



# Ethical Issues in Dementia Research

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## ABSTRACT

Dementia is a global public health issue with an urgent need for developing newer and more effective treatment strategies. Research in the area of dementia, however, poses unique ethical and legal challenges. Epidemiological studies, studies on pharmacological and non-pharmacological interventions have to deal with obtaining consent from persons with cognitive impairments, those from diverse cultural groups and need to contend with privacy and confidentiality issues. The caregiver support intervention research has not yet translated into policy change and effective clinical care. Biomedical research that involves invasive procedures may not translate into short- or long-term therapeutic benefits but is necessary research. Palliative care research in dementia has to deal with ethical issues involving people at end-of-life research. Proposed research may not receive approval, citing necessary safeguards to the vulnerable older people against invasive studies even when it is least invasive. This article aims to review the ethical aspects for safeguarding vulnerable older people with dementia and the potential challenges in conducting dementia research from a researcher's perspective.

Some of the safeguards for ethical research include determining capacity to consent, obtaining advanced directives in early stages and proxy consent from

caregivers, obtaining informed consent in cognitively impaired individuals. Future research policies need to consider the logistics of involving older people in research, enhancing caregiver support, and encouraging supportive decision-making. It will also need to address developing capacity assessment tools while addressing advanced care planning that will ensure the well-being of subjects in research.

**Background:** Dementia has become a global public health issue, with hospitalization rates being 65% higher in seniors with dementia than others.<sup>1,2</sup> The pressures on healthcare systems mean an urgent need to develop robust preventive and treatment strategies for dementia, which requires multidisciplinary research. However, the patient's stage of illness and ability to engage in discussions around the merits of participating in research and caregiver concerns is an important aspect of dementia research.

Hence, dementia research poses unique ethical challenges compared to populations with other diseases, which has led to the evolution of an ethical framework for dementia research. This article aims to review and give a viewpoint on the ethical aspects for safeguarding vulnerable older people with dementia and the potential challenges in conducting dementia research from a researcher's perspective.

**Keywords:** Dementia, Ethics, Research, Geriatric

## Materials and Methods

Systematic Review of PubMed was performed using the following search string to obtain studies on ethical issues in dementia research:

*(dementia[Title] OR ncd[Title] OR neuro-cognitive[Title] OR alzheimer[Title] OR cognitive[Title] OR cognition[Title] OR neuropsychology[Title] OR neuropsychological[Title] OR pick[Title] OR lewy[Title] OR frontotemporal[Title] OR huntington[Title] OR prion[Title]) AND (ethics[Title] OR ethical[Title]) AND (research[Title])*

Seventy six results were obtained, which included publications from 1984 to 2021. Results were filtered for the availability of free full text and, subsequently, 15 studies were left. References within the articles were reviewed to obtain a comprehensive review.

These articles were reviewed for relevance, and all were found suitable for inclusion in this review.

These articles were evaluated in detail (authors MC and HS ) to create the first draft. The second draft incorporated

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**HOW TO CITE THIS ARTICLE:** Chandra M, Harbishettar V, Sawhney H, Amanullah S. Ethical Issues in Dementia Research. *Indian J Psychol Med.* 2021;43(5S):25S–30S.

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**Submitted:** 25 Mar. 2021  
**Accepted:** 14 May. 2021  
**Published Online:** 12 Jul. 2021



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DOI: 10.1177/02537176211022224

FIGURE 1.

### Systematic Search of PubMed Using Search String

(dementia[Title] OR ncd[Title] OR neurocognitive[Title] OR alzheimer[Title] OR cognitive[Title] OR cognition[Title] OR neuropsychology[Title] OR neuropsychological[Title] OR pick[Title] OR lewy[Title] OR frontotemporal[Title] OR huntington[Title] OR prion[Title]) AND (ethics[Title] OR ethical[Title]) AND (research[Title])

76 Results were obtained  
Results were filtered for availability of free full text

15 Studies were reviewed. References within the article were reviewed as well and included in this review.

the clinical and research experience of the authors who had varying levels of experience. An in-depth discussion was held with all authors regarding various aspects of the paper on a virtual platform. The inputs from all authors were combined to formulate a viewpoint on ethical issues in dementia research.

The methodology is illustrated in detail in Figure 1.

## Ethical Issues Across Specific Types of Dementia Research

### Epidemiological Studies in Dementia

Epidemiological studies have dealt with consent issues in cognitively impaired populations with low baseline educational attainment or culturally diverse populations. Furthermore, there are often privacy and confidentiality issues in field settings, issues around medical care, and rehabilitative measures for identified persons with dementia (PwD). This raises questions about basic ethical issues of beneficence and non-maleficence. Another ethical aspect of dementia in low- and middle-income countries (LMIC) like India is the lack of culturally sensitive screening and evaluation instruments. Concerns about the validity of nosological criteria of dementia in uneducated, multiethnic, multilingual populations have not been adequately raised or addressed. There

is a genuine concern that instruments designed for the Western population may not be appropriate and may end up mislabeling and stigmatizing some with only age-related cognitive impairment. This is especially significant given that the treatment gap in dementia in LMICs is more than 90%.<sup>3</sup>

Dementia research has also investigated modifiable risk factors for dementia to identify targets for early intervention. Lower levels of educational attainment and decreased physical activity levels have been noted to be associated with Alzheimer's disease (AD).<sup>4</sup> Hence, the population-level increase in educational status and physical activity levels can potentially reduce the risk of cognitive impairment.

### Biomarker Research in Dementia

A major ethical issue in research on biomarkers in dementia has been a disproportionately excessive focus on AD, usually diagnosed as "probable AD"<sup>5</sup> even though other types of dementia commonly exist in clinical practice. Similarly, an emphasis on neuroimaging and biomarkers as indicators of dementia risk has not translated into clinical practice.<sup>6,7</sup> For example, it is known that up to 50% decrease in Cerebrospinal Fluid (CSF) A $\beta_{42}$  concentrations and twofold to threefold increase in CSF total tau increase in F<sub>2</sub>-isoprostanes occurs in AD or mild cognitive impairment. Still, these tests are

not routinely performed in clinical practice either for diagnosis or prognosis.<sup>8</sup>

This leads to a fundamental question on the nature of dementia research, which does not yield any diagnostic or therapeutic benefit to patients with dementia in the short or long term while subjecting cognitively impaired individuals for invasive and painful procedures.

## Research on Pharmacological and Nonpharmacological Interventions for Dementia

Both pharmacological and nonpharmacological interventions have been studied for dementia. While pharmacological intervention can be standardized, nonpharmacological interventions may not use a standardized treatment manual, which is ethically questionable. There is also a need to develop standardized methodologies for assessing nonpharmacological interventions to reach a more robust conclusion.

Among pharmacological interventions, there have been extensive trials on acetylcholinesterase inhibitors and memantine.<sup>9</sup> However, since 2003, no new drug has been approved by the FDA to treat AD. More than 200 therapeutic agents have been assessed, and then either they are abandoned or have failed investigational programs.<sup>10</sup>

Some Pharmaceutical companies like Pfizer have abandoned dementia research.<sup>11</sup>

A pertinent ethical question is about the rights of the participants with dementia who participated in these failed trials in good faith.

### Caregiver Support Interventions Research

Caregivers of patients of dementia face many challenges, with studies reporting 30%–55% of caregivers experience anxiety or depressive symptoms, which may adversely impact the quality of care provided to the patient.<sup>12–14</sup> Although studies have shown that psychosocial interventions may be effective in dementia caregivers to reduce their burden, they often face logistic barriers, stigma among caregivers, and a lack of structured instructional manuals.<sup>15</sup>

The beneficial impact of psychosocial intervention for dementia includes

delayed institutionalization of patients, improved symptomatology, and providing services that caregivers highly value.<sup>16</sup> However, despite robust evidence, caregiver interventions have not been translated into policy domain and clinical practice. This is not ethical considering caregivers have a significant burden because of caring for patients with dementia. The lack of translation of evidence-based, low-cost interventions for dementia in policy and clinical care across many nations globally raises important ethical questions for the future research.

## Clinical Trials

For developing new drugs for the treatment of PwD, clinical trials are essential, but it requires well written informed consent assent process and rigorous documentation before recruitment. Participants will need more intense monitoring compared to cognitively intact individuals.<sup>17</sup>

There is concern about the robustness of the informed consent process for clinical trials for dementia conducted in LMICs with a population with limited baseline educational attainment. In some situations, it may be necessary that an independent clinician may undertake capacity assessments and informed consent to get involved in research instead of those research staff involved in the study.

## Genetic Testing

Genetic testing for dementia includes testings for symptomatic individuals (diagnostic testing) and asymptomatic at-risk individuals (predictive testing).

Advance directives may be useful in such cases. As genetic testing results may affect the patient and other family members, familial genetic counseling is essential before testing and for disclosure of results.<sup>18</sup>

## End of Life/Palliative Care Issues in Dementia Research

It may be difficult to determine the lifespan of patients in advanced stages of dementia, and many patients receive palliative care in hospices in high-income settings.<sup>19</sup> Dementia research

may include some participants in palliative care or who enter palliative care during the research. This raises ethical dilemmas of prolonging life at the cost of quality of life to complete research. Transference of a patient in the end stages of life to an unfamiliar setting may also lead to ethical dilemmas. The ability to participate in research may vary based on the clinical condition, and this poses challenges for the researcher, having to reassess this every time. Many exclusions of research participants during research may not serve the purpose, and this poses an ethical question to those who are participating, whether the study serves its purpose.

## Ethical Dilemmas in Multicentric International Research

The 10/66 Dementia Research Group found that even though 66% of people with dementia live in developing countries, less than 10% of dementia research is conducted. Underrepresentation of LMIC populations with large absolute numbers of dementia is a fundamental ethical issue in dementia research and must be addressed by policymakers and grant agencies.

Even within LMICs, ethnic, linguistic, and religious minorities are underrepresented, necessitating the development of novel strategies to improve the participation of minority groups.<sup>20</sup> Equitable partnership and participation in research across social groups is an important ethical goal in dementia research pertaining to rights of participation and justice.

Researchers lead most multicentric international dementia research in LMICs from high-income settings. It is often found that many such protocols contain research instruments that have not been culturally and linguistically validated for the target population resulting in underreporting or overreporting of cognitive impairment and dementia. In addition, the informed consent documents in multicentric international trials may not be adequately translated to cater to the informational needs of target populations with low educational attainment, as is often the case in LMICs. They may result in a lack of awareness of rights and compensation to participants.

## Ethical Aspects of Data Sharing Agreement to Enhance Research Outputs

For dementia research to reach any breakthrough, it is important to use harmonized protocols and share anonymized data with strict precautions for confidentiality, privacy, and data stewardship for implementing big data analytics. Alzheimer Europe gave a report, "Data Sharing in Dementia Research," which reviews the recent changes in research policy and gives recommendations to aid data sharing in dementia research. This is ethical utilization of limited resources for dementia research, but such initiatives are lacking in the Asian context.<sup>21</sup>

## Ethical Issues Specific to Dementia Research

### 1. Consent

#### a. Capacity for Consent

Memory impairment, poor comprehension, hearing, or visual impairment at varying degrees is common in dementia patients. This poses a challenge for the investigators to obtain consent, and more participants with impaired ability to comprehend information will get excluded from the study. On the other hand, vulnerable PwD in institutional care may agree/disagree to participate in research due to possible coercion and fear. Some studies on PwD in advanced stages include PwD with sensory deficits, which are not likely to have competency. This makes such studies difficult due to ethical dilemmas and leaves a gap in the understanding of dementia and probable medical progress for the care of such patients.<sup>22-24</sup> The progressive and continuous nature of the illness may necessitate a periodic reassessment of capacity for consent to participate in the study.

#### b. Proxy Consent

If PwD cannot have impaired capacity to give consent, proxy consent from caregivers can be taken.<sup>25</sup>

An ethical issue with dementia research is that persons without supportive family or carers may be excluded from the research (and its benefits) because they lack adequate representation.<sup>26</sup>

In the case of proxy consent, the patient's beliefs must be kept in mind while making a decision.<sup>27</sup> Advanced directive may help in this aspect. However, some ethical issues emerge when proxy decision-makers decide as per their beliefs about the right decision for the patient.<sup>28</sup> Some research has shown that the data provided by proxies may differ from data provided by PwD.<sup>29-31</sup> In the decision-making in dementia research by caregivers, it is essential for researchers or the ethical committees to ensure that there is no secondary gain by the caregiver considering the late stage of illness and issues around property, will, or any other form.

#### c. Assent and Dissent

In dementia research, it is required to obtain both informed consent and assent.<sup>32</sup> Assent may be defined as "the agreement to participate in research-based upon less than full understanding."<sup>33</sup> In contrast to informed consent, which requires an individual to understand the research protocol,<sup>34</sup> to give assent, an individual must only have a minimal level of understanding to make a meaningful choice.<sup>35</sup> An individual's level of cooperation may be indicative of assent or dissent.<sup>36</sup> Frustration, discomfort, unhappiness, or passivity may indicate

a lack of cooperation in research or dissent.<sup>37</sup> A study which audio-taped informed consent encounters for research concluded that any interpretation regarding assent should be made with caution for PwD. Also, along with the cognitive aspect, the emotional and social dimensions of informed consent warrant attention.<sup>38</sup>

#### 2. Involvement of Older Age Group/ Severe Dementia

One of the main concerns for ethical issues in dementia is related to involving older people in research. Possible barriers may include physical and cognitive impairments, lack of transport, a lower threshold for burden, changes in routine, and negative beliefs about medication.<sup>39,40</sup> These factors may affect the risk-benefit ratio for participation in research. Issues of beneficence versus nonmaleficence may need to be addressed.

Recruitment and maintenance of older people in studies may also involve higher costs.<sup>41</sup>

On the other hand, failure to include older people in studies could lead to inequities in healthcare and biased results.<sup>42</sup>

A databases search (PubMed and CINAHL) has revealed that only 3%–6% of clinical trials were based on older populations.<sup>40</sup> Studies have shown that clinical trials may sometimes involve participants who are not representative of those for whom the medication is most likely to be used. Older individuals are often excluded from the trials.<sup>43,44</sup>

#### 3. Respect for Client Autonomy

Respect for autonomy may be difficult in PwDs on account of impaired cognition.

Researchers and Institutional Ethics Committees and Institutional Review Boards can uphold the ethical principles of respect, beneficence, and justice through the informed consent/assent process and objectively assess the risks and benefits of participation in research.<sup>45</sup>

#### 4. Caregiver Involvement

Higher involvement of caregivers in dementia research safeguards the rights of PwD.

Patient and caregiver should share a harmonious relationship. However, in some cases, PwD may object to being accompanied by a caregiver for participation in a study.<sup>46</sup> It has also been suggested that the involvement of the caretaker may amount to paternalism.<sup>47</sup> **Table 1** highlights the ethical issues in dementia research.

### Summary

The progressive nature of the disease in dementia with poor interepisodic recovery, involvement of older age group, high caregiver burden, and issues around consent poses unique ethical challenges around dementia research. Developing decisional capacity assessment tools, advanced care planning, and a standardized approach to research would help in addressing the ethical barriers

1. Involving the elderly population: Dementia research should include all age groups and all stages of severity so that results are not biased.
2. Research tools: Standardized manuals for nonpharmacological interventions need to be developed for a more structured research approach. Furthermore, developing culturally and linguistically validated instruments

TABLE 1.

### Ethical Issues Specific to Dementia Research.

1. (a) Capacity for Consent	Memory impairment and poor comprehension may interfere with the informed consent process. Periodic assessment of capacity for consent is needed, along with the development of capacity assessment tools.
(b) Proxy Consent	It is often needed in dementia research. Advanced directives are likely to help.
(c) Assent and Dissent	Useful when unable to obtain full consent. Cognitive, social, emotional/behavioral indicators, and level of cooperation may aid in deciding assent/dissent.
2. Involvement of Older Individuals	Medical comorbidities and lower threshold for burden may affect the risk-benefit ratio for participation in research. Issues of beneficence versus nonmaleficence may need to be addressed.
3. Respect for Client Autonomy	Difficult in dementia research due to cognitive impairment. Informed consent/assent and objectively measuring risk-benefit ratio would help.
4. Caregiver Involvement	Higher involvement of caregivers in dementia research safeguards the rights of persons with dementia, ensures a harmonious relationship between research participants and researchers, and minimizes conflict of interest.

TABLE 2.

**Recommendations for Ethics Committee and Regulatory Authority**

Expertise Involvement	Contribution of Expertise
Geriatric and dementia expert as member in the committee	To what extent the proposed research will make a difference? Does it need to be done on patients lacking capacity? Is there any least invasive alternative methodology to answer the research question, so could avoid including interviewing or examining or investigative procedures this proposed research? Is there a need for assessment of capacity to participate from an independent clinician? Safeguards against coercion in studies involving PwD residing in residential care home under-supported admission of Mental Healthcare Act 2017?
Representation through one caregiving family member in the committees	The views of family caregivers regarding the interests of the PwD are given importance. It is also possible that the concerned family members having experienced difficulties may wish to promote the particular research and be a better judge of risk and benefit, especially when the wider societal interest is considered.
Care providers' and trained caregiving staff members' views	In the case of PwD in residential care homes or receiving home nursing care, their views can add to the decision-making process for the Ethics Committee. Therefore, protocols must also involve finding out the potential harm.
Drug trials	The need for ongoing drug trials versus the potential harm: the trial may cause harm in the elderly patient population; which is to viewed differently compared to the adult population, as there is a lack of research. At the same time, the morbidity is anticipated to be higher in the years to come.

and harmonized protocols would help in a uniform approach to research.

3. Consent: Supportive decision/assent making should be done to ensure ethical safeguards. It should be assumed that PwD has capacity unless proved otherwise.
4. Advanced care planning: In the early stages of dementia, advanced directives should be formed not just for clinical care but also for research participation. This would enhance research participation while upholding ethics.
5. Decisional capacity assessment tools: Multiple approaches to assess capacity throughout the study would be useful.<sup>37</sup>

Along with capacity assessment tools that check decision making in specific areas, knowledge of the patient's hopes, beliefs, and personal history should also be used to document decision making and withdrawal of cons.<sup>48</sup>

6. Regulatory Frameworks: Each institution must also have a scientific committee to evaluate the feasibility and an ethics committee that upholds ethics of research and protects the rights of participants. Ethics committees may need to have representation of caregivers of PwD as well as experts in providing geriatric care, so to ensure a balance between the safeguards for vulnerable people and at the same time support growth of medical knowledge for serving greater societal interests.

Data Safety Management Boards—Serious Adverse Events reporting as per established protocols enhances ethical conduct of dementia research. Scientists should make the study results accessible to the wider scientific community by sharing them in institutional repositories. This allows for secondary data research and avoids unnecessary research in a vulnerable population. At the same time, data sharing and attendant scrutiny increase confidence in research implementation as per ethical and legal regulatory framework.

Recommendations for the ethics committee and regulatory authority are illustrated in **Table 2**.

**Declaration of Conflicting Interests**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The authors received no financial support for the research, authorship, and/or publication of this article.

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