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# From Brain to Behavior: Mechanistic and Therapeutic Insights into Mood and Anxiety Disorders

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## ABSTRACT

Among the most common neuropsychiatric conditions, depression and anxiety impact millions of people worldwide and present serious public health issues. These disorders cause significant emotional, cognitive, and functional impairments due to intricate interplay between neurobiological, psychosocial, and environmental variables. With an emphasis on their neuropsychological foundations, this study offers a thorough examination of both established and novel therapy approaches for treating anxiety and depression. For many individuals, traditional pharmaceutical treatments including benzodiazepines, serotonin-norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors continue to be the first choice. Nevertheless, these treatments frequently have drawbacks because of their partial response, delayed commencement of action, and adverse effects. Consequently, non-pharmacological and neuromodulator methods such as transcranial magnetic stimulation, electroconvulsive treatment, mindfulness-based interventions, and cognitive-behavioural therapy are gaining popularity. Ketamine, esketamine, and psychedelic-assisted therapies are examples of new medicines that have been developed recently and give quick and potentially life-changing results in situations that are resistant to previous treatments. Research on neuroinflammation, the gut-brain axis, and personalized medicine has also created new avenues for tailored treatment. There is potential for better results when various therapy methods that are customized for each patient's neurobiological profile are integrated. The significance of a multimodal treatment strategy that incorporates pharmaceutical, psychological, and developing therapies is emphasized by this review. In order to maximize the effectiveness of treatment and get a deeper understanding of the mechanisms behind these diseases, it also emphasizes the necessity of further study.

**Keywords:** Neuromodulation therapies (TMS, ect, DBS), Ketamine rapid-acting antidepressants, Psychedelic-assisted therapy

## Introduction

The causes and symptoms of depression vary greatly because of the intricate interactions between psychological patterns, biological vulnerabilities, and social pressures. Treatment for depression is equally complicated and necessitates a highly customized strategy that may include a mix of therapy, medication, and lifestyle modifications. Two of the most common mental health conditions in the world, depression and anxiety greatly increase the burden of disease worldwide. These symptoms rank among the most worrisome for people with Parkinson's disease and are associated

with a significantly reduced quality of life.<sup>1</sup> Appropriate dopaminergic therapy may be effective in treating depression and anxiety if affective dysregulation is connected to insufficient dopaminergic supplementation. The use of selective serotonin reuptake inhibitors (SSRIs) may be considered due to its demonstrated effectiveness.<sup>2</sup> Following symptom identification, a thorough symptom history is necessary to establish a diagnosis of major depressive disorder (MDD); excluding medical conditions including thyroid disease that may exacerbate depressed symptoms; and assessing for additional mental illnesses that exhibit depressed symptoms, including substance-related disorders, anxiety disorders, and bipolar I or II disorder.<sup>3,4</sup>

## Neurobiological Basis of Depression and Anxiety

**Neuroanatomical Pathways:** Alterations in the hippocampus, amygdala, and prefrontal cortex are among the brain regions associated with these illnesses. **Neurotransmitter Systems Involved:** Dopamine, serotonin, and norepinephrine imbalances are important. **Genetic and Epigenetic Contributions:** These illnesses are a result of a combination of environmental influences and genetic predispositions.<sup>5</sup> **Neuroinflammation and Oxidative Stress:** The pathophysiology of anxiety and depression has been connected to both chronic inflammation and oxidative stress. **Neuroimaging and Biomarkers:** Potential biomarkers for diagnosis and therapy response have been found thanks to developments in neuroimaging.<sup>6</sup>

## Conventional Pharmacological Treatments

The main All medications in the two main families of antidepressants (serotonin norepinephrine reuptake inhibitors [SNRIs] and SSRIs) share the same mechanism of serotonin reuptake inhibition. Individual agent differences are comparatively small. Nonetheless, it is typical to see that different patients within the same class tolerate or react differently to different antidepressants. Secondary pharmacologic features that differ among the different antidepressants<sup>4</sup> may have an impact on individual differences in medication response; genetic variations affecting the pharmacokinetics and pharmacodynamics of antidepressants may also have an impact on the variability observed in patient responses (Figure 1).

## Non-Pharmacological Therapies

Cognitive behavioral therapy (CBT) is a time-limited, systematic treatment that aims to change dysfunctional behaviors and thoughts. CBT is an important therapeutic option for depressive disorders in addition to medication therapies. Although newly created digital

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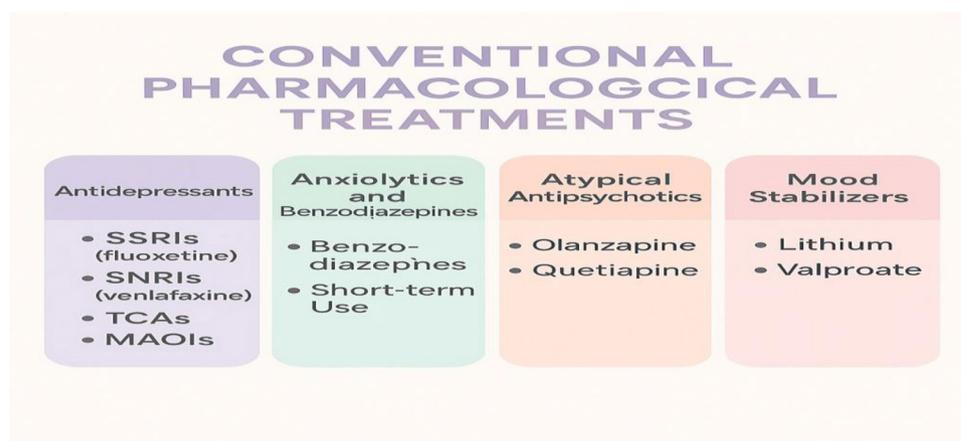


Fig 1 | Conventional pharmacological treatment

CBT techniques have significant benefits since they are more accessible, it is yet unknown how successful they are in comparison to traditional CBT.<sup>7</sup> To find every study that used a CBT-based intervention—whether in-person or online—for patients suffering from serious depression, we carried out a thorough literature search.<sup>8</sup> The acceptability and efficacy of guided iCBT for the treatment of anxiety and depression in routine care are supported by this study.<sup>9</sup> Because there is a great deal of variation among interventions and circumstances, health care professionals should only adopt interventions that have been validated in randomized controlled clinical studies. Successful application of iCBT could make it a valuable instrument for extending healthcare in a range of contexts.<sup>10</sup> Mindfulness-Based Interventions: Incorporate mindfulness practices to help individuals manage symptoms and reduce relapse rates. (a) Effectiveness of Mindfulness-Based Stress Reduction (MBSR): MBSR considerably lowers symptoms of anxiety and depression in both clinical and non-clinical populations.<sup>11</sup> (b) Mindfulness-Based Cognitive Therapy (MBCT). Effectiveness: MBCT helps patients with recurrent depression avoid relapsing and lessens the symptoms of anxiety.<sup>12</sup> (c) MBIs vs. Pharmacotherapy: Research revealed that MBSR was equally effective as escitalopram (SSRI) in treating anxiety disorders.<sup>13</sup> (d) Meta-Analysis Summary. Results: Meta-analyses indicate that MBIs improve well-being and offer moderate-to-large reductions in stress, anxiety, and depression.<sup>14</sup> (e) Proof from Neurobiology Results: MBIs improve activation in brain regions linked to self-referential processing, emotion management, and attention, according to neuroimaging research.<sup>15</sup> Psychodynamic and Interpersonal Therapies: Focus on unconscious processes and interpersonal relationships to alleviate symptoms.

#### Psychodynamic Therapy (PDT)

- Idea emphasizes how early experiences, unconscious processes, and unresolved issues impact mental health today. seeks to increase emotional intelligence and self-awareness.

- Effectiveness in Treating Depression and Anxiety: Research indicates that short-term psychodynamic therapy is highly beneficial in the treatment of anxiety and depression.

Results: A meta-analysis of 23 RCTs revealed that improvements were maintained after therapy ended and that effect sizes were moderate ( $g = 0.71$  for depression).<sup>16</sup>

#### Interpersonal Therapy (IPT)

Social isolation, role changes, conflict, grief, and interpersonal functioning are the main topics of IPT, which was developed to treat depression. It helps patients adapt to changes in their lives and strengthen their social ties.

Results: A meta-analysis found that IPT is as effective as CBT (effect size  $d = 0.63$ ), and it is better than a placebo or conventional treatment.<sup>17</sup>

#### Evidence of Efficacy in Anxiety Disorders

Modified IPT has demonstrated potential in the treatment of generalized anxiety disorder (GAD) and social anxiety disorder (SAD).

Findings: IPT for social anxiety was not inferior to CBT, according to RCT data.<sup>18</sup>

#### Long-Term Advantages

Following treatment, both PDT and IPT show a consistent reduction in anxiety and depression symptoms; some research suggests these improvements may remain for up to 2 years.<sup>19</sup>

#### Lifestyle Modifications (Exercise, Diet, Sleep)

It has been demonstrated that regular exercise, a healthy diet, and enough sleep can alleviate symptoms.

#### Exercise

- Contribution to Anxiety and Depression: Frequent resistance and aerobic exercise is linked to notable decreases in feelings of anxiety and sadness.

Exercise elevates mood by lowering inflammation, raising endorphins, and increasing brain-derived neurotrophic factor (BDNF).

- Proof: Exercise had moderate to large impacts (SMD = 0.66), as per a meta-analysis of forty-nine trials. Resistance and aerobic training are both beneficial; supervised programs produce superior results.<sup>20</sup>

**Nutrition and Diet:**

- Contribution to Anxiety and Depression: A Mediterranean diet rich in Whole grains, nuts, seafood, fruits, and vegetables are associated with a lower incidence of depression. Among the substances involved in the control of neurotransmitters include vitamins, zinc, magnesium, and omega-3 fatty acids.
- Proof: The SMILES experiment showed that, compared to a control group, dietary improvements decreased depression symptoms in patients with MDD (Figure 2).<sup>21</sup>

**Neuromodulation Techniques**

Electroconvulsive Therapy (ECT): Effective for severe or treatment-resistant depression (TRD), involving electrical stimulation of the brain under anaesthesia. ECT is a well-known somatic treatment that passes controlled electrical currents through the brain to cause brief seizures. It is mainly used for bipolar depression, severe depression, TRD, and some severe anxiety disorders.

Action Mechanism: Regulation of neurotransmitters (e.g., noradrenaline, serotonin, dopamine) Elevated expression of BDNF and increased neuroplasticity Normalization of hypoactivity in the limbic and prefrontal cortex, which are important in mood regulation.<sup>22</sup>

Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulation technique that uses magnetic fields to stimulate brain nerve cells. It typically targets the dorsolateral prefrontal cortex (DLPFC), a region of the brain involved in mood regulation.

Action Mechanism: TMS increases or decreases neural activity in specific brain regions by modifying cortical excitability and synaptic plasticity. Low-frequency

TMS ( $\leq 1$  Hz) is inhibitory, while high-frequency TMS ( $\geq 5$  Hz) is excitatory.<sup>23</sup>

The FDA-approved neuromodulation procedure known as vagus nerve stimulation (VNS) involves electrically stimulating the vagus nerve, also known as cranial nerve X. Although VNS was first approved to treat epilepsy, it has also shown promise in treating TRD.

Action Mechanism: Modulates monoaminergic neurotransmission (serotonin, norepinephrine) influences the hypothalamic-pituitary-adrenal (HPA) axis, which lowers the stress response. Increases cerebral blood flow and neuroplasticity in mood-related brain regions, including the prefrontal cortex and amygdala.<sup>24</sup>

By placing electrodes in particular brain regions, the invasive neurosurgery procedure known as deep brain stimulation (DBS) alters abnormal neuronal activity. Although DBS was initially intended to treat movement disorders like Parkinson’s disease, it also shows promise in treating chronic mental illnesses like major depression and obsessive-compulsive disorder.

Action Mechanism: Targeted activation of brain regions (e.g., nucleus accumbens, subgenual cingulate gyrus) modulates dysfunctional mood-regulating circuits (limbic, cortical, striatal, pallidal, thalamic loops) Influences neurotransmission (dopamine, serotonin) and neuroplasticity.<sup>25</sup> Emerging Brain Stimulation Methods: Techniques under investigation with promising early evidence.

**Transcranial Direct Current Stimulation (tDCS)**

A non-invasive method that regulates cortical excitability by applying mild electrical currents to the scalp. Cathodal stimulation reduces excitability; anodal stimulation increases it. tDCS targeting the DLPFC has been shown to alleviate depression symptoms.<sup>26</sup>

**Theta Burst Stimulation (TBS)**

A new repetitive TMS procedure delivering brief high-frequency stimulation bursts. FDA-approved intermittent TBS (iTBS) for MDD Similar effectiveness to traditional TMS but shorter sessions.<sup>27</sup>

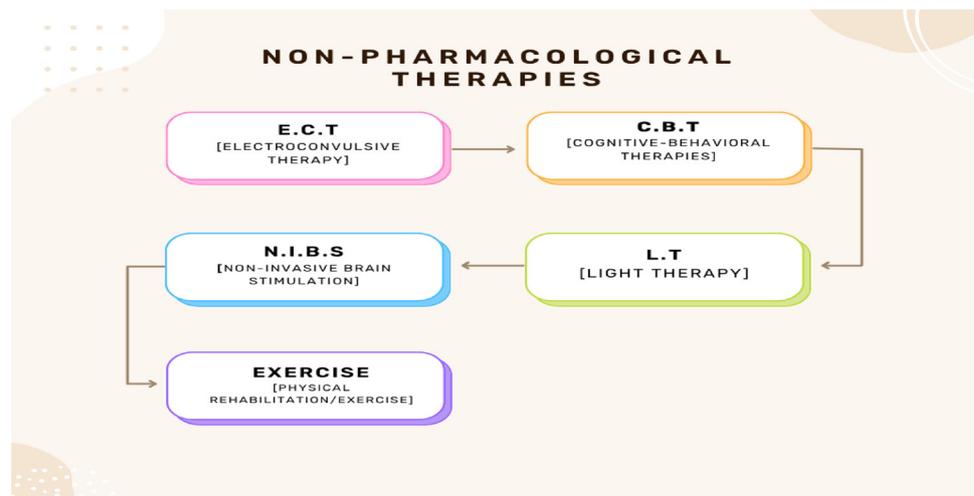


Fig 2 | Representing non – pharmacological therapies to neuropsychiatric treatments

**Low-Intensity Focused Ultrasound (LIFU)**

Uses ultrasonic waves to modulate neuronal activity in deep brain regions without surgery. Although human trials are limited, preclinical research indicates potential for mood and anxiety control.<sup>28</sup>

Using oscillating electrical currents, transcranial alternating current stimulation (tACS) synchronizes brain oscillations at particular frequencies (gamma, theta, and alpha). emerging as a possible treatment for anxiety and depression that can improve mood and cognitive function (Figure 3).<sup>29</sup>

**Magnetogenetics**

Using light to manipulate genetically altered neurons, optogenetics holds promise for dissecting mood circuitry. Magneto genetics, which uses magnetic fields to regulate cell activity, is being investigated for deep brain modulation in mood disorders.<sup>30</sup>

**Noval and Emerging Therapeutic Approaches**

**Ketamine and Esketamine**

Rapid-acting antidepressants used in TRD. Particularly in MDD and TRD, ketamine, an NMDA receptor antagonist, has shown quick antidepressant and anxiolytic effects. The FDA authorized esketamine, the S-enantiomer of ketamine, as a nasal spray for TRD in 2019.<sup>31</sup>

**Action Mechanism**

Inhibits the glutamate receptor known as the NMDA receptor, resulting in increased glutamate transmission, enhanced neuroplasticity and synaptogenesis in the hippocampus and prefrontal cortex, modulation of the mTOR signalling pathway, and mood elevation within hours.<sup>32</sup>

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cortex, Modifies the mTOR signalling pathway. Elevates mood within hours.<sup>32</sup>

**Ketamine’s Clinical Effectiveness**

Intravenous ketamine (0.5 mg/kg) reduces depression symptoms within 1–24 hours. Beneficial for acute suicidal ideation. Limitations include possible dissociation or psychotomimetic effects; benefits typically last 7–10 days.<sup>33</sup>

**Esketamine**

FDA-approved intranasal formulation for TRD with clinical efficacy. Long-lasting antidepressant benefits with repeated use. Fewer psychotomimetic side effects than racemic ketamine.<sup>34</sup>

**Applications**

Early trials suggest ketamine may benefit GAD, PTSD, and SAD, though more controlled studies are needed.<sup>35</sup>

**Therapies**

Substances like psilocybin are being studied for treating depression and anxiety. In psychedelic-assisted therapy (PAT), compounds including psilocybin, LSD, MDMA, and ayahuasca are used under psychotherapy supervision. Evidence shows these drugs can rapidly and effectively relieve PTSD, anxiety, and depression, particularly when conventional treatments fail.

Psilocybin-Assisted Therapy - Psilocybin, the active compound in magic mushrooms, is a serotonin 5-HT2A receptor agonist. Clinical trials show it significantly, rapidly, and sustainably reduces depressive symptoms, including TRD and end-of-life anxiety in cancer patients.<sup>36</sup>

MDMA-Assisted Psychotherapy - MDMA (3,4-methylenedioxymethamphetamine) reduces fear responses and enhances empathy and emotional processing.

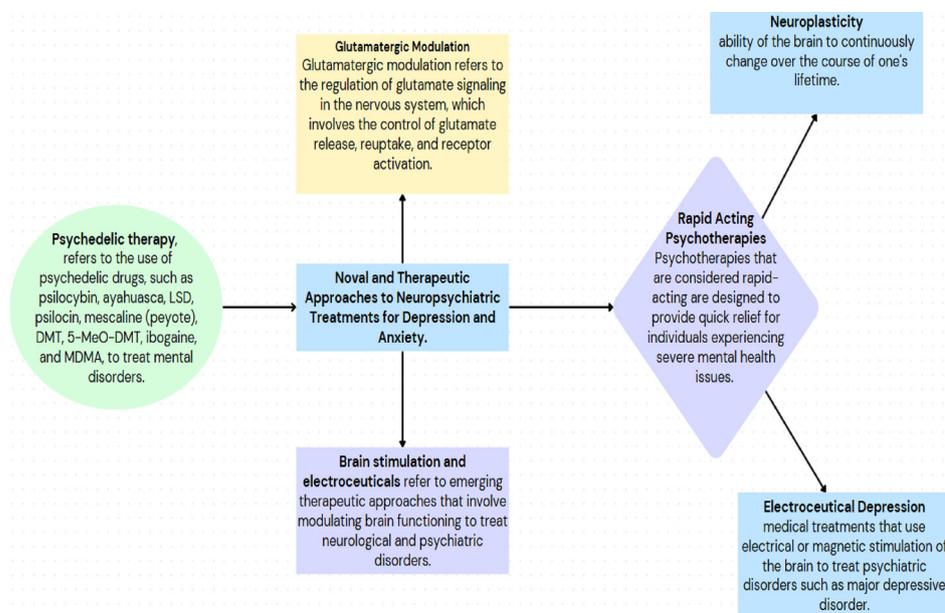


Fig 3 | Noval and therapeutic approaches to neuropsychiatric treatments for depression and anxiety

Controlled trials demonstrate its benefits for PTSD and anxiety-related disorders.<sup>37</sup>

### Anti-Inflammatory and Neuroprotective Agents

NSAIDs - One COX-2 inhibitor that has been investigated as an adjuvant treatment for serious depression is celecoxib. demonstrated to reduce inflammatory cytokines including TNF- $\alpha$  and IL-6 that are increased in depression.<sup>38</sup> PUFAs, or omega-3 polyunsaturated fatty acids. Neuronal membrane fluidity and cytokine production are regulated by EPA and DHA. Improvements in MDD are reported by clinical trials, and anxiety symptoms.<sup>39</sup>

Turmeric's major ingredient, curcumin, has strong anti-inflammatory, antioxidant, and neuroprotective effects. enhances BDNF expression, modifies monoaminergic pathways, and lowers oxidative stress. shown to have effects similar to those of antidepressants in people.<sup>40</sup> the connection between mental health and gut microbiome. There are two directions on the gut-brain axis. investigating the mechanism of communication between the gastrointestinal tract and the central nervous system (CNS). Anxiety and depression are associated with gut microbiota's effects on inflammation, immunological responses, and neurotransmitter synthesis.

### Gut Microbiota's Role in Mental Health

Gut bacteria produce neuroactive substances affecting mood and cognition, such as GABA and serotonin precursors. Dysbiosis (microbial imbalance) is associated with altered neurotransmission, increased inflammation, and heightened stress responses.<sup>41</sup>

Probiotics ("Psychobiotics") Some probiotic strains (e.g., Bifidobacterium, Lactobacillus) have anxiolytic and antidepressant-like properties. Influence neurotransmitter metabolism, reduce systemic inflammation, and modulate the HPA axis.<sup>42</sup>

### Prebiotics

Prebiotics like fructooligosaccharides and galactooligosaccharides promote beneficial gut flora. Certain prebiotics have been shown to improve emotional processing and lower cortisol levels.<sup>43</sup>

### Digital and Mobile Health Interventions

Mobile Applications (Apps) - Offer crisis support, mood tracking, guided meditation, and CBT-based therapy. Evidence suggests effectiveness for mild to moderate anxiety and depression.<sup>44</sup> Online Cognitive Behavioral Therapy (iCBT). Provides structured therapy through websites or apps. Effective for moderate-to-severe anxiety and depression, with outcomes comparable to face-to-face therapy.<sup>45</sup>

Virtual Reality (VR) Interventions - VR therapy enables immersive exposure therapy, social skills training, and relaxation. Demonstrated potential for treating social anxiety, PTSD, and phobias.<sup>46</sup>

Telepsychology and Telepsychiatry - Deliver therapy and psychiatric consultations via video calls. As

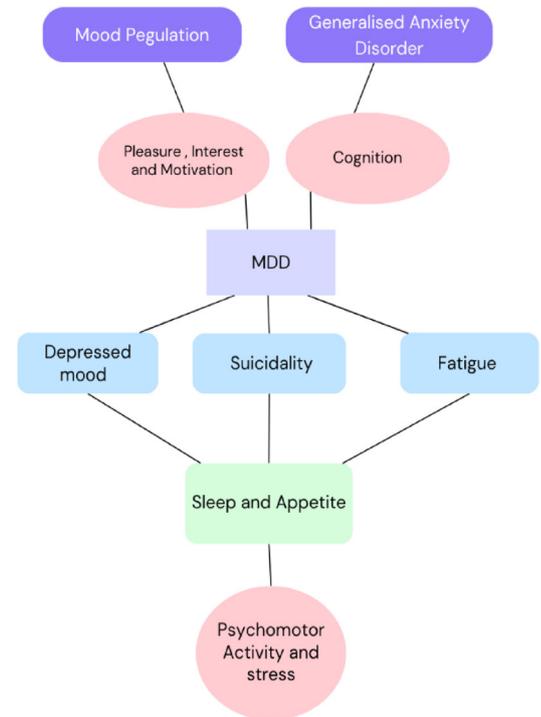


Fig 4 | Conditions associated with neuropsychiatric therapies

effective as in-person therapy for depression and anxiety, especially in underserved areas.<sup>47</sup>

Wearable Devices and Biofeedback -Real-time biofeedback on physiological stress signals (e.g., heart rate variability, sleep patterns) is provided via devices such as smartwatches and heart rate monitors. Proven to lower stress and anxiety and improve mood control.<sup>48</sup>

Telepsychiatry and Video Counselling - Provide remote access to mental health professionals via video sessions. Shown to be as effective as in-person therapy for various mental health conditions (Figure 4).<sup>47</sup>

### Conclusion

Anxiety and depression are complex neuropsychiatric conditions that have a major influence on mental health worldwide. This study emphasizes the wide range of therapeutic strategies, from cutting-edge neuromodulation methods and new digital health solutions to traditional pharmaceutical therapies. The mainstays of treatment continue to be traditional antidepressants, anxiolytics, and psychotherapy techniques such as mindfulness-based therapies and CBT. The investigation of new approaches, such as brain stimulation therapies (such as TMS, ECT, VNS, and DBS), ketamine and psychedelic-assisted therapies, and microbiota-targeted interventions through the gut-brain axis, is necessary due to treatment resistance and side effects.<sup>49</sup>

Furthermore, because they provide scalable, easily available, and customized interventions, digital and mobile health technologies are quickly changing the face of mental health care. Holistic management

also heavily relies on lifestyle changes like exercise, food adjustments, and sleep optimization.<sup>50</sup> Notwithstanding these developments, issues with long-term effectiveness, side effect reduction, and therapy customization still exist. Incorporating multimodal therapy, finding biomarkers for personalized medicine, and thoroughly assessing novel interventions like digital medicines and gut microbiome manipulation should be the main goals of future research. In conclusion, the most promising route to all-encompassing, patient-centered treatment for anxiety and depression is a mix of pharmaceutical, psychotherapy, neuromodulatory, and lifestyle approaches.<sup>41,51</sup>

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