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ABSTRACT

The application of stem cell transplants in clinical practice has increased in frequency in recent years. Many of the stem cell transplants in neurologic diseases, including stroke, Parkinson disease, spinal cord injury, and demyelinating diseases, are unproven—they have not been tested in prospective, controlled clinical trials and have not become accepted therapies. Stem cell transplant procedures currently being carried out have therapeutic aims, but are frequently experimental and unregulated, and could potentially put patients at risk. In some cases, patients undergoing such operations are not included in a clinical trial, and do not provide genuinely informed consent. For these reasons and others, some current stem cell interventions for neurologic diseases are ethically dubious and could jeopardize progress in the field. We provide discussion points for the evaluation of new stem cell interventions for neurologic disease, based primarily on the new Guidelines for Stem Cell Research and Clinical Translation released by the International Society for Stem Cell Research in May 2016. Important considerations in the ethical translation of stem cells to clinical practice include regulatory oversight, conflicts of interest, data sharing, the nature of investigation (e.g., within vs outside of a clinical trial), informed consent, risk-benefit ratios, the therapeutic misconception, and patient vulnerability. To help guide the translation of stem cells from the laboratory into the neurosurgical clinic in an ethically sound manner, we present an ethical discussion of these major issues at stake in the field of stem cell clinical research for neurologic disease. ***Neurology*® 2017;88:322–328**

GLOSSARY

FDA = Food and Drug Administration; **IRB** = institutional review board.

Stem cells have been of increasing interest in the treatment of neurologic disease in the last 2 decades. Early stem cell transplants in animal models in the 1990s showed significant improvement in the symptoms of debilitating neurologic diseases, particularly Parkinson disease.[1–5] In time, the research applications of stem cells expanded to include Huntington disease,[6,7] spinal cord injury,[8–10] and stroke,[11] with particular expansions in ongoing research occurring in the early years of the 21st century.[12–22] Many of these animal studies in recent years have shown remarkable and progressive success in the treatment of neurologic disease.[8,23,24]

In terms of clinical application, however, stem cell transplants remain largely unproven—they have often not been tested in prospective, controlled clinical trials and have not become accepted therapies.[25–27] Although some of the published data have suggested successful application of specific types of stem cells to specific diseases, these animal model applications have not been successfully demonstrated in human beings.[25,28–30] In the absence of rigorous clinical trials demonstrating the efficacy and safety of stem cell transplants for specific disease processes in humans, current efforts to move stem cell interventions forward have included many different

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strategies. One of the more concerning approaches is to offer patients autologous transplants without sufficient evidence, oversight, or informed consent.[9,25,27,28,31–34]

The controversy of stem cell procurement (particularly embryonic stem cells) notwithstanding, the application of stem cells of any type to clinical practice raises many ethical concerns that are relevant to neurologists and neurosurgeons (table).[25,26,29,35–37] These include true treatment efficacy, risks pertaining to stem cell behavior once transplanted into the human host, such as tumor formation or migration, patient vulnerability, informed consent, and adequate oversight.[38]

As unproven treatments using stem cells for neurologic diseases become more prevalent, how can the neurosurgical community promote professional standards that lead to more ethical conduct? While stem cells may play a key role in future treatments of neurologic disease, how can neurologists and neurosurgeons ensure that these treatments are researched, developed, and provided in an ethical way? Rather than continuing to proceed expediently but haphazardly, without the structure of clinical trials or other ethically acceptable research methods, it is imperative that stem cell clinical research for neurologic disease be standardized, tracked, regularly reviewed, and appropriately published.

Recent reports have demonstrated that potential complications of haphazard stem cell use can have devastating consequences specifically in neurologic patients, and that at least part of the neurosurgical community is currently not aware of the many ethical issues associated with translating stem cells to the clinic.[10] Therefore, we describe a series of discussion points for neurologists and neurosurgeons to consider in the evaluation of new stem cell interventions for neurologic disease, based primarily on the new guidelines for stem cell research and clinical translation released by the International Society for Stem Cell Research in May 2016.[39–42] Our hope is that these issues may help guide the translation of stem cells from the laboratory into the neurosurgical clinic in an ethically sound manner.

Table Ethical challenges of stem cell transplants

Issue	Description
Oversight	As a surgical innovation rather than a medical innovation, stem cell transplants have become difficult to regulate by typical oversight agencies like the US Food and Drug Administration
Conflicts of interest	Potential profits from stem cell interventions are massive, and may incentivize investigators to overstate successes or underreport adverse events
Surgical innovation	Restriction of surgical innovation to formal knowledge generation structures is nearly impossible, but some level of oversight is necessary
Informed consent	Once stem cells are implanted, patients cannot be guaranteed the right to leave a trial, due to possible migration and growth of cells
Risk-benefit ratio	Benefits unclear from current animal model studies, risks include both those of surgery and of the stem cells themselves
Patient vulnerability	Patients are often highly vulnerable due to terminal illness and may be more susceptible to unethical experimentation of unproven treatments

ETHICAL ISSUES

Oversight. Current clinical interventions involving the implantation of stem cells for neurologic disease often lack appropriate oversight on at least 2 distinct levels: the hospital or center level and the national level.

At the level of the center providing unproven stem cell interventions, stem cell interventions may be offered outside a clinical trial, as experimental treatment or in a compassionate use program without the oversight from an institutional review board (IRB) or otherwise. Independent overview of stem cell interventions is crucial for ensuring the ethical and scientific basis of clinical research.[40] In evaluating high-risk stem cell interventions, such as stem cell therapies directed at the nervous system, it is of key importance that normal membership of the IRB committee be supplemented by members who are experts in stem cell science, neurology, and ethics, whenever possible.

At the national level, inadequate oversight of stem cell treatments could be related to regulatory deficiencies within the Food and Drug Administration (FDA) and other national and supranational regulatory agencies, which make some unproven stem cell therapies technically legal.[27,43–45] Modifications to these regulations in the near future will be crucial to curbing the administration of stem cell treatments without appropriate preclinical in vitro and in vivo studies. The standards applied to stem cell interventions before they are approved for in-human use must at least match the standards applied to drug development, and in fact may necessarily exceed these standards. Stem cells are living transplants that may be tumorigenic if used improperly, and once injected, cannot easily be removed. Whereas drugs can be discontinued or appropriately titrated, the unregulated use of stem cells for neurologic disease has already been implicated in the generation of new, debilitating disease.[10]

Conflict of interest. Related to regulatory oversight is an ethical issue relevant in nearly all areas of clinical medicine: the existence, disclosure, and management of potential conflicts of interest. Financial and nonfinancial relationships and incentives of physicians providing stem cell interventions in today's clinical world may create potential conflicts of interest: a set of circumstances that creates a risk that professional judgement or actions regarding a primary interest will be unduly influenced by a secondary interest.[46] Although conflict of interest policies typically focus on financial incentives, several other kinds of potential conflicts exist.[46] For example, the potential for being the first to develop a successful therapy may incentivize physicians to overstate successful results, while large sums of money being paid to those who carry out dubiously efficacious interventions may also result in inappropriate or unethical applications.[35] Especially outside the context of a randomized, controlled, double-blind trial, physicians providing unproven stem cell transplants may be at risk for serious bias, both conscious and unconscious. In the context of neurologic disease, stem cell transplants may require skills that are exclusive to neurosurgeons, such as stereotactic implantation, that could engender exorbitant fees from terminally ill patients. These potential conflicts of interest must be disclosed to patients undergoing stem cell interventions, and clinicians who are not blinded to the treatment or who have a vested financial or commercial interest in the treatment being provided should recuse themselves from the patient's care.

Data sharing. Data sharing is of particular importance in translational stem cell science and must be ensured moving forward. Transparent sharing of data in both the preclinical and clinical phases of translational research has numerous potential benefits, including improved research efficiency, more thorough oversight, and earlier evidence-based applications to the clinic.[47,48] Since most surgical trials are of relatively small sample size, data sharing across a universal protocol may also reduce variability while improving power. Many recent efforts have been undertaken in the stem cell community to improve the registration and banking of stem cells and their associated metadata, yet significant barriers to true transparency in stem cell research exist. These range from personal/professional issues, like publication prestige, novelty, and promotion, to funding issues, like grant acquisition. It is possible that reasonable incentives may be able to overcome these barriers to promote responsible and widespread sharing of stem cell information.

Innovation inside or outside clinical trials. Specifically to clinical/translational studies of stem cells, clinical trials will be of paramount importance in the future development of stem cell therapies. While these trials will necessitate a high standard of informed consent (discussed in the following section), the generation of accurate, generalizable, useful data will necessitate the level of rigor provided by a clinical trial. It is imperative that these clinical trials be properly registered and published, so that patients undergoing stem cell interventions will at least be contributing to knowledge development, irrespective of the personal therapeutic benefit of their participation in research.

Given the devastating nature of some of the neurologic diseases for which stem cells are being attempted, this is, even though challenging, of particular relevance in the neurologic patient population. While some novel treatments have been developed outside the context of a clinical trial, this is both a rare and somewhat risky occurrence. Beyond just a few unique patients, clinical trials are imperative in stem cell research for neurologic disease moving forward.

Informed consent. Informed consent is a key component of ethical clinical research of any type. Concerns in this process include participant understanding of the many risks of undergoing experimental treatment weighed against the potential benefits of the research to the individual (if any) and to society in general. Participant autonomy mandates sufficient understanding of both risks and benefits, as well as an ability to consent to these features of the research freely and willingly, without undue coercion. Especially early in their development, the use of stem cell transplants for neurologic disease must be prefaced by explicit discussion of the therapeutic misconception. Patients must know that in many cases, they may not benefit at all from the experimental procedure they are undergoing, and may in fact be at risk of some harm. Consent made in the absence of this discussion is not sufficient to be considered consent at all.

While these issues are of concern to any clinical research, many of them are of heightened importance in stem cell research for neurologic disease. Consent procedures for stem cell interventions will need to disclose and detail both the surgical risks (e.g., direct injury to nervous tissue, infection, stroke) and the risks from the stem cells themselves (e.g., tumor growth). In general, the literature of medical ethics has confirmed the ethical acceptability of sham procedures when scientific necessity, reasonable risks, and valid and informed consent are present.[49] Nevertheless, trials that potentially include sham surgeries in comparison to surgical

trials should specifically disclose these studies as such, rather than the more benign use of placebo, while potential risk should be minimized and adverse effects tracked and reported.

Because these procedures will ostensibly involve the implant of permanent foreign tissue, it is of the utmost importance that preoperative consent procedures detail the risks associated with such procedures.[50] These include the possibility of stem cell rejection, stem cell migration, or tumor formation. In addition, a key concept of traditional clinical research has involved the right of the participant to withdraw from the clinical trial at any point. After the insertion of stem cells for research purposes, it is possible that a true exit from the study cannot be responsibly promised to the potential participant.

Informed consent is a means to secure patient autonomy. Patient autonomy is sometimes used to justify experimental therapies for compassionate use or by patient request.[51,52] In general, patient autonomy should not include a right to be treated with an experimental treatment outside of a trial, nor can compassion be invoked to justify an ultimum refugium treatment. It is a professional duty to evaluate treatments and restrict to those with sufficient scientific and clinical warrant.

In addition, many patients undergoing stem cell implantation procedures at for-profit clinics are not included in any formal investigation, so the protections provided by informed consent may be absent.[26,53] These clinics are operated as commercial entities rather than truly scientific experimental facilities, and the ethical risks are increased as a result.

Risk-benefit ratio. As with all clinical research, early studies of stem cell interventions may necessitate a higher risk-benefit ratio, simply because these interventions will not have been proven in human studies. Making the leap from rodent and other animal models to human application in the context of a clinical trial must be disclosed specifically to the patient, so that patients have a reasonable expectation of their potential to benefit from the study. Once implanted into the human body, stem cells may not be able to be retrieved, making the potential for complications such as tumor formation or inappropriate migration a major consideration of the benefit to risk calculus.[38] In the CNS, these complications could have devastating consequences, as recently shown.[10] If patients do not have a reasonable expectation to benefit from the study, this reality should be specifically stated to avoid the aforementioned therapeutic misconception. It is, however, a minimum requirement that an adequate rationale has been unequivocally established in preclinical trials before clinical applications should be considered.

Patient vulnerability. Finally, patients targeted by these interventions in the neurosurgical community will likely be particularly vulnerable.[25,54] Research in vulnerable populations is generally accompanied by significantly higher conditions for initiating research and higher standards for oversight. In patients with severe, end-stage neurologic disease like amyotrophic lateral sclerosis, informed consent procedures must be thoroughly vetted and designed specifically for these populations.

Patients are also vulnerable to sensational claims made in the media by proponents of stem cell interventions, which serve to popularize services provided by for-profit clinics.[37] Often, these exposures result in patients seeking stem cell clinics against the advice of their doctors, or in addition to the standard of care. In some cases, patients themselves may also be at risk of conflicts of interest in relation to their treatment, as stem cell clinics are often popularized by patient testimonials that may mislead new patients seeking care.[26,37,43,55]

Patients intending to undergo unproven or experimental stem cell interventions, especially in the context of stem cell tourism, must be warned against the many risks and unknown benefits of these procedures. In speaking with patients about stem cell therapies, it is important that neurosurgeons and neurologists take a nonjudgmental yet evidence-based attitude. While stem cell therapies may not yet yield medical benefits, patients are subject to many pressures, from family, friends, the media, and their own experiences with their health and the medical system, to seek care from all possible sources. Making it clear whenever possible that there are better options for these patients that are evidence-based and within the standard of care, or reasonably and ethically experimental, can help guide progress while avoiding patient mistreatment.

DISCUSSION Many current interventions using stem cell transplants for neurologic disease are not tested and established by appropriate studies and are ethically dubious. Although the majority of these interventions have not been proven in man, and many have not even been thoroughly vetted in animal models, they are often offered up as cures to vulnerable and desperate patients.[26,29,30,35,49]

A variety of factors have played a role in the development of this practice. On the one hand, regulatory oversight on stem cell clinical research from bodies like the FDA has been lacking, and the profitability for stem cell transplants remains high for those who provide them. The result is a series of pop-up clinics offering unproven, potentially dangerous interventions to vulnerable patients who

do not provide adequately informed consent. While not all stem cell transplants are being offered in this context, the vast majority are being offered outside of registered clinical trials, and thus not only may potentially harm patients, but also may not generate scientifically useful knowledge.[25,29,56] In this way, stem cell interventions share similarities with other innovative surgical procedures; similarly, many of the ethical challenges are also comparable. Stem cell therapies for neurologic diseases can also be seen as a mixture of medical and surgical intervention, however, and therefore may require unique ethical discussion.[5,29,43,57]

Beyond the potential harm to patients, one of the greatest challenges of current clinical interventions using stem cells is their lack of generalizability and scientific rigor. It is possible, based on research that has been carried out in animal models, that stem cell interventions may play a crucial role in the future treatment of neurologic diseases, including Parkinson disease, Huntington disease, and spinal cord injury. For this potential to be realized will require well-designed, well-regulated clinical trials in humans, after sufficient evidence has been provided via in vitro and in vivo models.

Much of the current work in this area fails to meet the ethical principles of quality research and lacks the standardization associated with productive clinical trials. As a result, physicians who provide these procedures are not only putting patients at risk, but are also preventing the generation of useful knowledge for further development and implementation of these interventions.

Improvement in these areas is already developing, and will continue to gain momentum as the practice of stem cell transplant enters the mainstream of clinical research. Professional guidelines on data sharing, oversight of stem cell research, and informed consent of patients undergoing stem cell transplant procedures will play a major role in setting ethical norms for these research projects, while continued laboratory research will provide further information on their feasibility and viability in human beings.

It is neither studied nor established that the untested therapies currently being provided are safe and effective. They may fail to do good and they may, indeed, do harm, frequently being offered in scenarios that violate the principles of fairness and justice. Finally, patients in these situations are typically faced with an overwhelmingly complex decision in a dependent and desperate situation, where basic requirements of an informed autonomous decision are difficult or impossible to meet.

Unproven stem cell interventions for neurologic disease are currently being offered in contexts that violate the ethical principles that are key to the practice of medicine and jeopardize progress in the field. These practices can have serious consequences, especially in vulnerable neurologic patients. We present an ethical analysis of the major issues at stake in the field of stem cell clinical research that can aid in translating novel findings to patients with neurologic diseases.

AUTHOR CONTRIBUTIONS

David J. Cote: study concept and design, drafting manuscript, critical revision of the manuscript. Annelien L. Bredenoord: study concept and design, critical revision of the manuscript. Timothy R. Smith: critical revision of the manuscript. Mario Ammirati: critical revision of the manuscript. Jannick Brennum: critical revision of the manuscript. Ivar Mendez: critical revision of the manuscript. Ahmed S. Ammar: critical revision of the manuscript. Naci Balak: critical revision of the manuscript. Gene Bolles: critical revision of the manuscript. Ignatius Ngene Esene: critical revision of the manuscript. Tiit Mathiesen: critical revision of the manuscript. Marike L. Broekman: study concept and design, study supervision, critical revision of the manuscript.

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