Innovation could help address the global burden of depressive disorders

In collaboration, Sage Therapeutics and Biogen have partnered with the broader scientific community of researchers and clinicians to address the growing global health and economic burden of major depressive disorder (MDD).

MDD is a serious and life-altering condition that can lead to significant functional impairment and is associated with considerable economic burden, morbidity and mortality. An increase in the global prevalence and burden of depression has been consistently reported since 1990; in 2021, there were 280 million people living with depression, according to the World Health Organization. In parallel, the economic burden of MDD in the US increased by 38% from US$237 billion in 2010 to US$326 billion in 2018, driven largely by the costs associated with comorbid conditions[1]. The coronavirus disease 2019 (COVID-19) pandemic was a mass-trauma event that disrupted daily living and exacerbated stressors (e.g., job loss, financial difficulties and deaths of loved ones), resulting in a greater than three-fold increase in the prevalence of depressive symptoms in the US[2].

As a heterogenous disorder, MDD manifests differently across patients. The causes of MDD are multifactorial and may result from brain-network dysregulation triggering low mood or loss of interest or pleasure in activities, leading to impaired functioning. Models of depression pathogenesis have advanced over the years. The 'monoamine hypothesis' primarily attributes the cause of depression to an imbalance or deficiency of monoamine neurotransmitters (e.g., serotonin and norepinephrine). However, this model fails to explain the variability in clinical presentations of depression, intra-patient and interpatient heterogeneity in responses to antidepressant therapies (ADTs), and the 6–8 weeks needed for clinical benefit of monoamine-based ADTs[3,4].

Scientific understanding of the aetiology of MDD has since shifted; although monoamines may play a role in the pathophysiology of MDD, there may be central physiological changes in brain networks that underpin depression and affect behaviour, mood, cognition and responses to stress. In one hypothesis, dysregulation in key neuronal networks (e.g., central executive, default mode and salience networks) generates functional alterations that contribute to the development of depression.

Additional areas of research include examination of the depression-associated changes found in hypothalamic–pituitary–adrenal axis signalling, which comprise increased stress-related cortisol release and decreased glucocorticoid receptor-mediated feedback inhibition. Inflammation has also been implicated as a cause of depression, with evidence of neuroinflammation found in the brains of patients post mortem[3].

As such, the recognition and treatment of MDD presents a challenge that may not necessarily be overcome with a single treatment course or therapy.

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PSYCHOTHERAPY, TELEMEDICINE AND DIGITAL TOOLS IN THE TREATMENT OF MDD

Treatment of MDD often involves psychotherapy, pharmacotherapy or a combination of both. Patients with milder forms of depression are more likely to be treated with psychotherapy alone, while those with moderate-to-severe forms are more likely to receive combination therapy or pharmacotherapy alone. To complement traditional psychotherapy, the treatment landscape for MDD is evolving to incorporate multiple modes of therapy that aim to improve care and access to care for patients.

The use of telemedicine for mental health treatment increased significantly during the COVID-19 pandemic, likely due to lockdowns that limited in-person visits and the removal of previously existing regulatory hurdles that allowed for greater virtual accessibility options. Between March and August of 2021, in the US, the proportion of telemedicine visits reached 35% of all outpatient visits for depression, according to the Kaiser Family Foundation. Digital psychotherapy, including person-to-person telemedicine visits or text-message exchanges with a therapist, has been demonstrated to be an effective way to deliver high-quality therapy to patients, especially those in remote settings. Given that digital psychotherapy has effectiveness comparable to that of in-person visits and has utility in reaching patients in both rural and urban areas, its use has been incorporated into clinical practice guidelines in several countries. Benefits of digital psychotherapy may include greater accessibility, convenience and cost-effectiveness, which reduce the likelihood of lost appointments, thus promoting continuation of care[5]. The COVID-19 pandemic may have indeed forged a path for expanded

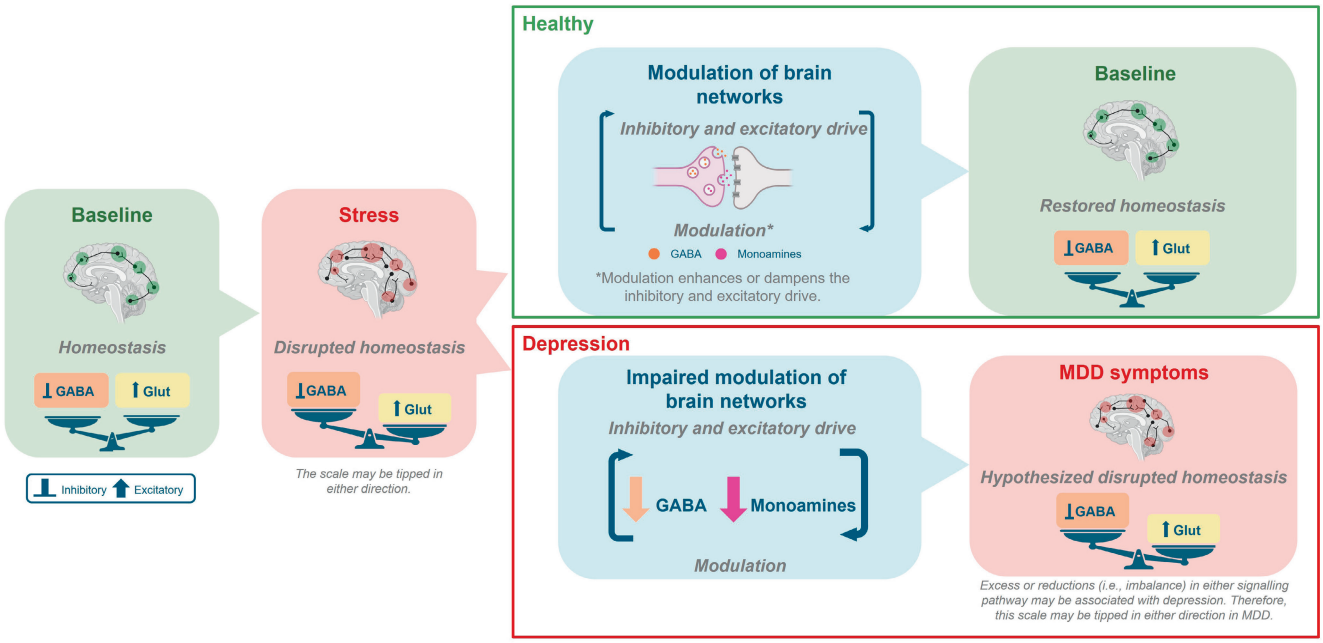

Figure 1. Dysregulated γ-aminobutyric acid (GABA) and brain-network modulation in depression[8]. Stress stimuli, such as acute stress caused by an unpredictable situation or chronic stress due to repeated exposure, are threats to baseline homeostasis (left). In response to acute or chronic stress, brain-network modulation is required to restore homeostasis. Healthy brain networks can self-regulate and restore homeostasis after stress (top right). Impaired modulation of brain networks and prolonged inability to restore homeostasis may give rise to the core symptoms and clinical presentation of major depressive disorder (MDD). Multiple signalling pathways are hypothesized to contribute to MDD, including monoaminergic, glutamatergic and GABAergic signalling pathways (bottom right). Glut, glutamate.

"Tools such as low-intensity, automated virtual reality interventions may offer additional options for exposure therapy in the management of depression."

adoption of telemedicine and digital psychotherapy.

Another route of digital innovation actively explores the use of wearable devices and mobile device applications that can easily integrate into patients' daily routines. Mental health status can influence parameters such as heart-rate variability, blood-pressure changes, sleep duration and quality, social activities and voice features, which can be recorded by sensors. Smartphones and smartwatches allow for active and passive collection of data related to physical and mental health. Collecting and analysing data from sensors embedded in the context of daily life has been widely used for monitoring mental health. With the ability of consumer-grade products to collect these data, and the prevalence of these tools, digital health offers another avenue for health-care professionals to obtain vital information to complement clinical visits.

Further research is needed to correlate the collected data with the mental health of the patient, such as investigation of useful data-labelling techniques to link measured digital biomarker data to a patient's condition. Although the US Food and Drug Administration (FDA) has provided a framework for agency approval, many digital tools lack a traditional evidence-based foundation and rely on alternative forms of data-driven evidence.

Several digital technology-based treatments are under investigation. For example, tools such as low-intensity, automated virtual reality interventions may offer additional options for exposure therapy in the management of depression. Because patients are best served when they are able to partner with their clinicians and build trust, future efforts to develop digital interventions for depression should address optimizing the use of these technologies in various phases of the patient journey.

PHARMACOTHERAPY CHALLENGES IN MDD

As of 2016, there were more than 20 ADTs approved by the FDA for the treatment of depression. Currently available ADTs can take weeks to months to produce therapeutic effect, which can contribute to poor adherence to treatment. Residual symptoms such as anxiety and insomnia may prevent patients from returning to daily lives, further delaying full physical, occupational and social recovery as well as increasing the risk of relapse[5]. The lack of novel and rapidly acting treatments for MDD is therefore a significant area of unmet need.

The clinical development of novel ADTs remains challenging. The placebo response in clinical studies for the treatment of MDD is implicated as a major reason for the failure of clinical trials of ADTs. Several factors can potentially contribute to the placebo response in these trials, including expectation bias,

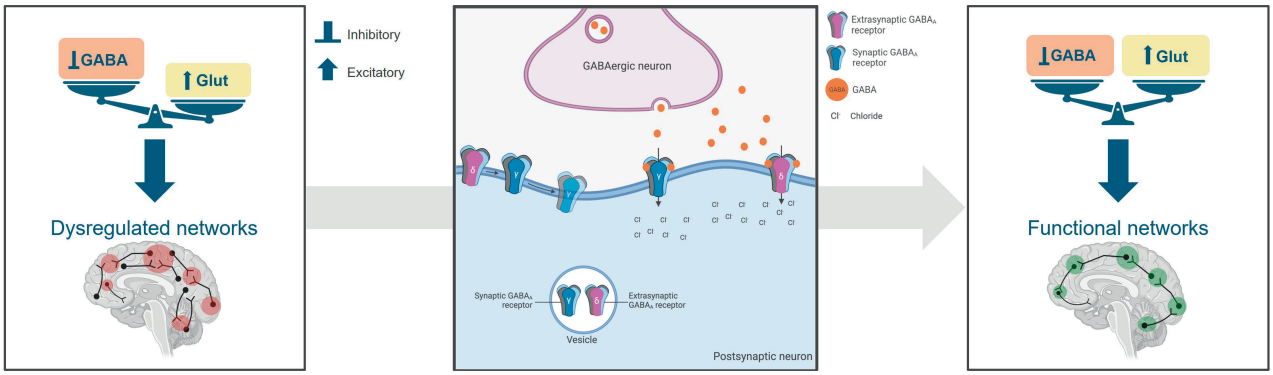

Figure 2. Hypothesized network rebalance in major depressive disorder (MDD) via modulation of γ-aminobutyric acid type A (GABA$_A$) receptors[8,10]. Hypothesized dysregulation in MDD (left): GABA–glutamate (Glut) imbalance alters inhibitory and excitatory signalling, which may lead to impaired modulation of brain networks in MDD. One approach to rebalance the network in MDD is modulation of GABAergic signalling via synaptic and extrasynaptic GABA$_A$ receptors to restore the function of key brain areas that are dysregulated in depression (centre). This modulation of GABA$_A$ receptors may upregulate GABA$_A$ receptor expression, increase GABA$_A$ receptor trafficking and enhance inhibitory GABAergic signalling. Hypothesized restoration of homeostasis (right): re-establishing the GABA and Glut balance is hypothesized to restore homeostasis in brain networks in patients with MDD.

patients' motivation to please their health-care providers, use of standard-of-care ADTs in trials and more frequent clinical visits compared with real-world experience outside of a trial[6].

Preliminary evidence presented in a poster at Academy of Managed Care Pharmacy (AMPC) Nexus 2019 indicated that although most patients receive psychotherapy or pharmacotherapy within 12 months of diagnosis of MDD, more than 80% have a change in treatment for MDD within 12 months, due to lack of improvement in depressive symptoms or side effects, with approximately 57% of patients discontinuing all pharmacotherapy and approximately 26% switching or augmenting their pharmacotherapy[7]. Patients with MDD often require multiple changes of ADTs in the first year after treatment initiation, which may include switching on and off therapies and changing ADT classes. In summary, nonadherence, lack of efficacy and intolerance to side effects remain challenges for currently available ADTs and can result in relapse and recurrence, further escalating health-care resource utilization and increasing the risk of suicide.

Consequently, health-care providers should consider multiple modes of treatment to address the heterogeneity of MDD manifestations and aetiologies observed among their patients. As previously discussed, most of the currently available ADTs are based on the monoamine hypothesis[4]. Although the monoamine hypothesis has been a forerunner as a foundational explanation for the pathogenesis of MDD, findings from clinical observations (e.g., delayed onset of treatment efficacy and inadequate response/remission rates) do not fully support monoaminergic drugs as the sole viable path to treatment.

NEXT-GENERATION THERAPIES

A novel mechanism that is being investigated for the treatment of MDD is to address the imbalance between excitatory and inhibitory neurotransmission in the brain (**Fig. 1**), which are primarily mediated by glutamate and γ-aminobutyric acid (GABA), respectively. GABA type A (GABA$_A$) receptors mediate both phasic and tonic inhibition in the brain, and evidence suggests that disruption of tonic inhibition may be a mechanism underlying the pathophysiology of depression. Naturally occurring GABA$_A$ receptor positive allosteric modulators (PAMs), including neuroactive steroids (NASs), are produced in the brain, where they amplify GABA$_A$ receptor signalling, resulting in a broad array of effects on network excitability and behaviour[8]. Modulation of neuronal networks and restoration of excitatory–inhibitory balance by GABA$_A$ receptor PAMs are hypothesized to play important roles in regulating mood (**Fig. 2**). As inhibitory GABAergic signalling is central to maintaining network balance, amplifying GABA-driven signalling may restore homeostasis to brain networks dysregulated in depression[8].

Zuranolone is an investigational NAS and a GABA$_A$ receptor PAM being co-developed by Sage Therapeutics and Biogen for the treatment of MDD and postpartum depression (PPD) as an oral once-daily 14-day treatment course. Zuranolone targets both synaptic and extrasynaptic GABA$_A$ receptors, modulating phasic and tonic GABAergic conductance, respectively[9]. Zuranolone has been studied in eight (seven completed and one ongoing) phase 2 and phase 3 trials in the LANDSCAPE and NEST clinical development

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NEST PROGRAM

LANDSCAPE DEPRESSION STUDIES

	ROBIN STUDY	SKYLARK STUDY	MOUNTAIN STUDY	WATERFALL STUDY	SHORELINE STUDY	CORAL STUDY	SHIONOGI
Clinical focus	**One-course PPD** Mono or add-on to existing ADT	**One-course PPD** Mono or add-on to existing ADT	**Initiation MDD** Mono or add-on to existing ADT	**Initiation MDD** Mono or add-on to existing ADT	**Initiation MDD** Mono or add-on to existing ADT	**Maintenance MDD** Mono or add-on to existing ADT	**MDD rapid response** Simultaneous start with new ADT	**Moderate-to-severe MDD patients in Japan** Mono or add-on to existing ADT
Study #	NCT02978326	NCT04442503	NCT03000530	NCT03672175	NCT04442490	NCT03864614	NCT04476030	JAPICCTI-205276
Design	RCT	RCT	RCT	RCT	RCT	OL; longitudinal; maintenance	RCT	RCT
Primary objectives	Efficacy: **zuranolone 30 mg** vs placebo	Efficacy: **zuranolone 50 mg** vs placebo	Efficacy: **zuranolone 30 mg** vs placebo	Efficacy: **zuranolone 30 mg** vs placebo	Efficacy: **zuranolone 50 mg** vs placebo	• Long-term safety: 1-year follow-up (zuranolone 30, 50 mg) • CORAL rollover	Efficacy: **zuranolone 50 mg** + OL ADT vs placebo + OL ADT	Efficacy: **zuranolone 20, 30 mg** vs placebo
Primary endpoint	CFB HAMD-17 total score at day 15	CFB HAMD-17 total score at day 15	CFB HAMD-17 total score at day 15	CFB HAMD-17 total score at day 15	CFB HAMD-17 total score at day 15	Safety/tolerability at week 52	CFB HAMD-17 total score at day 3	CFB HAMD-17 total score at day 3
Population	HAMD-17 ≥26	HAMD-17 ≥26	HAMD-17 ≥22	HAMD-17 ≥22 MADRS ≥32	HAMD-17 ≥24	HAMD-17 ≥20 MADRS ≥28	HAMD-17 ≥24	HAMD-17 ≥24
Status	Completed	Completed	Completed	Completed	Completed	Ongoing	Completed	Completed

Figure 3. Snapshot of the zuranolone clinical development program. Summary of the zuranolone clinical development programs LANDSCAPE and NEST for major depressive disorder (MDD) and post-partum depression (PPD), respectively. Zuranolone is being investigated as a monotherapy, an adjunct therapy to existing antidepressants and a co-initiation therapy for use when needed during major depressive episodes. Zuranolone has been studied in two phase 3 trials for the treatment of PPD in the NEST program and in five phase 2 and phase 3 trials for the treatment of MDD in the LANDSCAPE program. In Japan, Shionogi Inc. conducted a phase 2 clinical trial for the treatment of moderate-to-severe MDD. ADT, antidepressant therapy; CFB, change from baseline; HAMD-17, 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Rating Scale; OL, open label; RCT, randomized controlled trial.

programs for MDD and PPD, respectively (**Fig. 3**).

Zuranolone has not yet been approved for the treatment of MDD or PPD by any health authorities. If approved, zuranolone may add to the current armamentarium for depression and provide another option for people with MDD or PPD.

In combination with advances in digital health technology, patients with MDD should be provided with ever-increasing flexibility in their journeys to wellness. While standard-of-care ADTs are widely used to treat MDD, large-scale studies have demonstrated the need for additional pharmacotherapies with differentiated mechanisms and profiles. The evolution and innovation of the emerging treatment landscape described here show promise for patients with MDD. The joint vision of Sage Therapeutics and Biogen is for patients with depression to feel better as soon as possible, utilizing treatments that fit into their lifestyle.

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