FOR THE RECORD

Industry urges psychopharmacology incentives

Industry will require a more responsive regulatory environment, incentives to develop new therapies and more collaboration with governments and academe if the world is to adequately respond to the growing burden of mental and neurological disorders, according to the International Federation of Pharmaceutical Manufacturers & Associations.

A "robust collective response" is needed from all sectors in response to the globe's 700 million annually diagnosed cases (according to the World Health Organization, WHO) of mental and neurological disorders, the federation states in a report, *Mental and Neurological Disorders: Innovative therapies, innovative collaborations* (www.ifpma.org/fileadmin/content/Publication/2012/MNDs-Innovation.pdf).

Using WHO, World Economic Forum and Alzheimer's Disease International data, the report states that mental and neurological disorders account for 13% of the global disease burden. Some 350 million people live with depression, 90 million with a substance abuse disorder and 35.6 million with Alzheimer disease or dementia. The global cost to directly treat such disorders, combined with the indirect cost to the economy through lost productivity and sick leave, was pegged at US$2.5 trillion in 2010. That will increase to US$6 trillion by 2030. Depression is expected to be the globe's leading cause of disease burden by 2030, while a projected 115 million people are projected to have Alzheimer disease by 2050.

Such statistics point to the need for a reformulation of policy across all sectors of society, the federation argues.

With regard to innovation, "push and pull mechanisms, such as product development partnerships (PDPs), advanced market commitments, and grant-giving to research entities could help incentivize research and accelerate the development of new therapies," the report states. "The complexity of the brain, the multidisciplinary nature of research, and the longer time taken to bring new therapies to market can discourage investment in this area. New medicines offer hope of reducing the devastating impact of MNDs [mental and neurological disorders] globally, but innovative and holistic solutions will require a fundamental understanding of the diseases. Solutions will also require ending fragmentation across sectors, as well as leveraging the efforts between our industry, governments, patient organizations, the WHO and other stakeholders in partnership. Such an example is One Mind For Research, a broad consortium that aims to bring health actors together to accelerate the 'research-to-cure' time needed to deliver new therapies."

While calling for a "concerted approach to reprioritize brain research to match the burden from brain disorders," the report noted that "product development partnerships can integrate inputs from different sources to accelerate development of new therapies while dispersing the cost and risk of conducting R&D [research and development] amongst several actors. Particularly for MNDs, grant-giving to research entities is a policy incentive that can accelerate much-needed basic research to understand the basic functioning of the brain."

"Academic institutions and governments can devise supports for researchers and offer incentives for the commercialization of cutting-edge ideas. An example is working to make industry-liaison offices more effective so that ideas born in university laboratories can be transferred to experts with experience of turning this knowledge into medicines," the report added. "Similarly, scientists working in industry can support academia by transferring technologies and know-how to universities engaged in the fundamental science to feed applied research. The relationship is symbiotic but must be nurtured in order to reach its full potential. Furthermore, governments should allocate more funds into basic research. The complexities of studying the brain call for new insights and discoveries in brain research, which can be then translated into novel therapies."

Research and development costs are particularly tricky for industry to handle alone, the report argues. "New therapies for brain disorders take 35% longer to complete clinical trials and receive regulatory approval compared to other new prescription medicines. Add to that the fact that only 1 in 10 molecules entering clinical trials for MNDs obtain approval, compared to around one in six for other disease areas, and it becomes clear why investment in brain research is a risky prospect." — Wayne Kondro, *CMAJ*

First of UK off-label drug use summaries becomes available

The United Kingdom's National Institute for Health and Clinical Excellence (NICE) has launched the first of its proposed new evidence summaries for the use of unlicensed and off-label medicines (ESUOM).

The summary, *Significant haemorrhage following trauma: tranexamic acid*, indicates that in a study involving over 20 000 patients with trauma, those given transexamic acid had a greater chance of survival than those who were not. An extra 15 of every 1000 people (160 as compared with 145) who were given transexamic survived for longer than four weeks in comparison with those given a placebo, NICE concluded in its study (http://publications.nice.org

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.uk/esuom1-significant-haemorrhage-following-trauma-tranexamic-acid-esuom1). The study also found some evidence that the drug is more effective when administered within three hours of the trauma having occurred.

Tranexamic acid is licensed in the UK for use after surgery or in women with heavy bleeding during their periods, but it is not licensed to stop bleeding after major injury. As well, "a health economic analysis has found that tranexamic acid for the prevention and treatment of significant haemorrhage in trauma patients has an incremental cost of $64 international dollars (£43) per life saved," it notes.

NICE's new off-label summaries are intended to provide "information for healthcare professionals and patients to decide whether these medicines are safe and effective, and when they are most likely to yield good patient outcomes," the agency states on its website (www.nice.org.uk/mpc/evidencesummariesunlicensedofflabelmedicines/home.jsp). "Unlicensed and off-label medicines have a valuable role in the care of certain patients when there are no suitable licensed medicines available which meet their needs. However, information for healthcare professionals and patients to decide whether these medicines are safe and effective, and when they are most likely to yield good patient outcomes, can be difficult to find. It is estimated that around 1,000 specific requests for off-label drug use are made to NHS commissioners in England every year. The summaries will be the first nationally-available source of information for healthcare professionals and patients. They will allow evidence-based prioritisation, treatment and funding decisions to be made where there are no clinically-appropriate licensed alternatives. The strengths and weaknesses of the relevant evidence are critically reviewed, but the summaries do not constitute formal NICE guidance."

Two types of topics are to be considered for ESUOMs, specifically, "an unlicensed medicine: that is, a medicine that does not have a UK marketing authorisation and is not expected to do so in the next 2 years" and "an off-label medicine: that is, a medicine with an existing UK marketing authorisation that is used outside the terms of its marketing authorisation, for example, by indication, dose, route or patient population."

Forthcoming summaries that are now in the works include ones on the use of melatonin for sleep disorders in children, diltiazem cream 2% for anal fissure, metformin for polycystic ovary disease and clonidine for attention deficit hyperactivity disorder. — Wayne Kondro, *CMAJ*

Tuberculosis infection rate declining

Fewer people fell ill with tuberculosis (TB) in 2011 and access to TB care has been substantially expanded over the past few decades, but the diagnosis and treatment of multidrug-resistant TB remains a major challenge, the World Health Organization (WHO) says in its annual TB update.

An estimated 8.7 million people contracted TB in 2011 and about 13% of those cases involved coinfections with HIV, WHO states in its report, *Global Tuberculosis Control 2012* (http://apps.who.int/iris/bitstream/10665/75938/1/9789241564502_eng.pdf). There were 1.4 million deaths from TB in 2011, of which an estimated 430 000 involved people who were HIV-positive. "TB is one of the top killers of women, with 300 000 deaths among HIV-negative women and 200 000 deaths among HIV-positive women in 2011. Global progress also conceals regional variations: the African and European regions are not on track to halve 1990 levels of mortality by 2015."

The further decline in TB prevalence rates has helped the world to already reach the Millennium Development Goal of reversing the TB epidemic, the report notes. "The TB mortality rate has decreased 41% since 1990 and the world is on track to achieve the global target of a 50% reduction by 2015. Mortality and incidence rates are also falling in all of WHO's six regions and in most of the 22 high-burden countries that account for over 80% of the world's TB cases."

Over the course of the past 17 years, 20 million people have survived TB because they've received treatment, Dr. Mario Raviglione, director of WHO's Stop TB Department stated in a press release (www.who.int/mediacentre/news/releases/2012/tb_20121017/en/index.html). "This milestone reflects the commitment of governments to transform the fight against TB."

Nevertheless, there is a risk of stagnation if more money isn't made available for treatment, Raviglione argued. "The momentum to break this disease is in real danger. We are now at a crossroads between TB elimination within our lifetime, and millions more TB deaths."

The report notes that "progress in responding to multidrug-resistant TB (MDR-TB) remains slow. While the number of cases of MDR-TB notified in the 27 high MDR-TB burden countries is increasing and reached almost 60 000 worldwide in 2011, this is only one in five (19%) of the notified TB patients estimated to have MDR-TB. In the two countries with the largest number of cases, India and China, the figure is less than one in ten; scale-up is expected in these countries in the next three years."

"There are critical funding gaps for TB care and control. Between 2013 and 2015 up to US$8 billion per year is needed in low- and middle-income countries, with a funding gap of up to US$3 billion per year. International donor funding is especially critical to sustain recent gains and make further progress in 35 low-income countries (25 in Africa), where donors provide more than 60% of current funding," the report adds. "There are also critical funding gaps for research and development. US$2 billion per year is needed; the funding gap was US$1.4 billion in 2010."

The report also indicates that the TB burden is highest in Asia and Africa. "India and China together account for almost 40% of the world's TB cases. About 60% of cases are in the South-East Asia and Western Pacific regions. The African Region has 24% of the world's cases, and the highest rates of cases and deaths per capita."

"Worldwide, 3.7% of new cases and

20% of previously treated cases were estimated to have MDR-TB. India, China, the Russian Federation and South Africa have almost 60% of the world's cases of MDR-TB. The highest proportions of TB patients with MDR-TB are in eastern Europe and central Asia. Almost 80% of TB cases among people living with HIV reside in Africa. Estimating the burden of TB in children (aged less than 15) is difficult; estimates are included in the report for the first time. There were an estimated 0.5 million cases and 64 000 deaths among children in 2011." — Wayne Kondro, *CMAJ*

Malaria pilots a "dangerous distraction"

Canada's $20 million contribution toward an initiative that subsidizes sales of a treatment to fight malaria in eight African nations does far more harm than good and may even be "endangering lives," according to the international relief agency Oxfam.

The Affordable Medicines Facility–malaria (AMFm) initiative, which subsidizes sales of artemisinin combination therapy (ACT) through private providers such as shopkeepers and vendors, and for which the Canadian International Development Agency (CIDA) provided $20 million, has been a failure that does not save lives or delay drug resistance, Oxfam states in a briefing paper, *SALT, SUGAR, AND MALARIA PILLS: How the Affordable Medicine Facility–malaria endangers public health* (www.oxfam.ca/news-and-publications/publications-and-reports/salt-sugar-and-malaria-pills).

Renewal of the initiative, which is run by the Geneva, Switzerland–based Global Fund to Fight Aids, Tuberculosis and Malaria, is scheduled to be discussed in mid-November. Oxfam argued that CIDA and other donors such as the Bill and Melinda Gates Foundation and the government of the United Kingdom should terminate the scheme.

"A shopkeeper selling salt, pepper and malaria medicines cannot tell if a child has malaria or pneumonia," Dr. Mohga Kamal Yanni, senior health policy advisor for Oxfam Canada, stated in a press release (www.oxfam.ca/news-and-publications/news/put-end-risky-malaria-scheme-warns-oxfam). "The Affordable Medicine Facility for malaria is a dangerous distraction from genuine solutions like investing in community health workers and free medicine that have slashed the number of malarial deaths in countries such as Zambia and Ethiopia. The Global Fund board must act on the evidence and put a stop to the AMFm now."

The AMFm was piloted at nine sites in eight countries: Cambodia, Ghana, Kenya, Madagascar, Niger, Nigeria, Tanzania (including Zanzibar) and Uganda (www.theglobalfund.org/en/amfm/).

The paper argues that the AMFm has failed miserably with respect to its original aims of enhancing the availability of ACT and delaying the development of drug resistance by replacing artemisinin monotherapy with ACT.

"The main problems with the concept of the AMFm were, and remain, as follows:

- **Selling malaria medicines, even at a small cost, excludes poor people who cannot afford to pay for a full course of treatment.** Evidence shows that paying for health care leads to delays in seeking treatment, or even going without it. Women are the most likely to be excluded.
- **The informal private sector does not have the ability or incentive to provide correct diagnosis and treatment**. The concept of the private sector as applied to the sale of medicines in developing countries may be misleading. It includes not only pharmacies, but also unregulated informal private sellers, such as street vendors, market stall-holders and grocers — people without medical qualifications who are motivated by commercial interest, not public health outcomes. They lack the incentive and ability to deliver correct diagnosis and treatment for malaria.
- **Many fevers are not malaria, so an informal private sector provider is the wrong place for sick people to go**. Studies in the 1990s showed that malaria was responsible of 40 per cent of fever cases in children in sub-Saharan Africa, meaning that the majority of fevers — 60 per cent — were not due to malaria. Moreover, malaria cases have been decreasing in recent years. This makes it even more critical that children with a fever are diagnosed and treated appropriately — for malaria or non-malarial fevers. The informal private sector is not qualified to do so. The fact that many people currently get their malaria medicines from informal private providers is not a sound public health approach to be built on, but a dangerous outcome of a lack of investment in public provision. Not only is it dangerous for people to be given the wrong medicines, this may also contribute to worsening drug resistance.
- **The AMFm has the potential to increase resistance to malaria drugs**. The history of malaria treatment shows that chloroquine, once a cheap and effective medicine, was rendered useless against Falciparum malaria (the main strain in sub-Saharan Africa), partly because people could not pay for a full course of treatment. Far from delaying the development of resistance, the uncontrolled sale of subsidised ACT could lead to a similar outcome.
- **Moreover, it is unclear why AMFm is necessary**. Governments are able to use donor funding, for instance from the Global Fund and the US President's Malaria Initiative (PMI), to purchase ACT for both the public and private sectors, leaving no need for a new subsidy."

As well, "the AMFm caused excessive orders of ACT, which were not based on clinical needs and led to a crisis in the global market. For example, in 2010 there were 2,338 cases in Zanzibar, yet the private sector ordered 240,000 treatments, mostly for adults. There were also excessive orders in other countries, such as Nigeria and Ghana. The total number of ACT treatments purchased by AMFm for the eight pilots was 155,812,358, nearly five times the estimated number of malaria cases in 2010 in those countries. The global

crisis forced the AMFm secretariat to enforce rationing mechanisms, including basing orders on clinical need — a criterion that arguably should have been in place from the beginning."

The paper also argues that an evaluation of the AMFm conducted by the Global Fund failed to ascertain the level of use of ACT by vulnerable populations, such as children and the poor. Nor did it compare the cost-effectiveness of AMFm against public sector programs, such as the ones run in Ethiopia and Zambia.

Far more effective than the AMFm have been programs that delivered treatment through the public sector and community health workers, the paper adds. For example, "the deployment of over 30,000 health extension workers in Ethiopia (in addition to treatment and bed nets) has slashed the number of deaths caused by malaria by half in just three years." — Wayne Kondro, *CMAJ*

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