

## Ethics

# Ethics in Psychopharmacological Research

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**Abstract:** This paper raises some of the ethical issues that have become relevant as academia has increasingly relied upon a greater proportion of industry sponsorship for research. First, we must acknowledge, discuss and declare the appearance of conflict of interest, taking care not to fuel a public perception of bias. Researchers must be guaranteed academic freedom and professional autonomy, and contracts with undue confidentiality clauses should be avoided. Scrutiny by Research Ethics Boards (REBs) and standardization of policies in university departments and scientific journals help guide and regulate this potentially dangerous interface.

### Résumé : Éthique de la recherche psychopharmacologique

Cet article soulève certaines questions éthiques devenues pertinentes parce que les universités se fient de plus en plus à une proportion accrue de commandite de l'industrie pour la recherche. D'abord, nous devons reconnaître, discuter et déclarer l'apparence d'un conflit d'intérêts, en prenant garde de ne pas alimenter la perception publique d'un biais. Il faut garantir aux chercheurs la liberté universitaire et l'autonomie professionnelle, et éviter les contrats aux dispositions de confidentialité abusives. L'examen par le Comité d'éthique pour la recherche (CER) ainsi que la normalisation des politiques dans les départements universitaires et les revues scientifiques contribuent à orienter et à régulariser cette interface éventuellement dangereuse.

**Key Words:** ethics, conflict of interest, industry-sponsored research, psychopharmacology.

A recent Canadian case that involved research ethics arising out of industry sponsorship of an academic project attracted international attention and highlighted issues relevant to the entire academic community (1).

Dr. Nancy Olivieri is a specialist in the treatment of hereditary blood disorders. In the early part of the 1990s, her field of inquiry took her into the area of an experimental iron-chelation drug for the treatment of thalassemia. In 1993, she and a colleague signed a contract for a

randomized trial of this agent, based on some early promise shown in a pilot study. The negotiated contract contained a confidentiality clause giving the sponsor the right to control certain information and the right to terminate the trial. Dr. Olivieri subsequently identified an unexpected risk to the treatment. The company disputed this finding and attempted to block investigators' efforts to inform patients of this risk. That the company in question was currently making a multimillion-dollar donation for facilities at the university complicated the case. There are several plot twists that go beyond the scope of this paper and are more suitable to a work of fiction.

Another major case at Brown University in the United States involved an occupational health physician who conducted research as a consultant to a textile company. He discovered what he considered to be a work-related lung disease. After finding out that he planned to present this finding to his peers at a conference, the company threatened to sue him for breaking secrecy (2).

These cases highlight several issues that arise out of an increasing trend toward industry-sponsored research in academia. Increasingly, government and nonprofit organizations have been unable to provide a major proportion of grant money, and for this reason, industry has taken a larger role. This has set up a potential conflict whereby industry's aim to realize a profit for its shareholders could come into conflict with academia's aim—the search for truth and knowledge in the spirit of scientific inquiry (3). Although it is reassuring to think that psychiatry is immune to these problems, this most likely is not the case. Clearly, we should not consider this purely an American problem, because it certainly has Canadian connotations (1,4).

Patients generally participate in clinical research trials for altruistic reasons; that is, to advance the standard of care. As noted in the Tri-Council report (5), Canadian society expects that the benefits and the harms of research will be fairly distributed. The danger arises when a secondary economic impact exists, wherein clinical trials are used for marketing purposes (6). Bearing in mind that it takes

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\$500 million US to bring a new drug onto the market, for academics to be key players in this process depends on industry-sponsored research. In turn, academia is beginning to depend on industrial grants and faces competition from contract research organizations, both of which could lead to a compromise in principles when negotiating contracts. For academia to remain in control, an awareness of any potential conflicts of interest and restrictions on academic freedom is essential. Grant money, in and of itself, has become an outcome measure of an academic department; thus, when negotiating contracts, the quest for this Holy Grail may affect an academic institution's bargaining power. It is vital that these factors do not compromise the objectivity of investigators and their ability to disseminate their findings.

### **Conflict of Interest**

Many faculty members may not realize potential conflicts of interest, even with the best of intentions. Phillipson describes a classification of interactions that may create conflicts of interest (7). The first type typically involves drug companies sponsoring resident lunches at rounds—a situation he calls indirect nonpersonal interactions. He considers the purist view that one should avoid all sponsorship and considers it inappropriate. He believes that conflict is unlikely with some interactions that are at an acceptably low level, unless one evokes the slippery-slope argument. The key issue is not that support exists but that there may be failure to disclose to patients and the professional community. Most conflicts of interest are at the level of an appearance of conflict rather than an actual conflict. A recent paper looked at 136 trials that researched treatments of multiple myeloma and found that three-quarters of the industry-sponsored trials favoured new treatments over the standard, compared with only one-half of the trials funded by nonprofit organizations (8). It did not appear that the difference in results reflected a lower quality of scientific research or methodology. In fact, one study in the industry-sponsored group demonstrated better-quality research. Although this result could be interpreted as giving the appearance of conflict of interest, the authors of the paper sensibly note that only preselected drugs advance to clinical testing; thus, one would expect positive results in industry-sponsored trials that have reached this level. They also note that a publication bias exists, in that journals are prone to publish favourable results over unfavourable ones (6,9). Another study found that, of authors who supported the advantages of calcium channel antagonists (CCAs) over other treatments, 96 per cent had a financial relationship with the manufacturers, compared with only 37 per cent of the

authors who were critical of CCAs and 60 per cent of authors who were neutral (10). Again, the study appropriately notes that limitations exist—most notably, it did not inquire about a temporal relationship between the authors and the company, (drug companies may have sought relationships post-hoc with clinicians who had published supportive findings). Nevertheless, this study could be used to fuel a public perception of conflict of interest.

Lo and others reviewed the 10 medical schools in the United States that received the most research funding (11). They looked at the school policies regarding conflict of interest guidelines and found that they varied widely. These authors pointed out that the research subjects, the medical profession and the public rely heavily on clinical investigators to act impartially and with integrity, and universities should work to ensure consistent guidelines in this regard.

Further, we should remember that the common use of the amount of grant money as a measure of outcome in an academic department could be a potential conflict. In addition, most clinical research has the potential for conflicts of interest regarding the “intellectual gains” that may benefit the career of the investigators. In other circumstances, even in the mental health field, various benefits may accrue from establishing a standardized model or test (12).

### **Academic Freedom and Professional Autonomy**

The high-profile cases of Olivieri and Keen perhaps highlight the most crucial aspects concerning the ethics of industry-sponsored research. In any research, a scientist must have freedom to inform the subjects and patients and the scientific community about any concerns with respect to the treatment under review. The company may disagree, but this should be done in a forum where there is open and transparent debate (13). The scientific community must carefully investigate those involved in scientific debate—conference program committees, chairs of scientific meetings, and others—for conflicts of interest. Investigators must retain a primary duty to patients (13). One of the problems evident in the Olivieri case involves researchers' ability to publish results within an optimal period of time, without suppression or censorship by the sponsor. Even more pertinent to the Olivieri case is the right to disclose safety concerns to subjects immediately. This aspect involves careful scrutiny of confidentiality agreements. This also supports Phillipson's point that ignorance of these issues is unacceptable in today's climate (7). Researchers and investigators can no longer be taken

unaware. In the Oliveiri case, despite a dispute about the risk, Thomson and others identified the central issue: trial investigators with a reasonable basis to believe that they have identified a risk must ensure that trial participants are informed of this risk (1).

### Research Ethics Boards

The Tri-Council policy statement describes the policies of the Medical Research Council, the Natural Sciences and Engineering Research Council and the Social Sciences and Humanities Research Council (5). The authors note that modern research ethics requires a favourable harm–benefit balance, ensuring that any foreseeable harm should not outweigh anticipated benefits. In Section One, they outline the standards and procedures that Research Ethics Review Boards should use. This is done in some detail, ensuring the expertise, multidisciplinary and independence essential to the work of these boards. The document outlines how the scholarly review is part of the work of ethics review and advocates a proportionate approach to ethics assessment, based on the principle that the more invasive the research the greater the care should be in assessing and in balancing the harms and risks. Ferris notes the lack of communication among research ethics boards (REBs) and the lack of any central mechanism to coordinate REB decisions (14). She argues that REBs have a duty to protect the rights and welfare of research subjects but do not traditionally share confidential information because no formal system exists for doing this. She postulates the need for REBs to develop increased communication and coordination. To do this, however, they will have to be offered legal immunity for disclosing confidential communication. She suggests that REBs should report to Health Canada's Therapeutic Products Directorate, the coordinating agency. This, in turn, may help to clarify and highlight issues that concern policy and principles.

### Publication

We have already discussed some issues about publication that have grave importance relevant to the principles of academic freedom. These include giving investigators the right to publish results within a reasonable time period and researchers' obligation to be accountable for any publication. Publishing negative results may be as important as publishing positive results. Contracts that contain unduly restrictive confidentiality clauses should not be signed. Houston and Moher report on a single North American trial reported transparently and opaquely in six different publications and cited in several unpublished forms (4). They note that multiple renditions of the same

information are self-serving and profoundly misleading, calling into question the integrity of the results. Publications in the scientific sphere rely on author honesty and integrity. Authors, however, may not have access to or know about the totality of studies in multicentre studies. Dissemination of data should not carry a corporate or personal agenda but should be used for scientific purposes.

Davidoff and others argue that authors' rights to examine data independently and submit them for publication independently, if necessary, is also vital (6). Authorship carries with it accountability and requires the author to retain independence. Representing the editors of general medical journals, these authors note that they will collectively avoid reviewing or publishing articles based on studies conducted under conditions that allow the sponsor to have sole control of the data or to withhold publication.

They also note that authors, reviewers and editors can give the appearance of a conflict of interest if they have financial or personal relationships with organizations that could influence their actions. They note that, although financial relationships are most easily identifiable, other reasons could exist for a conflict of interest, including intellectual passion and academic competition. It is common practice for researchers to be given merit payments that, are in part based upon the grant money they have attracted and their publication records. Moreover, advancement within the university depends upon the same factors. Therefore, investigators, authors and academic departments need to monitor themselves closely for these possible conflicts.

### Conclusions

In this paper, we have outlined some of the ethical predicaments facing investigators in the area of industry-sponsored research. We have attempted to highlight some areas where an appearance of conflict of interest may be generated, sometimes without the conscious knowledge of the investigator. Discussion and dissemination is the first stage in dealing with this problem. Policy documents such as the Tri-Council policy will help regulate this sometimes difficult interface, ensuring the reasonable approach that will be productive for all parties and ultimately for society and science. Universities (9) have continued to be at the forefront of this regulation, though more standardization is necessary (11).

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## CMHA Conference to Stimulate National Dialogue on Mental Health Congrès de l'ACSM pour stimuler le dialogue national sur la santé mentale

*Tanya Baglole*

Take part in new conversations about mental health. The Canadian Mental Health Association plans to hold its national conference in Ottawa in mid-November.

The theme for the annual meeting, to be held Nov. 16–19 at the Crowne Plaza Hotel, is “People, Policy and Passion: New Conversations About Mental Health.”

Plenary sessions, debates and workshops are scheduled along five main topics: new conversations, recovery, children and youth, organizational leadership and health reform.

Notable invited speakers include Ian Green, deputy minister of Health Canada, Senator Michael Kirby and Maude Barlow, chair of the Council of Canadians.

CMHA aims for conference participants to learn about innovative programs and how to work with others in the community and government to achieve common goals.

For more information, please visit  
<http://www.cmha.ca>. ●

Prenez part à de nouveaux entretiens sur la santé mentale. L'Association canadienne pour la santé mentale organise un congrès national à Ottawa, à la mi-novembre.

Le congrès, qui aura lieu du 16 au 19 novembre à l'hôtel Crowne Plaza, aura pour thème « Les gens, la politique et la passion : de nouveaux entretiens sur la santé mentale ».

Des séances plénières, des débats et des ateliers sont prévus ainsi que cinq sujets principaux : de nouveaux entretiens, le rétablissement, les enfants et les jeunes, la direction d'entreprise et la réforme de la santé.

Les conférenciers de marque invités sont Ian Green, sous-ministre de Santé Canada, le sénateur Michael Kirby et Maude Barlow, présidente du Conseil des Canadiens.

L'ACSM souhaite que les participants acquièrent des connaissances sur les programmes innovateurs et sur la façon de collaborer avec des représentants de la communauté et du gouvernement pour atteindre des objectifs communs.

Pour de plus amples détails, veuillez consulter l'adresse <http://www.cmha.ca>. ●