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NATIONAL MENTAL HEALTH RESEARCH STRATEGY

BACKGROUND PAPER: Mood disorders (Session 7A)

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Introduction

There is international recognition of the premature death and disability costs attributable to common mental disorders.[1,2] The largest proportion of this excessive morbidity is attributable to depressive and other common mood (including bipolar) disorders – reflecting their early age of onset, high population prevalence, chronicity and comorbidity with physical illness.[3]

Many people live with persistent or recurrent mood disorders, and consequent functional impairment and secondary comorbidity. This takes the form notably of alcohol and other substance misuse and poor physical health, with specific emphasis on premature cardiovascular morbidity (with linked metabolic complications) and premature mortality. The contribution of mood disorders to premature death by accident and injury and suicide is also large. More effective treatments for depression and other mood disorders being implemented at scale are likely to result in reduced suicidal thoughts and behaviours, as well as premature mortality. However, there is recognition that the evidence base for choosing highly-personalised, new or existing treatments, especially for young persons with mood disorders, is limited. Additionally, the evidence for how to institute such treatment approaches or provide the most cost-effective treatments at scale is sparse.[4,5,6] Current treatment approaches are characterised by a lack of a clear primary or secondary preventive agenda[7] and, in the first instance, delayed access to the most appropriate evidence-based interventions.[5,7]

Functional outcomes from current pharmacological or psychological treatments remain limited, with accumulating evidence of poor long-term education and employment outcomes, even among those young people who do receive clinical care from early intervention networks in Australia.[8] Currently, our youth health service systems are not widely linked to clinical and neurobiological research capacity, thus inhibiting the testing of key hypotheses.[9,10,11] While very substantive government investments are being made in Australia, North America and Europe in new youth-focused mental health services, there is still a lack of evidence for optimal models of care.

For those with well-established mood (including bipolar) disorders, despite increased access to medical and psychological treatments, there is little evidence that the burden of disease or other key outcomes (i.e. participation in education, training or employment, suicidal thoughts and behaviour, secondary alcohol and other substance misuse, poor physical health) have improved substantially. Specifically, the extent to which new primary care-based systems (in Australia, notably the Commonwealth-funded Better Access scheme[12,13] which has emphasised increased access to services as distinct from access to high-quality interventions or improved long-term outcomes, or other models such as IAPT[14] in the United Kingdom) are well-directed is debated.

As mood disorders are rather broad and heterogeneous categories of illness, their relationship with development of much more personalised primary treatment selection, and secondary prevention strategies,

remains highly problematic. At the group level, the 'average' degree of improvement associated with any specific psychological or medical therapy remains relatively small. Hence ongoing public commentary typically reinforces only small degrees of difference between 'active' and 'placebo' therapies. By contrast, the range of responses of individuals to common therapies is very large – with significant subgroups showing very large positive responses while typically also significant subpopulations report very adverse outcomes. To date, there are no clear clinical or laboratory predictors that can be utilised at the individual level to predict such a range of outcomes.

Increased international emphasis on the possibility of preventing the onset of major depressive disorders by greater investment in potential risk factor modification (e.g. reduced childhood trauma); promotion of specific cognitive, behavioural or lifestyle strategies to children or young people; or selective or indicated interventions to relevant subpopulations (i.e. pre-natal cohorts, those with childhood anxiety, those young teenagers with sub-threshold depressive symptoms) is clear (e.g. Wellcome Trust[15]). The extent to which such preventive and linked early-intervention strategies are effective in reducing onset, preventing persistence or recurrence or improving long-term outcomes is not yet clear. However, the potential capacity to deliver such interventions at scale, specifically by linking them with new digital technologies and relevant educational or public infrastructure, has great appeal.

International research

International research in the mood disorders domain has been dominated by a range of investments, as outlined below.

Neurobiologically-focused

Genetics

Our understanding of the genetic pathways underlying the mood disorders has improved dramatically in recent years with the increasing numbers of large international genetic consortiums and genome-wide association studies (GWAS). Genome-wide genotyping and sequencing studies are providing evidence that psychiatric disorders are truly polygenic; that is, they have a genetic architecture of many genetic variants.[16] Contrary to expectations that there would be a specific mapping of genetic risk factors to specific mental health diagnoses, there is now strong evidence implicating that psychiatric disorders share common variant risk.[17,18,19,20] These findings challenge the existing nosology of psychiatric conditions and indicate that current clinical boundaries do not reflect distinct underlying pathogenic processes, at least at the genetic level.[17,18,21]

GWAS of common diseases have matured over the last decade, generating the knowledge base for increasingly informative individual-level genetic risk prediction.[22] The commonly applied approach for predicting the genetic risk of human disease is computing polygenic risk scores (PRS) from GWAS summary statistics.[22] Although PRS hold especially great promise in psychiatry because of the inaccessibility and complexity of brain tissue and lack of clinical biomarkers, they are not yet clinically useful, but they are useful for research and have provided insight into disease outcomes, correlated phenotypes and biological mechanisms.[22] The future of genetic risk prediction is anticipated to benefit several areas of research and clinical practice.[16,22,23] PRS may provide an estimate of how many at-risk individuals will be expected to exhibit clinical symptoms or be diagnosed, providing a measurable change from expectation for drug trials. Furthermore, PRS studies may lead to the identification of other biomarkers or may allow for the prediction of treatment response and, thus, facilitate the development of personalised treatment strategies. Genetically informed optimisation of pharmacological treatment can also be addressed by the development of pharmacogenomic tests and decision support tools.

Neuroimaging

Neuroimaging studies contribute to a better understanding of the neurobiological underpinnings of mood disorders, as they allow for examining of associated neuroanatomical and neurofunctional alterations. A number of anatomical brain abnormalities have been described in young adults with depression, bipolar disorder or anxiety,[24,25] such as changes in the volume and thickness of the anterior cingulate cortex (ACC),[26,27,28,29] the volume of the amygdala,[30,31] decreased grey matter volume in frontal brain regions[32] and poorer white matter integrity.[33,34,35,36,37] Interestingly, the volume reduction of the subcallosal gyrus, a part of the rostral-ventral affective subdivision of the ACC, was only observed in patients with more than three untreated depressive episodes, indicating that the volume loss is developing over the course of the untreated illness.[26] Grey matter loss in key frontal brain regions,[32] as well as the disruption of white matter tracts,[33] seem to occur during the course of mood disorders between early disease states characterised by attenuated symptoms and later discrete illness stages.[32] There is also mounting evidence of altered functional activations and connectivity in extended medial prefrontal network regions and closely related subcortical areas such as amygdala and striatum in youth depression,[25,38] bipolar disorder[25,39,40] and anxiety.[41]

Rather than using neuroimaging techniques to understand the neuroanatomical and neurofunctional basis of mood disorders, it has been suggested to utilise these techniques to identify biomarkers to guide differential diagnosis and risk assessment, as well as treatment selection and prediction.[25,42] However, despite advances in functional neuroimaging and promising neuroimaging data, the current knowledge is not yet mature enough to be translated into clinical practice.[25,40,42]

Animal models

Over the last decades, translational research, bridging the gaps between basic animal and clinical research as well as medical practice, has progressed.[43,44] Animal models are valuable tools for the understanding of disease pathophysiology, the identification of biomarkers and development of novel treatment targets and strategies. However, modelling mood disorders is extremely challenging, and continuous bi-directional translations – from animals to humans and back from humans to animals – are needed to improve the preclinical models and to inform clinical research and practice.

One major challenge is the complexity and unique nature of psychiatric disorders. Some symptoms can easily be translated (e.g. altered sleep-wake behaviours and circadian rhythms, change in body weight) or possess at least a significant similarity (e.g. anhedonia or anxiety), while other symptoms (e.g. sadness, feelings of worthlessness, guilt or suicidal thoughts and behaviour) are human-specific and cannot be modelled in animals. Thus, animal models can only focus on specific aspects of a disease but will never display its entire complexity. In addition, psychiatric symptoms need to be induced artificially. This can be done by using various methods based on plausible risk or aetiological factors, triggers and biological mechanism, such as selective breeding, genetic, engineering, brain lesions, electrical stimulations (including optogenetic approaches), pharmacological interventions (i.e. manipulating specific neurotransmitter systems) or environmental manipulations (e.g. chronic social or physical stress, disruption of the circadian rhythm).[43,45,46,47] Importantly, this requires already a certain basic knowledge or hypotheses regarding the underlying pathophysiological mechanisms.

Despite these challenges, meaningful animal models fulfilling a multidimensional set of criteria of validity[43,48,49] have been developed, contributing to a better understanding of the aetiology, pathophysiological mechanisms and the discovery of new drug targets.[45,46,47] Further investigation of bi-directional translations and technological advances will result in further refinement of animal models and tests ("readout measures"), and in consequence improved translation of preclinical findings to clinical research and practice.

Pharmacologically-focused

New targets

Although major mood disorders are highly prevalent, recurrent, and comorbid, and generate a substantial burden of disease,[50,51] multiple psychological and pharmacological treatments are often ineffective.[52] There are ongoing challenges with modest effectiveness, highly variable responses between individuals with the same diagnosis, frequent relapse and recurrence, and a lack of prior predictors that can be applied at the individual level to maximise impacts and minimise adverse effects. Recently, novel pharmacological agent development has departed from the traditional monoamine hypothesis of depression and focuses instead on the glutamatergic, GABAergic, opioidergic and inflammatory systems.[53] Pharmaceuticals that target the glutamatergic system include ketamine, esketamine and rapastinel; brexanolone and SAGE-217 target the GABAergic system; and minocycline targets the inflammatory system.[53] Furthermore, emerging evidence suggests that targeting one or more of the four opioid receptors – mu (MOR), kappa (KOR), delta (DOR), and the nociceptin/orphanin FQ receptor (NOP) – may yield effective therapeutics for stress-related psychiatric disorders and target symptoms of depression that were previously resistant to current antidepressant medications.[54] For example, the promising combinatory agent buprenorphine + samidorphan targets KOR and MOR,[53] and the effects of the rapidly acting antidepressant ketamine may involve opioid receptors as well.[54] In order to improve the personalisation of treatment selection for mood disorders, it is necessary to acquire a greater understanding of the mechanisms of antidepressant action of specific compounds and the neural systems that are targeted.

New psychological treatments

Adaptation of CBT

Over the past several decades, there have been vigorous efforts to adapt cognitive behavioural therapy (CBT) for treatment of mood disorders.[55] CBT provides a sophisticated, empirically grounded account of depression and an evidence-based therapeutic approach for people who suffer from depression. The typical model of CBT is represented in terms of dysfunctional schemas that are dormant until activated by congruent life experiences. Unlike traditional CBT, transdiagnostic CBT aims to modify dysfunctional cognitions, behaviours and emotions. Acceptance- and mindfulness-based interventions aim to change a person's perspective on, and relationship with, their cognitions and emotions. This process is facilitated through mindfulness, non-judgemental awareness and acceptance of psychological experiences.[56] Acceptance and Commitment Therapy (ACT) is a modern form of CBT based on a distinct philosophy (functional contextualism) and basic science of cognition (relational frame theory[57]). This is now generally considered part of a new generation of CBT approach focused on process-based treatments and a large body of research has shown its effectiveness in the treatment of depressive symptoms. The delivery format of CBT has evolved over time from individual to computerised. It is still unclear which delivery format leads to superior outcomes.

Clinical trials of novel treatments

Ketamine

Traditional antidepressant medications are thought to predominantly exert their effects via actions on the monoamines serotonin and norepinephrine, with lagged downstream effects on processes such as synaptic plasticity and neuronal excitability.[58] The effects of these medications are, however, often modest, can take weeks to affect the clinical state and have unfavourable risk-benefit profiles in certain patient groups.[59,60,61,62] Accordingly, international efforts are underway to identify novel antidepressants, which are efficacious, fast-acting and safe.[58] In 2019, the US Food and Drug Administration approved a form of ketamine – esketamine – for treatment-resistant depression (depression that is unimproved by two or more antidepressants). Esketamine is delivered intranasally under physician supervision and in conjunction with an oral

antidepressant. Evidence to date shows that esketamine works rapidly. Depressive symptoms are observed to be reduced in hours – rather than weeks – in around half of the patients with treatment-resistant depression, which may be due to its actions on the glutamate system, a key departure from traditional antidepressants.[63,64] While ketamine has high abuse potential, the World Health Organization's (WHO's) expert committee on drug dependence has concluded that the abuse potential of esketamine is not high enough to warrant scheduling.[65] Future studies will need to determine the long-term safety of esketamine, which is currently unknown, and to determine which groups of patients are most likely to benefit from this novel approach.[64,66]

Immune therapies

There is increasing recognition of the pathophysiological role of neuroinflammation and neuronal autoantibodies across neurological, paediatric and mental – in particular atypical mood and psychotic – disorders. Besides neuronal and other central nervous system (CNS) and systemic non-CNS autoantibodies,[67,68,69,70,71] a general immune dysregulation (including increased levels of circulating pro-inflammatory cytokines, granulocytes and monocytes, and concomitant activation of microglia)[72,73] has been found to be associated with psychiatric manifestations such as atypical mood disorders.

As a young person presenting with atypical neuropsychiatric syndromes may often be extremely sensitive to adverse neurological or motor-side effects from conventional antipsychotics or mood-stabilising agents,[74] there is an urgent need to detect immune-mediated mental disorders early and deliver alternative treatments. A range of active immune-modulating or anti-inflammatory therapies have been shown in case series, and very limited comparative trials, to be therapeutic – particularly with regards to the relief of mood-related symptoms.[75,76,77,78] These include anti-cytokine treatment (e.g. adalimumab, etanercept, infliximab, tocilizumab),[77] nonsteroidal anti-inflammatory drugs (NSAIDs, in particular, celecoxib)[75] and modulation of the kynurenine pathway (minocycline).[78] Furthermore, neuroactive steroids – such as brexanolone (formerly SAGE-457), SAGE-217, and ganaxolone – have been shown to affect brain function through multiple mechanisms, but mainly positive allosteric modulation of the $GABA_A$.[79] In March 2019, brexanolone received its first global approval in the USA for the treatment of postpartum depression (PPD) in adult women. This steroid-type drug rapidly decreases PPD symptoms in moderate to severe PPD.[80] In addition, the efficacy of SAGE-217 and ganaxolone in depression and PDD, respectively, is currently evaluated in clinical trials.[81]

Physical therapies

Individuals with a mental illness have a considerably shorter life expectancy (15–25 years) than those in the general population.[82] The reduced life expectancy for those living with major mood or psychotic disorders is now recognised as a major public health challenge, with a large proportion of the mortality gap being due to premature cardiovascular disease (pCVD). The poor cardiometabolic profile of these individuals was reflected in a recent commission report which showed that those with a mental illness are at a 1.4–2.0 times higher risk for developing obesity, diabetes and cardiovascular diseases than the general population.[83] Specifically, patients with depression have a 40% higher risk of developing cardiac disease, hypertension, stroke, diabetes, metabolic syndrome or obesity than the general population.[83] The comorbidity between mental health and physical conditions is associated with an increased burden of disease,[84] emphasising the importance in improving physical health outcomes and reducing the risk of pCVD.[9]

Furthermore, repetitive transcranial magnetic stimulation (rTMS) is also considered a physical therapy often used complementary to existing behavioural and pharmacological treatments for psychiatric disorders.[85] rTMS is a non-invasive brain stimulation technique, using brief duration, rapidly alternating or pulsed magnetic fields to modulate neural activity.[85,86] In particular, left prefrontal rTMS repeated daily for 4–6 weeks is regarded as effective and safe in adult individuals presenting with depression who have failed one

or more antidepressant treatment attempts.[85] However, in order to improve the response rate, it has been recommended to use fMRI-guided neuro-navigation. This allows for targeting and engaging specific functional brain networks by considering the individual differences in a region-specific way.[87]

Late-life depression

Depression predisposes to medical illnesses and advances biological aging indicated by shorter telomere length, accelerated brain aging and advanced epigenetic aging.[88] Old age is a risk factor for a poor course of major depression, which often cannot be explained by a range of risk factors.[89] Much focus has been on identifying modifiable risk factors in mid-life to prevent discourse into late-life depression. In particular, the targeting of risk factors for vascular disease in mid-life has been a logical approach in the prevention of vascular depression. Therefore, lifestyle alterations and treatment for hypertension and hypercholesterolemia can potentially mitigate the risk for late-life depression. Computerised cognitive remediation targeting functions of the cognitive control network may improve both executive functions and depressive symptoms of late-life major depression.[90] Furthermore, positive outcomes have been shown in neurostimulation treatments in depressed younger adults and promising potential to avert late-life depression.[88] TMS targeting deep structures responsible for mood regulation is well tolerated by older adults and mitigation of late-life depression, however the overall efficacy requires further investigation.[91] Streamlined, stepped psychotherapies targeting behaviours assumed to result from dysfunction of brain networks implicated in late-life depression can be easy to learn and have potential for dissemination[92] to further elevate efficacy.

Late-life depression is also characterised by a range of cognitive deficits and increased risk of dementia, even in elders with an early life depression onset. Fronto-subcortical regions are perturbed in the aetiology and perpetuation of late-life depression, particularly the disruption of subcortical and hippocampal elements in older patients.[93] Therefore, clearer differentiation of the underlying pathophysiological models is required to develop personalised treatments that will target the deficits arising from dysfunction in the underlying circuitry. Clinical trials need to be stratified with regards to underlying neuroimaging parameters and other neurobiological makers.[93] There is a need for future paradigms targeting early intervention and management of depression occurring in later-life, to shift from purely diagnostic models, toward those which incorporate early screening and management of underlying aetiological risk factors, as well as factors which perpetuate symptom persistence.[94]

Australian research: gaps

Australian-based mood disorders research has typically also followed these trends. There has been a relative lack of focus on the areas outlined below.

Personalisation

A major challenge for mental health care is the heterogeneous pattern of illness and diverse needs that people present with. Each person follows a trajectory over time, which may oscillate between health and disorder as a function of complex vulnerability, protective and treatment factors. Diagnostic manuals are often used to guide the diagnosis and treatment of these disorders, however these have been heavily criticised for their lack of clinical utility and inability to account for the huge heterogeneity of these disorders, which means it is challenging to match individuals to effective interventions.[95,96,97,98,99] Common reasons for poor matching include: (i) current syndrome-focused classification systems, and matching clinical guidelines, are largely generic and often fit poorly to young people presenting with sub-threshold mental health disorders (e.g. clinical features of one disorder may overlap with those of other diseases, or the most prominent presenting symptoms may not be those that most clearly define the established phase of the

disorder);[7,10,100,101] (ii) illness extending factors such as functional impairment, self-harm, suicidal thoughts and behaviours (STB), alcohol or other substance misuse and poor physical health are often neglected;[24,102] (iii) neurobiological profiles and pathophysiological mechanisms are often not recognised;[101,103,104] and (iv) the selected interventions do not recognise the significance of clinical stage[7,105,106] (i.e. the severity and persistence of the illness).

This challenge has largely driven the development of new personalised approaches for identifying and treating common mental disorders that reorientate care towards active interventions considering key factors including illness trajectory and pathophysiological mechanisms, clinical stage and broader multidimensional outcomes.[5,10,104,107] These approaches emphasise that beyond the clinical syndromes, people are particularly vulnerable to worse health, social and functional outcomes, and that interventions should be targeted to improve these outcomes transdiagnostically.[108] The importance placed on diverse outcomes aligns with the substantial burden associated with these disorders and the needs reported by people and their families who traditionally feel that health professionals and service providers lacked a fundamental understanding of their situations, and had unwillingness to address their specific needs.[109,110] The prevailing 'stepped-care' service model illustrates how current mental health care opts for a 'fail-first' model where the initial level of care is low regardless of needs, over and above a 'stage-appropriate' care model that aims to ensure that more intensive interventions are offered in a timely way and, thus, that people receive mental health care that is personalised to them.

Young people

Mental health research to date has predominantly focused on adults with established and chronic mental disorders, with considerably less attention paid to young people in earlier phases of illness. This narrow focus on adults to the detriment of young people is ill-informed based on epidemiological data from cohort and burden of disease studies. For example, most major adult-type mental disorders typically emerge early in life,[111,112] and birth cohort studies suggest that the majority of mental disorders experienced by adults are probably extensions of disorders people had when they were young.[113] While adult-type mental disorders frequently follow a chronic course with multiple episodes of relapse,[114,115] evidence is emerging suggesting that efforts made to intervene in early illness phases can modify this illness course.[116,117] Critically, mental disorders are also the leading cause of disability in young people aged 10–24 years, accounting for 45% of the overall burden of disease in this age-group.[50]

An important report by the WHO estimated that the age of maximum negative impact of a disabling illness, with respect to longer-term social and economic outcomes, is 22 years of age.[118] The magnitude of this impact is a consequence of the occurrence of peak risk for mental disorders within the foundational developmental phases of adolescence and early adulthood.[119] Thus, efforts to intervene in young people in early illness phases may be the most cost-effective and successful time to do so, with great potential to interrupt paths to lifelong disability.[119,120,121] There is a dire need to focus on young people, as it has the untold potential to reap a 'triple dividend' of benefits – for adolescents now, into their adult lives, and for the next generation.[122]

Health services and systems

Over the past decade, efforts have been made to create mental health service delivery models that better meet the unique needs of young Australians. This included substantive government investments, mainly through the *headspace* network, new PHN-funded youth intensive services, expanded roles in state-based services and private hospitals, and the Commonwealth-funded Better Access scheme.[12,13,123] Despite the priority of this area, a lack of health service innovation – that is scalable – is notable internationally. Effective care early in the course of illness is still not delivered to most young people with mood disorders.[124,125] Even

when care is delivered, the longer term functional outcomes are often disappointing.[126] The consequences of this failure remain large – personally, socially, and economically.[100] A major reason is that the mental health services in Australia are characterised by service fragmentation, late intervention, a lack of focus on an individual's needs and inequitable distribution of scarce resources.[127,128]

Recent policy directives from the Australian Government recommend the adoption of stepped-care services to improve the appropriateness of care, determined by the severity of need. Under simple stepped-care models, differentiation in the level of service provision usually occurs after the initial episode of care, mainly by identifying those who do not respond. So, only individuals who do not respond to the initial episode of care move to more intensive interventions (i.e. this can be described as a 'fail-first' approach to care). Consequently, these models will persistently fail to reduce disability associated with early onset mental health problems that are already associated with functional impairment or those that progress to more persistent, recurrent or severe forms of illness.[127] Thus, it has been proposed that these stepped-care models can be significantly improved by a highly personalised and measurement-based, technology-enabled care approach.[127]

There is a lack of substantive evidence for choosing which models of care are optimal. It needs to be tested if the new proposed model for youth mental health results in improved clinical and social outcomes compared to existing care models.[125] As the new youth health service systems are not widely linked to large-scale health services research capacity, the testing of key clinical and health-system hypotheses is currently inhibited.[9,10,11] Furthermore, if new models are shown to deliver more effective care, the challenge will be to deliver it at sufficient scale to have real population-level impacts in regions where specialist clinics are not available so that it connects with populations who are at high risk or traditionally under-represented in care.[125]

Prevention and early intervention

Internationally, clinical practice and mental health research has largely been dominated by the use of traditional diagnostic classification systems[129,130] specifying criteria for 'full-threshold' disorders. The categorical disorders defined by these instruments and their corresponding thresholds have determined who receives which treatments and how individuals are categorised in a large body of research into causes and treatments. As a consequence, health systems have largely ignored individuals who do not meet these 'full-threshold' criteria, resulting in a lack of care for those in the early stages of disorder or in 'at-risk' states. These early states often include complex combinations of subthreshold syndromes and a high degree of comorbidity, and do not fit clearly into the pre-specified diagnostic silos,[131,132,133,134] thus it is important to develop and direct prevention and intervention efforts in a transdiagnostic manner. Despite the fact that duration of untreated mental illness is consistently found to be associated with poorer outcomes,[135,136,137,138] identification and intervention at earlier stages of illness has not been prioritised alongside the continued development of interventions for those with more established illness. One exception to this is the development and implementation of early intervention programs for psychotic illness which have shown some success.[139,140] Similar progress for common mood disorders is lacking. Further, reform to implement improved models of care that incorporate early intervention is generally slow and results in highly variable outcomes between services.[141,142,143]

There is some evidence for the efficacy of various early intervention and prevention programs for mood disorders, including school or community-based education or skills training; individual, group, or family therapy; and exercise or other health promotion activities.[144,145,146,147,148,149] Other important components to support early intervention and prevention include improving mental health literacy[150] and reducing stigma,[151] so that adequate help-seeking can occur in the early stages or prior to the onset of mental illness.

However, few economic evaluations of prevention and early intervention have been conducted,[149] and there has been little progress in corresponding policy change and resource allocation to support change in this area. A greater understanding of the pathophysiological basis of common mood disorders and causal risk factors is also needed to further refine prevention and intervention strategies, and to focus the optimal use these in individuals most likely to benefit.[152,153]

An overreliance on consensus-derived, descriptive and categorical psychiatric diagnoses has very likely stalled discovery into prevention and early treatment targets for a range of mental health problems and presents difficulties for clinicians aiming to select optimal treatments for their patients.

Using new technologies effectively

The health sector has recently seen a major increase in the number of mobile applications, internet-based resources and platforms that target mental health.[154,155] Many of these promise to transform mental health treatments and the way mental health care is delivered, and have the potential to overcome many of the traditional barriers to conventional clinic-based care.[156,157] While it remains important to develop and assess the efficacy of online interventions, an equally important task is to determine how to integrate and use these new technologies effectively to improve the delivery and quality of mental health care.[156]

One of the biggest enablers for achieving significant improvements in quality of mental health service delivery is through the integrated use of health information technologies (HITs).[158,159,160] In conventional services, extensive time is often spent conducting thorough face-to-face assessments rather than providing skilled interventions. HITs assist the assessment, feedback, management and monitoring of mental ill-health by collecting personal and health information from individuals and their clinician(s), and promoting genuine collaborative care.[161] These technologies have already demonstrated utility for enabling an appropriate and timely response for people reporting higher levels of suicidality,[162] facilitating more broad assessment of the totality of a young person's needs, and enabling clinicians to move away from traditional evaluations towards detailed data-driven assessments.[163]

While research regarding the efficacy and effectiveness of HIT is growing, we still know very little about the implementation of HIT solutions into existing mental health care settings. Overcoming the implementation barriers associated with new HIT is critical to reach the full potential impact on patient outcomes and health service efficiencies. Recently, key technology, clinician and service factors have been identified that currently limit the effectiveness of new technologies to transform the quality of youth mental health care.[160] These factors include technology design, variation in the level of integration into existing service pathways and clinical protocols, process dynamics, contextual factors (e.g. local leadership, organisational support) and other factors (e.g. resourcing, training).[164,165,166] Addressing these technology and implementation barriers is critical to ensure these tools are developed and integrated with services in a way that truly transforms clinical practice.

Australian research: strengths

Early intervention

The past decade has seen a major shift towards early intervention and pre-emptive psychiatry, which recognises that trajectories of mental disorders and associated impairment are often not fixed, but instead malleable to change.[4,7,167,168] Australia has established itself as a world leader in this area by translating much of the early work carried out for psychotic illnesses, to more broadly address common mental disorders. Major health service limitations have been met by the development of early intervention services, to prevent or delay the onset and progression of these disorders and reduce secondary morbidity.[169,170] *headspace* is a primary care-based model for youth mental health care that aims to be highly accessible to young people

and provide care that addresses a range of social, physical and mental health problems with locally available specialist service partnerships.[171] This early intervention model has already demonstrated successes in reducing the stigma associated with common mental disorders and increasing overall access to mental health care among young people.[6,172,173,174,175] These successes have led to the international adoption of these models in the UK, Ireland, Israel, the Netherlands and the USA.[175,176]

The early intervention model moves away from traditional diagnostic criteria and arbitrary symptom thresholds in favour of recognising the complex and varied needs of young people. Critically, it recognises that longer periods of untreated illness contribute to poorer treatment outcomes and the development of chronic problems.[177,178,179,180,181] Prior work suggests that young people who present with greater impairment and more developed mental health syndromes require more intensive treatments and resources yet are less likely to recover. In contrast, those with milder symptoms and impairment are more likely to recover after a briefer period of care.[182] Therefore, much like other areas of medicine (e.g. physical health), it aims to provide effective care to people in the early stages of illness, before the onset of an acute or crisis situation, or before a disorder becomes a chronic problem.

Prevention

Prevention of major health problems includes early recognition and appropriate treatment of specific psychiatric disorders.[183] In particular, the promotion of active health care including suicide prevention and other secondary prevention strategies has been previously discussed and encouraged.[10] Prevention in depression, for example, has been examined in regard to pharmacological and psychological therapies, as well as programmes needing to combine both behavioural and lifestyle factors (e.g. diet and exercise, social engagement, sleep), in addition to good medical management (stabilising blood pressure, better glycaemic control and stroke prevention).[184] Australian prevention models recognise the importance of multidisciplinary strategies, a major strength in Australia challenging prevention. Previous reviews have highlighted specific Australian health services (such as *Orygen Youth Health*) that have focused on prevention.[169] Like other Australian services, prevention involves synergy between specialised early intervention, youth-specific mental health services, integrated research and clinical programs.[169] Strengths in Australia's focus on prevention also improves management of psychiatric disorders across settings.[162]

Health systems and services

Australia has a major strength in leading health services that are primary-level care, personalised and supported by varying comprehensive and multidisciplinary teams. Specialised mental health services (i.e. *headspace*) utilise clinical psychologists, psychiatrists and allied health professionals. Thus, health services that are well-designed have the capacity to attract higher numbers of young people.[6] Providing required health services at the necessary scale has been effective, specifically in transdiagnostic and stepped-care, having been applied to mental health services.[127,156] Studies have highlighted Australia's strength in leading targeted youth-specific services, and high levels of engagement in young Australians with mental disorders.[6]

Furthermore, Australian mental health services combine the use of online assessments, triage, early intervention and evaluation for targeted care.[185] Online mental health services for young help-seeking Australians has thus far demonstrated the value of involving users.[160] The use of online systems has already had major implications on actual health service practices for the youth mental health services; for example, improving patient and workforce management through systematic assessment, assisting clinical team review and decision-making processes, and the facilitation of systematic assessment and detection of help-seeking young people presenting with suicidality.[162]

Cohort studies

Longitudinal cohort study designs are critical for answering some of our field's most pressing questions: *What are the developmental pathways to mental disorders? Which individuals and which characteristics predict different types of mental disorders? Which trajectories of mental disorders most strongly predict disability? Where and when should we apply health services?*

Capturing and tracking groups of individuals in the community and clinical settings affords an excellent opportunity to improve our understanding of the evolution of mental disorders and their collateral impacts. Australia is home to a number of rich community and clinical cohorts, including the Brain and Mind Centre Youth Cohort (NSW),[186] Brisbane Longitudinal Twin Study (QLD),[187] NSW Child Development Study[188] and the Australian Rural Mental Health Study,[189] among others. Data from these cohort studies have been critical in shaping our understanding of the patterns and predictors of mental and physical health problems among Australians, identification and modelling of which is critical for the development and implementation of effective interventions and primary and secondary prevention efforts.[190]

To conduct meaningful analyses, detailed data tracking over the 5–15 year period after disease onset is needed. Data collection methods demand highly personalised and flexible approaches, so that the maximum data is collected not only at key points of biological or social transition, but also when a young person is exposed to a major new risk factor, experiences a major deterioration or receives an effective intervention. Previously, such responsive longitudinal research, and innovative clinical practice, relied largely on cohort studies confined to highly specialised clinical centres. Additionally, these studies required large investments in trained research staff, but typically resulted in only a limited number of data entry points over the course of illness. These traditional methods struggle to provide sufficient data for the type of modelling exercises that are now required to describe the many possible trajectories that are possible during this key developmental period.[191] Recent developments in health information technologies[192] provide new platforms to capture frequent repeated measures of mental health and wellbeing over extended periods of time.[192] These technologies allow enhanced charting of individual trajectories across key developmental phases (macro-level) as well as monitor reactions to life events (micro-level), capturing valuable data that might otherwise be missed by traditional cohort designs with long assessment intervals.[193] These rich and dynamic data will prove incredibly useful to clinicians and researchers alike, facilitating personalised and measurement-based models of mental health care and improvements to our understanding of the evolution of mental disorders over the life-course.[190]

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