

Recent Advances in Multimodal Non-Pharmacological Interventions for Late-Life Depression

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Abstract: Late-life depression (LLD) is a common mental disorder that significantly accelerates cognitive decline, increases the risk of somatic comorbidities, and increases all-cause mortality. Traditional pharmacotherapy for this population faces significant limitations, including increased pharmacokinetic sensitivity, anticholinergic burden, and adverse events associated with multiple medications. These factors collectively lead to poor adherence and limited long-term efficacy. This narrative literature review was conducted using studies retrieved from PubMed, ScienceDirect, and Google Scholar, with general search phrases on LLD and non-pharmacological interventions. The inclusion criteria were clinical trials, meta-analyses, and systematic reviews published between 2020 and 2025. Studies that were finally selected were comprehensively evaluated, with non-English literature and case reports excluded. Non-pharmacological interventions have become a core strategy for the management of LLD due to the advantages of high safety, fewer side effects, and a multi-target nature. Psychotherapy, physical intervention, digital technology, and lifestyle modification can effectively improve patients' depressive symptoms, improve quality of life, reduce the risk of relapse, and serve as possible alternatives and supplementary treatment options for older patients. There is a need for more in-depth research on non-pharmacological interventions for LLD. Future studies should explore the combined application of different non-pharmacological treatments to optimize treatment plans. Developing individualized non-pharmacological treatment plans to improve the accuracy of treatment and reduce the burden of disease should be considered.

Keywords: older adults, psychiatric disorder, therapy

Introduction

Late-life depression (LLD) is a major depressive disorder occurring in adults aged 65 years and older, with symptoms that often interact with cognitive decline, chronic pain, and social isolation.¹ LLD is among the most common psychiatric disorders of old age in later life, with a global prevalence rate of approximately 28.4%.² The increasing global burden of LLD varies by socioeconomic, gender, regional, and national differences.³ Compared with adult depression, LLD symptoms are often masked by physical illness and cognitive decline, leading to its untimely diagnosis and treatment.⁴ Although antidepressants can be effective in ameliorating some LLD symptoms, multiple medical comorbidities and drug interactions, in cases of polypharmacy, often pose a more serious adverse events risk.⁵ Studies have shown that less than half of older adults with major depressive disorder achieve remission when receiving medication alone.⁶ Notably, many patients with LLD achieve remission of mood symptoms but still have persistent neuropsychological deficits.^{7,8} The mechanism may be closely related to abnormal functional connectivity of the default mode network (DMN)⁹ (excessive activation of the DMN promotes ruminative thinking and cognitive rigidity, driving a vicious cycle of depression and cognitive deterioration), which may form the neurobiological basis of LLD relapse. Given that single-modal interventions cannot fully reverse the multi-dimensional pathological mechanisms of LLD, there is an urgent need

to achieve complementary and synergistic effects through multi-modal non-pharmacological intervention strategies that integrate neuromodulation, psychobehavioral, and lifestyle components. Such integrated strategies can act on the remodeling of neuroplasticity, regulation of metabolism during inflammation, and repair of social neural circuits, thereby optimizing clinical outcomes and reducing the risk of recurrence. Although previous studies on non-pharmacological interventions for LLD have mostly focused on single therapies¹⁰ or followed adult intervention models, such as standard cognitive behavioral therapy, they have generally overlooked the unique clinical complexity of LLD. Consequently, these studies have failed to fully reflect the adaptive adjustments that are tailored to the older adult population, and the intervention settings have mostly been limited to hospitals. This article transcends the traditional single-therapy perspective by integrating psychological, physical, nutritional, and community interventions for treating LLD. It emphasizes the exploration of multi-modal collaborative strategies and personalized treatment planning based on cutting-edge technologies. The article further focuses on bridging the gap between hospital-oriented treatment models and community-based practices, offering a novel perspective for establishing a comprehensive management model for LLD.

Non-Pharmacological Interventions for Late-Life Depression Treatment

Psychotherapy

Psychotherapy for LLD is a non-pharmacological intervention during which professional therapists use structured techniques aimed at modifying patients' maladaptive cognitive, emotional, and behavioral patterns to improve symptoms, functioning, and quality of life. Current guidelines recommend psychotherapy as the first choice for initial treatment in patients with mild-to-moderate LLD and a combined treatment of antidepressants and psychotherapy for patients with moderate-to-severe depression¹¹ to improve clinical efficacy and treatment adherence. A meta-analysis further confirmed that psychotherapy is significantly advantageous in moderating depression in older patients, with effect sizes of moderate or higher (standardized mean effect size $d = 0.72$).¹² Notably, all psychological interventions compared to conventional treatment were at least moderately effective in improving depressive symptoms in adults, while all 21 antidepressant medications had small-to-moderate effects on symptom improvement.¹³ Current psychological interventions for LLD include behavioral therapy (BT), cognitive behavioral therapy (CBT), cognitive bibliotherapy, problem-solving therapy (PST), brief psychodynamic therapy (BPD), and reminiscence therapy (RT).¹⁴

Cognitive Behavioral Therapy

CBT is a structured, problem-oriented psychotherapeutic model whose core goal is to alleviate emotional symptoms and promote adaptive behavior and cognitive remodeling.¹⁵ CBT can partially normalize neural patterns by modulating neural activity in brain regions related to affective and reward processing (eg, amygdala-hippocampus complex, anterior cingulate gyrus, and prefrontal cortex), thereby improving mood and cognitive flexibility.¹⁶ Meta-analysis results have shown that CBT is significantly more effective than conventional treatment and wait-list control groups in alleviating depressive symptoms, and this advantage persists at the 6-month follow-up.¹⁷ Adaptations have been proposed to better accommodate the changes in sensory deficits, frailty, and mild cognitive impairment associated with aging and may facilitate the effectiveness of CBT for this older population,¹⁸ such as enhanced group CBT for older adults (CBT-OA), internet-based CBT (iCBT), and virtual reality (VR)-enhanced CBT (VR-CBT).

Enhanced Group Cognitive Behaviour Therapy for Older Adults (CBT-OA) modifies standard CBT to better meet the needs of older adults. Skosireva et al¹⁹ recruited 49 older adults aged >65 years between 2015 and 2019 who presented with symptoms of depression and/or anxiety and underwent five CBT-OA therapy sessions. They demonstrated a significant decrease in Beck Depression Inventory-II scores, with participants aged <78 years showing the greatest gains.

iCBT can effectively address the treatment gap in LLD caused by limited mobility, stigma, or geographical barriers. Meta-analyses have confirmed that iCBT has a positive impact on improving depression and mental health in older adults.²⁰ Moreover, it demonstrates sustained long-term efficacy across all age groups, with observed consistent reductions in depression severity.²¹

VR-CBT, an innovative intervention, promotes emotional regulation and cognitive flexibility of older patients through multi-sensory stimulation by integrating traditional CBT with VR technology, making up for the limitations of traditional talk therapy. In the treatment of severe depression, VR-CBT has shown potential efficacy, which is comparable to

standard pharmacological treatment, effectively alleviating depressive symptoms, suicidal tendencies, and associated anxiety and perceived stress.²²

CBT-OA and iCBT can serve as non-pharmacological intervention options for most older adults with depression. VR-CBT is particularly suitable for those seeking an immersive therapeutic experience or for individuals who have not responded adequately to conventional antidepressant medications or standard psychological interventions. Although CBT and its technology-assisted forms represent effective approaches for treating LLD, offering diverse implementation pathways and good adaptability, research within the geriatric population remains limited. In the future, more clinical practice and technological iterations are needed to develop safe, effective, and humanized intervention programs.

Mindfulness-Based Cognitive Therapy

Mindfulness-based cognitive therapy (MBCT) is a novel treatment for depression that combines mindfulness meditation with elements of CBT to reduce negative emotions and anxiety, thereby helping to alleviate depressive symptoms.²³ MBCT may improve rumination in this population by modulating the over-activation of the DMN,²⁴ making them more capable of negative emotion regulation to become more competent. MBCT is increasingly being used in the older population, with age-related modifications, such as more sedentary meditation and shorter session durations. Age-modified MBCT is more helpful in controlling depressive symptoms in older patients.²⁵ Further studies have shown that older populations receiving web-based mindfulness intervention do not only exhibit cognitive and emotional improvements but also demonstrate adaptive modulation of neural oscillatory rhythms in specific brain regions.²⁶ MBCT is effective for treating LLD and preventing its recurrence, but individualized program adjustments are needed for groups with low cognitive reserve and acute severe illness.

Problem-Solving Therapy

PST, often considered a form of CBT, is a practical approach focusing on problem solving and action taking and aims to promote problem solving by instilling an optimistic and assertive attitude toward the problem.²⁷ At present, the neural mechanism underlying the effect of this therapy remains unclear. One possibility is that PST improves depressive symptoms by enhancing the activity of the amygdala.²⁸ PST is an effective treatment for LLD, and in a significant number of older adults with major depression and executive dysfunction, it results in significant therapeutic response and remission.²⁹ For patients with LLD who have cognitive decline, a modified PST can significantly reduce depressive symptoms and improve response and remission rates within a 12-week intervention cycle through structured adjustments in therapist-led problem simplification and action planning.³⁰ Modified PST (MPST) directs more focus on the relevance of knowledge transfer, empowering effect of group interaction, and establishment of early trusting relationships, which are more relevant to the cognitive characteristics and psychological needs of older adults.³¹ PST is efficient for addressing the real-life dilemmas of patients with LLD, especially suitable for patients with mild cognitive impairment. Its structured problem-solving process can significantly enhance functional independence; however, for those who have severe executive impairment and lack social support, it should be applied with caution. MPST can be used to enhance the feasibility of PST through family collaboration and simplification techniques.

Reminiscence Therapy

RT aims to promote patients' sense of wholeness and adaptability, which emphasizes the review of life and recognition of life's meaning and purpose. Neuroimaging studies have confirmed that it alleviates negative emotions by modulating the thalamocortical pathway and suppressing activity in pain-related brain regions, including the lingual and parahippocampal gyri.³² Liu et al³³ found that RT does not only significantly improve depressive symptoms in older patients with chronic diseases but also positively affects LLD groups treated with antidepressant drugs. More notably, group-based RT was superior to individual interventions in terms of efficacy and cost-effectiveness. VR-RT, an innovative intervention, can significantly improve depressive mood and cognitive functioning in older groups without significant adverse effects and has the potential to be useful in more varied settings.³⁴ Trauma history should be screened prior to RT implementation to avoid triggering agitated behaviors or worsening mood.³⁵ RT may likely play a more important role in aging societies, but further research is needed to investigate its long-term effects on depression alleviation. The application of

RT is varied in different cultural settings, and in the future, nostalgia intervention protocols should be further developed and standardized to promote its global use.

Cognitive Reading Therapy

Cognitive reading therapy guides patients to self-adjust their cognition through self-help books or materials, which can be understood as a process of reading, reflection, and discussion. In recent years, mental health scientists have studied reading therapy separately from traditional interventions to improve the lives of readers.³⁶ Cognitive reading therapy works by guiding patients to engage in emotional projection and cognitive universalization, thereby effectively alleviating their negative emotions and enhancing their self-efficacy.³⁶ It appears effective in reducing depressive symptoms in adults, and its use as an accessible, cost-effective, and timely intervention can reduce the need for antidepressant medication use.³⁷ Floyd et al's study³⁸ involving 31 community-dwelling patients aged ≥ 60 years demonstrated that individual psychotherapy and reading therapy significantly outperformed the delayed-treatment control group. Notably, the reading therapy group exhibited sustained improvement trajectories, with therapeutic effects converging between the two interventions at the 3-month follow-up. This confirms both approaches as viable therapeutic alternatives for LLD. However, cognitive reading therapy lacks interpersonal interaction, has limited effect on those with strong feelings of loneliness, has independent efficacy in the older population, and still needs to be verified in randomized controlled trials (RCTs). Studies related to cognitive reading therapy for LLD treatment are few, and further explorations are still needed in the future.

As summarized in [Table 1](#), the comparative analysis of psychological treatment methods for LLD shows that each method has unique advantages and disadvantages in terms of core mechanisms, target populations, accessibility, and other aspects. For patients with LLD who are frail or bedridden, BT or PST can be implemented using video conferencing to reduce the burden of travel. Caregiver assistance can be incorporated into this process to reinforce the intervention by recording daily activities or providing problem-solving support. For patients with severe somatic debilitation, any BT regimen requiring physical activity should be avoided in favor of supportive talk or RT. For those with severe cognitive impairment, CBT or cognitive reading therapy should be used with caution. Instead, simplified BT approaches—for instance, sensory stimulation activities—or fragmented recall during RT may be more appropriate. The use of tactile object aids (including old photographs and mementos) rather than only verbal recall can also help to reduce cognitive load in RT interventions. During a psychological intervention, the intensity and form of intervention should be dynamically adjusted according to the patient's functional status. Moreover, physical exertion and emotional response should be continuously monitored. In the future, researchers can further explore joint models, such as “PST+RT”, to enhance the self-efficacy of patients in coping with current challenges by recalling their previous successful problem-solving experiences.

Physical Therapy

Physical therapy for LLD is a non-pharmacological biological intervention based on neuroplasticity. It involves the precise modulation of physical energy (such as electricity, magnetism, or light) on specific brain regions to directly modify abnormal activity in emotion-processing neural circuits, thereby alleviating depressive symptoms and reducing suicide risk. Neuromodulation techniques currently applied to treat LLD include electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), deep brain stimulation (DBS) and transcranial direct current stimulation (tDCS).³⁹ Furthermore, physical therapy for LLD includes exercise therapy and bright light therapy (BLT). Physical therapy does not only have a faster onset of effectiveness than that observed with single drug therapy but is also more suitable for the older population with coexisting multi-morbidities, as it does not impose systemic drug metabolism burden. The defining features of these neuromodulation and physical therapies for LLD are presented comparatively in [Table 2](#).

Electroconvulsive Therapy

ECT is a therapeutic method of stimulating the patient's head with electric current to cause a grand mal seizure, which results in clinical symptom relief. The therapeutic mechanism of ECT stems from its ability to induce structural

Table 1 Comparative Analysis of Psychotherapy Methods for Late-Life Depression

Interventions	Core Intervention Mechanisms	Applicable Symptom Characteristics	Advantages	Limitations	Implementation Flexibility	Cognitive Demand
BT	Behavioral activation	Behavioral withdrawal, loss of interest, social isolation	Simple to operate, suitable for patients with cognitive limitations	Limited effect on complex cognitive problems	High (support for homework, caregiver assistance)	Low (Focuses on behavior recording and execution)
CBT	Modifying negative cognitions and behavior modification	Presence of negative thought patterns and ability to complete structured training	Effective in preventing recurrence	Requires high cognitive engagement, limited effect in people with severe cognitive impairment	Moderate (Requires structured sessions; can be delivered remotely)	High (Requires identifying and modifying thought patterns)
BPD	Environmental stimulus modulation and adaptive behavior training	Depression with anxiety or obsessive-compulsive behavior	Rapid relief of outward symptoms	Long-term mood improvement weaker than CBT	Low-moderate (Requires in-person therapist guidance)	Low-moderate (Relies on repetitive behavior training)
PST	Developing Realistic Problem-Solving Skills	Depression triggered by real life problems	Increased self-efficacy and improved daily functioning	Insufficient intervention in non-realistic issues	High (Can involve family participation)	Moderate (Requires logical reasoning ability)
Cognitive Bibliotherapy	Self-reading cognitive materials and writing reflection assignments	Mildly depressed, treatment-motivated patients with high literacy levels	Low-cost, autonomous implementation	Lack of interpersonal interaction and low adherence of critically-ill patients	Low (Dependence on patient autonomy)	Moderate-High (Requires basic literacy skills)
RT	Enhancing self-continuity and sense of meaning through life review	LLD accompanied by the presence of meaning deficit or appropriate for mild cognitive impairment	Improvement of self-esteem and reduction of aggressive behavior	May trigger traumatic memories (need to screen for history of PTSD)	Moderate (Requires therapist guidance)	Moderate (Basic memory extraction skills required)

Abbreviations: LLD, late-life depression; PTSD, post-traumatic stress disorder; BT, behavioral therapy; CBT, cognitive behavioral therapy; BDT, brief psychodynamic therapy; PST, problem-solving therapy; RT, reminiscence therapy.

Table 2 Comparative Analysis of Physical Interventions for Late-Life Depression

Interventions	Core Intervention Mechanism	Applicable Symptom Characteristics	Advantages	Limitations	Implementation Flexibility
ECT	Induces seizure-like discharges via electric current to remodel neuroplasticity	Severe, treatment-resistant LLD with rapid onset	Fastest onset, high remission rate	May cause transient memory impairment	Low (requires hospital setting under general anesthesia)
rTMS	Magnetic pulses target and modulate DLPFC excitability	Medication intolerance/ineffectiveness, relatively intact cognitive function	Non-invasive, safe	Heterogeneous individual response, insufficient evidence for long-term efficacy	Moderate (requires specialized equipment and personnel, can be performed outpatient)
tDCS	Low-intensity direct current modulates cortical neuronal excitability and synaptic plasticity	Mild-to-moderate depression, as adjuvant or first-line treatment	Non-invasive, safe, accessible via portable home devices	Superficial stimulation intensity, mild efficacy per session	Moderate-High (potential for remotely monitored home-based treatment models)
VNS	Electrical stimulation of vagus nerve afferent fibers modulates limbic-prefrontal circuitry	Chronic, treatment-resistant depression requiring long-term maintenance	Significant long-term cumulative efficacy	Invasive VNS requires surgery, high cost; non-invasive forms being developed	

Abbreviations: DLPFC, dorsolateral prefrontal cortex; ECT, electroconvulsive therapy; LLD, late-life depression; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; VNS, vagus nerve stimulation.

neuroplasticity in the brain, particularly, increased hippocampal volume and neurogenesis. This process is accompanied by the upregulation of neurotrophic factors at the molecular level and the reorganization of brain network function.⁴⁰ Studies have demonstrated that ECT is most effective for severe LLD treatment, and the older the patient, the quicker the response to ECT and subsequent remission (remission rate, up to 80.1%).⁴¹ Novel and more tolerable forms of ECT are currently being investigated for LLD treatment, and preliminary results have suggested that right unilateral ultrashort ECT (RUL-UB ECT) is a promising intervention with antidepressant efficacy comparable with that of conventional short-pulse ECT, with less cognitive impact.⁴² RUL-UB ECT in combination with antidepressants significantly improves acute-phase remission rates and reduces relapse risk compared with that of single-agent therapy.⁴³ Notably, the clinical efficacy of ECT was consistently superior to antidepressants in patients of all ages.⁴⁴

Modified ECT (MECT) is also known as convulsion-free ECT due to the use of muscle relaxants prior to treatment. For refractory LLD, MECT is an effective, well-tolerated, and safe method.⁴⁵ MECT is preferred in older patients; it reduces discomfort and anxiety during treatment. It can be used in combination with antidepressant medications, which can improve therapeutic efficacy, especially in the acute treatment phase.⁴⁶

The specific mechanisms of ECT in the aging brain remain inadequately studied. It is currently unclear how to optimize key parameters such as electrode placement and stimulation dosage based on individual patient characteristics including brain structure and comorbidities. Although ECT is highly effective for acute symptom control, predicting and preventing post-ECT depressive relapse remains a critical research priority. Further exploration is needed to optimize treatment parameters for achieving the optimal balance between therapeutic efficacy and cognitive side effects.

Repetitive Transcranial Magnetic Stimulation

rTMS is a neuromodulation technique that non-invasively regulates the excitability of the cerebral cortex using a time-varying magnetic field. TMS modulates whole-brain network function by remodeling signal transmission among the dorsolateral prefrontal cortex (DLPFC), subgenual and dorsal anterior cingulate cortex, and salience-network regions. Additionally, it can promote the transition of behavioral states to positive patterns to exert an antidepressant effect. Its long-lasting therapeutic effect relies on synaptic plasticity, mediated by dopamine and NMDA receptors.⁴⁷ The application of rTMS in LLD has yielded clinically significant and sustained improvements in quality of life. This is similar to the outcomes observed in younger patients and is comparable to or superior to the benefits of antidepressant medications.⁴⁸ Remission rates for LLD treated with rTMS range from 20% to 63%, with bilateral stimulation modalities or high-frequency regimens generally showing superior efficacy.⁴⁹ In addition, the new theta burst stimulation (TBS) patterns, especially bilateral intermittent TBS, have also proven to effectively improve depressive symptoms and executive functions with excellent tolerability.⁵⁰ Compared with unilateral stimulation, sequential bilateral rTMS can regulate a broader range of neural networks, and higher remission rates and better tolerability have been observed.⁵¹ Notably, a bilaterally-combined stimulation regimen (left iTBS + right sustained TBS) for LLD may further optimize efficacy,⁵² and its short-session characteristics significantly enhance treatment accessibility. In addition, an accelerated rTMS regimen (twice-daily high-frequency stimulation [20 Hz]) of the left DLPFC can significantly shorten the treatment cycle in older patients with refractory depression, with strong evidence of safety.⁵³ Currently, rTMS application is still limited by the heterogeneity of individual responses and the lack of evidence supporting its long-term efficacy. By optimizing target localization and individualized therapeutic parameters while considering age-related brain changes, the precision and effectiveness of this intervention can be enhanced. With further research, rTMS is expected to become a more universal non-pharmacological alternative for LLD treatment.

Transcranial Direct Current Stimulation

tDCS is a safe, noninvasive neuromodulation technique that modulates cortical neuronal excitability and synaptic plasticity through low-intensity direct current (0.5–2 mA).⁵⁴ tDCS can induce neuroplasticity and ultimately trigger structural changes in brain gray matter by functionally regulating the DLPFC and its network.⁵⁵ The effects were comparable to those of antidepressant medication and rTMS.⁵⁶ In most studies, the left DLPFC was stimulated. However, a study reported that in patients with first-episode unmedicated major depression, stimulation targeting the frontal cortex and both papillae significantly improved symptoms.⁵⁷ In addition, high-definition tDCS (HD-tDCS) precisely focuses the

current on the target brain area by adjusting the electrode layout, which greatly improves spatial resolution. HD-tDCS can significantly alleviate depression and effectively improve cognitive function in patients with LLD.⁵⁸ Notably, a remotely-monitored home-based tDCS program has been shown to be effective and well-tolerated in patients with major depression after a 10-week intervention.⁵⁹ The continued development of home-based portable tDCS devices is expected to provide a new pathway for long-term maintenance therapy with greater accessibility for LLD treatment. The specific mechanisms by which tDCS induces neuroplasticity in the aging brain remain inadequately studied, and large-scale RCTs confirming its long-term efficacy and value in relapse prevention are lacking. Future advancements should focus on parameter optimization, mechanism elucidation, and integration into multimodal treatment frameworks.

Vagus Nerve Stimulation

VNS is a neuromodulation technique that utilizes an implanted device to deliver electrical pulses to stimulate the vagus nerve. VNS activates vagal afferent fibers through electrical impulses, transmits signals to the nucleus tractus solitarius, and subsequently affects the amygdala, prefrontal cortex, and other brain areas related to emotion regulation, achieving antidepressant and neuromodulatory effects.⁶⁰ An observational study of an older subgroup confirmed that the long-term efficacy of the adjunct VNS group was significantly better than that of the conventional treatment group, with a significantly higher 5-year cumulative remission (67.6% vs 40.9%) and first remission (43.3% vs 25.7%) rates.⁶¹ Transcutaneous auricular VNS, a non-invasive alternative, can prevent the invasive risk and high cost of VNS by modifying the topology of brain networks, which can effectively alleviate the symptoms of depression. It is easy to operate and is more suitable for the elderly.⁶² Currently, studies on VNS in LLD are insufficient, and the sample size is limited. In the future, expanding the scale of clinical trials, exploring the optimal stimulation target and dosage parameters of VNS treatment, providing more effective individualized targeting means for patients, and continuously optimizing the treatment protocol are needed.

Exercise Therapy

Exercise therapy is a non-pharmacological therapy that uses regular physical activity as a core intervention method, combining safety, effectiveness, and cost-effectiveness. Physical activity and exercise are potential therapeutic interventions for depression and are incorporated into guidelines as adjunctive treatment for mild-to-moderate depression.⁶³ Exercise stimulates endorphin release and promotes neurotransmitter secretion, such as serotonin and dopamine secretion, thereby directly improving mood. Furthermore, exercise induces irisin secretion via the muscular PGC-1 α /FNDC5 pathway. The induced irisin enters the brain via circulation, thereby enhancing the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus and promoting neural plasticity.⁶⁴ Simultaneously, exercise can reverse the atrophy of brain regions associated with depression such as the hippocampus, prefrontal cortex, and anterior cingulate cortex, contributing to symptom improvement.⁶⁵ Clinical research has confirmed that implementing structured exercise interventions in older adults with significant depressive symptoms significantly reduces depression severity.⁶⁶

The National Institute for Health and Clinical Excellence recommends incorporating group exercise, especially aerobic exercise, into depression treatment, and they recommend structured and supervised moderate-intensity exercise more than once a week for 10 weeks.⁶⁷ Aerobic exercise involves sustained, rhythmic activity that engages large muscle groups, during which the body consumes oxygen to generate energy. Previous meta-analyses have robustly confirmed its efficacy in treating LLD.⁶⁸ Resistance training interventions also hold substantial therapeutic value in LLD, with core objectives centered on augmenting muscular strength, endurance, and power. Meta-analytic evidence has confirmed that resistance training significantly reduces depressive symptom severity and improves self-perception and quality of life among affected individuals.⁶⁹ Notably, resistance training combined with aerobic exercise is an effective strategy for alleviating depression-related symptoms and is particularly effective in middle-aged and older patients with moderate depression.⁷⁰

Mind-body exercise can improve quality of life by increasing perceived social support and psychological resilience in older adults.⁷¹ A meta-analysis showed that mind-body exercise showed the greatest improvement in depressive symptoms, followed by aerobic and resistance exercise.⁶⁸ Various forms of mind-body exercise are applicable to the older population, with Tai Chi and Qigong showing the most significant benefits in terms of improvement in general

health indicators.⁷² A review suggested that Tai Chi may be superior to non-orthogonal exercise in alleviating anxiety and depression and improving overall mental health⁷³ and can be practiced safely by those with cardiovascular disease or risk factors.⁷⁴ Given that physiological changes due to aging generally reduce motor skills and movement precision in older adults, affecting the safety and effectiveness of their fitness activities, artificial intelligence (AI) interventions are practical. Studies have shown that AI precision intervention by wearing a smart armband equipped with an inertial measurement unit (IMU) can effectively enhance the understanding and execution precision of complex taijiquan movements and significantly improve balance in older adults.⁷⁵ The key to this technology lies in its adoption of the temporal convolutional neural network, an emerging neural network architecture capable of processing IMU data in near real-time. This capability enables the system to concurrently analyze movement standardization during practice, establishing the technical foundation for instant corrective feedback and guidance, thereby endowing the training regimen with a “digital coaching” function.⁷⁶ Existing studies have mostly focused on the overall efficacy of exercises, such as mind-body exercise, and lack in-depth exploration of their neural mechanisms that affect LLD (specificity, specific mechanisms, optimal solutions, and universality are unclear). Future research should involve designing longitudinal studies, harmonizing data collection, and integrating insights from traditional methodologies with the strength of data-driven techniques.

Bright Light Therapy

BLT is a physical intervention that treats mood disorders by exposing individuals to light of a specific intensity. BLT is an effective option for seasonal major depression; its prevention of relapse requires a combination of antidepressant medications and other strategies.⁶³ In patients with LLD, BLT has been shown to improve depressive symptoms, as well as improve sleep efficiency through supraoptic nucleus stimulation to correct circadian rhythm disturbances and modulate the hypothalamic-pituitary axis.⁷⁷ As a convenient and accessible treatment modality, meta-analyses have affirmed its positive effects in alleviating depressive symptoms, and it can enhance the effects of psychotherapy and pharmacotherapy.⁷⁸ In addition, BLT, an adjunct treatment to antidepressants, can significantly enhance the remission and response rates of non-seasonal depression and accelerate the process of treatment response.⁷⁹ BLT has a favorable safety profile and accessibility for patients with LLD who are resistant or intolerant to conventional antidepressant therapies. However, ocular diseases, such as macular degeneration, are common in older people,⁸⁰ and BLT is contraindicated in people at high risk of retinopathy.

Critical gaps persist regarding the neurobiological mechanisms of BLT in the aging brain and the establishment of standardized, effective treatment protocols for LLD. Current evidence supports its role in alleviating depressive symptoms and improving sleep efficiency. Future studies are needed to clarify the optimal treatment protocols, long-term efficacy, and underlying mechanisms of BLT in LLD management.

Dietary and Nutritional Interventions

Dietary and nutritional interventions are non-pharmacological strategies that improve depressive symptoms by adjusting overall dietary patterns or supplementing specific nutrients. Their core principle involves harnessing the neuroprotective and anti-inflammatory properties of food to support LLD management. Studies have shown that diets high in glycemic index or saturated fat increase depressive symptoms and inflammatory markers in healthy populations.⁸¹ In contrast, the Mediterranean Diet has been shown to increase plasma BDNF levels, which can help alleviate depressive symptoms.⁸² The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet, which integrates the core concepts of the Mediterranean and antihypertensive diets, is an exemplary balanced pattern. The MIND diet, which is rich in antioxidants, Omega-3 fatty acids, and polyphenols, enhances BDNF levels and cognitive performance, thereby supporting neuroprotection and mood regulation.⁸³ The health value of this model has been validated in the older Chinese population, following the Chinese version of the MIND diet, and it significantly reduced the risk of depression and anxiety symptoms.⁸⁴ In addition, those who adhered to a high-scoring DASH or MIND diet over a long period had a lower incidence of depressive symptoms.⁸⁵ The core characteristics of these diets are summarized and compared in Table 3.

Table 3 Nutritional Interventions for Late-Life Depression

Interventions	Core Intervention Mechanism	Applicable Symptom Characteristics	Advantages	Limitations	Implementation Flexibility
n-3 PUFAs	Anti-neuroinflammatory, promotes neurogenesis	LLD with high inflammation marker levels or cardiovascular comorbidity	High safety profile, additional cardiovascular protection	Slow onset, requires long-term adherence	High (dietary supplementation)
Vitamin D	Regulates BDNF and immunity, inhibits neuroinflammation	Homebound older adults with low serum vitamin D levels and limited sun exposure	Improves bone health, reduces fall risk	Effects are not significant in individuals with normal vitamin D levels	High (oral supplementation)
Probiotics/ Prebiotics	Modulates the gut-brain axis, reduces inflammatory mediators	LLD with gastrointestinal symptoms or history of antibiotic use	Improves overall gut health, potential multi-system benefits	Strain-specific effects, optimal dosage and duration require further research	Moderate (requires selection of specific strains and regular intake)

Abbreviations: LLD, late-life depression; n-3 PUFAs, Omega-3 polyunsaturated fatty acids.

Omega-3 Polyunsaturated Fatty Acids

Omega-3 polyunsaturated fatty acids (n-3 PUFA), a core component of the MIND diet, have neuroprotective and mood-regulatory functions attributed to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). n-3 PUFA have been recommended as a comprehensive treatment for major depressive disorder,⁸⁶ and their antidepressant mechanisms may involve the modulation of neuroinflammation, including competitive replacement of pro-inflammatory fatty acids, inhibition of NLRP3 inflammatory vesicles, and facilitation of anti-inflammatory mediator production.⁸⁷ Clinical evidence has suggested that EPA-based preparations have significant clinical benefits compared to that of a placebo in patients with depression. However, DHA-based preparations did not show equivalent effects, and further RCTs using EPA-based omega-3 highly unsaturated fatty acids are recommended in patients with established or sufficient clinical severity and duration of depression.⁸⁸ Despite the existence of supportive studies in dietary supplementation in LLD populations,⁸⁹ current evidence is still insufficient to recommend their systematic clinical use.

Vitamin D

Vitamin D, a fat-soluble vitamin obtained mainly through limited dietary intake and sunlight exposure, plays a key role in physiological processes, such as the maintenance of calcium homeostasis, bone health, and immune regulation.⁹⁰ Vitamin D targets key pathways in depression pathogenesis through multiple mechanisms: regulating monoamine neurotransmitter synthesis, inhibiting neuroinflammation, promoting BDNF-mediated neuroplasticity, and stabilizing hypothalamic-pituitary-adrenal axis function,⁹¹ with particular neuroprotective value. Previous studies have confirmed that specific nutrients—vitamin B-complex, by regulating homocysteine metabolism, and vitamin C via scavenging free radicals—jointly constitute a mood-regulatory network together with vitamin D.⁹² A large body of research evidence has suggested that low vitamin D levels are associated with an increased risk of depression. Previous meta-analyses have further indicated that vitamin D supplementation in individuals who are deficient demonstrates antidepressant efficacy comparable to conventional antidepressant medications, whereas it provides no significant benefit to those with normal vitamin D levels.⁹³ Notably, vitamin D and omega-3 fatty acids are synergistic in inhibiting neuroinflammation and regulating mood, and the combination of the two is expected to be an adjunctive therapeutic strategy for depression.⁹⁴ Current evidence relies on observational studies, lacking large-scale RCT validation. Future research must verify efficacy through robust trials and establish precision strategies, integrating deficiency status and nutrigenomics to realize vitamin D's potential in comprehensive LLD treatment.

Probiotic Metabolites

Probiotic metabolites (short-chain fatty acids [SCFAs] and γ -aminobutyric acid) transmit signals to the nucleus tractus solitarius by activating receptors on the afferent fibers of the vagus nerve, thereby inhibiting the overactivation of the hypothalamic-pituitary-adrenal axis and reducing the overproduction of cortisol and its disruption of neurotransmitter homeostasis.^{95,96} SCFAs elevate the intestinal tryptophan utilization rate and promote 5-HT synthesis;⁹⁷ their metabolic derivatives also down-regulate pro-inflammatory cytokine expression and inhibit the progression of mood disorders through anti-inflammatory effects.⁹⁸ Therefore, intervention strategies targeting the gut microbiota (eg, probiotic supplementation with dietary modification) are valuable in alleviating depressive moods in LLD. In the future, precise nutritional intervention programs including specific probiotic or prebiotic combinations and anti-inflammatory nutrient packages can be designed based on individualized metabolomic profiling of gut microbiota to achieve the synergistic efficacy of neuroinflammation modulation and reconstruction of brain metabolic homeostasis.

Social Support and Community Interventions

Social support and community interventions are non-pharmacological strategies that alleviate social isolation and improve mental health through the building of social networks, provision of community resources, and organization of group activities. Social isolation, a cumulative risk factor for LLD, has negative effects that increase over time. Studies have further demonstrated that social network structure and functioning are strongly correlated with depressive symptoms in older adults, and that subjective loneliness can be reduced by promoting social network integration and community involvement, thereby preventing the development of depressive mood.⁹⁹ Being socially active significantly inhibits the expression of pro-inflammatory factors, such as interleukin-6, and mediates anti-inflammatory, anti-stress,

and immune homeostatic effects by activating the paraventricular nucleus of the hypothalamus oxytocinergic neuron release pathway.¹⁰⁰ LLD treatment requires the integration of high-quality social contact as a non-pharmacological intervention and targeted improvement of social determinants at an early stage to enhance efficacy.¹⁰¹ As indicated previously, the landscape of social support and community interventions for LLD is diverse. Their key attributes are succinctly summarized in [Table 4](#) to facilitate comparison.

Social prescription activities, such as soccer, gardening, and art are accessible with associated low cost. These interventions do not only provide direct health benefits but also effectively promote the establishment of social connections among emotionally-disturbed older adults by enhancing social support and reducing loneliness,^{102,103} which has been shown to be positively effective in multiple scenarios. In the future, it will be necessary to combine precision medicine and community ecology to construct a scalable, low-cost, and high-compliance intervention model.

Intergenerational interaction programs rebuild social bonds through age-complementary resource exchange to enhance self-efficacy and social motivation. Intergenerational relationships, serving as social bonds across age groups, encompass not only intra-family interactions and support but also non-family intergenerational interactions such as community mutual aid and communication across ages.¹⁰⁴ For example, in the Chinese culture of filial piety, a negative correlation exists between intergenerational relationships and depressive symptoms, which can alleviate depression by improving older adults' self-assessed health and well-being.¹⁰⁵ The sustainability of intergenerational relationships in LLD should be enhanced through standardized designs in the future. In addition, the use of some new technologies has been welcomed by older adults. For example, the long-term care companion robot PARO (Social Seal Robot),¹⁰⁶ which simulates vital body responses through multi-sensor interactions and provides alternative social connections for older adults, has a significant positive impact on reducing depression and loneliness in older adults.^{107,108} Current evidence has suggested that technological-based interventions, such as PARO, can alleviate negative emotions, including feelings of emotional numbness, social disconnection, and worthlessness by alleviating LLD. Research has demonstrated significant synergistic effects between intergenerational support, community services, and smart health devices, indicating the substantial value of integrating a "family-community-technology" model in alleviating depressive symptoms in older adults.¹⁰⁹ Current evidence on social and community interventions for LLD remains constrained by fragmented implementation and inadequate cultural adaptation, necessitating the future development of more ecologically-valid models that integrate digital tools.

Multimodal Integration

Combining non-pharmacological interventions is a therapeutic strategy that employs two or more modalities to enhance overall efficacy through multi-target synergistic effects. Considering the heterogeneous pathological mechanisms of LLD, the multimodal intervention strategy can achieve synergistic effects by simultaneously targeting neuroplasticity remodeling, metabolism regulation during inflammation, and social neural circuit repair. In neuroplasticity, the combination of physical therapies, such as neuromodulation and psychotherapy, can simultaneously enhance prefrontal neuroplasticity, as well as promote hippocampal BDNF expression and synaptic regeneration, accelerating cognitive pattern consolidation. Moreover, clinical studies have demonstrated that light therapy combined with rTMS is significantly more effective than rTMS alone in refractory LLD.¹¹⁰ The combination of psychological and exercise interventions has also demonstrated the advantages of CBT and exercise interventions in reducing suicidal ideation and improving daily functioning compared with that observed using CBT alone.¹¹¹

Regarding metabolism during inflammation, inhibition of NLRP3 inflammatory vesicle-mediated neuroinflammation using probiotics and anti-inflammatory diets and activation of the iris pathway through individualized exercise effectively blocks the primary inflammatory cascade. This integrated dietary and exercise intervention showed prominent protective effects in Chinese older adults, implying that a combination of various diets and regular exercise resulted in psychological benefits that exceed those of a single intervention.¹¹²

Multimodal interventions are also effective for psychological aspects. The integration of CBT and social skills training significantly improved the self-esteem and quality of life of older adults in nursing homes.¹¹³ Moreover, the efficacy of an integrated program that combined psychotherapy, positive thinking training, and family education was significantly better than that of a single treatment.¹¹⁴ Evidence has indicated that integrating comprehensive

Table 4 Community and Social Interventions for Late-Life Depression

Interventions	Core Intervention Mechanism	Applicable Symptom Characteristics	Advantages	Limitations	Implementation Flexibility	Cognitive Demand
Social Prescription	Increases social connection and support, reduces loneliness	LLD with significant social isolation and loneliness	Breaks social isolation, integrates naturally into life, low cost	Effectiveness depends on group dynamics and participant engagement	Moderate (requires community organization, but diverse formats)	Low to Moderate (depends on activity complexity)
Intergenerational Interaction Programs	Rebuilds social bonds through complementary resource exchange across ages	Elderly feeling socially disconnected or lacking family support	Promotes social integration, utilizes cultural resources	Requires careful design to ensure interaction quality and sustainability	Moderate (requires organization and coordination across generations)	Moderate (requires basic communication and interaction skills)
Technology-Assisted Companionship (eg, PARO Robot)	Simulates social connection via multi-sensory interaction, provides alternative companionship and comfort	LLD with limited mobility and very few social opportunities	Available anytime, provides constant companionship, reduces negative emotions	Lacks the depth of real human interaction, device cost	High (can be used individually on a scheduled basis)	Low (allows for passive interaction)

Abbreviation: LLD, late-life depression.

interventions, comprising physical, psychological, social, and lifestyle dimensions, into routine care plans for LLD may not only alleviate individual clinical symptoms and enhance quality of life but also contribute to the optimization of the healthcare system.¹¹⁵ These findings collectively highlight the need for future comprehensive treatments for LLD to transition from single-target interventions to an integrated model aimed at restoring brain homeostasis and overall bodily health.

Current relevant studies have several limitations. First, sample sizes are generally small, and long-term follow-up data are relatively scarce. Second, for studies on combined non-pharmacological interventions targeting the older adult population, the empirical evidence accumulated so far remains insufficient. Furthermore, existing studies have not yet provided clear answers regarding the optimal combination of different intervention models, appropriate treatment courses, and the specific neurobiological mechanisms underlying the synergistic effects of these models. Therefore, future studies should rely on large-scale, rigorously-designed RCTs to further verify and optimize personalized multimodal intervention protocols.

A major challenge in managing multimodal non-pharmacological interventions for LLD is the effective integration of scattered therapies into routine medical practice. Consequently, the Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT) model provides an excellent operational framework for the systematic coordination and implementation of non-pharmacological interventions. Through clear role division for the interdisciplinary team, this model ensures the feasibility and continuity of non-pharmacological interventions: primary care physicians are responsible for initial identification and referral of such patients; psychiatrists focus on formulating and reviewing personalized non-pharmacological plans; and care managers, as the core of execution, control patient education, guide treatment, coordinate resources, and provide continuous monitoring.¹¹⁶ Studies have shown that this model, which focuses on collaboration and emphasizes integrated care, can significantly improve the management outcomes of LLD.¹¹⁷ Health administration departments should prioritize the adoption and funding of evidence-based collaborative care models such as the PROSPECT, promote their popularity by establishing standardized procedures and compensation mechanisms, and encourage clinicians to actively participate in flexibly selecting intervention measures based on patients' specific conditions—for example, providing a simplified problem-solving therapy for those with impaired executive function and introducing VR-based intervention programs for those with limited mobility.

Discussion

This article systematically integrates the latest evidence across multiple dimensions, including psychological, physical, nutritional, and social support interventions. It connects neurobiology with non-pharmacological interventions and explicitly proposes a core framework of “multimodal synergistic intervention”. Multimodal interventions involving combinations of non-pharmacological approaches may have unique advantages in the treatment of LLD. Existing evidence has indicated that strategies such as psychotherapy, physical therapy, nutritional interventions, and community support can alleviate LLD symptoms through specific mechanisms, such as regulating DMN function, enhancing neuroplasticity, reducing neuroinflammation, and repairing social neural circuits. However, due to LLD's etiological heterogeneity and multidimensional pathophysiology, no single intervention can fully reverse the disease. Multimodal interventions effectively generate synergies, simultaneously acting on multiple pathophysiological links to potentially yield more significant and lasting clinical benefits, especially in patients with LLD.¹¹⁸ For example, neuromodulation may “reset” the brain into a learning-conducive neural environment, boosting the subsequent cognitive remodeling effects of psychotherapy.¹¹⁹ Similarly, combining anti-inflammatory diets with regular exercise may have additive or complementary effects in inhibiting systemic inflammation by acting on the gut microbiota-brain axis and muscle-brain axis, respectively.¹²⁰ Notably, studies on multimodal interventions for LLD—exclusively non-pharmacological—remain scarce.¹²¹ However, most of these synergistic mechanisms are still hypothetical, with limited research among older adults.

Negative Outcomes and Risk Management of Non-Pharmacological Interventions

In psychotherapy, some approaches such as CBT and cognitive reading therapy require patients to have certain cognitive function and educational levels, potentially causing frustration in older adults with cognitive impairment or low

education. RT risks reactivating traumatic memories, while poor therapeutic relationships may also have negative effects.³⁵ Digital therapies, lacking real interpersonal interaction, have limited effect on alleviating loneliness.¹²²

Neuromodulation techniques, as physical therapies, have side effects: ECT may cause memory impairment and anesthesia risks;¹²³ rTMS often induces headaches and scalp discomfort;¹²⁴ and the efficacy of tDCS remains uncertain. Exercise therapy poses injury risks to frail older adults, and patients often struggle with adherence due to insufficient motivation. BLT may cause eye discomfort and is contraindicated for certain groups.⁸⁰

Nutritional interventions have slow and uncertain efficacy, may trigger gastrointestinal discomfort and drug interactions, and pose financial and adherence challenges during its long-term use. Social support and community interventions depend on activity quality for efficacy, while technology-assisted companionship may fail due to the digital divide.

Most importantly, integrated multimodal interventions may create an “intervention burden”. Simultaneous participation in multiple therapies can excessively drain older patients’ energy, time, and cognitive resources, leading to increased stress, reduced adherence, and even premature treatment discontinuation. Therefore, clinicians must carefully weigh these potential risks and optimize therapeutic benefits through individualized plans and tailored pacing.

Key Limitations in the Field

Despite the promising prospects, this field faces several important limitations. Methodologically, most cited RCTs are constrained by small sample sizes and short follow-up periods, limiting the reliable assessment of long-term efficacy and safety. As a narrative review, this article lacks the methodological rigor of a systematic review, potentially introducing selection and publication biases. Furthermore, the exclusive inclusion of English articles may omit significant findings from other cultural contexts.

Regarding implementation, the generalizability and accessibility of interventions present challenges. Many psychological interventions require relatively intact cognitive function, while digital therapies pose barriers in older adults with low technology adoption rates or in resource-limited settings. The sustainability of community interventions significantly depends on external resources and policy support, with a notable absence of mature, scalable business or public policy models.

Finally, significant gaps remain in mechanistic research and clinical translation. The understanding of how multimodal interventions produce synergistic effects at the cerebral, immune, and metabolic levels remains superficial, lacking robust evidence in the field of systems biology.

Future Research Directions and Practical Recommendations

To address these gaps, future research must conduct large-scale, long-term multicenter RCTs to establish high-level evidence for multimodal interventions. Studies should include cross-cultural comparisons to develop culturally-adapted protocols and integrate precision medicine approaches to identify treatment-guiding biomarkers. Technological developments must incorporate age-friendly designs to enhance usability and adherence. The ultimate goal is to create an integrated hospital-community-home care model, supported by innovative policies and funding, to translate these technological advancements into accessible, effective, and humane care for older adults with depression.

Conclusion

Non-pharmacological interventions have been emphasized in LLD treatment due to advantages, such as fewer side effects and higher patient compliance. The use of such interventions has shifted from monotherapy to comprehensive multidimensional interventions. To facilitate the translation of these interventions from evidence to practice, clinicians should define their roles within collaborative care models, such as the PROSPECT, to systematically integrate multimodal interventions. Concurrently, public health policy makers must establish a robust support framework by institutionalizing these collaborative structures and reforming payment systems. In the future, research in this field should advance along two critical pathways: first, for clinical practice, precision medicine, digital technologies, and community ecology should be integrated to establish an accessible and integrated personalized biopsychosocial care model and second, for research, multicenter, large-sample longitudinal, and cross-cultural comparative studies should be conducted to evaluate

the long-term efficacy and feasibility of multimodal interventions, ultimately establishing an efficient, accessible, and humanized mental health care system for older adults with LLD.

Data Sharing Statement

No dataset was used for this study.

Author Contributions

Tianmei Xu: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Conceptualization. Yanping Mao: Validation, Methodology. Ye Wang: Validation, Supervision. Yi Gong: Project administration, Methodology. Enyan Yu: Investigation, Formal analysis, Conceptualization. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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