EDITORIAL

Launching the ‘War on Mental Illness’

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It is time for a concerted effort, the ‘War on Mental Illness,’ to be launched.

On 23 December 1971, the then US President Richard Nixon signed the National Cancer Act of 1971, a United States federal law. The act was intended ‘to amend the Public Health Service Act so as to strengthen the National Cancer Institute in order to more effectively carry out the national effort against cancer’.¹ This has been widely perceived as the official launch of the War on Cancer. If one looks back at 1971, we were technologically unprepared to launch such a war then. At that time, medical research was severely limited by insufficient technology—there was no magnetic resonance imaging (MRI), no positron emission tomography (PET), very rudimentary molecular biology, no genetically modified animals, no automated DNA or human genome sequencing, no personal computers, no databases, and no universal access to bibliography. Scientific manuscripts were handwritten and then typed with manual typewriters, with no possibility for cutting and pasting. A revised version of a scientific article had to be typed in its entirety from scratch. Obviously, all our current ‘omics’ platforms, such as genomics, proteomics, metabolomics and lipidomics had not even been dreamed of. Yet, the enormity of task, the audacity of the goal, and the technical limitations of the era did not prevent the launch of that ambitious and immensely successful effort. While some cancers, such as pancreatic carcinoma and glioblastoma multiforme, remain uniformly fatal, others have been, for the vast majority of patients, either cured or transformed from a death sentence into chronic illnesses that one manages and lives a long time with.

We propose that it is now the time for a ‘War on Mental Illness’ to be officially and rapidly launched, both as national efforts within various countries and also as an international initiative. The goal of that effort will be improved translation of science into health care, resulting in more efficacious treatments than what we have available today.

THE NEED FOR THE ‘WAR ON MENTAL ILLNESS’

Psychiatric disorders represent a substantial burden to the world. Depression is an excellent case example, as it is in average the second cause of disability in developed countries and the fourth in the entire world.² In Australia, depression represents the largest cause of nonfatal disease burden.³ Moreover, suicide, which is in most cases an outcome of depression, is the third cause of fatal disease burden in Australian men. It is noteworthy that depression precipitates a variety of negative mental and physical outcomes that contribute to poor health both in children and adults. Nearly one-third of people with major depressive disorder also have an alcohol problem, according to the US National Institute on Alcohol Abuse and Alcoholism (NIAAA). In many cases, depression may be the first to occur, thereby leading to alcoholism. Research shows that children with depression are more prone to develop alcohol problems once they reach adolescence. Teenagers who have had an episode of major depression are twice as likely as those who are not depressed to start drinking alcohol. Alcohol abuse in adolescence and adulthood is a cause of physical illness as well as

traffic accidents. Furthermore, depression also contributes to obesity. Depressed patients gain weight during the course of the disorder,⁴ and also as a result of antidepressant treatment.⁵ Having depression makes the treatment of obesity particularly challenging, as the symptoms of depression preclude adherence to diet and exercise guidelines and are a major obstacle to healthy lifestyles. Depression by itself also increases the risk of type 2 diabetes by 60%⁶ and doubles the risk of cardiovascular disease.⁷ Recent studies have documented that by shortening telomeres, depression has a negative effect on the ageing process.^{8,9} If one adds to the burden of depression those of bipolar disorder, schizophrenia, autism, eating disorders and many other psychiatric disorders, it is easy to see that the cumulative impact of these disorders in the world is truly staggering.

THE TIME IS RIGHT FOR THE ‘WAR ON MENTAL ILLNESS’

One could make the case that psychiatric disorders are harder to study than cancer, which can be put into cell cultures or in animals to be dissected in the lab. While that may be right, it is also true that the infinitely better tools that we have today, compared with what was available for the ‘War on Cancer’ in 1971, give us a stunning advantage that our oncology colleagues of the early 70’s did not have. In a way, the higher complexity and inaccessibility of psychiatric disorders are more than offset in 2014 by the astoundingly superior tools available to us. Therefore, we are at the present time far better positioned and therefore readier to launch a ‘War on Mental Illness’ than our oncology colleagues of 1971 were to start their exceptionally successful ‘War on Cancer.’

It is unquestionable that a ‘War on Mental Illness’ is necessary, timely, and technically feasible. That being the case, how can we get started? In our opinion, this new ‘war’ needs to be fought along all the steps of translation. Therefore, it is worthwhile to define those.

THE SIX STEPS OF TRANSLATIONAL SCIENCE

The process of translation in all areas of medicine, including psychiatry, can be conceptualized as occurring along six steps, from T0 to T5, as follows (see Figure 1).

T0: Discovery

Because T1 has already been used by many as a level of translation, we call a preceding step T0 (T zero). This refers to the fundamental process of discovery, which is sometimes forgotten in discussions on translational science. Translation cannot be a pipeline only, or a bridge from nowhere. It is not the case that all fundamental discoveries have occurred and that if we bring to the clinic all the advances of recent years, disease will be conquered. Much fundamental discovery work still needs to be done so that proper translation can occur. Hypothetically, one could have the best translation pipeline, but without translatable new fundamental science, such pipeline becomes meaningless. This step is also critical if we are to distinguish translational science from purely applied research.

T1: First in humans or proof of principle

This refers to the now ‘classical’ step of bench to bedside—first in human studies.

T2: Clinical trials

The step of translation from bedside to clinical care: clinical trial studies, for example, are in this domain.

T3: Health-care policy and guidelines

This term has been emerging but needs further definition. We believe that this is best defined as translation of new evidence into health-care guidelines and health policy.

T4: Long-term effectiveness and safety

We define this step as a research on the outcomes assessment of translation. Once translation occurs from T0 to T3, from novel fundamental discovery to health policy, the outcomes of such changes in practice need to be meticulously and critically evaluated, as not all new guidelines and policies will be shown over time to work out. Careful research is needed to determine what is successful in the long run and what is not in order to guide the health care of the future.

T5: Global health

This consists of global implementation of new guidelines that emerge, as the outcome of translation after research at the T4 level further validates effectiveness and utility.

The Six Steps of Translation

Figure 1. The six steps of translational medicine: T0, discovery; T1, first in humans or proof of principle; T2, clinical trials; T3, health-care policy and guidelines; T4: long-term effectiveness and safety, and T5, global health.

Translation: A process with three major gaps

Figure 2. Three major gaps are identified along the pathway of translation, at the levels of knowledge, practice or implementation and adherence.

THE THREE GAPS IN THE PATHWAY OF TRANSLATION

We have identified the following three major gaps along those six steps that constitute the pathway of translation, at the levels of knowledge, practice and adherence, which we refer as G1–G3 (see Figure 2).

G1: Knowledge gap

This is the gap caused by the lack of discovery and the absence of usable data. It is remedied by translation steps T0, T1 and T2. The take home message at the level of this gap is that in the absence of knowledge or evidence, there can be no evidence-based medicine.

G2: Practice gap

On many occasions, existing knowledge is simply not translated into actual, real-life clinical practice. This is also known as translation into practice or implementation. It has been estimated that it takes ~17 years for research evidence to reach clinical practice.¹⁰ Overcoming this gap is challenging, as it requires a process of ongoing education by practitioners so that new knowledge can be consistently translated into the clinic.

G3: Adherence gap

It is common that both clinicians and patients agree on a therapeutic course of action, which is then not followed. As an example, a large European study showed that 56% of patients prescribed an antidepressant stopped taking them on their own within 4 months.¹¹ The critical issue at this level is the modification of behaviors, which is tremendously challenging.

THE NECESSARY ELEMENTS FOR THE 'WAR ON MENTAL ILLNESS'

Keeping in mind these six steps and three gaps in the translational process, how can we then proceed to successfully launch a 'War on Mental Health'? Our vision for that is summarized in Figure 3 and Table 1.

Investigator-initiated research

First, we believe that there is a key role for existing investigator-initiated efforts, either as single projects (known as R01 grants in the USA or as project grants in Australia) or as clusters of projects (known as center grants in the United States of America or program grants in Australia). Obviously, for a 'War on Mental Health' to be successful, a higher number of investigator-initiated grants needs to be funded. Furthermore, targeted calls for research, with dedicated budgets, need to be established. Those are known in the United States of America as Request for Applications or RFA's and in Australia as Targeted Calls for

Figure 3. A strategy summary for the 'War on Mental Illness'.

Table 1. Components of the 'War on Mental Illness'

- **Increases in existing investigator-initiated single grants** (R01's in USA, project grants in Australia)
- **Increases in center grants** (Conte Centers in USA, program grants in Australia)
- **Call for applications with dedicated funding for**
 - Basic discovery
 - Psychiatric neuroscience translation
 - Translation into practice (implementation)
- **Well-structured and well-funded national consortia**
- **Well-structured and well-funded international consortia**
- **Creation or expansion of dedicated translational psychiatry centers and institutes**
- **Federal requirement for inpatient and outpatient psychiatric services in academic medical centers**
- **Global treatment efforts: an issue of human dignity**
- **Promotion of wellbeing, including positive psychology and resilience building, as well as adoption of health lifestyles.**
- **Philanthropy: support of new hypotheses and approaches.**
- **Infrastructure and seed funding for sole proprietor labs**
- **Effective commercialization**
 - Facilitation and support of start-up/incubators
 - Efficient tech transfer
 - Ethical and appropriate interface with big pharma

Figure 4. The structure for an international translational psychiatry consortium, developed to address the six stages of translation.

Research or TCR's. They should cover, in separate mechanisms, basic discovery, psychiatric neuroscience translation and translation into practice (implementation). It is essential that funding streams for these three domains be completely separate from one another, each with their dedicated budget, so that one approach does not compete with the others. There has to be a particular emphasis on funding mechanisms for discovery in the domains of mental health and psychiatric neuroscience, as fundamental knowledge related to psychiatry still needs to be drastically advanced.

National and international networks

While investigator-initiated efforts are indispensable, it is highly unlikely that a disease like schizophrenia will be conquered by advances accomplished in one single lab, funded by one single grant. All mental illnesses are common and complex disorders of gene–environment interactions. Those are best approached by well-structured and well-funded consortia, which have existed with great success in other areas of medicine, including cancer, heart disease and endocrine–metabolic diseases. Such consortia

should be funded in translational psychiatry both at the national level and internationally. Figure 4 summarizes the elements for a proposed International Translational Psychiatry Consortium. That type of international partnership would be structured to fully cover the six steps of translation. T0—Discovery: to identify and integrate the most promising discovery efforts. T1—First in humans or proof of principle: partnerships among leading clinical psychiatry research centers. T2—Clinical trials: to create a rigorous international academic clinical trial network. T3—Health-care policy and guidelines: Interface with relevant health agencies in various countries. T4—Long-term effectiveness and safety: is what we are doing working well over time? T5—Global health: international partnerships and outreach with innovative international clinical and training programs, such as a Global Masters in Translational Psychiatry.

Global mental health

The issue of global mental health is very timely. The miserable, inhumane and appalling conditions faced by the mentally ill in some low- and middle-income countries constitute one of the great human rights scandals of our era.¹² Efforts analogous to those of the Bill & Melinda Gates Foundation, that is doing so much to address infectious diseases, must be created for worldwide mental health, as vital for human dignity. Such global mental health efforts should be an important constitutive element of the 'War on Mental Health.'

Mental health in academic medical centers

In developed countries, the stigma of mental health manifests itself in a more insidious way. Groundbreaking advances in treatment tend to occur in academic medical centers. Because psychiatric services do not offer intensive and invasive procedures that can be billed at top dollar, profit-oriented hospital administrators, who increasingly lack any medical background, have in many cases greatly reduced or simply terminated psychiatric services in academic medical centers.^{13,14} A 'War on Mental Health' should include a federal requirement for academic medical centers to have inpatient and outpatient psychiatric services in a fixed formula that would be proportional to their size. This way, large academic health sciences centers would have large psychiatric services.

Translational psychiatry centers and institutes

There are very few dedicated translational psychiatry centers and institutes in the world. The number of those needs to be increased, both as independent entities and as national intramural research programs, where new ideas can be tested and developed without the long delays caused by the search for external funding. Such translational centers and institutes should be structured to promote integration along both vertical and horizontal axes, as we recently described (see Figure 5).¹⁵ Briefly, vertical integration is what is presented in Figure 1, from T0 to T5. Horizontal integration cuts across disease states along either scientific themes, such as inflammation and neuroendocrinology, or along technical domains, exemplified by imaging and the 'omics platforms: genomics, proteomics, metabolomics and lipidomics.

Philanthropic initiatives for new and untested ideas

In contrast to cancer and heart disease, philanthropy in psychiatry is still in its infancy. We are grateful for the support offered by Connie Lieber and the Brain and Behavior Research Foundation (formerly NARSAD) and the Stanley Medical Research Institute. Nevertheless, many more similar bodies should be created in our field so that there can be adequate support for new initiatives, innovative approaches and untested hypotheses, leading to the collection of pilot data and positioning for competitive application to government funding.

Figure 5. A conceptual framework for psychiatry. Top panel: in the brain-defined structural changes, such as the plaques and tangles of Alzheimer's disease, or to be discovered or confirmed microstructural or functional changes can lead to key symptoms. Bottom panel: parallel and simultaneous tracks of integration along both thematic and technical horizontal axes and at the vertical translational level are needed in psychiatry (from Licinio and Wong,¹⁵ with permission).

Sole proprietor researchers (biohackers)

In traditional medical research settings, investigators are typically given very little to nothing by the institutions that employ them. Vast numbers of medical researchers are 100% self-funded, bringing in the entirety of their own salaries from external sources. Moreover, the infrastructure they use is all paid for by the direct and indirect budgets of their own grants. Additionally, they have to teach (usually for free), to contribute to committees and to engage in other administrative tasks for which they are not paid and that distract from their core research mission. As a reaction to what they perceive as an exploitative type of structure, some researchers, also known as biohackers, are becoming *de facto* sole proprietor businesses, engaged in noninstitutional science and technology development. They lease their own bench space and infrastructure and operate like micro-companies.¹⁶ There are new funding programs, such as SynBio axlr8r and the Thiel Foundation, that provide early-stage support to high-risk, high-reward independent ventures. SynBio axlr8r is a program that jump starts synthetic biology companies with funding from SOS Ventures, a venture capital firm in Kinsale, Ireland, with a goal of taking an idea through proof of concept to form a company within 90 days. The Thiel Foundation from San Francisco, CA, USA, created by Peter Thiel, cofounder of PayPal, supports fellows to 'pursue innovative scientific and technical projects, learn entrepreneurship from the ground up, and begin to build the innovative companies of tomorrow' (Thiel Fellowships <http://www.thielfellowship.org>). Europe's budding biohacker scene includes La Paillasse in Paris that is growing rapidly and, with public funding and support from the Mayor of Paris, will soon move to a larger building in the city center.

Commercialization

Eventually, new treatment approaches need to be effectively commercialized in order to reach vast numbers of people and make a difference in their lives. This requires facilitation and support of start-up and incubators and efficient tech transfer, which tend to be a roadblock and source of delayed translation in academic institutions.

Given recent conflict of interest scandals in Psychiatry, it is absolutely essential that the 'War on Mental Health' not be tainted by such egregious misconduct. Therefore, guidelines and frameworks for interaction with big pharma companies need to be developed to ensure expediency and feasibility in the context of the highest ethical standards.

Prevention: wellbeing, resilience and early-life intervention

While a war on established mental illness is very much needed, according to Benjamin Franklin 'an ounce of prevention is worth a pound of cure.' In that context, efforts to promote wellbeing, such as positive psychology and resilience building,^{17,18} as well as the adoption of health lifestyles, including stress reduction, proper nutrition and exercise, ought to be an integral part of the 'War on Mental Illness.'

It will be likewise crucial to develop and apply preventive strategies for those who are vulnerable to mental illness in childhood and adolescence, before psychiatric disorders become established chronic conditions. This represents a difficult challenge with two factors that need to be delicately counterbalanced. On the one hand, it is logical to propose early intervention before psychiatric disorders become a chronic burden; on the other hand, it is detrimental to prematurely label children and adolescents as mentally ill and to treat, sometimes with undesirable outcomes, young people who may in the long run do well without intervention. Given the potential pitfalls of applying diagnostic labels and exposing any vulnerable group, such as children and adolescents, to treatment and treatment-related adverse events, we believe that it must be absolutely required for early-life preventive and treatment strategies to be supported by the most rigorous science.

ADDITIONAL CONSIDERATIONS

This 'war' needs to be launched simultaneously on multiple fronts. There is much that can be done within the existing structures and of course more resources are needed to either create or enhance the constitutive elements of the 'War on Mental Illness', which are summarized in Figure 3 and Table 1. As the 'war' evolves, other elements will undoubtedly emerge. Over time, the 'War on Mental Illness' will certainly become bigger and more powerful than the sum of its parts, leading to truly innovative treatments, improved therapeutic approaches and effective prevention.

It is tempting, but unwise, to disregard current approaches as having at best reached a plateau and focus resources solely on the search for new treatments. Many patients with psychiatric disorders achieve full remission with existing interventions, whereas others have only partial or no response. Importantly, some patients may respond very well to some treatments and not to others. They may also stop responding, without reasons that are clear at this time. Pharmacogenomics is aimed at unraveling the genetic basis of treatment response. When we discover *a priori* through genomics, or other types of biomarkers, which patients will respond to which drugs, therapeutics in psychiatry will be much further ahead than it is now.¹⁹ Consequently, efforts to discover new treatments should be complemented by an equally strong emphasis on personalizing and optimizing existing interventions or drugs.

Much emphasis has been placed in recent years on research that is peer reviewed before it is done, as is the case for existing grant mechanisms. In this context, many intramural research institutes have either been reduced in size or dismantled over time.

The US National Institute of Mental Health (NIMH) Intramural Research Program (IRP) has suffered considerable erosion in the last two decades. When we first joined the IRP in the early 90's, its

budget was 16% of NIMH's budget. In 1994, Cassell and Marks chaired a blue ribbon panel on the NIH's Intramural Research Program, of which the NIMH IRP is part, (http://www.sourcebook.od.nih.gov/oversight/NIH-IRP_Redbook.pdf) and specifically recommended that 'the total IRP budget for institutes, centers and divisions (ICDs) should not exceed the current rate of 11.3 percent of the total NIH budget.' The NIMH IRP budget is today 11% of that institute's total budget, as recommended by Cassell and Marks. This represents a relative reduction of 31% in 20 years. Having faced many challenges over the last two decades, it is hoped that with newly appointed leadership the NIMH IRP will again achieve new heights in mental health research.

In Australia, The John Curtin School of Medical Research (JCSMR) at the Australian National University in Canberra used to be entirely block-funded by a direct allocation from the Australian Commonwealth government. This allowed its scientists to rapidly attain world renown, with milestones such as the award of the Nobel Prize in Physiology or Medicine to three individuals who performed their award winning work there, including neuroscientist Sir John Eccles. However, federal block-funding dedicated directly to JCSMR has ceased to exist and that institution's research projects are now entirely supported by competitive grants. At present, Australia does not have a National Institute of Mental Health or any stable, secure, long-term sources of funding for research in psychiatric neuroscience or mental health. Other international institutions, which used to be 100% supported by direct funding allocations, have also become increasingly grant dependent.

We believe that while there is a key role for research grants, rapid progress at the cutting edge research can benefit from secure, stable and dedicated revenue streams. For example, the Manhattan project was launched by President Franklin D. Roosevelt's Executive Order 8807, signed on 28 June 1941, and resulted in the first atomic bomb successfully detonated in New Mexico on 16 July 1945 (Trinity test). Such spectacular success would not have been achieved as rapidly if instead of an intramural Manhattan project the US government had relied on the process of investigator-initiated grants that currently exists in medical research. Under the right conditions, a well run, solidly funded and dedicated program can be more far more efficacious, expeditious and cost effective than dispersed efforts.

The 'War on Mental Illness' needs be fought on many fronts, with a variety of strategies and mechanisms. For our success, it is vitally important that different approaches do not compete with another. Instead, they should coexist and work cohesively together towards a common target: the generation of new knowledge and its rapid translation to improve mental health.

LAUNCHING THE 'WAR ON MENTAL ILLNESS'

We have already reached the threshold in which our efforts to launch the 'War on Mental Illness' represent medical, scientific, humanitarian and moral imperatives. Hillel (הלל) (Babylon, c.110 BCE–Jerusalem, 10 CE) famously stated, 'if I am not for myself, who will be for me? And if I am only for myself, then what am I? And if not now, when?' If we do not stand up, not only for ourselves, but also for the hundreds of millions afflicted by mental illness the world over, who will? And if not now, when?

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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