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**TREATMENT AND
THERAPEUTIC INTERVENTIONS**

Use of gene regulatory network analysis to repurpose drugs to treat bipolar disorder

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Bipolar disorder (BD) presents challenges in drug discovery, prompting exploration of drug repurposing and computational techniques. Supported by expanding biomedical data, these approaches represent opportunities for new treatment avenues. Network analyses, particularly gene regulatory networks, could provide insights into pathophysiological transcription factor (TF) effects in BD. This study used gene regulatory networks to identify regulatory changes in BD, employing network-based signatures for drug repurposing. The PANDA algorithm analysed differences in gene regulatory networks between BD patients and controls, incorporating binding motifs, protein interactions, and gene co-expression data. Differential network signatures identified potential drugs targeting the disease-associated gene signature via the CLUEreg tool in the GRAND database. Analysing an RNA-seq dataset of 216 post-mortem brain samples from the CommonMind consortium, we constructed gene regulatory networks for BD and healthy control individuals. Our findings highlighted significant TF influences on pathways related to immune response, energy metabolism, cell signalling, and cell adhesion in BD. Through drug repurposing, we identified 10 promising candidates for BD treatment, including kaempferol and pramocaine, which previously showed preclinical efficacy and need further investigation. Impact statements: The identification of promising compounds, alongside novel targets such as PARP1 and A2b, underscores the potential of drug repurposing for quicker, cost-effective therapeutic solutions. Featured in the "Paper of the Week" series by REPO4EU, a €22 million EU-funded drug repurposing initiative, the study helps advance the understanding of BD's molecular underpinnings and paves the way for future research and clinical applications, ultimately aiming to improve the lives of those affected by this condition.

Falls and fall-related injuries: Prevalence, characteristics, and treatment among participants of the Geelong Osteoporosis Study

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Background: Falls are a significant public health challenge, especially among older adults. In Australia, they cost \$2.3 billion annually. This study examined the prevalence, characteristics, and treatment of falls and related injuries in a population-based sample of Australian men and women. **Methods:** Participants from the Geelong Osteoporosis Study provided cross-sectional data: baseline for men (2001-2006) and 10-year follow-up for women (2004-2008). Falls over the previous 12 months were self-reported by 2,631 participants aged 20-97 years (1,533 men and 1,098 women). The study described the timing, location, causes, and treatment of falls. Data collection included self-reported fractures, medication, disease conditions, anthropometric, and biochemical tests. Binary logistic regression identified factors linked to fall-related injuries. **Results:** Fall rates by age group: 20-29 (24.4%), 30-39 (21.5%), 40-49 (18.7%), 50-59 (24.9%), 60-69 (25.0%), 70-79 (34.6%), 80+ (40.5%). The age-standardized prevalence of falls was 25.0% (95% CI: 23.4%-26.7%), increasing to 32.4% (95% CI: 29.3%-35.5%) for adults ≥ 65 years. Fallers were typically older, less mobile, with higher BMI, and cholesterol levels, and more likely to have musculoskeletal conditions, cancer, and polypharmacy. Most falls occurred outdoors (62.1%), from extrinsic causes (58.5%), and on the same level (78.5%). Fall-related injuries were more common in women, elevated falls, and falls outside the home. Nearly half (45.7%) of those injured sought medical attention, primarily from general practitioners (25.7%). **Conclusion:** Falls are common, affecting about a quarter of adults. This research identifies fall characteristics and circumstances, informing targeted prevention strategies to reduce occurrences and alleviate burdens on healthcare systems and individuals.

Mental Health Australia General Clinical Trial Network (MAGNET) – The Impact of Connecting People and Places across Australia.

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13. University of Queensland

Mental Health Australia General Clinical Trials Network (MAGNET) is Australia’s first adult facilitating clinical trials network funded by an Australian Medical Research Future Fund (MRFF), 2020 Million Minds Mission MHR grant. MAGNET is a collaboration with over 40 leading Australian organisations bringing together researchers, clinicians, and Lived Experience Research Partners and First Nations Research Partners in mental health to improve the quality, reach and translation of clinical trials. Working collaboratively with the mental health community, MAGNET is in the process of developing seven platform resources: Assessments, Biostatistics and Data Management, Governance and Policy, Health Economics Knowledge and Translation, Recruitment Resources, Lived Experience Research Partners, and First Nations Social Wellbeing and Governance Platforms. Four signature trials are part of MAGNET’s mandate. These platforms provide critical resources and skillsets to facilitate the design and implementation of trials, and to minimize duplication. MAGNET has also launched a trial endorsement process to support and facilitate transformative mental health research that addresses major national and international unmet needs and unanswered questions. At the heart of MAGNET are our Lived Experienced Research Partners, First Nations Partners, researchers, and clinicians, incorporated at all levels of MAGNET’s governance. United together we aim to facilitate and impact the delivery of scalable, high-quality, translatable mental health clinical trials to serve community needs.

Associations between defining components of sarcopenia with symptoms of depression and anxiety

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Background: Sarcopenia is the age-related progressive loss of muscle mass and function associated with adverse physical outcomes. Little is known about the relationship between muscle parameters and mental health. We aimed to establish whether components of sarcopenia are associated with depression and anxiety. **Method:** This cross-sectional study involved 682 adults aged >60 years from the Geelong Osteoporosis Study. Symptoms of depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS-D>8, HADS-A>8). Low handgrip strength (HGS) was assessed by dynamometry, appendicular lean mass (ALM) by dual energy X-ray absorptiometry, and physical performance by the timed up-and-go (TUG) test. Multivariable logistic regression models adjusting for potential confounding sociodemographic and lifestyle variables were employed. **Results:** Fifty-six older adults had depression (8.2%) and 122 had anxiety (17.9%). Among women, decreasing ALM was associated with an increased likelihood of anxiety (OR 0.83 95%CI 0.73-0.95) whereas increasing HGS and slower TUG were associated with an increased likelihood of depression (OR 0.91 95%CI 0.84-0.98; OR 1.10 95%CI 1.01-1.19). No associations were identified for men after accounting for differences in sociodemographic and lifestyle factors. **Conclusions and Impact:** Our data underscore the importance of preserving muscle health with advancing age. Interventions aimed at preventing sarcopenia (e.g., resistance exercise training) may have the added benefit improving mental health and warrant further investigation. Clinicians should consider screening older adults with poor muscle health for symptoms of depression and anxiety.

OPTIMISM: A Proof-of-Concept Trial

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Background: Depression affects 185 million people worldwide. Medication has low efficacy and psychotherapy may not be accessible or acceptable to all patients. Emerging evidence supports the use of dietary intervention for depression. However, it is unclear whether the benefits are due to diet or behavioural activation. We aim to address this gap by conducting a controlled feeding trial in people living with depression. **Methods:** In this 4-week double-blind, placebo controlled, randomised controlled trial, 44 participants aged 18-65 years with moderate-severe major depressive disorder, recruited from the community, will be randomised to one of two dietary patterns. The nature of the intervention diet patterns is withheld to minimize expectation bias of future participants. All food will be provided and delivered to participants. Weekly monitoring calls by unblinded dietitians will support adherence. Depressive symptoms will be measured using the Montgomery-Åsberg Depression Rating Scale (MADRS), and together with anxiety and quality of life will be measured at baseline and 4 weeks. Diet feasibility, acceptability and tolerability will also be evaluated. Stool and blood samples will be collected for analysis of microbiome and its metabolites, and inflammatory markers and neurotransmitters, respectively. The primary outcome is mean difference in change in MADRS score between the groups at 4 weeks, analysed using generalized estimation equation models and an intention-to treat approach. **Conclusion:** If the intervention diet leads to a greater reduction in depressive symptoms compared with the control diet, this will provide proof-of-concept evidence that diet alteration can alleviate symptoms of depression.

Preliminary findings from the BipolarWISE trial: An innovative online psychosocial intervention for people with bipolar disorder

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Bipolar disorder has a lifetime prevalence of 2.4% and is associated with significant morbidity, disability, and the highest suicide completion rates of all mental illnesses. While medication is the mainstay for mood stabilisation and prophylaxis, medication adherence is often low and episode relapse and inter-episode residual depressive symptoms are common. There is a need to improve symptom management and reduce the negative impact of the illness on everyday functioning and quality of life. Face-to-face psychosocial interventions have robust evidence as adjunctive treatment for bipolar disorder, not only in terms of symptom management but in improving wellbeing and functioning. However, these interventions are costly, have limited availability, and are inaccessible to many people with bipolar disorder. Online interventions offer promise to increase accessibility, however existing online interventions for bipolar disorder are mostly self-guided and have limited success in helping to reduce relapse. BipolarWISE is a novel digital intervention combining group and individual psychotherapy with a web-based app. The BipolarWISE program was designed in consultation with individuals with lived experience and with the philosophy that living well with bipolar disorder is about more than relapse prevention. This presentation will provide an overview of the BipolarWISE program for individuals with bipolar disorder and present the preliminary findings from the feasibility pilot study. Ultimately, if it proves to be helpful, BipolarWISE could be made available within the Medicare Better Access Scheme as an adjunct to medication treatment and offers an opportunity to improve access to evidence-based psychosocial treatment for Australians with bipolar disorder.

Exploring and evaluating the link between mental and physical health using evidence synthesis methods

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Evidence synthesis is the process of bringing together information from various sources, disciplines, or fields. The information garnered can be used to inform decision making on specific issues by policymakers, institutions and clinicians, and guide researchers and educators. Evidence synthesis can also provide information to and build public awareness of how to make informed decisions. In the Population Health theme, our team is utilising evidence synthesis methods to understand what is known about a range of topics related to the connection of mental and physical health such as the relationships between depression, anxiety and personality factors, and physical health conditions including musculoskeletal and bone health as well as consequences of those, such as falls, fractures and mortality. We will present the key findings of a suite of scoping and systematic reviews, as well as knowledge gaps identified on these topics, and propose recommendations for future research. Our evidence synthesis projects have uncovered the extent and types of evidence concerning the comorbidity between a range of mental and physical health conditions, explored underlying mechanisms, and have pathed the way for new studies.

DepressionASSIST: A psychoeducation website for close family/friends of adults with major depressive disorder

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Around 1 in 6 Australians will experience major depressive disorder in their lifetime and virtually all will rely on family and friends for support. Through providing good support, family and friends can improve outcomes in people with depression and reduce relapse and suicide risk. However, poor support can worsen depressive outcomes and family and friends report distress and decreased wellbeing when taking on this caregiving role. Given the prevalence of depression and strain on health services, there is an urgent need to find novel and effective ways to equip family and friends for this role. Therefore, we are developing DepressionASSIST, a psychoeducation website based on the research literature and a Delphi study involving clinicians, carers, and people with depression. DepressionASSIST includes online courses, videos, and information sheets, as well as interactive tools to help users reflect on and apply the material to their own situation. Using a co-design approach, our current research aims to further refine this website to make it useful, engaging, and relevant. By helping family and friends provide support while taking care of themselves, DepressionASSIST has the potential to empower informal carers and reduce the cost of depression on health services. DepressionASSIST could work alongside existing treatment options to provide a holistic approach to depression treatment and help prevent the development of depression in family and friends. As an online resource, DepressionASSIST could be adapted for use in other countries and cultures and used to guide the development of other carer resources.