Journal of Parkinson's Disease xx (2021) x–xx
DOI 10.3233/JPD-212639
IOS Press

Review

Bringing Advanced Therapies for Parkinson's Disease to the Clinic: An Analysis of Ethical Issues

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Accepted 3 May 2021
Pre-press 04 June 2021

Abstract. Advanced therapies for Parkinson's disease (PD) constitute a broad range of treatments, each presenting specific ethical challenges. Some of these therapies are established and in clinical use, like device-aided therapies, and others, based on advanced therapeutic medicinal products (ATMPs), are still in early stage of clinical trials. This paper focuses on some common ethical issues arising in these two categories of advanced therapies, especially challenges arising when advanced therapies are proposed to PD patients in the form of advanced care, under a clinical trial, or, in case of ATMPs, under the "hospital exemption" rule. The ethical issues covered here relate mainly to ensuring informed consent in these different contexts, to the stakeholder role of patient's non-professional caretakers, such as family, and to patient safety in treatments under "hospital exemption". To illustrate the points discussed in connection with "hospital exemption" rule, the example of the EU has been chosen. This paper does not claim completeness of ethical issues raised by bringing advanced therapies for PD to the clinic, but rather presents examples of ethical challenges in this context.

Keywords: Parkinson's disease, advanced therapies, advanced therapeutic medicinal products, ethics

INTRODUCTION

Advanced therapies for Parkinson's disease (PD) include a broad range of treatments, each presenting specific ethical challenges. Some of these therapies, such as device-aided therapies, are established and in clinical use. Others, based on advanced therapeutic medicinal products (ATMPs), are still in early stage of clinical trials.

PD affects patients of all social backgrounds worldwide [1], their caregivers, and society in general [2]. It is one of the leading causes of disability in humans, the most common serious movement disorder in the world affecting 1% of adults older than 60 [3], and is increasing in incidence due to an aging population [4, 5]. It significantly reduces quality of life both for patients and families supporting them: it is a progressive course towards the loss of patient's independence, dignity and, eventually, life itself [2].

This paper reviews some common ethical challenges for clinicians and investigators contemplating applying device-aided therapies and ATMPs for PD and lists some practical suggestions in these different contexts. While many of the issues raised in this paper are relevant to efforts being undertaken across the globe, EU regulatory examples are chosen to illustrate the ATMP-related ethical challenges.

ADVANCED THERAPIES: A BROAD CATEGORY

Advanced therapies for PD can be divided into 1) symptomatic treatments (used clinically as conventional therapies) and 2) disease-modifying treatments

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Table 1
Advanced therapies for PD

Features Name	Category	Conventional or experimental?	Disease-modifying?	Way of action
Deep brain stimulation (DBS)	Device-aided therapies	Conventional	No	Surgical procedure where electrodes are inserted into a targeted area of the brain, using MRI (magnetic resonance imaging) and recordings of brain cell activity during the procedure, done with the aim to treat a variety of neurological symptoms of PD such as tremor, rigidity, stiffness, slowed movement and slowed walking [9]. DBS also involves implantation of an impulse generator battery providing electrical impulses to a part of the brain involved in motor function, where the device can be turned on or off by the patient with the help of controller [9].
Infusion therapies	Device-aided therapies	Conventional	No	Infusion of medicated gels (levodopa-carbidopa intestinal gel or dopamine agonist apomorphine) into the small intestine through percutaneous endoscopic gastrostomy [6, 7, 10].
Somatic cell medicinal products	ATMPs	Experimental	Yes	Introduction of cells or tissues that have been subject to substantial manipulation to change their biological characteristics, physiological functions or structural properties relevant for the intended clinical use, or cells or tissues not intended to be used for the same essential function(s) in the recipient as in the donor [11].
Gene therapy medicinal products	ATMPs	Experimental	Yes	Introduction of an active substance which contains or consists of a recombinant nucleic acid with the aim to regulate, repair, replace, add or delete a genetic sequence, and where the therapeutic effect relates directly to the recombinant nucleic acid sequence it contains or to the product of genetic expression of this sequence [11].
Tissue-engineered products	ATMPs	Experimental	Yes	Introduction of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered; or cells or tissues that are not intended to be used for the same essential function(s) in the recipient as in the donor, with the aim to regenerate, repair or replace a human tissue [11].
Combined ATMPs	ATMPs	Experimental	Yes	Combination of ATMP technologies with a medicinal product or medical devices [12]. An example of a combined ATMP could be cells embedded in a biodegradable matrix or scaffold [11].

(still in the experimental stage). The first category, although life-quality improving, does not slow or stop the progressive course of PD [3, 5] and develops adverse effects over time [3]. Here belong device-aided therapies, indicated for improvement of health-related quality of life when after a few years of peroral/transdermal PD medications a majority of patients develop motor fluctuations and dyskinesias [6, 7] despite more frequent dosing [7]. Device-aided therapies do not prevent or replace the progressive loss of mDA neurons in PD [5]. The second category, contrary to the first, aims at modifying the progression of PD. Here belong ATMP-based therapies, expected to offer potential cure, but still some years off and the efficacy of which cannot be guaranteed [8]. Both categories include a number of different treatments, the main features of which are summarised in Table 1.

SELECTED ETHICAL CHALLENGES IN ADMINISTERING DEVICE-AIDED THERAPIES

The main purpose of device-aided therapies is to improve the patients' quality of life by reducing motor symptoms [6, 13, 14]. For example, infusion therapies reduce "off time" (time with PD symptoms)

[13] by at least 60%–65% [6]. Device-aided therapies are not risk-free. In DBS, electrodes are surgically implanted into the subthalamic nucleus and *globus pallidus* [15]—a procedure associated with adverse effects such as the worsening of cognitive, motor or psychiatric symptoms and cerebral hemorrhages or stroke [16]. The mechanisms behind the underlying efficacy of DBS are not well understood [17], and unexpected harms can sometimes be induced [18]. Although DBS is considered a "reversible" treatment, there are concerns that non-stimulation-dependent effects of DBS can occur [19]. In infusion therapies, complications mainly relate to infusion equipment and the establishment of the percutaneous endoscopic gastrostomy, or local inflammation at infusion site [6]. Many of these risks affect mainly the patient. But risks like worsening cognitive or psychiatric symptoms affect both the patient and the patient's caretaker or family.

In order to be able to improve a patient's health-related quality of life, it is essential to first identify what is important to that particular patient. The ethical challenge here is manifold, e.g.: 1) balancing the patient's best interests against those of the caretaker without compromising the patient's interests, in treatments with high potential to affect patients' caretakers; 2) helping the patient make the best decision, when it comes to early decisions about advanced therapies; and 3) making personalised recommendations considering that patient's values and aims over time.

For clinicians, the first ethical challenge starts with identifying "target patients"—should they consider the patient alone or the patient-caregiver "tandem"? Different advanced therapies suit different types of patients and vary in effectiveness on health-related quality of life, side effects and safety. These effects may be of different value to individual patients who choose these therapies to improve their quality of life, a highly personal and value-laden concept [20]. Therefore, choosing the right type of therapies for the right type of patients from the clinical perspective is only half the job; knowing patients' preferences and goals [20] is as important as the clinical parameters. Should the caregivers' perspective also be considered, especially when their daily lives are also affected by the care they are providing, as is often the case with family members and other non-professional caregivers? Some argue that knowing the family's goals is important to clarify and align expectations of patients and caregivers with what can be achieved from a particular type of advanced therapy [20, 21]. Knowing the caretakers' capabilities and limitations is equally important—what could actually work for that family or other persons caring for the patient? Agreeing on treatment decisions jointly between PD patients, their caregivers and health care professionals can optimise individual therapy [21].

Why is the caregivers' perspective important? For the first, caregivers play an important role in supporting patients: from assistance with daily life activities and management of PD-related tasks (appointments, medication) to treatment decisions [21]. The family is also an important pillar in patient's process of adapting to the disease and integrating it into daily living [22]. Secondly, caregivers are affected by treatment options chosen. PD implies emotional, cognitive and personality changes, influencing the patient's behaviour in daily situations [23] which affects caregivers. For example, neuropsychiatric symptoms (impulsivity, hypomania [14]) resulting from DBS contribute to burden on caregivers [24] who are sometimes deeply troubled by the effects of this therapy [25].

Despite all these good reasons to take the caregiver's perspective into consideration, the question still remains what weight this perspective should have in the case of conflict with the patient's perspective. This question merits an ethical evaluation (and a paper) of its own, without which it is difficult to give a straightforward answer. At least the caregiver's perspective should be considered to evaluate what therapeutic approach could work in practice for that caregiver-patient "constellation".

Other ethical challenges are related to the necessity to make treatment decisions in light of possible changes in the patient's cognitive capacity or change in the patient's values and priorities over time. As device-aided therapies are chosen considering the patient's personal preferences, and not only clinical indications/contraindications and the patient's symptom profile, it becomes important to discuss advanced therapies early, well before excessive deterioration of PD symptoms [6], especially nonmotor ones. Bringing up advanced therapies first when they have become acutely necessary may require careful consideration when the patient's cognitive capacity is already reduced. Advance planning would enable collaboration to identify values, goals, and preferences early and facilitate care concordant with patient's wishes [26]. But early discussions about advanced therapies have their own challenges – patients may worry that this would reduce the quality of their care or that such conversations indicate that the health professionals expect immediate progression of PD [26].

At this point, reassurance may be needed that such conversations are intended to help patients reflect on both their current goals and values and foreseeable selves in the future early in the disease and should be seen as a dynamic process rather than a one-time event [26]. Early and multiple discussions are also important considering possible changes in patients' values and priorities over time or difficulties to make hypothetical decisions about future care when the disease has advanced.

SELECTED ETHICAL CHALLENGES IN BRINGING ATMPS TO THE CLINIC

The injured brain has a limited ability to repair itself. Finding ways to restore damaged networks is a challenge for scientists [4]. The main task for ATMP-based therapies is to provide such restoring possibilities. To date, the biggest potential for PD treatment using ATMPs is within stem cell-based therapy [8], distinguished by its potential to replace nerve cells to compensate for those lost in the degenerative process [16, 27]. To date this approach remains experimental and a number of first-in-human clinical trials (CTs) using cells derived from both human embryonic stem cells and induced pluripotent stem cells are on the way [28, 29]. The road to clinical application of certain types of cell-based therapies is estimated to be long, entailing challenges in controlling differentiation into defined subtypes of cells, reducing the immune response that occurs in the central nervous system [16] and assuring that the produced cells are safe (e.g., with reduced risks of tumorigenesis [15]) and efficacious, as well as Good Manufacturing Practice – compliant, which is necessary for their use in patients [28]. Another significant advance is in the area of gene therapy where a single injection of a gene into a nerve cell could give rise to a continuous production of the associated protein [8], which could potentially stimulate dying nerve cells to regrow and thus reverse the progression of PD [8]. Importantly, to enter clinical application, ATMP-based therapies need to hold sufficient competitiveness compared with conventional therapies, both when it comes to their availability and therapeutic effectiveness [15]. Their testing in clinical trials is highly regulated and subject to prospective ethical review, where balance between potential benefit and potential harm is extensively debated, among other things, making sure that potential research subjects can be asked to consider given risks. Ethical challenges in this field are very diverse, relating to informed consent process, methodological issues or diverse application of legal requirements. Here follow some examples.

The particular difficulty in obtaining informed consent for participation in CTs using ATMPs is the high degree of complexity to be communicated to the patient. For a patient without a solid medical or scientific background it can be difficult to grasp how ATMPs are produced and what they do in the body. Likewise, risks associated with ATMPs, especially in interventions using pluripotent stem cells, may be difficult for patients to perceive. Moreover, many cell-based therapies are irreversible, meaning that a patient would become a trial participant for life in the sense that transplanted cells cannot be taken out from the body and would continue to affect the patient even if they withdraw from the study. This may become an exclusion criterion for entering some other clinical trials in the future, thus limiting the patient's future choices. To be able to choose, one has to understand what the options are. Therefore, participant information should provide all relevant facts about a given trial [30] and a lot of effort should go to increase layperson-adapted understandability of participant information sheets.

Cell or gene therapies for PD are still some years away [31] and experimental. Attitudes toward CTs in general are encouragingly positive among PD patients [32]. Enrolling a sufficient number and appropriately diverse group of patients with PD is important for the success of first-in-human clinical trials [15, 33]. But it is of utmost importance to prevent the therapeutic misconception. One empirical study found that older patients and those with lower education often had inadequate knowledge of the nature and purpose of clinical research in general and were more likely to suffer therapeutic misconception [32], but patients may also become vulnerable for therapeutic misconception due to other factors such as despair.

Prevention of hype is likewise important. For the first, to date there is no scientific evidence that patients suffering from neurodegenerative diseases treated with disease-modifying experimental interventions would have better outcomes than their counterparts in placebo arms. A recent empirical study, examined whether clinical trial participants randomised to unapproved, disease-modifying interventions in neurodegenerative disease, including PD, had better outcomes than those randomised to placebo [34]. It provided evidentiary grounds for clinicians to

temper patient expectations in informed consent discussions, but did not rule out benefits from accessing investigational treatments to some individuals [34]. Secondly, unrealistic expectations as to personal health benefits associated with a CT may lead to distrust in CTs among trial participants [32].

Among CT methodology-related ethical challenges is the difficulty to compare the safety and efficacy of studied therapies and to inform patients adequately. To obtain relevant safety and efficacy information scientists need to collect robust and comparable evidence, e.g. in cell therapy, high variability in CTs in terms of donor tissue source, culture conditions, PD stage in which a studied therapy was applied, route of administration, dose, clinical evaluation criteria, and timing of evaluation can lead to inconsistent results [35]. This difficulty to obtain robust knowledge makes it hard to properly design

Table 2
Interpretation difficulties of EU legal documents' requirements regarding the use of ATMPs without marketing authorisation

Present in: Requirements	Art. 28 of Regulation (EC) No 1394/2007 [36]	Art. 83 of Regulation (EC) No 726/2004 [41]	Art. 5 of the Medicines Directive (2001/83/EC) [42]	Interpretation difficulties
For special needs/ on a non-routine basis	Yes		Yes	Unclear evaluation of whether an ATMP is prepared on a non-routine basis [43]. Lack of clarity what particular number[1] of ATMP constitute "non-routine" preparation [44]. Different interpretations can lead to "hospital exemption" being used in large series of patients in some EU Member States [37].
For patients with chronical, seriously debilitating or life-threatening disease who cannot be satisfactorily treated by an authorised product		Yes		Unclear whether the "hospital exemption" rule might be applied *only* when there are no treatments available or in situations of high unmet medical need [43]. This might lead to misuse of this clause [43].
For use by individual patients / by individual medical prescription for a custom-made product for an individual patient	Yes		Yes	Ambiguous: it should not overlap with the field of autologous therapies which could be considered in a wrong way as therapy for individual patients. Some autologous therapies may be addressed to a large population [39]. Unclear meaning of "custom-made product"; the definition is left to the competence of EU Member States [44, 45]. Subject to interpretation of what exactly "tailored for individual patient" should mean in practice. Unclear meaning of individual patient group [45].
For use under exclusive/direct personal responsibility of an authorised healthcare professional	Yes		Yes	Difficulty to identify one specific person responsible for the whole treatment process (it usually involves a number of medical personnel) [43].
Preparation according to specific quality standards	Yes			Undetailed quality standards, except requirement that relevant Community rules on quality and safety should not be undermined [43].
Used in a hospital	Yes			Unclear whether prescription and use of ATMP under the hospital exemption have to be in the same hospital, or the manufacture process can be separated and performed outside of the hospital [43]. Unclear whether manufactured ATMP in the same Member State would be used in several hospitals [43].

[1] In response to the requirement for "non-routine" production of ATMPs under the hospital exemption clause, most Member States, but not all, have annual limits to the numbers of a specific product type which can be manufactured under a hospital exemption clause license [46].

Table
Take-home messages

When undertaking discussions about the use of established advanced therapies:

- Discuss them several times: 1) information obtained overtime can help surrogate decision-makers when the patient's decision-making capacity becomes affected by the progression of PD; 2) frequent review of goals throughout the disease can help find care which reflects that patient wholly [26].
- Encourage PD patients to plan their advanced care accompanied by those who understand their history, values, and preferences. Considering their views can reveal otherwise invisible "blind spots" [26] and provide different perspectives, since patients, families and healthcare professionals all have different levels of knowledge about PD [20].
- Help patients focus on their current goals and values by presenting decision-making about advanced care as a dynamic process rather than a one-time event [26].
- Encourage patients to reflect on past, present, and foreseeable selves [26] early in the discussions. Reflection on foreseeable self becomes difficult for patients when cognitive impairments begin [47].
- Become acquainted with patients at the outset (e.g., hobbies, professions, willingness to participate in decision-making about their own medical care. This information may help make a personalised recommendation [26].
- Anticipate that it can be difficult for those affected by PD to accept and cope with the disease. Despite its high prevalence, PD is largely unknown to society [22].

When recruiting patients to clinical trials involving ATMPs:

- Ensure comprehensibility of trial participant information. Increased knowledge about how clinical trials work can help them make an informed choice and increase willingness to participate [32].
- Make sure patients understand the irreversibility of applied treatment, when that is the case. Having received an irreversible therapy may become an exclusion criterion for entering other clinical trials in the future and thus limit the patient's future choices.
- Beware that altruism and self-interest are two primary motivations for enrolment in clinical trials, but they can become contingent upon each other complicating understanding what that patient's true motivation is [48].
- Beware of hype in patients, temper patient expectations and reassure patients who fear missing out on therapeutic benefit through, e.g., trial ineligibility. Evidence suggests that patients with neurodegenerative diseases are not, on the whole, harmed by lack of access to unapproved disease-modifying treatments [34].

When giving an experimental advanced therapy under a "hospital exemption" rule:

- Beware of possible variability of implementation of this rule in different countries due to interpretation differences of legal requirements (see examples in Table 2). This can have a bearing on patient safety.
- Beware of possible implications on patient safety if processes elaborated for a very low number of patients are performed in less closed systems implying a higher contamination risk. That many production sites rely on similar but slightly different manufacturing processes raises safety risks which are mitigated by manufacturing sites relying on a unique standard manufacturing [49].

new studies and has a bearing on trial participant safety.

The therapeutic use of ATMPs outside clinical trials, and thus outside research enterprise in the strict sense, under the so-called "hospital exemption" rule[1], poses another type of ethical challenge. Different interpretation of legal requirements regulating the use of ATMPs as hospital exemption can lead to disparities between countries regarding the implementation of the hospital exemption rule, which raises concerns about patient safety. To illustrate this point, the example of the EU has been chosen (for examples see Table 2).

Besides applying ATMPs outside clinical trials under the "hospital exemption", controversial uses, such as marketing and provision of unproven cell therapies by "stem cell clinics" have been around

[1]The hospital exemption rule in the European legislation (EU ATMP Regulation) [36] makes products available to individual patients on a non-routine basis at the request of the treating physician [37]. This rule enables patients to receive an ATMP under controlled conditions in cases where no authorised medicinal product is available for an indication with a high unmet medical need [37]. These single-use therapies can then become justification to run a trial after having obtained a scientific and an ethical approval [38]. Some other countries have a concept similar to "hospital exemption": in the US the "compassionate exemption", "compassionate use" or "special exception" is for patients who do not meet the eligibility criteria for a clinical trial of an investigational drug [39], and in Japan, the "compassionate use" or "expanded access" applies for investigational drugs, medical devices, or regenerative medicine products when the patients who could not meet the eligibility criteria need such access during a clinical trial or after completing the clinical trial prior to approval [40]. Receiving an experimental therapy under "hospital exemption" and under a clinical trial are thus two different things, undergoing different kinds of ethical review.

for a while and are difficult to regulate internationally. It can be very challenging for patients and their caregivers to navigate among participating in clinical trials and seeking help from clinics selling unproven therapies. These issues are outside the scope of this paper but are so important that they would merit an article of their own.

CONCLUSION

This paper has reviewed different types of ethical issues arising when advanced therapies, device-aided or ATMP-based, are proposed to PD patients either in the form of advanced care, or a clinical trial, or, in case of ATMPs, under the "hospital exemption" rule, using EU legislation as an illustration. The ethical challenges reviewed relate mainly to ensuring informed consent in these different situations, to the role of patient's familial caretakers as potential source of information about patient's goals and values, but also as stakeholders affected by treatment choices, and to patient safety in treatments under "hospital exemption". Common ethical concern across both types of advanced therapies is the need for greater patient involvement in decision-making about their present and future care and facilitating greater understanding of their own goals and motives as well as suggested treatment, either conventional or experimental. This paper does not claim completeness of ethical issues raised by bringing advanced therapies for PD to the clinic, but rather presents examples of common ethical challenges which arise when advanced therapies such as device-aided therapies and ATMPs are applied for treatment of PD.

ACKNOWLEDGMENTS

The author would like to thank all three anonymous reviewers for constructive comments, which have indeed helped to make this paper better.

CONFLICT OF INTEREST

The author has no conflict of interest to report. This work has not been funded.

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