Nonpatentable drugs and the cost of our ignorance

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The pharmaceutical industry spends over US$10 billion to fund some 90% of the 40 000–80 000 randomized controlled clinical trials (RCTs) being conducted across the world at any given time.[1–3] By its own estimation, the pharmaceutical industry in Canada spent Can$501.8 million on clinical trials in 2004.[4] In comparison, in 2003/04 the Canadian Institutes of Health Research spent Can$31.8 million in direct grants to RCTs.[5]

The RCT business is profitable for private pharmaceutical companies because the large trials they invest in are focused on patentable drugs. The patent system enables innovator firms to charge consumers prices that are above marginal cost and make a profit.[2,6] In contrast, research on drugs without patent (i.e., nonpatentable or off-patent drugs) or with insufficient marketing prospects (orphan drugs) is funded by nonprofit or charitable organizations only. The numbers presented above show that for economic reasons alone, drugs for which a patent cannot be granted are not being developed, even when they respond to a public health need. Patients, pharmacists, physicians and other caregivers consequently cannot take full advantage of potentially effective treatments.

Must we remain ignorant of the potential efficacy of drugs simply because of their nonpatentability?

Omega-3 polyunsaturated fatty acids (*n*-3 fatty acids) for the prevention and treatment of Alzheimer's disease are a good example of this problem. These chemicals are essential for synapse function, but their concentrations in our cellular membranes depend on our dietary intake. Underconsumption of *n*-3 fatty acids is commonplace in our modern society; indeed, in the United States the average intake of docosahexaenoic acid (DHA) is 60–80 mg/d, in contrast to expert-panel recommendations of 200–300 mg/d.[7,8] Several preclinical and epidemiologic studies suggest that long-chain *n*-3 fatty acids such as DHA may be beneficial for Alzheimer's-related dementia.[7,9–11] In animal models, DHA deprivation leads to aggravation of pathological signs of Alzheimer's disease, especially at the level of the synapses.[9,10] In an epidemiologic study,[11] patients with a diet high in DHA (a median of 0.10 g/d) were at lower risk of Alzheimer's disease than those who consumed less DHA (median 0.03 g/d; relative risk 0.3, 95% confidence interval 0.1–0.9) after adjustments for sex, race, education, total energy intake and the presence of the ε4 polymorphism of the apolipoprotein E gene, the ApoE ε4 allele. Furthermore, various studies[12–15] (though not all of them)[16] have indicated that blood concentrations of DHA and other *n*-3 fatty acids are lower in patients with Alzheimer's-related dementia. Because *n*-3 fatty acids are readily incorporated in cellular membranes, adverse effects from high consumption are rare.[17]

To translate these observations into evidence-based recommendations, we need large, state-of-the-art RCTs. For primary prevention trials, it is reasonable to estimate (assuming an annual probability of Alzheimer's of 3% in the placebo-treated population) that sample sizes of at least 4500 patient-years per group are required to achieve sufficient statistical power (80%) to detect a 25% relative difference in the risk of Alzheimer's disease.[18] RCT costs average some $5000/yr per patient; investments in the area of $50 million are therefore required, which, because *n*-3 fatty acids are a natural product that cannot be patented, could come only from nonprofit agencies. The cost of these studies nevertheless constitutes a fraction of the money spent around the world on mildly efficient palliative drugs for treatment of Alzheimer's disease, such as cholinesterase inhibitors. Indeed, if we assume that 1 million patients worldwide who have Alzheimer's disease are treated with cholinesterase inhibitors at an annual cost of Can$1000 per patient, this amounts to more than Can$1 billion yearly.[19–21] Pfizer's own data[22] state that 717 million patient-days of Aricept were purchased in 1997–2002; assuming $3 per patient-day, this represents more than Can$2 billion. Meanwhile, it is quite possible that suboptimal consumption of *n*-3 fatty acids, in combination with population aging, will soon translate into increasingly more patients with dementia related to Alzheimer's disease.

> Studies of omega-3 fatty acids would cost a fraction of what is spent on palliative drugs for Alzheimer's.

Can we afford to invest in clinical research for nonpatented drugs? The answer, in many cases, is yes. What we tend to forget is that everyone pays at the pharmacy for the cost of private pharmaceutical research. By entrusting drug development almost entirely to the pharmaceutical companies, we may enjoy short-term savings; but in the long term, either as citizens or as patients, we will have to pay.[2]

Competition between manufacturers generally causes the pharmacy prices of nonpatentable drugs to be lower than those of patented ones.[23,24] Thus, many nonpatentable drugs such as *n*-3 fatty acids may turn out to be cheaper in the long term than a patentable drug of the same efficacy. Folic acid, mineral and vitamin supplements are good examples of low-cost nonpatentable drugs commonly recommended by health professionals. It is estimated, for example, that 1.5 million

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Americans experience osteoporotic fractures each year, with an annual cost of nearly US$14 billion in health care alone (ignoring lost income and other indirect costs).[25,26] A 400-UI vitamin D and 1000-mg calcium supplement, which has been shown to reduce the risk of fracture by at least 15%,[27,28] costs less than Can$200/patient/yr.[29] This example, like possibly that of *n*-3 fatty acids in Alzheimer's disease, suggests that some (perhaps many) nonpatentable drugs can reduce pharmacy and other health care costs.

Pharmaceutical companies play a pivotal role in drug discovery; yet they develop and test only those drugs for which they can get a patent.[30] Instead of relying exclusively on pharmaceutical companies to determine the effectiveness of drugs and to develop new treatments, nonprofit agencies should take up the relay for nonpatentable, off-patent and orphan drugs. As of today, such propositions seem utopian, but the problem calls for economic studies on a global scale to determine where public money for health research is better invested. Since the benefit of research-generated knowledge is not limited to a nation's borders, funding could come from international organizations as well as individual governments.

To meet the health research challenges of tomorrow, the present dynamic, in which public money is focused on basic research while private funding is concentrated on clinical research, should be carefully analyzed and revised if necessary. At present, we all should realize that ignoring the potential efficacy of nonpatentable or orphan drugs carries a social cost that clearly needs recognition.

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