

Proven or Unproven? Panel Report on Ethics in the Translation of Neuroscience

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Within the field of neuroscience, advances in the basic scientific understanding of neurological disorders has led to some translation into new therapeutic and diagnostic applications. Given the intricacies of the brain, such translations present important medical and ethical challenges. And even if the products of research are successfully translated into new therapeutic or diagnostic applications, the pluralistic nature of contemporary societies means that not everyone will agree on what counts as an “advance”. Perhaps even more fundamental is the difficulty of establishing the criteria by which we first determine how and when promising advances in basic science are tested in clinical research. For example, what are sound criteria for funding and initiating a clinical trial? How should the knowledge-driven interests of science be balanced with the competing practical interests of a patient group? What happens if refusal to initiate clinical trials for an intervention drives medical tourism? Should the justification for initiating clinical trials take into account requests from patients and other social pressures? Such questions have come to the forefront for the Canadian medical and research community in recent months due to the controversy surrounding an experimental intervention for multiple sclerosis based on the hypothesis of chronic cerebrospinal venous insufficiency (CCSVI) (see: <http://www.cih-risc.gc.ca/e/43951.html>).

In an attempt to better understand the medical and ethical challenges posed by the translation of neuroscience in the Canadian context, we asked an interdisciplinary panel to provide perspectives on the translation of research to patient care. The panel discussion was open to the public, and was held as a preconference event launching an international neuroethics conference. The subsequent conference was designed to elicit expert reflections on the ethical challenges of translations in neuroscience.¹

The pre-conference panel discussion entitled “Proven and Unproven Therapies: Issues in the Translation of Neuroscience Research to Patient Care”² involved four Canadian experts (Shannon MacDonald, patient advocate; Dr. Eugene Bereza, physician and clinical ethicist; Dr. Jonathan Kimmelman, research ethicist; and Dr. Richard Riopelle, neurologist) representing different research, clinical, and health policy

expertise and interests. Panellists were invited to each answer two of the four questions pre-identified by our team (see Table). To generate this report, a full transcript was prepared, major topics were identified, and a manuscript was drafted and circulated between authors. Panellists were then consulted on the manuscript and asked to comment and give feedback on the panel report. Ensuing exchanges and reflections are summarized here.

Prominent themes

The content of the panel discussion clustered around five themes: (1) the role of evidence in research and care; (2) patient and physician involvement in advocacy for translational efforts; (3) limitations on translation related to problems within the health care system; (4) the role of relationships in the translation of neuroscience; (5) research ethics governance and research translation.

1. Role of evidence in research and care

Panellist Dr. Jonathan Kimmelman explained that the complexity of the central nervous system introduces a basic challenge for clinical translation of basic neuroscience research. This complexity means that despite pre-clinical evidence of a treatment’s potential, remarkably few treatments prove safe and effective in clinical trials. Furthermore, there is a fundamental distinction between the demonstration of efficacy and the later provision of access to interventions in the health care system. At times, our healthcare system struggles to provide those interventions that have a demonstrated effectiveness. This raises important questions about the balance between innovation and provision of established effective therapies.

From a clinician’s perspective, Dr. Richard Riopelle stressed the role of evidence in clinical decision-making and proposed six conditions to determine when to support an intervention: (1) the research agenda should be hypothesis driven; (2) evidence of effectiveness should be generated through clinical trials; (3) there should be a consensus based on synthesis of best available evidence; (4) best practice recommendations should emerge from the consensus of evidence synthesis; (5) there should be

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Table: Questions for pre-conference panel on ethics in translational neuroscience**Question 1: Clinical trials and research^{1,2}**

Clinical trials and the general process of translating basic neuroscience research into new therapies create key ethical issues for neurological patient groups, their families, and health care professionals

When and how should we decide what treatments are available or unavailable to patients?

Question 2: Clinical care^{3,4}

The availability (or unavailability) of proven and unproven treatments presents a dilemma for front line clinical care, as patients, often desperate for new therapies, seek the advice of clinicians.

What are the challenges for patients and clinicians when requests for proven or unproven enter clinical consults?

Question 3: Follow-up care^{2,3}

In the absence of clinical proof, or evidence, in support of a biomedical intervention, clinicians may struggle to provide their patients with an adequate standard of care.

How should we ensure support of these patients? Do the ways you offer follow-up care to patients differ if they have sought proven or unproven treatments?

Question 4: Advocacy^{1,4}

Lack of access to a proven therapy, or lack of evidence for an unproven one, often presents itself as an area that requires attention and advocacy.

In your opinion, what is the role of practitioners or stakeholders in advocating for coverage or implementation of proven or unproven therapies (or more clinical trials)?

Discussants: 1. Jonathan Kimmelman; 2. Richard Riopelle; 3. Eugene Bereza; 4. Shannon MacDonald

linked performance standards for providers; and (6) a systematic approach should guide the implementation of therapies. Best practices, implemented without fidelity to guidelines, can result in unfavourable outcomes and therefore Dr. Riopelle also pointed out the value of incorporating patient reported outcome measures and qualitative research to capture health-related quality of life for patients in clinical trials.

All panellists acknowledged the importance of clinical trials as a process to ensure that interventions are vetted before they become widely available. Ultimately, however, it is physicians who provide information to their patients regarding available treatments and physicians who offer patients a clinical assessment of the existing evidence. Dr. Kimmelman suggested that clinicians could also be encouraged and better supported to systematically collect data about their patients when applying interventions that are not yet fully validated.

2. Patient and physician involvement in advocacy for translational efforts

Discussions on the topic of evidence intersected and overlapped with discussions about the tension between scientific rationales for initiating a clinical trial and political pressures for initiating trials. Such pressures can now take various forms including social media campaigns. Panellists reinforced the value of hypothesis driven clinical trials based on pre-clinical or prior clinical studies. They debated whether patients should be able to use political means to initiate clinical trials. One recommendation was that, as an alternative or a complement to advocacy, different groups such as clinicians, patients, pharmaceutical companies, government representatives, and

others could be consulted and engaged from early stages of pre-clinical research through clinical development.

3. Limitations on translation related to problems within the health care system

Panellists brought attention to systemic and long term issues, which Canadian provincial healthcare systems face and that shape the debates regarding proven and unproven interventions. For example, a focus on scientific and clinical breakthroughs in treatments risksoften overlooks important basics (e.g., pain treatment in palliative patients). Similarly, neurological patients frequently need sustained and long-term support yet our systems falls short of optimal performance in this area. Dr. Riopelle suggested that in order to cover all facets of the evolving life of neurological patients, healthcare providers should work in multidisciplinary teams which incorporate the provision of community care and that focus on enabling individuals to function within their home environment. Community services provide an essential component of the necessary support structure for these patients.

Further, Shannon MacDonald suggested a need to consider not only challenges related to funding in our healthcare system but also related to organization and resource allocation. Although practitioners can be identified as the protagonists who could take up a role in such discussions, Dr. Kimmelman cautioned that “[p]ractitioners wear two hats. At the bedside they are expected, and rightly so, to be tireless advocates for the welfare of the patients. When they are back in their office they wear the second hat. They have obligations to be stewards of a sustainable and fair healthcare system, but those are imperfect duties and

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Jonathan Kimmelman, Research ethicist

clinicians are very very busy people (...) I think it is a lot to expect practitioners to be taking a reactive role in these larger more macroscopic questions.”

4. The role of relationships in the translation of neuroscience

One-on-one patient-provider relationships were often described as a reservoir of solutions to the challenges created by unproven interventions and translational research. Shannon MacDonald pointed out that if a physician explains how he or she practices medicine early in the relationship with her patients, the groundwork is laid for difficult discussions that might later arise: “I would suggest that clinicians and patients are people, and people live and function in relationship, and your ability to work through problems and your ability to navigate difficult situations always comes back to the quality of your relationship.” In a context where online access to information about clinical

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Shannon MacDonald, Patient advocate

trials can complicate clinical encounters, a strong patient-physician relationship and honest discussion about unproven interventions can facilitate treatment and follow up care.

Doctors are expected to provide the best care possible, but in some situations the “best care” is unavailable or unclearly defined. Dr. Eugene Bereza suggested that instead of pretending that our healthcare systems are perfect and that the “best care” is known and accessible, doctors should be honest with their patients. If physicians are providing an unproven treatment, they should be able to explain that there is no developed standard of follow-up care. Such an approach calls for an important commitment to patient autonomy and the best interest of the patients as well as transparent shared decision-making processes.

5. Research ethics governance and research translation

With the goal of stimulating discussion, Dr. Bereza questioned whether current research ethics guidelines and their implementation hinder the development and uptake of clinical innovation. Perhaps research ethics has evolved to a point where it constitutes a significant obstacle in this uptake process or does not reflect the concerns of research subjects? Dr. Bereza also questioned the correlation in the Canadian context between, on the one hand, increased research ethics bureaucracy and paperwork with, on the other hand, enhanced subject information and protection. Dr. Bereza asked us to consider whether current regulations and modern ethics have evolved to “confuse protectionism with paternalism”. Research Ethics Boards (REB) can represent increased cost for conducting research. But, as panel discussions explored, it is still very difficult to assess the effectiveness of REBs in protecting and better informing research subjects. For instance, Dr. Kimmelman pointed out major methodological challenges in seeking evidence to determine if regulatory frameworks have either been beneficial or harmful. Yet the need for reflection on evolving trends in research ethics remained an important question for the panel. One potential solution to any stifling effect of REBs on research (brought forward by an audience member) was to foster a collegial approach for REBs akin to the more consultative model of clinical ethics committees.

Questions and recommendations

The panel discussion “Proven and Unproven Therapies: Issues in the Translation of Neuroscience Research to Patient Care” provided an opportunity to bring together a diverse and thoughtful group of panellists who raised a set of under-examined medical and ethical questions and voiced some noteworthy recommendations (Boxes 1 and 2). We hope that by reporting highlights of the discussion we can share with colleagues and members of the public their insights on important questions worthy of further collaborative discussion and research.

Box 1: Example of questions raised by panellists and audience

Should patients be given greater freedom to determine the level of acceptable risk in a clinical trial?

What is the appropriate relationship between politics and medicine with respect to clinical trials?

How much individual judgment by physicians should be allowed within a regulatory framework, especially in relation to unproven or potentially harmful treatments?

Box 2: Example of key recommendations formulated by panellists and audience

Health related quality of life assessments should be included in more clinical trials.

Clinicians should be more engaged and better supported to systematically collect data about their patients when using interventions which are not yet fully validated.

Diverse groups (industry, patients, researchers, government) should be consulted early in clinical research.

A strong physician-patient relationship should be developed whenever possible. Investing in relationships can help doctors and patients engage in honest discussions and make difficult decisions about proven and unproven interventions.

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REFERENCES

1. Brain Matters 2: Ethics in the Translation of Neuroscience Research to Psychiatric and Neurological Care, May 26-27, Institut de recherches cliniques de Montréal, IRCM.
2. The panel took place at the Institut de recherches de Montréal (IRCM), on the evening preceding the conference (May 25, 2011). The event was open to the general public as well as participants from the Brain Matters 2 conference.