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The Therapeutic "Mis"conception

An Examination of its Normative Assumptions and a Call for its Revision

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Abstract: This article examines some of the assumptions and implications associated with the Belmont era context in which the concept of therapeutic misconception was forged. We argue that the justification of therapeutic misconception should be reconsidered based on less paternalistic and more participatory models of research. Finally, we identify conceptual and practical approaches that might better reflect contemporary research practice.

Keywords: therapeutic misconception; Belmont Report; paternalism; research practice

Introduction

Since its introduction in 1982, the concept of therapeutic misconception has played a significant role in understanding the informed consent process in clinical research.[1] Paul Appelbaum and colleagues originally defined therapeutic misconception as an inappropriate assumption on the part of a patient enrolled in research "that decisions about their care are being made solely with their benefit in mind," which hampers proper informed consent by compromising an individual's ability to make appropriate risk-benefit appraisals. However, in the 30 years since Appelbaum and colleagues' article, the research landscape has changed in significant ways. Research today is more participatory and patient focused; many patients advocate for a right to participate in rather than be protected from research. The nature of early cancer trials in which much of the research on therapeutic misconception has taken place, has shifted away from strict Phase I trials and toward hybrid trials that admit the possibility of individual benefit. In response to these shifts and others, human subject research policy in the United States is being reconsidered, as the government tries to determine how best to ensure that the system as a whole upholds the central tenets

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of respect for persons, beneficence, and justice.[2] One important aspect of this reconsideration should be the understanding and use of the concept of therapeutic misconception.

Over time, therapeutic misconception has been broken down (or expanded, depending on one's perspective) into its constituent parts, including the core of therapeutic misconception (misconstruing research as clinical care) and the related concepts, therapeutic misestimation (incorrectly estimating the probability of risk or benefit) and therapeutic optimism (belief that one is more likely to benefit than statistically predicted). There has been discussion and debate regarding the value of therapeutic optimism, in particular, with oncologists arguing that it is beneficial to treatment, and others asserting the opposite. We suggest that whereas therapeutic misconception and its brethren were important concepts in the Belmont era, when the focus was on protecting vulnerable populations, the utility of such concepts as therapeutic mis-estimation and therapeutic optimism, and in some cases the core of therapeutic misconception, should be reconsidered.

"Therapeutic Misconception" and Related Concepts

Concerns about the misunderstanding of the distinction between clinical care and research (the "core" of therapeutic misconception), supported by the Belmont Report's definition of research, led to studies attempting to understand and prevent therapeutic misconception. Over time, the definition of therapeutic misconception was expanded, spawning the related concepts of therapeutic mis-estimation and therapeutic optimism. These concepts have been developed and studied, like the core of therapeutic misconception, as problematic understandings on the part of a (prospective) research subject, the presence of which compromises fully informed consent. These derivative concepts related to therapeutic misconception have persisted despite the perceived value of optimism and hope in the oncology community[3] and the failure by well-respected groups to include them in their definitions of therapeutic misconception.[4] It is of note that Henderson et al. (2007), in their attempt to develop a consensus definition, struggled with the evolution of the term over time, ultimately focusing instead on the goal of research: "Therapeutic misconception exists when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the participants enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial." Horng and Grady[5] have gone so far as to say that "[o]ptimism alone should never be ethically problematic" and in many cases should be actively preserved or supported, though others strongly disagree with this view.[6]

Therapeutic Misconception in Context

Therapeutic misconception, first noted by Appelbaum and colleagues in psychiatric patient-subjects, grew out of the same history of abuse that spawned the Belmont Report, including the history of abuse of psychiatric patients.[7] The focus, understandably and appropriately, in the 1970s and 1980s was on protecting research subjects from abuse by researchers. Psychiatric patients, in particular, had been identified as an especially vulnerable population in need of protection.[8] In a context in which oversight was absent or nascent, norms had yet to be developed, and investigators routinely behaved in ways that failed to respect research subjects as

ends and treated them as mere means, research subject protection was (and still is) a high priority, both in policy and in practice.

Over time, the research environment has improved, oversight structures are now well established, and norms with regard to human subject protection are in place (although certainly neither of these are perfect or perfectly functioning). Perhaps most importantly, attitudes toward the mentally ill have changed. It is now appreciated that individuals with psychiatric conditions are more capable of participating in the consent process than once was thought, making paternalistic protections less necessary. Recent data suggest that people with serious psychiatric disease, such as treatment-refractory depression and obsessive compulsive disorder, for example, are no different from others with severe, chronic conditions with regard to their capacity to consent to treatment or enrollment in clinical research.[9] Further, our attitude toward patients broadly has changed. Although the regulation of research remains protectionist, theoretical work in bioethics and notably neuroethics—as well as many patients and patient advocates—has convincingly argued for the rights of individuals (independently or through a surrogate decisionmaker) to participate in the research process rather than be subject to it.[10] In clinical care, patient-centered outcomes reflect a similar rationale. Inclusive language such as "therapeutic alliance" has gained traction, and partnerships between researchers and patients are, if not common, unsurprising. Finally, early oncology trials—a focus of therapeutic misconception research—are increasingly designed to include the possibility of individual benefit. Given these and other changes in the landscape,[11] the concept of therapeutic misconception, in its original form, needs to evolve, and its ethical justification needs further clarification and refinement for the concept to remain valid and useful.

Although understandable given the history and context of its development, therapeutic misconception represents Belmont era language, and is reflective of the paternalistic stance that was perhaps necessary at the time, although ironically this occurred during the age of autonomy. Therapeutic misconception was viewed as an inherently problematic characteristic of the vulnerable patient, which compromised informed and, therefore, autonomous decision-making. Now, it is recognized that the concept has a more global impact because of its negative connotations. The moral valuation placed on the term, parsed or not, is that if a (prospective) research subject has it, it is bad. The implication is that in all cases, when therapeutic misconception, therapeutic mis-estimation, or therapeutic optimism is detected, corrective measures should be taken.

The problem with this situation is twofold. First, the moral valuation of the core concept of therapeutic misconception has been extended to states of the research participant[12] (e.g., optimism) that might be adaptive and whose absence should give pause. Second, it is unclear that the moral problem lies essentially in the (potential) participant's conceptions of a research project, rather than in the interaction between the participant and investigator, and the results of that interaction. That is, the locus of concern may be wrong.

Reconsidering the Therapeutic Misconception

Moral Valuation

Therapeutic misconception has been so ingrained in the thought processes (and regulatory structures) about research and

informed consent that we have come to think of it and its more recent kin as always disqualifying, and as undermining fully informed consent, but is this justified? In the oncology community, Horng and Grady ask, "should we insist that subjects not have any expectation or hope or benefit?" Is that not part of our nature? Hope has been described as an active engagement with life that brings meaning and purpose to one's existence and experiences.[13] On their face, the presence of engagement, meaning, and purpose do not seem to threaten informed consent. One could argue that the opposite might be true. Might not one worry about someone who consented to a trial, but who was completely devoid of hope or optimism about his or her prospects in that trial? In a recent investigation of therapeutic misestimation and therapeutic optimism, Pentz et al. found that more than one third of their sample were actually therapeutic pessimists.[14] Is therapeutic pessimism also disqualifying?

It is true that there are levels of unrealistic optimism (and pessimism) that are problematic and should be addressed, but to disabuse patients of hope seems both wrongheaded and in itself a misunderstanding of normal human functioning and adaptation. Importantly, when Pentz et al. probed their participants displaying therapeutic optimism (an inappropriate estimate of personal benefit), only 18% (17 responders) said that they were stating a fact. The majority (78%) of these participants said that their estimate was what they hoped would happen, or that they felt that it was important to maintain a positive attitude. Likewise, Kim et al. concluded that the disjunction between their participants' understanding of randomization and the application of that understanding to their own chances of being in the treatment arm was a result not of unrealistic hope, but rather of the participants' understanding of the question in the context of the interview: they were not attempting to demonstrate their knowledge of statistical likelihood, but rather were conveying their hopes about what would happen.[15] To label those individuals as suffering from therapeutic or unrealistic optimism in such contexts assumes that such people cannot be both hopeful and appreciate that they are in an investigational trial without a promise of therapeutic benefit. Further, such a belief reveals a misunderstanding on the part of the investigator, not a problem within the participant. Indeed, evidence is growing that those who hope against the odds are not necessarily deluded or confused, but might simply be hopeful.[16] People can hold multiple understandings of reality in their heads simultaneously[17] – to wit, Cubs fans.

Locus of Concern

In addition to reconsidering the moral valuation of labels and patients, it is also important to recognize that there are two individuals, perspectives, and understandings in each interaction, rather than one individual (the patient) with imperfect understanding. To accurately reflect this reality, all the questions and labels that we as researchers might study with respect to participants ought also to be studied for investigators, as some have done with respect to therapeutic misconception.[18] Given the importance of the relationship between participant and investigator, the concept of therapeutic optimism, as a continuum and unrelated to the core of therapeutic misconception, should also be appreciated and studied in both partners in this dyad. For example, should one want the surgeons who place deep brain stimulators or who perform heart transplants to be optimistic that their ministrations or investigations are going

to prove beneficial and instructive? Would adaptation necessary to invading the brain or chest of another human be called confidence? Would it be called hope, or rather, therapeutic misconception? Having a surgeon with no interest in the individual patient/participant in front of him or her, focused solely on the science at hand, who proceeded happily to cut into the person's skull, would arguably be highly problematic. What constitutes acceptable or unacceptable levels of confidence/therapeutic misconception in surgeons?

In extreme form, therapeutic misconception or therapeutic optimism could distort the consent process, as many individuals enrolling in research do so because of their relationship with and trust in their physicians,[19] and should be ameliorated with the aid of consent monitors, recruitment, and consent scripts. In its usual form, therapeutic optimism should be framed as an understandable, expected and entirely normative aspect of clinical research.

Post-Belmont Explorations

Normative Assumptions of the Therapeutic Misconception

Given the evolution of research ethics and regulation since Belmont, and the aforementioned issues, it is time to step back and reconsider the normative and conceptual aspects of therapeutic misconception, most notably the bias about the participant's understanding of research inherent in this and related terms. Labeling of the presumed "vulnerable" patient is more reflective of the research ethics born of the abuses that spawned Belmont, than of a well-regulated research enterprise, and the more participatory tone and trend that there is in research today. Individuals enrolling in research make decisions based on many factors, not all of which align with researchers' and institutional review board's (IRBs) views of the facts relevant to the decision.[20] Taking into account or relying on factors other than those deemed legitimate by researchers for their decisions does not necessarily imply that these prospective participants are irrational or vulnerable.

Given this, and in line with Henderson et al. (2007), we maintain that "therapeutic optimism" should not be part of the definition of therapeutic misconception. Rather, both therapeutic optimism and therapeutic mis-estimation should be considered separately and studied independently in both participants and investigators, with neither a positive nor negative valance ascribed to these states. Assigning a negative prefix to these terms and labeling what in many cases may be a reasonable and perhaps even adaptive view of research as a *mis*-conception or unrealistic comes from a separate judgment. This secondary judgment should be independently examined for its potentially paternalistic, rationalistic, or reductionistic assessment of individuals' understanding of the information presented by or to them during the informed consent process.

Our proposal enables optimism in research to be evaluated independently and objectively, without prejudgment as to whether it will ultimately be found to be helpful or a hindrance with respect to informed consent and trial participation, and leaving open the possibility that at least some levels of hopefulness are positive and should even be supported. Further, this frame allows one to think of optimism not as binary, but as a matter of degree, thus opening up space for specific questions such as, "How much optimism is too much?" And conversely, "How much is instrumental?" For example, it seems clear that those who understand that a given trial has only a 10 percent chance of benefit, yet are *convinced* that they personally

will benefit, have a problematic level of therapeutic mis-estimation. But what of those who, faced with the same odds, says that they are optimistic that it will help them, "because I have to be, right?" On the other hand, if there is some prospect of benefit, but the probability and magnitude are unclear, should researchers be comfortable enrolling individuals who are entirely hopeless about their prospects? We as researchers would certainly not want to enroll individuals who are suicidal or so depressed that their decisionmaking capacity is compromised, but is there a level of hopelessness not as extreme as clinical depression that should also be concerning? Hope gives purpose and meaning, even to suffering, but hope, as therapeutic optimism, has been swept up in the therapeutic misconception debates and tarred with the same brush. Perhaps there is a "Goldilocks" level of optimism or hope that is not too much, but not too little, and within this range, therapeutic optimism, or hopefulness, ought not be considered disqualifying or even problematic.

A New Model: From Rational Congruence to Reasonable Coherence

The conventional view (rational congruence; Figure 1a) on therapeutic misconception is that a basic misunderstanding on the part of the participant exists relative to a rational and objective observer (i.e., the researcher or IRB), who understands the activity as a "study" or a "research project." According to this view, the researcher or IRB stands in a privileged position as the initiator of the study and also as the one who truly understands its goals. When the participant's understanding does not mirror the investigator's, this is detected as a defect to be rectified and short of that, a reason to exclude a participant from the study. The virtue of the congruence standard is its apparent objective determination of problematic distances between expert and participant perspectives. Remediation is, therefore, defined as an alignment of those perspectives. However, this view fails to capture the richer relational, contextual, and positional aspects of the researcher–participant interaction, in which misalignment can stem from either or both sides of the dyad. For example, the researcher could be an active contributor to the gap between the participant's perspective and the researcher's own. Investigators are not impartial observers, especially given that their own interests motivated the study.[21]

The congruence standard requires that there be no negotiation of this understanding because the "value" (assessment of risk and benefits, optimism) arrived at by the participant must closely match that of the researcher, as the objective standard. This framing of the situation lacks psychological plausibility and undermines respect for participants,

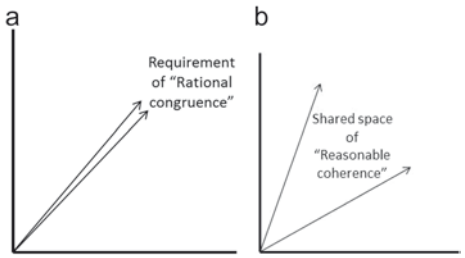

Figure 1. (a) Standard of rational congruence. Therapeutic misconception describes lack of agreement between participant and expert perspectives. Ideally, the participant's understanding of the study should concur with that of the investigator or expert assessor. **(b)** Standard of reasonable coherence. Therapeutic misconception does not simply describe lack of congruence between participant and expert perspectives but rather a problematic distance between these perspectives. X= assessment of benefits; Y= assessment of risks; arrows indicate separate assessments of research participant and investigator.

their decisionmaking processes, and their autonomous analysis of the value associated with trial participation. As John Dewey once wrote, the layman is an expert in determining where the shoe hurts.

In contrast to rational congruence, a standard of reasonable coherence (Figure 1b) would acknowledge differences in assessment between researcher and patient, and creates an opportunity for a negotiated understanding. The standard of reasonable coherence implies that some disagreement is admissible—perhaps even expected—given differences in knowledge, experience, and perspective. Space is, therefore, opened to establish some coherence between the investigator's and patient's understandings of the benefits and harms of the study. Rather than reflexively and pejoratively labeling the lack of congruence as therapeutic mis-estimation or optimism, the coherence model seeks to understand the magnitude of the difference between what the investigator expects (and presents to the IRB) and what the patient expects, and the significance of this difference for study participation. This metric is more nuanced than the categorical of the rational congruence model and is also variable from study to study, based on the context of the trial and the stakes at play; for example, divergence on the expectations about a minimal risk study carries different consequences, and, therefore, different weight, than the same divergence in an invasive, high-risk trial.

Although we believe that the reasonable congruence model is more suited to the research enterprise, it is challenged by the risk of potential relativism without any reference to an objective benchmark. This potential liability can be tempered by empirical work that seeks to build external reference standards, based on the understanding of the "average" or "reasonable" participant, similar to that which emerged out of the legal history of informed consent in clinical practice (e.g., referring to the information that a reasonable patient would want to have to make a decision about a given treatment).[22] Such a standard would acknowledge that it is critical that investigators—and oversight structures—allow for reasons, justifications, and hopefulness that do not necessarily map cleanly onto their own decisionmaking and ways of thinking about and experiencing the world. The further definition of a reasonable congruence standard will require empirical data on participant expectations within or across trials of a given class, defined by the type of intervention, the level of risk, and the probability of individual harm and benefit, as well as the actual impact of differences in expectations. The standard might also take into account—but not be defined by—expert knowledge (e.g., IRB, expert group/peers), which, if considered in isolation of patient perspectives, would risk perpetuating the paternalistic stance reflected in a congruence standard. Common sense red flags can be triggered when there is an obvious lack of coherence as a result of problematic distortions of risk or benefit on the part of the participant or investigator. The interpretation of smaller differences in perspective, and the assessment of what constitutes reasonable coherence, require further conceptual specification and empirical investigation.

Conclusions

In the decades since therapeutic misconception was first introduced into the literature, the research landscape has evolved with regard to the conduct of research and clinical care, research oversight, and understanding of the psychology of decisionmaking and coping. A concept of the Belmont era, therapeutic

misconception is at once defensive and protective, rather than collaborative, with a misplaced paternalism that was intended to protect vulnerable patients but actually undermines respect for persons by discounting and even discarding the legitimate perspectives of research participants. Further, therapeutic misconception in its different forms, including therapeutic mis-estimation and therapeutic optimism and pessimism, connotes a paternalistic and overly "rationalistic" or cognitive understanding of the research enterprise. Changes in the research landscape and the literature must be accommodated, and a plausible, evidence-informed, appreciation of relational and personal dynamics needs to be brought to this collection of concepts. Once gross therapeutic misconception-based problems of patient abuse and protection are excluded, a space opens up for collaborative and deliberative negotiation to assess a range of research conceptions. By disaggregating value judgments about the participant's understanding of a trial and degrees of optimism or pessimism, and refocusing on the participant–researcher dyad, we can better capture the complexity of the consent process and work toward more collaborative and truly respectful approaches to research participation.

Notes

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