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HISTORY OF RESEARCH INVOLVING MENTALLY DISABLED PERSONS - FROM EXPLOITATION THROUGH EXCLUSION TO APPROPRIATE INCLUSION

ISTORIJA ISTRAŽIVANJA NA MENTALNO OBOLELIM LICIMA – OD EKSPLOATACIJE PREKO ZABRANE DO ADEKVATNE INKLUZIJE

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Summary
Introduction. The inability to protect their own interests makes mentally disabled subjects particularly vulnerable; they face an increased likelihood of being wronged or harmed in the context of research. Therefore, they are due to having extra protection and safeguarding. History of research misconduct and abuse of mentally ill patients. The 20th century abounds with examples of ethically inadmissible experiments conducted on decisionally impaired patients. The most infamous among them are surely the atrocities of the Nazi doctors, whose fraudulent experiments resulted in death of hundreds of thousands of imprisoned innocent and mentally ill individuals. Current and previous regulations and recommendations on research involving the mentally ill. Extreme use of potentially vulnerable mentally ill persons in research has led to a set of policies and practices for protection from exploitation and abuse of human research participants. While the regulations initially protected these vulnerable patients by prohibiting research including the mentally disabled, current guidelines propose appropriate safeguarding so that they may be involved in appropriate research. Conclusion. Protection measures for the mentally disabled persons who are unable to consent to their involvement in research, by banning all biomedical research including the mentally ill are restrictive and unnecessary. Even if well-intended, such overprotection is discriminatory and implies that new treatments for conditions that directly affect the incapacitated subjects will not be developed. Providing that they are properly protected from unnecessary harms, appropriate inclusion of vulnerable mentally ill patients in research is necessary in order to meet their health needs in a safe manner.

Key words: History of Medicine; Mentally Ill Persons; Codes of Ethics; Human Experimentation; Patient Rights; Informed Consent; Bioethics; Psychiatry

Sažetak

Ključne reči: istorija medicine; mentalno obolele osobe; etički kodovi; eksperimenti na ljudima; prava pacijenata; informisani pristanak; bioetika; psihijatrija

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Introduction

Mental health care has a well-documented history of patient neglect, patient-subjects abuse, and stigmatization [1]. Since the World War II (WW II), through dubious experiments on humans that earned the investigators Nobel Prizes, to various misconducts in the developed world up until the late 20th century, mentally ill patients have suffered from being inappropriately included in medical research. Inclusion of potentially vulnerable mentally ill individuals in research, especially in research they were unlikely to benefit from, has led to a set of policies and practices to protect human subjects from exploitation and abuse in research [2]. The main goal of this study is to provide a comprehensive historical overview of abuse of mentally ill patients in research, demonstrate how reactions to research misconduct shaped previous and current regulations and recommendations on research including the mentally ill, and outline how and why those regulatory documents have shifted their focus from protective exclusion to appropriate inclusion of these vulnerable patient-subjects into research.

History of research misconduct and abuse of mentally ill patients

Like ghosts from a dark past, the victims of research haunt the dream of biomedical progress, returning again and again to raise the harsh reality of dignity violated, integrity invaded, and lives destroyed [3, p. 25].

When the horrors of the Nazi doctors were revealed after the WW II, it was realized that the atrocities of the Holocaust were preceded by a systematic program designed to eradicate the disabled and others whose lives were “unworthy of life” [4]. The emphasis was placed on the burden that the mentally ill and their facilities represented for the healthy who supported them. “Selective breeding” and “special treatment” were cover-names for forced sterilization of the mentally and physically disabled. Once the war began, efforts were made to realize the T4 euthanasia program, in which 70,000 were killed in “hospitals of death” by 1941 in the name of “racial health” and in order to eliminate the financial burden of caring for those deemed unworthy of living [5]. There is evidence that, under the Action T4, more than 200,000 children and adults who were identified as “defective” were killed at the institutions that once provided care for them [4].

Moreover, experiments were conducted on mentally ill patients primarily to improve mass-murder techniques, as a rehearsal for the subsequent persecution of Jews, Roma, homosexuals and others demonized by the ruling Nazi party. This included improving the effectiveness of the gas chambers from the T4 program, which were later shipped to concentration camps and used for the extermination of ethnic and social minorities. As the mentally ill have already been sentenced to death, medical professionals of the time “put them to use” justifying their inclusion in all kinds of tortuous, unethical and unscientific experiments [5].

Unfortunately, the dark times of the Nazi-era were not the first time that the unwilling and unaware mentally ill patients were abused under the veil of medical research. Their ready availability, powerlessness, and lack of autonomy made them extremely vulnerable to exploitation. Many praiseworthy discoveries used unwitting and non-consenting patients, such as the discovery of malaria-induced fever treatment for paralytic dementia caused by tertiary syphilis fever that earned Julius Wagner von Jauregg a Nobel Prize in Medicine or Physiology in 1927. Another psychiatrist won the Nobel Prize for his “discovery of the therapeutic value of leucotomy in certain psychoses” [6]. In 1949, António Egas Moniz was so rewarded for his experiments on severely mentally ill patients using frontal lobotomy. The use of non-consenting patients as research subjects by von Jauregg, Moniz and others was a common practice at that time [7].

Unlike these two Nobel Prize winners, whose research included non-consenting patients with the goal of benefiting the subjects or address the conditions of disability, there were others who took advantage of institutionalized and decisionally impaired individuals for research on conditions not related to mental disorders. Two prominent examples of such non-therapeutic research experiments were conducted at two Massachusetts schools for “mentally retarded” children and adolescents. In the 1940s and 1950s, for instance, residents of the Walter E. Fernald School were given oatmeal containing minute amounts of radioactive material, as part of a study that was designed to establish how the body absorbed minerals from dietary sources and explore the effects of different compounds on mineral absorption. Similarly, in 1961, residents of the Wrentham State School were administered small amounts of radioactive iodine, with the goal of determining the amount of nonradioactive iodine that could block the uptake of radioactive iodine in the event of a nuclear war [8]. In 1995, the Final Report to the President by the Advisory Committee on Human Radiation Experiments found that:

Even at the time, government officials and biomedical professionals should have recognized that when research offers no prospect of medical benefit, whether subjects are healthy or sick, research should not proceed without the person’s consent. It should have been recognized that despite the significant decision-making authority ceded to the physician within the doctor-patient relationship, this authority did not extend to procedures conducted solely to advance science without a prospect of offsetting benefit to the person. This finding is supported by the moral principle, deeply embedded in the American
experience, that individuals may not be used as mere means toward the ends of others [8, p. 788].

Unfortunately, these were not the only examples of ethically egregious experiments conducted on decisionally impaired patients during the 20th century. There are numerous studies that did not obtain valid informed consent, used deceit, and subjected patients to unjustified risks in poorly designed scientific studies. One was the 1963 experiment performed on chronically ill, mostly demented patients at the Jewish Chronic Disease Hospital in New York. Live cancer cells were injected to unsuspecting and incapacitated patients, for the purpose of determining if the immunologic systems of debilitated individuals reacted any differently to the introduction of cancerous cells than those who were healthy, and also exploring how a chronically ill and weakened immune system affected the spread of cancer. There was no ethical review of the study, no prospect of benefit for the subjects, these individuals of diminished autonomy were not given adequate information on the research, did not consent to it, nor could they leave the study, and the investigators had no evidence that the subjects will not, in fact, develop cancer [9].

Another controversial experiment took place at the University of California at Los Angeles (UCLA), from 1983 into the 1990s, in which patients with schizophrenia were taken off their medication. Half of them suffered severe relapses, with symptoms that included hallucinations, paranoia, and severe decrease in functioning. One of the subjects consequently committed suicide, and another dropped out of college and attempted to kill his parents [10]. A United States federal agency later ruled that the UCLA failed to get a valid consent from the patient-subjects, by failing to inform them of the extent of risks they will be exposed to and that ordinary treatment would be safer for most of them [10]. At the time, federal ethics officials estimated that there were anywhere from 100 to 300 experiments in which psychiatric patients were taken off their medicines for the purpose of observation of their illness once they relapsed; these studies involved high levels of risk and no prospect of direct benefit to the participants, while providing subjects and their families little information about the true nature of the research and the foreseeable harms resulting from it [11].

The historical abuse of mentally ill patients who lack the ability to consent thus emphasizes the need for careful scrutiny and protection of study subjects who are unable to protect their own interests. However, despite this ethical imperative, they should not be “protected” to the degree that they are completely excluded from the research. Understanding the very conditions that deem them incapacitated requires research [12].

Current and previous regulations and recommendations on research including the mentally ill

The Nuremberg trial’s revelations about the horrors performed on unwilling imprisoned individu-
als, including experiments that killed hundreds of thousands of mentally ill and “racially and cognitively compromised” individuals in psychiatric hospitals, prisons and death camps during the WW II [13], resulted in the first international code of ethics principles for research on human subjects. Of the key principles of the resulting Nuremberg Code [14], promulgated in 1947, the very first requires the informed and voluntary consent of the subject, regardless of their specific attributes:

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision [14, p. 181].

This formulation, however, completely prohibits research on children, the decisionally impaired, or emergency room patients, who lack the legal, mental or physical capacity to consent, respectively [7]. Although there is evidence to suggest that the chief medical advisor to the Nuremberg Tribunal insisted that the mentally ill should be excluded and given special consideration and protections, the judges omitted this reference from their final ruling. This seems to be justified by their intention not to interfere with potential medical advancements, but only to address highly risky non-therapeutic research on the easily coerced population [7]. Since research on human subjects should “yield results for the good of society that are unprocurable by other methods or means of study” [14], such a wide-reaching policy of exclusion would have negative consequences for society. It could, for example, deprive it of important knowledge related to those whose conditions result in vulnerability or loss of competence [15]. This concern is reflected in well-known contemporary codes and regulations that do allow research on persons unable to provide consent, as long as there is justification and additional safeguarding for them. It is at present widely agreed that research on persons whose capacity to consent is compromised may be undertaken if research of comparable effectiveness cannot be carried out on individuals capable of providing consent, the research is likely to benefit the subjects themselves or others with the same competence-undermining condition, and that the risks are minimized. It is additionally required that permission for participation is acquired from a legally authorized representative of the subject, and that the subjects themselves assent to participation in research [16].

According to the Additional Protocol to the European Convention on Human Rights and Biomedicine, concerning Biomedical Research [17], research including a person whose capacity to consent is compromised may be undertaken only if there is a likely benefit to the subject and if the research cannot be performed on persons capable of providing informed consent. Alternatively, if the research does not have
the potential to directly benefit the subject, it needs to be intended to promote the health of the group the subject belongs to, and should entail only minimal risk and minimal burden. It means that the experimental interventions will inflict only a very slight and temporarily discomfort, or have a slight and temporary negative impact on the health of the person concerned. Other necessary preconditions for research on subjects who lack the capacity to provide consent include: 1) a necessary authorization given in writing by the legal representative or an authority, person or body provided for by law, taking into account the person’s previously expressed wishes or objections, 2) the prospective subjects shall be informed of their rights, 3) the subject shall take part in the authorization procedure as far as possible, and 4) their dissent to participate shall be respected.

The 2013 revision of the Declaration of Helsinki [18] reaffirms these agreed upon recommendations for research subjects who are incapable of giving informed consent, and proposes an additional requirement that research involving these subjects may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population.

Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization, recently issued the International Ethical Guidelines for Health-related Research Involving Humans [19]. These 2016 guidelines seek to avoid characterizing entire groups of individuals (i.e. the mentally ill) as vulnerable, and instead emphasize the importance of including adults who are not capable of giving informed consent in health-related research. Similarly, the newly-revised CIOMS guidelines recognize the need for specific protections to safeguard the rights and welfare of persons who, due to a lack of capacity, may not be able to protect their own interests.

Like other modern-day recommendations, the CIOMS guidelines require that researchers must obtain permission from the legally authorized representative of the prospective subject, and that this permission takes into account the participant’s previously expressed preferences and values, if known. CIOMS also recommends that the subject’s assent to participate should also be obtained, if possible, and that a potential participant’s refusal to take part in the research should be respected. It does, however, allow overriding the subject’s dissent in exceptional circumstances, for example, in cases where the incapacitated person needs treatment that is not available outside the context of research. In these circumstances, research participation would be the best available medical option and thus in the person’s best interest. CIOMS guidelines incorporate the usual requirement to maximize benefits and minimize risks for the research participants, or, for research interventions that have no potential individual benefits for participants, to ensure that the risks must be no more than minimal. Additionally, the guidelines allow for research ethics committees to permit a minor increase above minimal risk, in cases when the social value of the research is compelling.

Conclusion

The not-so-distant past of the modern world offers numerous examples that reaffirm the concern that individuals who lack the understanding or power to refuse participation may be overrepresented in research. Given that persons who suffer from mental disorders that render them unable to protect their own interests are easily abused and exploited, it is not difficult to understand how the need to protect them from harms of research reflected across the regulations in the form of complete prohibition of research including these subjects. However, the concern that their exclusion from research altogether also entails their exclusion from the benefits of research and access to treatments for which research evidence is needed prevailed at some point. It is now recognized that while there is a moral obligation to safeguard vulnerable individuals and groups in research, this obligation must not stand in the way of their right to the best available treatments and the highest attainable standard of health. Based on this premise, their exclusion from research was perceived as unjust, and their inclusion in research recognized as realization of their entitlement to proper, effective, scientifically researched, evidence-based care.

Mentally-ill subjects should neither be inappropriately included nor automatically excluded from participation in research on the basis of their vulnerability. Instead, they should be appropriately included, especially in research on those conditions that render them vulnerable. Contemporary legislation, regulations and guidelines on research including mentally-ill subjects reflect this requirement to adequately address the health needs of those suffering from mental disorders and enable them to benefit from research, while ensuring that appropriate safeguards for their wellbeing are in place.

References

