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NATIONAL MENTAL HEALTH RESEARCH STRATEGY

BACKGROUND PAPER: Comorbidities and trans-diagnostic research (Session 2A)

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Introduction

Mental Disorders[1] rarely occur on their own – other conditions and concerns are typically present. Many of these comorbid or co-occurring issues may complicate our ability to recognise, provide assistance and organise health services for people experiencing mental disorders. Physical health,[2] housing and homelessness, under or unemployment, family violence, stigma and discrimination, and legal and financial issues are among the many other issues and concerns that co-occur with mental disorders. In addition, diversities across indigeneity, ethnicity, gender, sexuality, age and disability influence all aspects of mental disorders but are not covered in this briefing.

Comorbidity is an issue across health, for example Caughey et al (2008) report 80% of elderly people have three or more chronic conditions. It is common to see statements like "Comorbidity is common, costly and complicates intervention leading to greater burden, disability and impact on people with mental disorders, their carers and the community".

Most of our research and understanding of mental disorders is based on selected samples of people without comorbid problems (O'Hara et al., 2017). More recently there has been progress in identifying some common patterns in the experience of people with mental disorders, developing and evaluating techniques for recognising these patterns, and developing and evaluating techniques for providing assistance. There is a significant need for research in all these areas of comorbidity.

Feinstein (1970, p 467) first used the term comorbidity: "In a patient with a particular index disease, the term co-morbidity refers to any additional co-existing ailment". Since, then the related term multimorbidity has also been used to refer to complexity (the presence of two or more long term health conditions) without a focus on an index condition.

This briefing provides some stimuli for discussion of research priorities to improve our understanding, recognition and treatment for comorbidity.

Background

Research to date has focused on establishing the size of the problems of co- and multimorbidity and there have been isolated successes in how to best recognise these problems and provide assistance. The overarching consensus is that there is a dearth of research on comorbidity compared with the apparent need.

Without a thorough bibliometric analysis of health and medical literature, it is difficult to encompass how well it addresses the needs of end users. Some indications can be gained from the Cochrane Library – while there are 857 Cochrane reviews with a subject heading encompassing mental health,[3] there are only 3 reviews that have comorbidity in their subject heading,s two of which are concerned with mental health. In

the PubMed database there are 38,283 records with both a subject heading from the Mental Disorders tree and from the Comorbidity tree, 5,815 are likely to be reviews.

These numbers are total numbers of publications and may represent a range of publications (editorials, letters, opinion pieces, etc). Despite this, the numbers give some indication of how little there is in the health and medical literature and hence how big the gap is between the information provided by research and the information needs of consumers, carers, health professionals and planners and policy makers. A more detailed Campbell Collaboration style, evidence and gap maps (EGMs) would be very useful (e.g. Hempel et al., 2019). In the absence, I provide the following observations with caution.

High levels of comorbidity have been one contributor to a rethink of the taxonomy or nosology of mental disorders – a number of efforts are underway to develop more empirically-based taxonomies. The Hierarchical Taxonomy of Psychopathology (HiTOP) consortium and the NIMH Research Domain Criteria are two large ongoing programs of work.

There is more work on the comorbidity of common mental disorders with areas of major disease burden such as cardiovascular disease, cancer and diabetes. This work includes the use of standardised assessments to screen for comorbid anxiety or mood disorders. Separate bodies of work have focused on the content of a treatment interaction and on the organisation of care. In terms of the organisation of care – the *no-wrong-door* approach has reasonable consensus across different clinical practice guidelines (e.g. Marel et al., 2016). Bouncing people from one service to another on the basis that one part of their problem needs attention first (without careful coordination) is very unlikely to lead to good outcomes.

Before going on to consider gaps, challenges and opportunities, it may be useful to consider how comorbidity may influence the outcome of health care. Comorbidity may indicate severity, it may complicate response to any intervention or it may interact with intervention so that some interventions are uniquely effective (or ineffective).

a) Comorbidity may be associated with greater severity. Is this effect additive, multiplicative or does it take some other form? For example in the 1997 National Survey of Mental Health and Wellbeing (ABS 1998, p 33), people with only a self-reported physical condition took on average 2.4 days out of role[4] in 4 weeks prior to the interview; people with only anxiety disorders took 2.1 days; and those with mood or affective disorders took 2.7 days. When anxiety and physical conditions were comorbid, the average days out of role was 3.7, which is less than an additive effect (2.4+2.1=4.5). Those with affective and physical health reported an average of 6.3 days, which is more than additive (2.4+2.7=5.1). Here it is important to consider severity as measured by what – ideally a broad measure such as quality of life or overall functioning.

b) Comorbidity may be associated with a lesser or slower response to all treatments. Comorbidity may be associated with greater severity before treatment and in addition, it might change or slow the response to any treatment. Such an effect is harder to demonstrate and requires a greater sample size among other things.

c) Comorbidity may be associated with a differential response to one treatment compared to another. Very rarely is this sort of evidence available, yet this is the evidence required to make the case for a different treatment approach to comorbidity.

Gaps and uncertainties

The overarching consensus in recent reviews is that there is a dearth of research in co- and multimorbidity. This is particularly so when compared with the need for research as indexed by the size and complexity of comorbid concerns. In the following sections I have attempted to blend the results of other recent research prioritisation processes – the Lancet Commission on Psychiatry, The Global Alliance on Chronic Diseases (2018) *Researcher Statement on Multi- morbidity*, The UK Academy of Medical Sciences (2018) and the James Lind Alliance Research Prioritisation Partnerships in some areas of mental health – with my own impressions.

The Lancet Psychiatry Commission blueprint on *Protecting Physical Health in People with Mental Illness* (Firth et al., 2019) provides expert consensus-based recommendations including clear research gaps. I recommend this paper to the workshop participants. A key area of need is the mortality gap between those with and without chronic psychosis (Lawrence et al., 2013). While understanding the benefits of psychotropic medications, the Lancet Psychiatry Commission noted their adverse effects on physical health – in antipsychotics and potentially the cardio metabolic effects of antidepressants. There is a need to understand these effects and develop new ways to reduce adverse effects. Consistent with the Lancet Commission's report, Barber and Thornicroft (2018) recommend research needs to be conducted on how to increase the uptake and effectiveness of lifestyle promotion programs with proven efficacy in people without mental disorders.

The UK Academy of Medical Sciences published research priorities for multimorbidity in 2018 and these are summarised in Table 1.

Table 1: UK Academy of Medical Sciences 2018 Research priorities in multimorbidity

1. What are the trends and patterns in multimorbidity?
2. Which multimorbidity clusters cause the greatest burden?
3. What are the determinants of the most common clusters of conditions?
4. What strategies are best able to facilitate the simultaneous or stepwise prevention of chronic conditions that contribute to the most common multimorbidity clusters?
5. What strategies are best able to maximise the benefits and limit the risks of treatment among patients with multimorbidity?
6. How can healthcare systems be better organised to maximise the benefits and limit the risks for patients with multimorbidity?
See https://acmedsci.ac.uk/policy/policy-projects/multimorbidity

The Global Alliance on Chronic Diseases Researcher statement on multi-morbidity (CGHE, n.d.; Hurst et al., 2018) was prepared for the 3rd UN General Assembly meeting on Non-Communicable Disease in 2018. The common themes identified in the statement reflect policy and service delivery priorities as well as priorities for research. While it was conducted independently and in parallel with the UK Academy review, the conclusions are consistent and add further weight to that document.

The James Lind Alliance in the UK facilitates Research Priority Setting Partnerships (PSP). They have developed a method for establishing common questions asked by health professionals, consumers, and carers for which there is no good answer in the health and medical literature and developing consensus priority for these uncertainties or questions. I scanned the online listing of research priorities (The James Lind Alliance, n.d.) for Autism, Bipolar Disorder, Dementia, Depression, Eating Disorders, Mental Health in

Children and Young People, Safe Care for Adults with Complex Health Needs and Schizophrenia. Aside from the complex needs PSPs, those that reflected some aspect of comorbidity are shown in Table 2.

Table 2: Research priorities related to comorbidity taken from James Lind Alliance Research Priority Setting Partnerships across mental disorders

Name of JLA Priority Setting Partnership	Priority (out of 10)	Text of uncertainty
Autism	1	Which interventions improve mental health or reduce mental health problems in autistic people? How should mental health interventions be adapted for the needs of autistic people?
Eating disorders	4	What is the most effective treatment (and order of treatment) for patients with an eating disorder and a comorbid disorder?
Schizophrenia	4	How can sexual dysfunction due to antipsychotic drug therapy be managed?
Schizophrenia	10	What interventions could reduce weight gain in schizophrenia?
See www.jla.nihr.ac.uk for process to develop and the context of these questions		

A couple of issues here: these are the results of a process conducted in the UK (or, in the case of the Eating Disorders, Netherlands) and may differ for Australia. The priorities in Table 1 should be addressed. The coverage of mental health is sparse. I did not consider examining all the PSPs in the "physical" disorders for uncertainties related to mental health.

The Safe Care for Complex Needs Priority Setting Partnership prioritised 10 uncertainties that are relevant to the organisation of care for people with comorbidity (*Safe Care for Adults with Complex Health Needs Top 10 | James Lind Alliance*, n.d.). These are summarised in Table 3.

Table 3: Top 10 uncertainties from JLA Safe Care for Adults with Complex Health Needs

1. When people with complex health needs require care from more than one specialist or department, how can their needs be addressed in a way that considers the whole person through better organisation and team-working?
2. How can communication be improved amongst professionals working in different organisations who are involved in the care of a person with complex health needs?
3. How can health professionals be encouraged to listen to and value the expertise of people with complex health needs, in relation to treatment and management of their health condition(s)?
4. How can we ensure that people with complex health needs are discharged safely from hospital, in a way that ensures their individual treatment, support and care needs will be met? How can we ensure that all of the services involved are committed to this?
5. How can communication be improved amongst the health professionals within a single organisation who are all involved in the care of a person with complex health needs?
6. When people with complex health needs receive care from different specialists, should one health professional oversee that person's treatment and care to improve safety?
7. How can important information about a person with complex health needs be recorded in a way so that health professionals can access the key facts quickly?

8. How can health and social care be better joined up, more flexible and responsive, so that a person with complex health needs can be regularly reviewed and their care plans changed as necessary?
9. How can (paid and unpaid) carers' knowledge of a person with complex health needs and their specific healthcare needs be recognised and used to improve and inform the care provided by professionals?
10. To what extent do health professionals read patients' medical records before providing care to people with complex health needs? How can this be improved?
See http://www.jla.nihr.ac.uk/priority-setting-partnerships/safe-care-for-adults-with-complex-health-needs

Many comorbidities that are reported in clinical settings appear to be sparsely researched. These may include but are not limited to: externalising disorders and substance use, cognitive impairment and substance use/externalising (fetal alcohol spectrum disorder and language disorders in prisons).

My conclusion is there is a need to establish and maintain more formal methods to identify gaps between what is known; and what consumers, carers, health professionals, planners and policy makers need to know.

Challenges

There is a lack of clarity about what comorbidity is and how it might impact health care – somewhat reduced by the UK Academy's recommendation for more rigour in conceptualising and defining comorbidity in research.

The number of different combinations of disorders presents a challenge which is partly offset by the examination of common combinations (e.g. Ng et al., 2018). Showing that single disorder focused research gives similar outcomes (allowing for differences in severity) in multimorbid populations is a start. Focusing on the organisation of care rather than a narrower focus on the content of care may also be a useful priority.

Consensus taxonomies (ICD-11 and DSM-5) have provided definitions from which research in mental health has benefited. Over time, they have also provided increasing numbers of disorders, which may have resulted in an increase in apparent or superficial comorbidity.

While Australia has a proud record in health and medical research, we remain limited by a relatively small population more widely dispersed over a larger geographic area than other countries. Thus, recruiting sufficient people into research can present problems even for common combinations of comorbidity. It also presents problems for the development and maintenance of expertise. Cooperation and collaboration rather than competition between researchers and clinicians is likely to be the way ahead here.

The siloing of researchers, health professionals, and clinical services is a significant barrier to integrated care and to research in comorbidity. While there is some small progress, the organisation and training of researchers and health professionals is a barrier to understanding and responding to comorbidity.

Many of the commonly understood research methods (such as randomised clinical trials) are focused more on efficacy (can this work under ideal circumstances?) not effectiveness (does it work under typical conditions?) and implementation (can this be delivered at scale?).

There is considerable value and continuing need for blue sky, discovery oriented, researcher initiated, research funding – we don't always know what we will discover when we set out on research. However, there is also a clear need for research that is more directly targeted at knowledge gaps and priorities set with users of research – consumers, carers, health professionals and policy makers.

Opportunities

Further examination of common patterns of multimorbidity will enable improved identification of phenotypes and that will enable further developments in understanding common mechanisms. Efforts such as the HiTOP and Research Domain Criteria should be supported and extended.

Advances in neuroscience, genomics and other basic sciences will no doubt continue. To be of maximum benefit and facilitate translation, research should include phenotypes that represent comorbidity and ensure new methods are tested with diverse samples that reflect multimorbidity as soon as is possible.

Research to identify the early signs of multimorbidity and to prevent or slow the progress is needed.

Integration of lived experience and end users of research into research at an early stage will result in more definitive and more implementable research. Practitioner/clinician researcher, consumer researcher and carer researcher provide integration of lived experience and research skills within the individual. Integration of these diverse perspectives within research teams is also a priority.

The "Learning Health Care System" (Riley et al., 2013) is an aspiration for a closer relationship between research and health care delivery. Routine methods (like the James Lind Alliance Research Priority Setting Partnerships) to identify areas of uncertainty in health care and prioritise those for research are needed. Researchers need to develop and employ optimal research methods to ensure that studies optimally resolve uncertainty.

As multimorbidity is the norm, new research proposals should be assumed to include people with common comorbid conditions and argue for why exclusion is necessary. New proposals should have adequate statistical power to detect the effect of comorbidity.

The UK Academy of Sciences (2018) report on multimorbidity and the Global Alliance on Chronic Diseases (2018) researcher statement of multimorbidity both highlight the difference between high and low/middle income countries. The differences in socioeconomic status are likely to be found within countries as well (Pathirana & Jackson, 2018). Research on multimorbidity needs to consider geographic diversity in mortality and morbidity, clustering of risk and the importance of engagement with, not marginalisation of, the vulnerable.

Implementation science is building methods and expertise to understand and reduce the barriers to innovation in health systems. Health services have invested in quality improvement methods and need to support the development of capacity in implementation science.

What are the unique skills sets and competencies to work in research on comorbidity – how many Australian researchers based here or around the world have expertise at pre- and postdoctoral levels? In addition to disciplinary skills and knowledge, research in comorbidity requires:

   a) multidisciplinarity – solutions are unlikely to come from within a single discipline

   b) consumer and end-user engagement – without an intimate understanding of the day-to-day issues facing consumers, carers, health professionals and other end users, research is unlikely to deliver answers

   c) skills in Data Science, and

   d) skills in Implementation Science.

Increasing the number of consumer researchers and supporting clinician researchers are key to encouraging diversity of expertise within research teams.

The National Health and Medical Research Council (NHMRC) Centre of Research Excellence in Mental Health and Substance Use (CREMS) led to a significant increase in the number of researchers skilled in and producing research in comorbidity. Related Centres of Research Excellence (CREs) in mental health have produced similar increased capacity. Yet the magnitude of the problem and the need to reduce the disease burden will likely need an order of magnitude beyond what they achieved at peak funding. What structures are there to support development of research capacity beyond the NHMRC CRE program?

Inspired by the Global Alliance of Chronic Disease researchers' statement on multimorbidity, how do interventions developed for single disorders impact on comorbidity and multimorbidity (increase the secondary analysis of existing data and broaden the secondary outcomes of planned studies, increase awareness of measurement of broader outcomes among investigators in mental health)?

What are the impacts from uncoordinated attempts to deal with multimorbidity (e.g. polypharmacy) in mental health?

Electronic medical records and other data exhaust from healthcare are an often touted as a source of answers to improve healthcare. Carefully designed data collections might allow feedback to end users about research priorities. The risks of selecting the wrong indicators, and providing the wrong feedback at the wrong time and to staff that are not empowered to make changes, will be barriers to achieving this potential.

Digital technology is likely to provide opportunities to provide information, assist in recognising comorbidity and provide assistance. The opportunity for digital health to fill gaps in local knowledge is profound – the challenges are to engage vulnerable members of our communities and to ensure the care provided from disparate sources is coordinated.

Examples of successful e-therapy interventions for comorbidity are Inroads and SHADE (Kay-Lambkin et al., 2006). Coordination of care may be provided by portals such as eCliPSE.

Conclusion

There is international consensus that:

- co- and multimorbidity is the norm and not the exception
- co- and multimorbidity is burdensome on individuals, their families and communities
- prevention, recognition and treatment is complicated by co- and multimorbidity
- there is a dearth of research to provide the knowledge base to improve this situation.

To further improve healthcare for people with mental and comorbid disorders, there is a need for significant increases in research funding.

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Notes

[1] I will use the term "Mental Disorders" as this is the closest to international consensus on the naming of problems and conditions in mental health from the ICD-11 and DSM-5 taxonomies and nosologies, understanding that this term is not universally accepted.

[2] "Physical health" is used by convention here because many health services are organised into separate physical and mental health streams and common conceptions often make a separation of mental and physical health. There is no implication intended here that the causes or treatments of mental disorders are "mental" nor that the causes or treatments of physical disorders are "physical".

[3] All tree exploded MESH Mental Health

[4] Defined in the 1997 National Survey of Mental Health and Wellbeing (ABS 1998) as: "The number of days in the 4 weeks prior to interview that the respondent was totally unable to work or carry out normal activities (or had to cut down on their usual activities) because of their health."