

IN THE LITERATURE

When Does Therapeutic Misconception Affect Surrogates' or Subjects' Decision Making about Whether to Participate in Dementia Research?

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Abstract

"Therapeutic misconception" (TM) refers to inappropriate assumptions and beliefs on the part of research participants regarding key distinctions between the purpose, methods, intended benefits, and potential disadvantages of research compared to those of clinical care. Despite an extensive literature describing TM across varied types of research and populations, minimal work has addressed TM in the context of dementia research. This is a serious gap, for several reasons: people with dementia are at significant risk of diminished capacity; surrogate decision makers are typically asked to provide consent on behalf of the person with dementia; and available treatments for dementia are quite limited. More research is needed on the prevalence, nature, and impact of TM in the context of clinical dementia research.

Introduction

Over 30 years ago, Appelbaum, Roth, and Lidz coined the term "therapeutic misconception" (TM), which they initially defined as the inappropriate assumption by research participants "that decisions about their care are being made solely with their benefit in mind" [1]. For example, citing the work of prior authors, they noted that randomized assignment sacrifices, to a degree, research participants' interests (or right to "personal care") for those of research design in order to advance science for potential future benefit of others. Participants' incorrect assumption that decisions are made to advance their personal therapeutic benefit is the crux of therapeutic misconception and may compromise informed consent. In a seminal article titled "False Hopes and Best Data: Consent to Research and the Therapeutic Misconception," Appelbaum and colleagues [2] provided further descriptive evidence of TM based on interviews with 88 patients with a range of psychiatric disorders, conducted immediately after the participants provided informed consent to participate in one of several clinical studies. The findings indicated that many participants failed to appreciate key distinctions between the purposes, methods, intended benefits, and potential disadvantages of research compared to those of clinical care. For example, a 25-year-old woman with a high school education, who consented to participate in a randomized, placebo-controlled trial of medication for a nonpsychotic psychiatric disorder, stated that she believed "the

placebo would be given only to those subjects who ‘might not need medication’ [3].

In this commentary, we first briefly examine the general importance of considering TM and advances in assessment of TM. We then describe its application to research involving people with dementia.

The Construct of Therapeutic Misconception

A review article on informed consent found that a large proportion of research participants, in medical as well as psychiatric or dementia trials, show poor comprehension of various key aspects of consent-relevant information [4]. However, misunderstanding the intent of a clinical trial as designed to provide individualized therapeutic benefit has special weight and importance beyond evidencing poor general comprehension of disclosed information. Although there is substantial overlap between [research ethics](#) and clinical ethics, they are not synonymous, and the ethical obligations of a researcher to the individual participant are not fully equivalent to those of a clinician to an individual patient. Most notably, clinicians are ethically compelled to act in the best interest of their individual patients. Researchers, by the very nature of research design (such as use of placebo control, fixed dosing, and assessments that are not needed for clinical management) sometimes violate the ethical mandates of personalized clinical care. As Appelbaum notes, “insofar as the justification for a departure from the principle of personal care is premised (at least in part) on the subject’s knowing relinquishment of an entitlement to a physician’s undivided loyalty, a subject’s failure to appreciate that this is occurring renders consent invalid” [5]. Appelbaum and colleagues recommended steps to mitigate the therapeutic misconception through better education of participants about differences between research and clinical care in order to help them better assess the risks and benefits of participating in research [2].

Many articles describing, defining, and debating TM have been published in the years since the emergence of the concept. Empirical studies have painted a detailed portrait of TM as pervasive across nearly all types of research studies and clinical populations [6-10]. The definition of TM has been discussed at length, with attempts at an expert consensus definition [11] as well as further refinement of the concept into several subtypes [6, 12]. A recent article by Lidz and colleagues offered a conceptual basis for TM, in which the authors argued that

TM does not primarily reflect inadequate disclosure or participants’ incompetence. Instead, TM arises from divergent primary cognitive frames. The researchers’ frame places the clinical trial in the context of scientific designs for assessing intervention efficacy. In contrast, most participants have a cognitive frame that is personal and focused primarily on their medical problems [13].

This conclusion implies that efforts to mitigate TM require challenging participants' cognitive frame, i.e., invoking a paradigm shift within participants away from interpreting disclosed information within a clinical-care schema toward interpreting it within a research schema. Finally, the ultimate question of the ethical significance of TM has been thoroughly discussed and debated as well, with some commentators arguing that the laxity of definitions might lead to overheated concerns about TM [14-16].

Attempts to measure TM have also been made, although assessment of the prevalence of TM has been hampered by the absence of a standardized measure of TM. Most recently, Appelbaum and colleagues have developed a psychometrically strong ten-item instrument to screen for TM based on semistructured interviews coded for the presence of several types of TM [12].

Therapeutic Misconception in Dementia Research

Despite the extensive general literature on TM in a broad range of clinical research participants, there has been minimal work specifically examining TM in the context of dementia research. This is a serious gap, for several reasons.

Participants' diminished capacity. First, people with dementia are at significant risk of diminished capacity to consent to research as a result of cognitive impairments, which can impede their ability to understand disclosed information, appreciate the significance of that information for their own situation, reason with the information, and express a decision about participation [17-19]. Studies of capacity to consent to research among people with dementia consistently demonstrate loss of capacity around the time of transitioning from mild to moderate dementia [17-19]. Persons with mild cognitive impairment (MCI) also demonstrate impairments in decisional capacity [20]. Therefore, even in people with MCI or mild dementia, the ability to understand the distinctions between research and clinical care and how these distinctions may affect one's own well-being in a clinical trial may be cognitively out of reach. Of note, in a study of capacity to consent to research among people with mild-to-moderate AD [17], 20 of 37 in the AD group scored 4 or lower (on a 6-point scale) on the "Appreciation" subscale of the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) [21] that arguably most closely targets elements of TM, whereas none of the 15 control participants scored lower than 5. Because the MacCAT-CR Appreciation subscale does not explicitly target TM, these data do not definitely establish that AD is associated with greater risk of TM, but they do at least strongly suggest that possibility, warranting further empirical attention.

Surrogate TM. Second, when people with dementia participate in research, the most common method used by researchers and accepted by institutional review boards (IRBs) for dealing with loss of capacity is the use of "double consent"—i.e., informed consent

provided by a surrogate decision maker (usually the patient's spouse or adult child), alongside the individual patient's assent to participate [22, 23]. Because of a confusing legal landscape surrounding [surrogate consent](#) for dementia research, however, the regulations and guidelines for obtaining surrogate consent remain somewhat ad hoc. The relevant sections of the Code of Federal Regulations do not clearly establish the qualifications for surrogate consent (or the qualifications of a legally authorized representative for research consent) beyond referring to applicable federal, state, or local laws [24]. This lack of clarity leaves each investigator and IRB responsible for ensuring adherence to applicable state laws (which frequently do not directly address the issue) and assuring adequate participant safeguards [25]. As is the case with consent provided by decisionally capable participants, there is no strict requirement that surrogate decision makers prove that they do not hold a therapeutic misconception about the specific research in question. As long as applicable state law recognizes the surrogate as the person legally authorized to provide consent on behalf of the research participant, and as long as the participant does not actively resist participation, the surrogate is allowed and assumed to provide informed consent for the participant.

Implications of limited treatments and surrogates' "informed" consent. Third, the limitations, in terms of both number and effectiveness, of available therapeutic agents for dementia [26] raise important questions. Most importantly, could "false hopes" or even desperation make surrogate decision makers particularly susceptible to TM in the context of clinical trials for dementia research? Also, how can an investigator or an IRB be assured that surrogate decision makers adequately understand the purpose of the research as distinct from clinical care, assess the research-related risks appropriately, and appreciate limitations on direct personal benefit for the individual patient? And, when making a decision on behalf of the patient, how should surrogates weigh risks and benefits? Does TM affect their decision making, even to the point of overriding the patient's preferences? The latter is an empirical question warranting further study.

Studies of Surrogate Decision Making in AD Research

Unfortunately, minimal research has been conducted that can address the questions posed in the above section. In order to better understand the research-related motivations and perspectives of surrogate decision makers of people with dementia, the first author (LBD) and colleagues conducted two studies of surrogate decision making for dementia research. In the first study, Dunn and colleagues interviewed 82 surrogate decision makers for people with any stage of Alzheimer's disease (AD), randomizing them to informed consent for one of three hypothetical protocols that differed in described levels of risks and potential for direct benefit [27]. Among surrogates who stated they would enroll their relative in the study, reasons given included the potential for direct benefit to their relative, altruism, and trust in researchers. Those who stated they would not enroll their relative cited risks, inconvenience, and stage of illness. Dunn and colleagues did not explicitly attempt to measure TM in this study; however, at least

some of the surrogates' statements reflected awareness that while the patient might not benefit directly, other patients might benefit. As one surrogate put it (speaking about the patient's feelings as well), "We both feel her experiments with AD may not help her but can help others" [28].

In another study of surrogate decision making for AD research, Overton and colleagues [29] and Dunn and colleagues [30] interviewed a total of 65 surrogate decision makers (primarily spouses and adult children) for people with AD. Each surrogate was randomly assigned to one of four hypothetical clinical trials for a fictional investigational drug for AD created by crossing two levels of risk and two levels of potential benefit. In-depth interviews assessed potential influences on the surrogates' decision making and willingness to enroll the patient in the protocol, their perceptions of protocol risks and benefits, and their willingness to override the patient's preferences for research participation. The authors were particularly interested in understanding, through in-depth interviews, how surrogates considered, interpreted, and acted upon abstract ethical principles (e.g., substituted judgment, best interests) in different aspects of research decision making, including whether there was an apparent influence of TM on such decisions. Based on qualitative analyses of two subsets of interviews, the authors reported that surrogates translated these ethical principles into specific duties. Substituted judgment was framed as honoring the patient's wishes and values. Best interests took the form of a perceived duty to do their best to maintain the patient's quality of life and avoid burdens or risks. The authors found that surrogates also were trying to discern (e.g., by reading into the patient's behavior) the patient's current preferences about research, either in conjunction with or in contrast to trying to base their decision on the patient's premorbid preferences regarding research.

There is reason for both hope and concern in the above findings. On the one hand, some of the reasons for consent (and refusal) provided by surrogates are very much in accord with ethical standards. One of the quotes above suggests a shared realization by the surrogate and person with AD that the research may have no personal benefit, while emphasizing their shared desire to participate in light of the possibility that the research might lead to help for others with AD in the future. This is indeed the core scientific motivation for the conduct of clinical research. There was also evidence that surrogates were trying to engage their loved ones and consider their current preferences, to the extent possible, in making the decision. This is very much in honor of the principle of autonomy, as an individual's lack of capacity to fully understand and legally consent to a protocol does not mean that he or she no longer has ongoing preferences that should be weighed in the decision. However, there were also some aspects of the findings that did suggest the potential influence of TM, e.g., when surrogates cited direct benefit to the person with AD even though the nature of the trial made such direct benefit unlikely. Together, these findings suggest there can be no "one size fits all" determination or conclusion about the influence (or lack of influence) of TM in surrogate decisions in AD

research.

Conclusion

Empirical research on TM among surrogate decision makers for participants in dementia research is desperately needed to guide policy and practice. What surrogate, patient, protocol, or environmental (e.g., consent method) characteristics foster or diminish TM? What is the nature of TM in dementia research, and how does it specifically manifest in reference to various types of AD research or at various stages of the disease? The answers to such questions are simply not available at present, but it is ethically imperative that the data needed to answer these and related questions be generated. Given the 2017 changes to the Common Rule overseeing research [31], which will be policy for the foreseeable future, such empirical data are needed immediately.

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