Australian Government
National Mental Health Commission

NATIONAL MENTAL HEALTH RESEARCH STRATEGY

BACKGROUND PAPER: Treatment research (Session 1B)

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Introduction

Notwithstanding the fact that mental health remains the largest driver of disability in developed nations, little progress has been made to date to identify the core biological pathophysiology of these disorders and to develop novel therapies. This stands in contrast to the situation in many other communicable and non-communicable disorders where, latterly, impressive progress has been made. The reasons for this are complex, but include historic under-appreciation of burden and hence, under-investment in the area. This has led to inadequate capacity in the mental health research space. This task is not aided by the fact that the brain is the most complex biological system known. Notwithstanding impressive progress in basic neuroscience, this has yet to translate into meaningful change at a clinical level. A further challenge is the withdrawal of many industry players from the mental health space and a consequently declining pipeline of novel treatment developments.

Background

Research to date has been in a number of distinct areas. These include epidemiology and disease burden, basic neuroscience, pharmacology, psychotherapy and social interventions, lifestyle based interventions and clinical trials. Much of the current research has been driven by independent investigators and has been relatively small scale. In contrast to what has been seen in other disorders, research in the mental health space has not seen many large scale, well-resourced and extensively coordinated efforts such as those that have underpinned progress in, for example, infectious diseases such as HIV. In the clinical trial space we have not seen coordinated, very large-scale clinical trials tackling the agreed priority areas in a manner that is commonplace in disorders like cardiovascular disease and cancer. While large-scale coordinated investments have been made in basic neurosciences, for example, in the USA Decade of the Brain, these have not been replicated nationally and have not been sustained, and hence have not led to the expected benefits in terms of solution of clinical problems. Lastly, we have not seen coordinated multidisciplinary approaches based on philosophies like convergence science, which aim to harness multiple diverse disciplines, skill sets and groups of researchers from different backgrounds to meet the complex challenges of these disorders.

While accepting that because we lack a coherent understanding of the core biology of these disorders, and consequently, diagnosis remains predicated on phenomenology, we have a reasonable understanding of the epidemiology, course and outcome of these disorders using existing classifications.

While our nosology is admittedly imperfect, given the absence of pathophysiology, there have not been overt benefits from recent attempts to refine our classifications, and until neurobiology and pathophysiology is available, these are probably settled. Churchill's maxim of this being the worst possible system except for the alternatives probably applies.

We have a reasonable understanding of the burden and impact of these disorders at a personal, social and economic level. But we need to translate this knowledge into health policy and health systems development.

We have made reasonable progress in psychotherapy and have usable models of intervention capable of addressing the need of fairly diverse groups of disorders. Models of individual therapy are fairly mature, although adaptation to internet and digital platforms is a promising area.

While acknowledging that these are sub-optimal for many individuals, we have pharmacotherapies that are capable of targeting most of the major disorders. Unfortunately, few of these get the bulk of people in a given disorder to remission, although sub-groups of people, such as with mood disorders, can respond very well to treatments. Treatments for many disorders such as obsessive-compulsive disorder and schizophrenia are however sub-optimal for the majority of individuals. We have many disorders such as autism for which no really useful treatments exist.

Gaps and uncertainties

We do not, as yet, have a coherent understanding of the underlying pathophysiology of most psychiatric disorders. While it is true that there has been substantial progress and many new pathophysiological insights, the core biology of these disorders remains unknown. This is a major roadblock for the development of biomarkers and rational therapy development.

The development of biomarkers for psychiatric disorders has substantive intrinsic appeal. In theory these are capable of clarifying state, trait, course, treatment response and outcome domains. However, these have been singularly disappointing. While individual biomarkers have been associated with some of these clinical domains of interest, it is probably fair to say that none of these have the sensitivity or specificity required for translation to clinical practice. This, at least in part, reflect the heterogeneity of psychiatric disorders, the vast number of pathways dysregulated to a subtle extent across multiple of these disorders, and the lack of coherent pathophysiology informing the classifications used.

While we do have many effective therapies, and a fairly good understanding of how to use many of these, we still need ongoing research to clarify exactly how many of these therapies could or should be used, as well as to better delineate the disorders or phenotypes that might respond to these. There is considerable interest in precision psychiatry, which promises to marry biomarkers of diverse types with treatments in order to inform, more specifically, who might or might not benefit from a particular therapy. It is nevertheless probably true to say that we have not yet had sufficient progress in this area to impact clinical care.

Despite the promise of neuroimaging, which admittedly has provided important insights into the pathophysiology of many disorders, neuroimaging has not yet contributed to the routine clinical care of people with mental health disorders.

Similarly, although genetics has provided meaningful insights into pathophysiology, it's explanatory capacity is limited by the fact that a very large number of genes, each of very low variance, uncertain physiology and interactions and, at times, inconsistent validation, have constrained the capacity of genetics to impact clinical care. It remains uncertain whether, without major methodological breakthroughs in genetics or imaging, that these domains will be able to substantially contribute to clinical care in the foreseeable future. Data from

other disorders is informative in this regard. Sickle cell anaemia, Huntington's and Cystic Fibrosis are genetic disorders with a single gene affecting a single protein. None of these have been cracked therapeutically. The task in mental health is many orders of magnitude more complex, and until the science of genetics advances enough to tackle the simple questions, it's unrealistic to expect them to crack the really hard ones.

A significant problem is in the domain of implementation. The majority of people with psychiatric disorders do not receive adequate or evidence-based care, even in well-resourced environments. There is a degree of between-disorder-heterogeneity in this regard. The routine management of some disorders such as bipolar disorder is noteworthy for normative and substantial divergence from guidelines. Most people do not receive evidence-based mood stabilisers and receive agents like antidepressants, which are not recommended as monotherapy - substantial progress is required to be made in the translation of evidence into clinical care.

There is uncertainty as to the optimal method for the development of novel therapies. The NIH has chosen to pursue a path requiring singular targets with proof of target engagement. While this is desirable methodologically and is capable of imputing pathophysiological salience, it has not succeeded in discovering meaningful new treatments, not least, because almost all psychiatric disorders are associated with multi-system dysregulation evident in multiple pathways. Systems based approaches are required. In addition, given that most pathophysiological insights are reverse engineered from understanding the mechanisms of known agents, these insights can be engineered to develop therapeutics.

Areas in need of further research

To preface the question, 'what further research is needed?' it is probably necessary to make two points. Firstly, relative to almost all areas of medicine, research is undercooked and substantial development is required in almost all areas. Secondly, it is essential to engage community stakeholders in this question, although we do know that more effective treatments and services are a consumer priority.

We still lack a coherent understanding of underlying neurobiology and pathogenesis of mental illness, and pre-clinical work in this domain remains essential. Pursuant to the second point raised earlier, more work in treatment development is essential. Areas requiring investment would include novel models of candidate molecule screening and drug repurposing, pharmaco-epidemiology and other target validation methodologies, as well as creating the infrastructure to support large-scale collaborative clinical trials. It is probably worth noting that psychiatry stands unique against other medical disciplines in the absence of any clinical trial networks. Service evaluation and implementation research remains immature compared to other medical disciplines. There is potential in digital and Internet interventions, an area where Australia has particular strength. There remains a need for high quality longitudinal and cohort studies to contribute to the understanding of burden of disease, course and outcome.

As noted earlier, there are a number of areas where research endeavours have been immature and preliminary, relative to the burden of illness. These include service evaluation and implementation research. There remains considerable uncertainty as to the optimum model for mental health service delivery, which requires evaluation. Drug repurposing has considerable potential and, to date has been inadequately pursued. Psychiatry urgently requires clinical trial networks similar to those in existence for other medical disciplines, scaled to the burden of disability. Lifestyle approaches show potential as a nascent area of investigation, and this merits validation in large-scale trials and research on implementation and integration with service delivery models.

Challenges

There has been historic under-investment in mental health relative to the burden of disability. This has created an absence of infrastructure capable of meeting the need. It's commendable that infrastructure has begun to be created in selected areas such as youth, but comparable efforts are required for other mental health research needs. Successes in other branches of medicine, which have reduced the burden of those disorders, together with likely increasing prevalence of mental health disorders, has spotlighted the prevalence and burden of mental health disorders. It's only recently that policy makers and the general public have taken ownership of this burden of disability resulting in a significant lag in investment and hence, breakthroughs. Secondly, the brain remains the most complex system known and the complexity of the brain confounds research endeavours.

Funding rates for mental health research, while always being competitive, have reached historic lows. The most recent NHMRC round had success rates in the 5-10% range. The risk of this scenario on a workforce that is largely funded by competitive grant funding, is that a substantial proportion of the early and mid career workforce will be eliminated by this Darwinian process, as an early or mid-career researcher only needs one or two years without grant funding to terminate their careers. This risks exacerbating the capacity limitations highlighted earlier. While there have been isolated examples of success in the philanthropic space, compared to countries like the USA, philanthropy is relatively undeveloped and is not systematised.

The old chestnut continues to hold true, that mental health is 16-18% of the burden of disability, 6% of clinical spend and 3-4% of the research spend. For us to make progress in this space, we need funding that is equitable to the burden of disability. Early and mid-career researchers face a particular barrier with significant job insecurity, a paucity of funding options and poor success rates. Psychiatry does not have much of the infrastructure available to other disciplines. Clinical trial networks are an example alluded to earlier, but another gap is that many other disciplines have national or state-wide centres of excellence where clinical and research expertise are integrated. The Peter McCallum Cancer Institute or the Baker Institute, where substantial discipline-specific capacity exists, would be an aspirational model. Internationally, the Institute of Psychiatry, Psychology and Neuroscience would also be a model worth studying.

For those participating in research, the disease state itself can be a barrier to research. For example, the hopelessness and lack of motivation in depression inhibits the drive to seek novel solutions. The negative symptoms of schizophrenia and lack of insight inhibit self-perception of perceived need. These symptoms can also pose barriers to consent, particularly in participants who are floridly psychotic or who have cognitive difficulties. As a counterpoint, there is active consumer demand for access to clinical trials in oncology to access cutting-edge treatments; both clinicians and patients in oncology perceive research and novel trials as a desirable and often essential aspect of clinical care. In psychiatry, this is seldom the case. There is frequently a passive acceptance of sub-optimal therapy by clinicians, predicated at least in part, on unsustainable patient loads and the need to turn over cases to optimise capacity. Again, unlike oncology, where publically accessible resources are available to inform potential participants of the availability of trials of novel agents, no such resource exists at a national level for psychiatry. While most people are treated in primary care settings, these are very rarely engaged, let alone, optimised for collaborative research endeavours.

Opportunities

There has been a substantial shift in public opinion emphasising the unmet need in the mental health sector. Consumers and the general public are now acutely aware of the gaps that exist and that there is a very large shortfall between expectation and reality. This can potentially be a trigger to greater investment in the sector. Hopefully, this can translate into a greater sense amongst the funders of mental health services that investment in the area more broadly is required. This includes not only services themselves but also integration, teaching, active research and quality improvement activities into the mental health sector. It is slowly becoming more acceptable for philanthropists to acknowledge that they or their loved ones have been touched by mental illness and invest in the sector. We still have a long way to go before we are as mature in this domain as our American colleagues, but there is progress. It is also hoped that the NHMRC and MRFF would recognise this need and allocate funding on a basis that is comparable to burden of disability.

It is probably true that public attitudes are shifting faster than those of politicians, and hence, funders. We need public pressure to ensure equitability of service and research funding comparable to burden of disability. As noted above, we need infrastructure for large projects, particularly clinical trial networks, and national and state-wide centres of excellence.

Conclusion

Despite being a tiny country, Australia punches way above its weight in the quantity and quality of its mental health research. Indexed by the ISI highly cited ratings, fully 10% of the world's top ranked scientists in mental health are in Australia. In particular, Australia has world leading capacity in disorders such as psychosis, addictions and mood disorders, as well as domains such as Internet psychotherapies, youth mental health and novel therapy development. Given the American RDoC experiment, which has effectively decimated clinical research, Australia's lead is likely to be extended and its international role even more necessary. This capacity, paralleled by the described clinical need, needs to be a spur for substantial investment in the sector. Essentially, what is required, is funding comparable to the burden of disease and investment in infrastructure capacity to bring mental health up to speed in comparison with what's available to researchers in other disciplines.