ETHICAL ISSUES OF PHARMACOTHERAPY AND CLINICAL TRIALS IN PATIENTS WITH DEMENTIA

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Dementia raises many ethical issues associated with stages of dementia such as the appearance of preclinical and asymptomatic patients who are, however, at risk of dementia. Thus, physicians come across ethical issues about preventive measures, disclosure of risks and protection from stigmatization and discrimination. Despite efforts to prevent dementia, it is also necessary to solve ethical issues related to the study of ways to alleviate the symptoms of clinical dementia, with the need for additional protection of patients with dementia when prescribing pharmacotherapy. One of the possible ways to solve these issues should be to use an integrated approach to conducting clinical trials and analyzing the ethical, legal and social consequences of dementia, for which it is necessary to include the collection of ethics-related data in the design of the dementia study itself.

Keywords: dementia, ethics, pharmacotherapy, clinical trials

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ЭТИЧЕСКИЕ ПРОБЛЕМЫ ПРОВЕДЕНИЯ ФАРМАКОТЕРАПИИ И КЛИНИЧЕСКИХ ИССЛЕДОВАНИЙ У ПАЦИЕНТОВ С ДЕМЕНЦИЕЙ

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Деменция поднимает много этических проблем, связанных со стадиями прогрессирования деменции, таких, как появление доклинических и бессимптомных, но подверженных риску развития деменции категорий пациентов, что ставит перед лечащими врачами этические вопросы о профилактических мерах, раскрытии рисков и защите от стигматизации и дискриминации. Несмотря на усилия по профилактике деменции, также приходится решать этические проблемы, связанные с изучением способов облегчения симптоматики клинической деменции, с необходимостью дополнительной защиты пациентов с деменцией при назначении фармакотерапии. Одним из возможных способов решения данных проблем должно быть использование комплексного подхода к проведению клинических исследований и анализу этических, правовых и социальных последствий деменции, для чего необходимо включать сбор данных, связанных с этикой, в дизайн самого исследования деменции.

Ключевые слова: деменция, этика, фармакотерапия, клинические исследования

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Progressively diminishing decisional capacity of patients, dementia raises ethical issues, which vary as the disease progresses from early biomarkers in the blood that predict the risk of dementia to early clinical symptoms and more severe stages.

Discovery of biomarkers associated with pathophysiology of Alzheimer's disease and other neurogenerative disorders transformed the way how the disorders were detected and diagnosed, and changed the contours of ethical issues faced by both healthcare professionals, and patients. According to available scientific data, pathophysiology of Alzheimer's disease, which is the most common cause of dementia, begins long before a person becomes a patient with observed signs and symptoms of dementia [1]. During another trial, a group of patients with 'asymptomatic risk of Alzheimer's disease' is revealed, and the role of biomarkers in determining the stage of the disease is confirmed [2]. Thus, detecting biomarkers based on genetic testing or cerebrospinal fluid analysis at the preclinical and symptomless stage of the disease raises a number of complex ethical issues associated with pharmacotherapy of patients with dementia.

First, what are the ethical consequences of shifting the focus of medical research from studying pharmacotherapy approaches in patients with symptomatic Alzheimer's disease to examining the same (including preventive pharmacotherapy) in symptom-free patients with a risk based on biomarkers? Second, how can we protect patients with a high risk of dementia from stigmatization and discrimination that accompany the majority of forms of irreversible cognitive impairment? The third ethical issue arising at this stage is as follows: what is the clinical and social benefit from knowing the risk status if developing effective methods of treatment of Alzheimer's disease and other dementias has proved difficult?

Several large clinical trials related to secondary prevention of Alzheimer's disease and other dementias and also preventing

cognitive impairment among persons with already manifested signs of dementia have been conducted [3–5]. The clinical trials were conducted because other clinical trials that investigated approaches to pharmacotherapy in patients with symptomatic forms of dementia (for instance, pharmacological substances aimed at beta-amyloid) failed to slow the progression of dementia. The obtained negative findings of the conducted trials resulted in new trials with involvement of patients without noticeable symptoms of memory loss but with biomarker-based risk factors. The purpose of the trials is that the beginning of pharmacotherapy prior to neurodegeneration can be more effective than that among patients who have already lost a part of neurons.

Clinical trials aimed to prevent the development and progression of dementia raise three ethical issues. First and most importantly, in some clinical trials participants get to know their risk factors for dementia, as the risk is an inclusion criterion for the trial [4]. The ethical issue means that the trials aimed to prevent development and progression of dementia require thorough development of algorithms and procedures to reduce harm, which can accompany disclosure of data about the risk of dementia. Second, some participants of clinical trials aimed at prevention and progression of dementia could probably never shift from a biomarker-based positive status (entitling to be included into a trial) to clinical symptoms. As a result, the risk represented by the clinical trials for the subgroup with positive biomarkers, which would never progress to clinical dementia, should be included into the total risk-benefit ratio of the conducted trial. Third, the clinical trials aimed to prevent the development and progression of dementia have, on the one hand, an ethical advantage, as they involve persons whose cognitive capabilities allow to weigh the risks and benefit [4]. On the other hand, it means that the clinical trial participant is made totally responsible for the independent dealing with complex ethical issues arising during the trials (such as disclosure of biomarker status, assessment of preventive pharmacotherapy benefit and harm, etc.).

As risk ethics issues focus on the possible development of dementia in cognitively normal subjects or patients with indistinct symptoms, dementia resulting in significant cognitive impairment is developed in some of them. Progression of cognitive impairment raises a number of other ethical issues. They are about how to achieve a balance between the possible benefit of pharmacotherapy aimed at reduced dementia symptoms and protection of the group of patients from possible risks associated with increased vulnerability.

Since 1950, numerous national and international codes such as the Declaration of Helsinki establish guidelines regulating clinical trials, including their independent inspection, risk-benefit ratio for potential participants, so that the vulnerable groups of population are not the objects of trials at risk [6]. Several ethical issues arise here as well. First, if it is assumed that respect for the identity means that people can take their own decisions about participation in clinical trials, how can decision-making ability and competence among people with dementia be determined and assessed?

Second, if a patient with dementia is not competent enough to consent to the trial, can the legal representative provide consent instead of the patient from an ethical perspective and to which type of the trial? The issues are still important even today. Though a number of trials aimed at development and progression of dementia is increased, various clinical trials involving persons with clinically pronounced dementia whose cognitive impairment cause complex ethical issues concerning obtaining consent to participation are being continued as well.

A doctor decides which patients with dementia can consent to medical procedures or participation in a clinical trial based on the human abilities to take decisions such as comprehension (ability to think over a respective situation), assessing the situation (ability to apply the data to own situation), speculation (ability to compare the suggested options and conclude about potential consequences of choice) and uttering a choice (ability to report the taken decision) [7]. Estimating the four abilities, the doctor concludes whether the person can take a respective decision about subsequent therapy or participation in a clinical trial [8].

Trials examining the abilities of patients with dementia to take decisions independently show that the probability of being classified as those capable of taking independent decisions depends not only on total severity of cognitive impairment, but also on the risks of suggested pharmacotherapy or a clinical trial: the risky the drug-induced intervention is and the more severe manifestations of dementia the patient has, the more likely it is that the patient will be treated as incapable of taking decisions [8,9].

Nevertheless, some trials show that in case of many neurological and psychiatric diseases a corresponding diagnosis does not make a person legally incapable [9,10]. Diagnostics of Alzheimer's disease or another dementia should also not be perceived as the determining factor for human incapacity. Over a half of patients with a very mild form of Alzheimer's disease can provide an informed consent to medical procedures, whereas the majority of (but not all) patients with a moderate form of the disease are not capable of giving the same consent [8,11]. These and other trials show that mild and moderate forms of Alzheimer's disease can't be automatically interpreted as an inability to provide an independent informed consent to suggested pharmacotherapy or participation in a clinical trial [12,13].

Thus, research of an ability of patients with dementia to take decisions about treatment results in three key conclusions with respective ethical consequences. First, patients with mild and early moderate forms of Alzheimer's disease should not be treated as those who are incompetent in making decisions about clinical treatment. It is so because some patients, and those who better understand their condition and have mild dementia, in particular, are competent in taking decisions about treatment. Second, at a certain point the competence is evidently lost. It means that early diagnostics and disclosure of diagnostic data are essential, as then the patients can report their preferences in treatment beforehand. Third, patients want to participate in taking treatment-related decisions insofar as their abilities permit, mentioning importance of the patients' involvement even if this doesn't allow them to take a final decision about treatment. A possible perspective trend in solving various ethical issues that occur during drug-induced therapy of dementia includes an integrated approach to conducting clinical trials and analyzing the ethical, legal and social consequences of dementia, for which it is necessary to include the collection of ethics-related data in the design of the dementia study itself. The integration can be helpful while solving many ethical issues, including when trying to find a balance between potential advantages of early interventions and potential harm of stigmatization and discrimination.

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