



# Mechanism-Driven Translation of Electroacupuncture for Depression: Bridging the Gap Between Preclinical and Clinical Research

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**Abstract:** Electroacupuncture (EA) has demonstrated multi-level antidepressant effects, yet the strength of clinical evidence remains insufficient and its efficacy consistency is highly contested. The key bottlenecks include heterogeneous research designs, a lack of standardized stimulation parameters and acupoint selection, insufficient attention to disease biological subtyping, and a disconnect between mechanistic studies and clinical outcomes. To address these gaps, this review proposes a mechanism-driven precision translation pathway centered on patient stratification. By integrating neural circuitry, immune-inflammatory pathways, biomarkers, and multimodal assessment tools, we argue that the primary translational bottleneck is not a lack of mechanisms but the failure to systematically integrate them into a clinical decision-oriented paradigm. Enhancing interpretability and clinical scalability through parameter optimization, targeted neural network modulation, and objective indicator integration may transform EA from a complementary therapy into a precision intervention with clear mechanisms and reliable evidence.

**Keywords:** electroacupuncture, depression, basic research, clinical translation, challenges, strategies

## Introduction

Depression is a complex, highly heterogeneous psychiatric disorder whose high prevalence and substantial disease burden have made it one of the leading causes of global disability.<sup>1</sup> The heterogeneity of depression manifests not only in diverse symptom clusters such as anhedonia, depressed mood, or somatic complaints,<sup>2</sup> but more profoundly in its intricate etiological network. Genome-wide association studies have revealed a polygenic inheritance pattern, where genetic variations interact with environmental effects, life course experiences, and gender differences to collectively form the complex biological foundation of the disease.<sup>3,4</sup> However, current mainstream diagnostic frameworks (eg., DSM-5/ICD-11) primarily rely on symptomatic phenomena. While providing unified standards for clinical practice, this approach has limitations in mechanism research and treatment efficacy prediction. Symptom-based classifications often mask underlying physiological and pathological heterogeneity, leading to repeated setbacks in drug development targeting single pathways.<sup>5</sup> This situation underscores the critical need to transcend mere symptom descriptions and identify “endophenotypes” or biomarkers associated with specific pathophysiological pathways (eg., inflammation, metabolic abnormalities, or circuit dysregulation) to overcome current diagnostic and therapeutic bottlenecks.<sup>6</sup>

Against this backdrop, electroacupuncture (EA) has garnered attention as a non-invasive neuromodulation therapy due to its multi-target regulatory potential and favorable safety profile. Extensive preclinical studies have confirmed its multifaceted antidepressant mechanisms: at the molecular level, EA exerts central anti-inflammatory effects by activating and inhibiting the NF- $\kappa$ B pathway;<sup>7</sup> at the plasticity level, it upregulates BDNF and hippocampal  $\beta$ -calmodulin-dependent protein kinase II

(CaMKII $\beta$ ) expression, remodeling hippocampal synaptic structures;<sup>8</sup> At the systems level, EA has been shown to specifically modulate key neural circuits such as the “motor cortex-parabrachial nucleus-nucleus of the solitary tract”.<sup>9</sup> This multi-dimensional evidence of mechanisms provides a robust scientific basis for EA as an integrative therapy. Despite increasingly deep mechanistic exploration, translating these findings into solid, reproducible high-level clinical evidence remains a significant challenge. A “translational gap” persists between the depth of current basic research and the scarcity of clinical evidence. This impasse stems not from a lack of mechanisms, but from disconnects in intervention protocols (parameter standardization), evaluation systems (reliance on subjective scales), model validity (species differences), and dose definition during the transition from laboratory to clinical settings. Simply replicating the drug development model is insufficient to resolve this issue. Future research urgently requires establishing a closed-loop translational framework linking “mechanism-biological dose-clinical phenotype.” Against this backdrop, this paper aims to systematize the key mechanisms of electroacupuncture’s antidepressant effects, dissect current translational barriers, and propose a mechanism-driven translational approach. This endeavor seeks to bridge the gap between preclinical discoveries and clinical applications, providing a reference for the rational design and clinical translation of EA interventions for depression.

## Clinical Evidence: Stratified Presentation and Methodological Bottlenecks

The research value of EA in treating depression primarily lies in its potential for multi-target neuromodulation, favorable safety profile, and integration possibilities with existing therapies.<sup>10</sup> However, these advantages also present challenges in protocol heterogeneity and evidence-based practice. As an intervention integrating traditional acupuncture with modern electrical stimulation, EA features adjustable stimulation parameters. This technical characteristic theoretically enables personalized neuromodulation targeting distinct pathological pathways of depression.<sup>11</sup> In clinical practice, practitioners can adjust frequency, intensity, waveform, and treatment duration based on patient symptoms and clinical judgment. This parametric flexibility constitutes a key potential advantage over fixed-dose pharmacotherapy but also increases the complexity of protocol heterogeneity and outcome comparability. Regarding safety, EA exhibits a lower incidence of severe adverse events compared to conventional antidepressants,<sup>12</sup> with no clear safety signals observed in populations such as those with depression and insomnia.<sup>13,14</sup> This characteristic confers advantages for patients with drug intolerance, comorbid physical illnesses, or requiring long-term treatment. However, existing evidence primarily stems from small-to-medium sample studies, necessitating systematic evaluation. Furthermore, EA demonstrates strong potential for integrated treatment, serving as an adjunct to pharmacotherapy or psychotherapy. Studies indicate that combining EA with medication or psychotherapy may yield superior outcomes in improving depressive symptoms, cognitive function, or sleep compared to monotherapy.<sup>15,16</sup> This suggests that future research should clarify EA’s optimal role within comprehensive treatment pathways, rather than positioning it solely as an alternative therapy.

To facilitate comparison of methodological differences, control types, and primary outcomes of electroacupuncture interventions across various clinical settings, this section summarizes representative RCTs and systematic reviews stratified by population, as shown in [Table 1](#).

Beyond the studies summarized in [Table 1](#), several international clinical trials have reported neutral or mixed findings. One US study showed that depression-specific acupuncture during pregnancy significantly accelerated symptom improvement,<sup>24</sup> however, another US randomized controlled trial found that a depression-specific EA protocol did not outperform non-meridian scalp sham stimulation.<sup>25</sup> Meanwhile, a Hong Kong-based randomized controlled trial evaluating EA-assisted benzodiazepine tapering revealed no significant differences between the EA and placebo acupuncture groups in either complete discontinuation rates or dose reduction at 12 weeks.<sup>26</sup> These diverse international findings highlight the heterogeneity of EA effects across different populations and control conditions, further reinforcing the need for the critical appraisal that follows.

## Challenges Hindering Evidence Strength Enhancement

Clinical research on EA for treating depression faces a series of challenges in enhancing evidence strength, limiting the causal attribution of its specific physiological effects and the reproducibility of outcomes. From the perspective of the disorder itself, first, the high heterogeneity and continuum characteristics of depression constitute major obstacles to outcome reproducibility.<sup>27</sup> As Li J et al noted, Major Depressive Disorder (MDD) is not a discrete disease category but

**Table 1** Evidence Characteristics and Methodological Limitations of Electroacupuncture Interventions for Depression in Different Clinical Settings

Research Subjects	Research Type	Sample Size	Comparison Type	Treatment Course	Outcome Indicator	Conclusion	Transformation Constraints
Post-stroke depression (PSD) <sup>17</sup>	RCT	150	Escitalopram	40 days	HAMD-17, SDS	Electroacupuncture efficacy is non-inferior to SSRIs; at certain time points, it is superior to SSRIs.	Non-inferiority margin/blinding and allocation concealment require verification; Long-term recurrence and maintenance efficacy data are insufficient.
PSD <sup>18</sup>	RCT	65	Sham acupuncture	4 weeks	Depression score, neurological function	Electroacupuncture significantly improves neurological function.	The success rate of sham acupuncture versus blinded methods requires clarification; endpoints and time windows need to be completed.
PSD <sup>19,20</sup>	System Evaluation/ Meta	–	Bringing together diverse perspectives	–	Depression scales (such as HAMD)	Equivalent efficacy to drugs with higher safety.	Heterogeneity (between controls/ parameters/populations) and publication bias must be reported; evidence grades (GRADE) must be completed.
Perimenopausal Depression <sup>21</sup>	RCT	242	Escitalopram	12 weeks	Symptom Scale, Quality of Life	Improved symptoms and quality of life; sustained response signals during follow-up period.	Mechanistic heterogeneity (sleep/ cognitive/hormonal-quality of life pathway) obscures “who benefits”; the outcome system requires optimization.
Depression with insomnia (symptom dimension enrichment) <sup>13</sup>	Multicenter randomized controlled trial	270	Sham acupuncture + Standard Care	8 weeks	PSQI; Depression/ Anxiety Score	Sleep quality was significantly better than in the control group; depression and anxiety also improved.	Parameter report integrity and blinded testing require verification; it is recommended to incorporate digital phenotypes/objective sleep and autonomic nervous system indicators as bridging endpoints.
Chronic pain (such as postherpetic neuralgia) with anxiety/ depression <sup>22</sup>	RCT	180	Sham acupuncture	4 weeks	Anxiety/ Depression Symptoms	Along with improvement in emotional symptoms.	Non-specific effects are strong, requiring strict controls; primary endpoints and comorbidity dimensions must be pre-registered.
Chronic low back pain with emotional symptoms <sup>23</sup>	RCT	125	Sham acupuncture	5 weeks	Pain intensity; Emotional symptoms	Pain intensity was not superior to placebo injections; the difference in frequency was not significant.	The message “non-specific effects/ suboptimal parameters/insufficient sample size” may lead to false negatives; dose-response and mechanism endpoints should be included.

should be conceptualized as a continuum along neurobiological dimensions.<sup>27</sup> This continuum implies extremely high intrinsic heterogeneity within study populations, meaning patients enrolled in different clinical trials may exhibit divergent underlying pathophysiological mechanisms. Consequently, they may respond inconsistently to the same intervention (eg., EA). Thomas JT et al further confirmed this heterogeneity through genomics research, revealing gender-specific genetic risk structures in MDD, suggesting that female and male patients may involve partially distinct pathogenic pathways.<sup>28</sup> Consequently, attributing treatment efficacy to the intervention itself and expecting replication across different samples poses significant challenges without precise patient subtyping. Second, extensive comorbidity and confounding factors severely disrupt causal inference. Depression frequently coexists with multiple physical illnesses, such as a bidirectional relationship with obesity that creates complex feedback loops, necessitating multidimensional interventions integrating psychological and metabolic approaches.<sup>29</sup> This comorbidity renders controlling confounding variables in clinical studies exceptionally complex. Furthermore, severe mental illnesses (eg., depression, bipolar disorder) themselves constitute risk factors for long-term health problems,<sup>30</sup> while conversely, physical illnesses may trigger or exacerbate depressive symptoms.<sup>31</sup> Against this backdrop of multifaceted disease interactions, it is challenging to attribute observed improvements in depressive symptoms solely to specific physiological effects of EA, rather than indirect outcomes stemming from concomitant treatments or confounding factors.

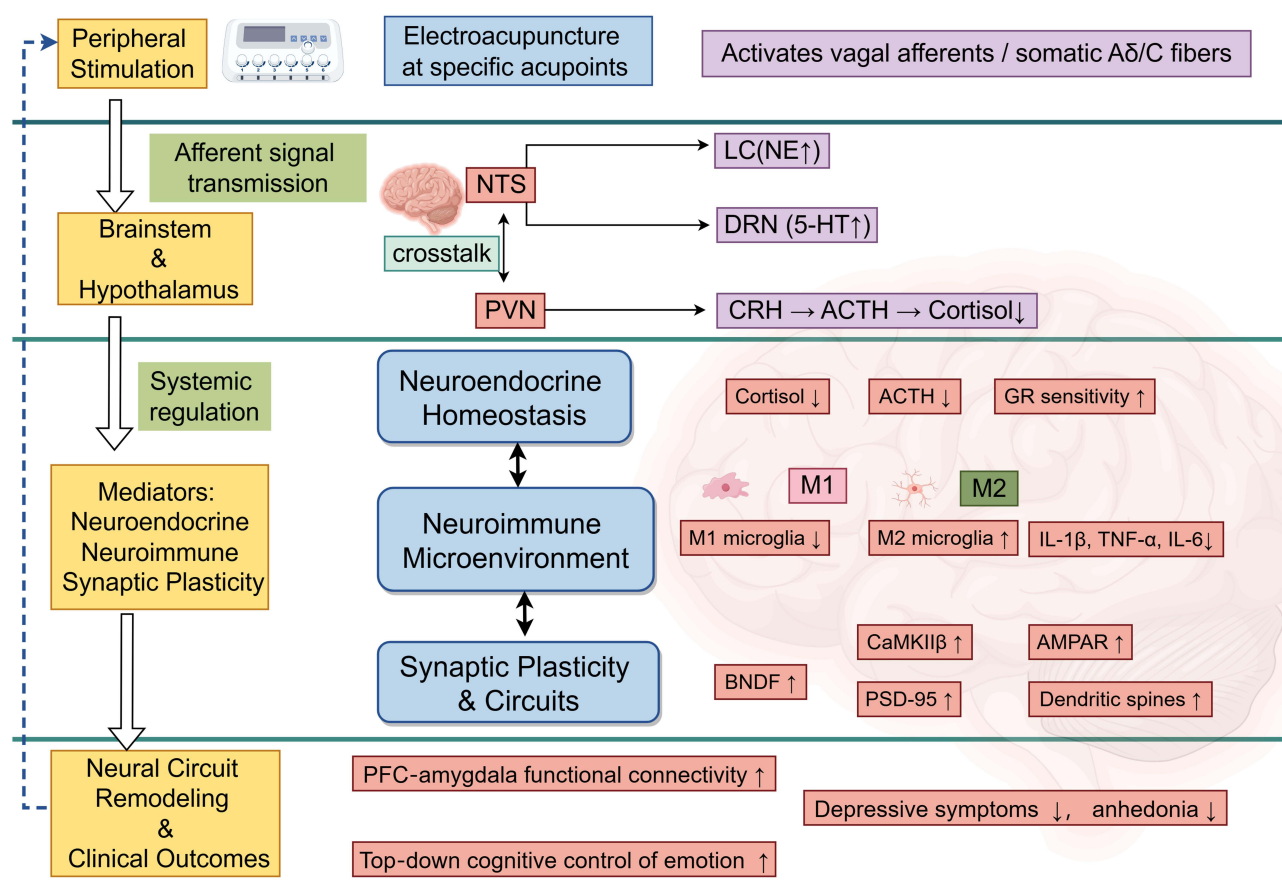
From a methodological perspective, first, the placebo effect and nonspecific factors are difficult to fully control, creating uncertainty regarding the biological attribution of EA's specific therapeutic efficacy. Although multiple randomized controlled trials have demonstrated EA's superiority over sham acupuncture in improving depressive symptoms,<sup>12</sup> nonspecific effects are particularly prominent in complex clinical scenarios such as pain and mood comorbidity. For instance, Torres SF et al found that in a study of elderly patients with chronic low back pain, EA did not outperform sham acupuncture in pain reduction,<sup>23</sup> suggesting that treatment context and placebo effects may significantly influence outcomes. Even with sham controls, achieving true equivalence in terms of needle sensation and therapeutic interaction remains challenging, thereby undermining blinding success rates and compromising the reliability of efficacy attribution. Second, there is a lack of mechanism-driven standardized consensus on electroacupuncture stimulation parameters such as frequency, intensity, duration, and treatment course. Few studies have systematically explored the relationship between these parameters and treatment effects, leading to highly heterogeneous treatment protocols that are difficult to compare and replicate. Existing studies predominantly rely on empirically set parameters. For instance, no significant efficacy differences were observed between EA at different frequencies (2 Hz vs. 100 Hz),<sup>23</sup> suggesting either that frequency is not a critical variable or that current dose exploration remains inadequate. Although some basic research indicates specific parameters may modulate prefrontal energy metabolism or hypothalamic transcription profiles,<sup>32,33</sup> these findings have yet to translate into clinically actionable dosage frameworks. Furthermore, efficacy assessments overly rely on subjective scales like the Hamilton Depression Rating Scale,<sup>12,34</sup> which are susceptible to rater bias and patient self-reporting, limiting mechanistic interpretation and inter-study comparability.<sup>35</sup> In recent years, a few studies have attempted to incorporate mechanism-related objective measures, such as cortical activation patterns reflected by functional near-infrared spectroscopy<sup>34</sup> or changes in inflammatory markers.<sup>17</sup> However, no widely validated biomarker system has emerged, making it difficult to directly translate basic mechanism discoveries into clinical practice. Finally, existing studies exhibit high heterogeneity in control group design, participant inclusion criteria, and treatment duration. Most trials have limited sample sizes and insufficient statistical power, with a severe lack of long-term follow-up data.<sup>12,13,23</sup> Only a handful of studies report mid-term follow-up results,<sup>13</sup> and evidence regarding relapse prevention and long-term maintenance efficacy remains scarce. This limitation constrains EA's positioning and guideline recommendations for the chronic management of depression. Collectively, these methodological challenges constitute bottlenecks in advancing the evidence base for EA in depression research, necessitating systematic improvements in trial design, parameter standardization, and outcome measurement systems.

Despite the promising signals from existing studies, a balanced interpretation requires explicit acknowledgment of several persistent limitations that are directly attributable to the absence of standardized EA parameters. First, inter-trial heterogeneity remains substantial: variations in acupoint selection, stimulation parameters (frequency, intensity, duration), control conditions (sham acupuncture, waitlist, pharmacotherapy), and outcome measures preclude definitive meta-analytic conclusions and limit the generalizability of any single study. Second, risk of bias is non-trivial. Many trials lack adequate allocation concealment, blinding of outcome assessors, or intention-to-treat analysis. Even when sham controls are used, the credibility of blinding is often suboptimal because patients may distinguish real from sham EA based on needle sensation (deqi), introducing performance bias. Third, effect sizes are generally modest. Although statistically significant in some trials, clinical relevance remains uncertain, especially given the absence of established minimal clinically important differences for EA in depression. Fourth, sham acupuncture controls face inherent conceptual and practical challenges. No consensus exists on an ideal inert comparator that mimics all non-specific aspects of EA (eg., needle insertion, electrical sensation, therapeutic ritual) without physiological activity. Penetrating sham needles may still produce peripheral afferent activation, while non-penetrating devices may not blind patients or practitioners effectively. This ambiguity complicates the attribution of specific physiological effects versus placebo responses. Notably, the modest effect sizes reported in many EA trials are frequently attributable to unexpectedly high response rates in the sham control groups, reflecting a substantial placebo component that masks specific treatment effects.<sup>36</sup> Beyond average treatment effects, the phenomenon of non-responders, defined as patients or animal models that show minimal or no improvement despite adequate EA stimulation, deserves explicit attention. In clinical settings, a substantial proportion of depressed patients fail to achieve a clinically meaningful response to EA. Potential contributors to non-response include genetic factors that may affect neuroplasticity and pain modulation, baseline severity (eg., patients with higher baseline

anhedonia may respond less favorably), and biological subtypes (eg., those with predominant inflammatory or metabolic dysregulation may require different EA parameters). In preclinical models, non-responders can be identified through behavioral screening, such as sucrose preference non-responders after chronic stress, enabling mechanistic studies of resistance to EA. Identifying predictors of non-response is as critical as defining responders for the precision application of EA. Future studies should prospectively stratify patients by these candidate factors and test whether parameter optimization can convert non-responders into responders. Collectively, these limitations do not invalidate EA's potential but demand greater caution in interpreting the current evidence base. Future trials must adhere to rigorous methodological standards (eg., Consort for acupuncture), report effect sizes with confidence intervals, and incorporate sham validation checks (eg., blinding questionnaires). Until such high-quality evidence accumulates, claims about EA's efficacy in depression should be framed as preliminary or supportive rather than definitive.

## Mechanistic Evidence

The biological effects of EA against depression do not rely on a single target but are achieved through systematic remodeling of the multidimensional complex network encompassing “stress-endocrine-neuroimmunity-synaptic plasticity-neural circuits”,<sup>37,38</sup> as shown in Figure 1. As a physical neuromodulation method, EA primarily acts on the upstream initiation phase of depression onset—the dysregulation of the stress response system. In classical models such as chronic unpredictable mild stress (CUMS) and chronic restraint stress, persistent stressors trigger excessive



**Figure 1** Hierarchical and directional mechanisms of EA in depression. EA activates peripheral afferents (Layer I). These signals then ascend to the brainstem and hypothalamus, including the nucleus tractus solitarius (NTS), locus coeruleus (LC), dorsal raphe nucleus (DRN), and paraventricular nucleus (PVN), and further trigger the hypothalamic-pituitary-adrenal (HPA) axis (Layer II). Downstream mediators (Layer III) include neuroendocrine factors (cortisol, ACTH), neuroimmune processes (microglial M1 to M2 polarization, IL-6, TNF- $\alpha$ , IL-1 $\beta$ ), and synaptic plasticity pathways (BDNF, CaMKII $\beta$ , PSD-95). The net effect leads to prefrontal-limbic circuit remodeling and alleviation of depressive symptoms (Layer IV). Solid arrows indicate causal direction; bidirectional arrows represent reciprocal interactions; the dashed arrow denotes a positive feedback loop. The symbols  $\uparrow$  and  $\downarrow$  indicate increase (upregulation) and decrease (downregulation), respectively. Abbreviations are defined in the main text.

activation of the hypothalamic-pituitary-adrenal (HPA) axis, forming a difficult-to-interrupt neuroendocrine cascade.<sup>39,40</sup> EA intervention has been demonstrated to restore glucocorticoid receptor (GR) sensitivity and negative feedback regulation by modulating key gene expression profiles in the paraventricular nucleus (PVN) of the hypothalamus.<sup>41</sup> This significantly reduces abnormal levels of circulating adrenocorticotrophic hormone (ACTH) and corticosterone, thereby blocking the neurotoxic damage caused by high-concentration glucocorticoids to brain regions such as the hippocampus at its source.<sup>42</sup> However, neuroendocrine markers are highly influenced by individual stress states, disease stages, and external environmental factors, and existing studies still exhibit limited control and stratification of these variables in their research designs. This instability in endocrine responses may further amplify the variability observed across EA clinical studies. Moreover, the neurotransmitter changes documented across different studies show significant discrepancies in model types, stimulation parameters, and detection time windows, with results not always exhibiting consistent directionality.

The restoration of this neuroendocrine homeostasis is intrinsically linked to improvements in the central immune microenvironment. Normalization of HPA axis function creates the prerequisites for suppressing neuroinflammation, and EA exerts particularly precise effects at the neuroimmunomodulatory level. Extensive research confirms that EA reverses the pathological polarization of microglia—inhibiting pro-inflammatory (M1) and promoting anti-inflammatory (M2) transformation—thereby reshaping the brain's immune microenvironment.<sup>43–45</sup> Its molecular mechanisms involve regulating multiple key signaling pathways: on one hand, EA blocks the maturation and release of critical pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  by inhibiting NLRP3 inflammasome assembly and activation;<sup>46,47</sup> on the other hand, EA further consolidates its anti-inflammatory effects by blocking the TLR4/p38/NF- $\kappa$ B signaling cascade mediated by oxidative stress in specific comorbidity models (eg., post-stroke depression or inflammatory bowel disease with depression).<sup>46,48</sup> However, the role of inflammation-related mechanisms in depression exhibits significant heterogeneity, with substantial variations in immune status across different patient cohorts.<sup>49</sup> Existing EA studies rarely employ stratified designs based on inflammatory phenotypes. This undifferentiated research strategy may undermine the reproducibility and predictive value of inflammatory regulatory mechanisms at the clinical level.

Suppressing inflammatory responses and clearing neurotoxic substances facilitates structural repair in damaged brain regions, forming the structural basis for EA's long-lasting antidepressant effects. In the dentate gyrus (DG) and CA1 region of the hippocampus, EA has been demonstrated to significantly reverse stress-induced downregulation of brain-derived neurotrophic factor (BDNF) and its receptor TrkB.<sup>50</sup> By activating the Wnt/ $\beta$ -catenin signaling pathway and Tet1-mediated epigenetic modification mechanisms, EA not only promotes the proliferation and differentiation of endogenous neural stem cells,<sup>51,52</sup> but also upregulates the expression of key synaptic proteins such as CaMKII $\beta$ , PSD-95, and AMPAR.<sup>8,53,54</sup> This directly drives the restoration of neuronal dendritic spine density and enhanced synaptic transmission efficiency, effectively counteracting astrocytic atrophy in the prefrontal cortex and hippocampal neuronal apoptosis. This provides material support for the physical reconnection of damaged neural circuits. Although these studies provide important clues for EA regulation of emotion-related neural circuits, inconsistencies in the circuit nodes, stimulation sites, and functional endpoints examined across different studies make it difficult to directly translate these findings into clinical intervention strategies. This disconnect between circuit-level evidence and clinical research design may be a key reason for the inconsistent translation of EA's neuromodulatory effects.

Although EA is administered peripherally, its antidepressant effects ultimately depend on the transmission of afferent signals from somatic or vagal nerves to the central nervous system. A critical but underemphasized aspect is the neuroanatomical circuitry through which peripheral EA stimulation engages brainstem nuclei and subsequently modulates limbic and prefrontal circuits.

Vagal afferents represent a major entry route. EA at specific acupoints (eg., ST36, PC6) has been shown to activate vagal sensory fibers, which project directly to the nucleus tractus solitarius (NTS) in the medulla oblongata. The NTS serves as a pivotal relay station, integrating visceral and somatosensory information. From the NTS, noradrenergic projections ascend to the locus coeruleus (LC), while serotonergic projections extend to the dorsal raphe nucleus (DRN) – both of which are deeply implicated in mood regulation. More directly, the NTS sends glutamatergic and GABAergic projections to limbic regions (eg., amygdala, hippocampus) and prefrontal cortex (PFC), either monosynaptically or via the parabrachial nucleus and thalamus.

Activation of this vagal–NTS–limbic/PFC pathway by EA has been associated with reduced amygdala hyperreactivity, normalized PFC–amygdala functional connectivity, and enhanced top-down cognitive control over emotion – effects that parallel those observed with direct vagus nerve stimulation (VNS), an approved neuromodulation therapy for treatment-resistant depression. For instance, animal studies demonstrate that EA at ST36 increases c-Fos expression in NTS and LC, and that cervical vagotomy abolishes EA’s antidepressant-like behavioral effects and its suppression of hippocampal pro-inflammatory cytokines.

Importantly, different EA parameters (eg., low-frequency 2 Hz vs. high-frequency 100 Hz) may differentially recruit distinct peripheral afferent subtypes (eg., low-frequency 2–10 Hz preferentially activates vagal C-fibers, whereas higher frequencies >50 Hz may recruit A $\delta$  fibers), leading to distinct NTS output patterns and divergent modulation of downstream limbic circuits. This parameter-specific neuroanatomical engagement provides a mechanistic rationale for optimizing EA protocols to target specific depression endophenotypes (eg., anxiety-driven vs. anhedonic subtypes).

In summary, explicit recognition of the vagal–NTS–limbic/PFC axis not only improves mechanistic coherence but also positions EA within the broader framework of established neuromodulation therapies (eg., VNS, transcutaneous auricular vagus nerve stimulation). Future mechanistic studies should routinely assess whether observed molecular or circuit effects are dependent on the integrity of this ascending pathway.

## Translation Challenges

### Species Differences and Uncertainty in Cross-Species Extrapolation

Cross-species differences complicate the direct mapping of effective parameters from animals to humans. The absence of equivalent models hinders the standardization of clinical prescriptions. Research on the mechanisms of EA in treating depression relies heavily on rodent models. However, translating effective parameters derived from these animal studies into human clinical applications faces significant challenges due to species differences.<sup>37</sup>

First, rodents and humans exhibit significant differences across multiple levels, including brain structure, neural circuits, behavioral content, and physiological responses,<sup>55–59</sup> leading to inherent uncertainty in extrapolating animal study results to humans. At the neuroanatomical and functional levels, key brain regions involved in emotional regulation—such as the prefrontal cortex (PFC)—exhibit significantly greater relative size, neural connectivity complexity, and integration of higher cognitive functions in humans compared to mice or rats.<sup>60</sup> Lin SS et al demonstrated that EA alleviates depressive-like behavior in mice by preventing astrocytic atrophy in the PFC.<sup>61</sup> Building on this, Lai S et al further revealed that EA modulates mitochondrial fission mediated by the SENP3/FIS1 pathway within neurons of this region.<sup>62</sup> Simultaneously, Yin X et al observed through functional magnetic resonance imaging (fMRI) that EA down-regulates abnormal functional connectivity in limbic system regions like the amygdala of depressive model mice.<sup>63</sup> However, direct evidence remains lacking to confirm whether these cellular, molecular, and circuit-level changes observed in animal models occur with identical mechanisms and efficacy within the more structurally complex and functionally diverse human prefrontal cortex and affective neural networks. At the behavioral level, animal “depression-like behaviors” are primarily assessed through tests like sucrose preference and forced swimming, reflecting anhedonia and despair-like behaviors.<sup>61,64</sup> However, the complex subjective experiences characteristic of human depression—such as persistent low mood, self-blame, and suicidal ideation—remain difficult to authentically simulate and quantify in animal models.<sup>65</sup> Second, physiological responses associated with EA may exhibit significant species specificity.<sup>41,66,67</sup> For instance, Qiu X et al found that animal studies suggest EA can improve depressive-like behaviors by modulating gut microbiota (eg., increasing *Lactobacillus* abundance).<sup>68</sup> However, significant differences exist between mouse and human gut microbiota composition, and the clinical relevance of key bacterial genera requires further validation.<sup>69</sup> Similarly, while EA’s mechanisms in modulating the hypothalamic-pituitary-adrenal (HPA) axis and suppressing neuroinflammation are relatively well-established in animal models,<sup>47,70</sup> its relative weight and interaction patterns within the highly complex human pathological network may not be entirely consistent.

Second, existing mechanistic studies heavily rely on singular, homogeneous animal models such as chronic unpredictable mild stress (CUMS).<sup>71,72</sup> While the CUMS model reliably induces depression-like behaviors like anhedonia and is widely used to elucidate EA’s mechanisms—such as upregulating hippocampal brain-derived neurotrophic factor

expression,<sup>73</sup> enhancing neurogenesis,<sup>74</sup> or preventing prefrontal cortical astrocyte atrophy.<sup>61</sup> However, this model significantly oversimplifies the profound complexity of human depression, which involves genetic predisposition, environmental exposures, and psychosocial factors.<sup>75</sup> Given the marked heterogeneity in the etiology of human depression, involving multiple factors such as genetic susceptibility, early trauma, and chronic comorbidities, mechanism discoveries derived from the single CUMS model may struggle to account for the specific pathophysiological processes of other depression subtypes (eg., postpartum depression, post-stroke depression).<sup>64,76</sup> This limitation constrains its universal explanatory power and clinical guidance value for complex human diseases.

Finally, the “effective dose” and intervention model established in animal studies face significant methodological challenges when translating to human treatment protocols. On one hand, existing basic research often retroactively derives electroacupuncture parameters deemed “effective” in animals through behavioral endpoints (eg., sugar water preference, forced swimming test) or molecular biological endpoints (eg., specific protein expression levels).<sup>70</sup> For instance, studies by Lai S and Zhang JR et al demonstrated antidepressant-like effects in CUMS or chronic social defeat stress (CSDS) models using 2 Hz electroacupuncture stimulation at acupoints including Baihui (GV20), Yintang (GV29), or Zusanli (ST36).<sup>62,77</sup> However, these parameters are established based on the physiological scale, tissue impedance, and neural excitability of mice or rats. How to scientifically and systematically translate them into safe and effective therapeutic parameters for humans based on biophysical equivalence principles (eg., current density) or neurophysiological equivalence principles (eg., thresholds for inducing neural oscillations in specific brain regions) Currently, there is no universally accepted model for this conversion, leading to insufficient standardization of clinical electroacupuncture protocols and limited reproducibility of therapeutic outcomes. On the other hand, to pursue experimental controllability and reproducibility, basic research often employs simplified intervention protocols with fewer acupoints and fixed parameters. Numerous studies select only a single or a few fixed acupoints (eg., Baihui, Zusanli) and use fixed stimulation parameters (eg., 2 Hz).<sup>8,70,74</sup> This approach contrasts significantly with clinical practice, which relies on individualized, multi-point combinations based on pattern differentiation. Clinical treatment often requires flexible adjustments to point selection and stimulation parameters according to specific syndromes (eg., liver qi stagnation, heart-spleen deficiency) and comorbid conditions (eg., chronic pain or post-stroke states).<sup>76,78</sup> While simplified designs in basic research facilitate elucidating the independent mechanisms of specific acupoints or parameters, they struggle to simulate and explain the holistic effects of multi-target, multi-pathway synergistic regulation observed in clinical treatment. For instance, Zhang Y et al found that the combination of Baihui paired with Taichong induces distinct transcriptional changes compared to single-point stimulation.<sup>79</sup> Consequently, the dual constraints of parameter translation uncertainty and simplified intervention models collectively diminish the practical guidance value of basic mechanism research for optimizing individualized electroacupuncture treatment protocols, constituting a core bottleneck in translating findings from animal studies to clinical applications.

To systematically present the structural limitations of current preclinical electroacupuncture antidepressant research in terms of models, interventions, and endpoint evaluations, and to clarify their specific impact on clinical translation, relevant paradigm characteristics and issues are summarized in [Table 2](#).

Moreover, the neuroanatomical pathways through which peripheral EA engages central circuits – particularly the vagal–NTS–limbic/PFC axis – exhibit both conservation and divergence across species. While rodents and humans share a basic vagal–NTS projection, the relative density, cortical projection targets, and synaptic integration patterns differ significantly. For example, the human prefrontal cortex receives more extensive and differentiated inputs from thalamic and brainstem nuclei than the rodent medial PFC. Consequently, even if EA activates the same subdiaphragmatic vagal afferents in both species, the resulting modulation of higher-order cognitive-emotional circuits may not be directly scalable. This underscores the need for parallel neuroanatomical mapping studies in non-human primates or humans using high-resolution neuroimaging (eg., diffusion MRI tractography) to validate cross-species translation of EA’s circuit-based mechanisms.

## The Gap Between “Simplified” and “Complex” Intervention Approaches

Clinical practice may rely on the systemic effects of multi-point combinations, yet basic research predominantly focuses on single points or fixed prescriptions, creating an evidence gap regarding synergistic mechanisms. Basic studies often

**Table 2** Key Limitations of Preclinical Research Paradigms and Their Translational Barriers

Level	Common Practices	Main Limitations	Impact on Clinical Translation
Disease model <sup>61,74,75</sup>	Primarily relies on a single CUMS model	Over-simplifying the genetic, environmental, and psychosocial heterogeneity of human depression.	Treatment response is difficult to predict across different subtypes of depression, such as PSD and PPD.
Model Coverage <sup>61,64</sup>	With anhedonia as the core phenotype	Unable to reflect dimensions specific to human symptoms such as self-blame, rumination, and suicidal ideation.	Behavioral improvements are difficult to map to core clinical symptoms.
Intervention Protocol (Acupoints) <sup>8,70,74</sup>	Single or a few fixed acupoints (eg., GV20, ST36)	Inconsistent with clinical multi-point acupuncture and syndrome differentiation formulae.	The unexplained synergistic therapeutic effects across multiple clinical targets.
Stimulus parameters <sup>70,74</sup>	Fixed frequency and intensity (eg., 2 Hz)	Lack of dose-response exploration.	Difficult to guide the optimization and standardization of clinical parameters.
Mechanism of Acupoint Combination <sup>79</sup>	Rarely compared: single-point vs. paired-point	Unclear synergistic/overlay mechanism	Clinical experience is difficult to systematize and standardize.
Species Differences (Brain Structure) <sup>80</sup>	Rodents have a simple prefrontal cortex structure.	Significantly different from human PFC in structure and function.	Uncertainty in the extrapolation of loop-level mechanisms.
Behavioral Endpoints <sup>64,80</sup>	Preference for sugary drinks, forced swimming	Reflecting only an absence of pleasure and despair-like behavior.	Difficult to encompass the complex dimensions of cognition and emotion.
Gut-Brain Axis Research <sup>68</sup>	Changes in the mouse microbiota as a mechanism	The composition of the microbiota in mice differs significantly from that in humans.	The clinical significance of key bacterial genera requires further validation.
Mechanism Weighting Assumption <sup>47,70</sup>	Mechanisms observed in animals can be extrapolated to humans.	Ignoring the hierarchical structure and interactions within human pathological networks.	May overestimate or underestimate the clinical significance of a mechanism.

concentrate on simple points to elucidate mechanisms, while clinical efficacy likely stems from the synergistic or cumulative effects of multiple points (eg., Baihui paired with Yintang, Neiguan paired with Taichong). Research on the synergistic mechanisms of point combinations remains severely inadequate. For instance, Wei X et al successfully improved depressive-like behavior in olfactory bulb-resected mice and restored dendritic complexity and electrophysiological activity in hippocampal CA1 neurons by stimulating the single acupoint Neiguan (PC6) with electroacupuncture (EA).<sup>80</sup> Ma F et al focused on EA combinations like Baihui (GV20) and Yintang (GV29), demonstrating efficacy comparable to escitalopram in patients with post-stroke depression (PSD) while modulating neuroinflammatory responses.<sup>17</sup> However, the underlying synergistic mechanisms underlying this transition from single acupoints to clinically used combinations remain unclear. Xu H et al found in PSD rats that EA stimulation of the “Four Gate Points” (a combination of Hegu and Taichong) improved depressive-like behaviors, potentially through regulating fecal short-chain fatty acids and thereby influencing colonic serotonin release.<sup>81</sup> This suggests that acupoint combinations may exert more comprehensive therapeutic effects by regulating multi-system interactions, such as the brain-gut axis. In clinical practice, acupoint combination is a core principle—for instance, treating PSD often employs Baihui paired with Yintang to calm the mind and stabilize the spirit, or Neiguan paired with Taichong to soothe the liver and resolve depression. This represents a crucial attempt to translate clinical experience into testable scientific questions.<sup>82</sup> However, the vast majority of current mechanism studies remain confined to single acupoints or fixed prescriptions, lacking systematic comparisons of the neurobiological effects of different combinations across specific depressive subtypes. This disconnect between basic research and complex clinical interventions makes it difficult to directly interpret laboratory-discovered single mechanisms or use them to guide the comprehensive therapeutic effects achieved by multi-point, individualized treatments in clinical practice.

## Definition and Quantification Challenges of Therapeutic “Dose”

EA dose encompasses a multi-layered structure comprising “physical parameters + needle sensation experience + physiological responses,” and its definition and quantification represent one of the key challenges currently facing clinical translation. Traditionally, the concept of EA “dosage” extends far beyond mere physical stimulation parameters.

It encompasses two interrelated yet distinct dimensions: first, objectively measurable physical parameters such as current intensity, frequency, waveform, and stimulation duration;<sup>83</sup> second, the patient's subjective experience of “deqi” sensation—a complex sensation of soreness, numbness, distension, or heaviness following needle insertion. Traditional Chinese medicine theory posits this as the critical mechanism where “qi reaches the affected area,” thereby generating therapeutic effects.<sup>84</sup> However, reliable and widely accepted methods for objectifying and standardizing this highly subjective and individually variable “deqi” experience remain elusive. For instance, in a randomized controlled trial by Xia J et al targeting mild-to-moderate first-episode depression, while the treatment frequency (3 sessions weekly for the first 8 weeks, then 2 sessions weekly for the subsequent 4 weeks) and total duration (12 weeks) of EA were clearly defined, no quantitative assessment was conducted regarding the intensity, nature, or association with treatment efficacy of the “deqi” sensation during each session.<sup>85</sup> This absence of objective measures makes it difficult to achieve consistent treatment “dosage” across studies or even among different practitioners within the same study. Consequently, the comparability and reproducibility of research findings are compromised, presenting a significant barrier to translating clinical experience into evidence-based medicine.

Meanwhile, there is a lack of research within the field that can systematically elucidate the dose–response relationship between electroacupuncture stimulation parameters, neurophysiological effects, and clinical outcomes. Most current studies remain at the level of observing “the presence or absence of efficacy,” failing to delve into mapping the dose–response curve connecting specific stimulation parameters with particular biological effects.<sup>86</sup> For instance, research by Zhang J et al suggests that electroacupuncture at different frequencies may exert effects through distinct mechanisms. A study on methamphetamine-induced depressive-like behavior found that low-frequency EA improved depressive-like behavior and cognitive impairment by suppressing hippocampal microglial activation, downregulating pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$ , and inhibiting the NF- $\kappa$ B/NLRP3 signaling pathway.<sup>87</sup> This suggests frequency may be a critical parameter that specifically modulates neuroinflammation as a distinct pathological process. However, this study did not systematically compare the gradient effects of different EA frequencies (eg., 2 Hz, 100 Hz) on the same set of neurobiochemical markers and behaviors, nor did it establish a quantitative relationship model linking “specific frequencies to behavioral improvement magnitude.” Exploration of such dose–response relationships remains scarce in clinical research. Multiple clinical trial designs primarily focus on outcome differences between treatment and control groups,<sup>85,88</sup> but typically do not stratify studies by variables such as current intensity or frequency to explore which parameter combinations optimize improvement for specific symptom clusters (eg., pain, insomnia, depression). This absence of dose–response research means that formulating EA treatment plans still relies heavily on experience rather than precise “dosage” prescriptions. This hinders its widespread adoption as a standardized therapeutic approach and its personalized application (As shown in Table 3).

To ensure replicability across different laboratory and clinical settings, we propose a minimal set of physical parameters that must be reported in all EA studies. Beyond the commonly reported frequency (Hz) and duration (minutes per session), the following parameters are critical for defining the biological dose of EA: current intensity (measured in milliamperes, mA, with specification of whether it refers to peak-to-peak or root-mean-square), pulse width (microseconds,  $\mu$ s), and waveform (eg., square, sine, or asymmetric biphasic). Additionally, electrode placement (distance between electrodes, skin preparation, and impedance monitoring) and stimulation regimen (ramp-up/ramp-down time, intermittent vs. continuous delivery) should be documented. We recommend that future studies adopt a standardized reporting checklist adapted from existing guidelines (eg., STRICTA for acupuncture, supplemented with

**Table 3** Potential Mapping Between TCM Syndrome Differentiation Types of Depression and Biological Phenotypes

Level	Common Practices in Basic Research	Clinical Practice	Translation Challenges
Acupoints	Single point or simple point combination	Multi-cavity combination	Collaborative mechanism unclear
Parameters	Fixed frequency	Individual adjustment	No dose-response relationship
De Qi	No evaluation	Core factors	Difficult to standardize

neuromodulation parameters). Without such detailed reporting, the “dose” of EA remains ill-defined, precluding cross-study comparisons, meta-analyses, and reliable dose-response modeling.

## Operationalization Challenges in Syndrome Differentiation and Treatment Research

Syndrome differentiation and treatment constitute the clinical advantage of Traditional Chinese Medicine (TCM), yet its lack of objectivity and standardization hinders integration into modern randomized controlled trial (RCT) designs, making its individualized benefits difficult to capture within evidence-based frameworks. TCM pattern differentiation and treatment form the core of EA clinical practice. However, translating diagnostic classifications like “liver qi stagnation” or “heart-kidney disharmony” into objective biological markers (phenotypes) suitable for standardized research poses significant challenges. This creates difficulties in integrating the principle of individualization into modern clinical study designs. Modern clinical research emphasizes standardization and reproducibility, creating an inherent tension with TCM’s emphasis on individualized pattern differentiation and treatment. Although randomized controlled trials (RCTs) have demonstrated the overall efficacy of EA for treating depression—such as EA combined with psychological intervention proving superior to psychological intervention alone for post-stroke depression,<sup>89</sup> and EA combined with medication outperforming medication alone in improving cognitive symptoms, mood, and executive function in depressed patients<sup>34</sup>—these studies typically treat patients as a homogeneous group, failing to incorporate TCM syndrome differentiation as a stratification or analytical factor. Objectivizing syndrome differentiation is key to bridging this gap. Some studies have begun exploring the biological basis associated with specific syndromes or symptom clusters. For instance, Zhou JH et al found that the primary symptom of perimenopausal depression is cognitive impairment, and that hormone levels do not directly correlate with depression scores but exert effects through the mediating variable of quality of life (MENQOL).<sup>21</sup> This suggests that syndromes associated with “kidney deficiency” or “disorder of the Chong and Ren vessels” may manifest by influencing specific quality-of-life dimensions and related neurocognitive circuits. Yuan J et al used functional near-infrared spectroscopy (fNIRS) to demonstrate that EA combined with medication more effectively enhanced cortical activation in depressed patients,<sup>34</sup> offering insights into translating pathomechanisms like “inadequate nourishment of the heart-mind” or “obstruction of brain orifices” into observable neural activity indicators. Basic research has attempted to link syndromes with molecular pathways. For instance, Cai HQ et al demonstrated that EA improves depressive-like behavior by activating the SIRT1 signaling pathway to promote oligodendrocyte differentiation and myelin repair.<sup>90</sup> These mechanisms may hold potential connections to syndromes like “liver qi stagnation invading the spleen” or “disorder of qi movement.” However, systematic research remains lacking to precisely correlate clinically common TCM syndromes of depression (eg., liver qi stagnation, deficiency of both heart and spleen, heart-kidney disharmony) with specific neuroendocrine, immune, metabolic, or brain network characteristics, and to validate the specific regulatory effects of EA intervention on these “syndrome-phenotypes.” This gap in translational research hinders the design of EA clinical studies from fully embodying and leveraging the essence of TCM pattern differentiation and treatment. It also limits the demonstration and promotion of personalized treatment advantages within the framework of modern evidence-based medicine.

## Mismatch in Dimensions of Efficacy Evaluation Systems

The absence of bridging biomarkers between molecular/circuitry endpoints in basic research and clinical-scale endpoints hinders the alignment of mechanisms with clinical benefits. Basic research focuses on quantifiable alterations at the molecular, cellular, or circuitry levels. For instance, Wang Y et al found that EA upregulates hippocampal BDNF and CaMKII $\beta$  expression in depressive model mice, modulating neuronal plasticity.<sup>8</sup> In IBD-depression models, Cao S and Li Z et al both demonstrated that EA improves neuroinflammation by inhibiting NLRP3 pathway activation via oxidative stress or activating IL-4/JAK-STAT pathways to regulate microglial phenotypes.<sup>46,48</sup> These studies clearly elucidate the mechanisms of EA. However, clinical endpoint assessments rely almost exclusively on subjective symptom scores such as the Hamilton Depression Rating Scale (HAM-D) and Self-Rating Depression Scale (SDS), with numerous RCTs and meta-analyses citing these as primary efficacy evidence.<sup>12,15,19,20</sup> Currently, there is a severe lack of rigorously validated biomarkers (such as specific neuroimaging patterns or blood miRNA profiles) that bridge these two levels. This absence of a “bridge” makes it difficult to objectively link the effects observed in basic research—such as enhanced neuroplasticity or suppressed

inflammation—to improvements in patients' subjective experiences, creating a disconnect between mechanism studies and clinical efficacy evaluations.

Additionally, a gap exists between animal behavioral tests and complex human clinical symptoms. Basic research commonly employs forced swimming tests and sugar water preference tests to simulate despair and anhedonia,<sup>91</sup> but these dimensions are extremely limited. Complex cognitive-emotional symptoms unique to human depression, such as self-blame, feelings of worthlessness, and rumination, are nearly impossible to simulate in rodent models. For instance, Fang X's meta-analysis on postpartum depression (PPD) showed that electroacupuncture outperformed controls in overall response rates. However, it failed to demonstrate significant superiority over sham electroacupuncture in reducing HAMD and EPDS scores—which assess complex dimensions like self-blame and anxiety.<sup>92</sup> Therefore, “efficacy” predicted based on animal behavioral improvements (eg., reduced immobility time) may be biased when translated to clinical settings due to inadequate coverage and improvement of complex cognitive symptoms unique to humans, exacerbating translation challenges.

## Systemic Constraints from Non-Biological Factors

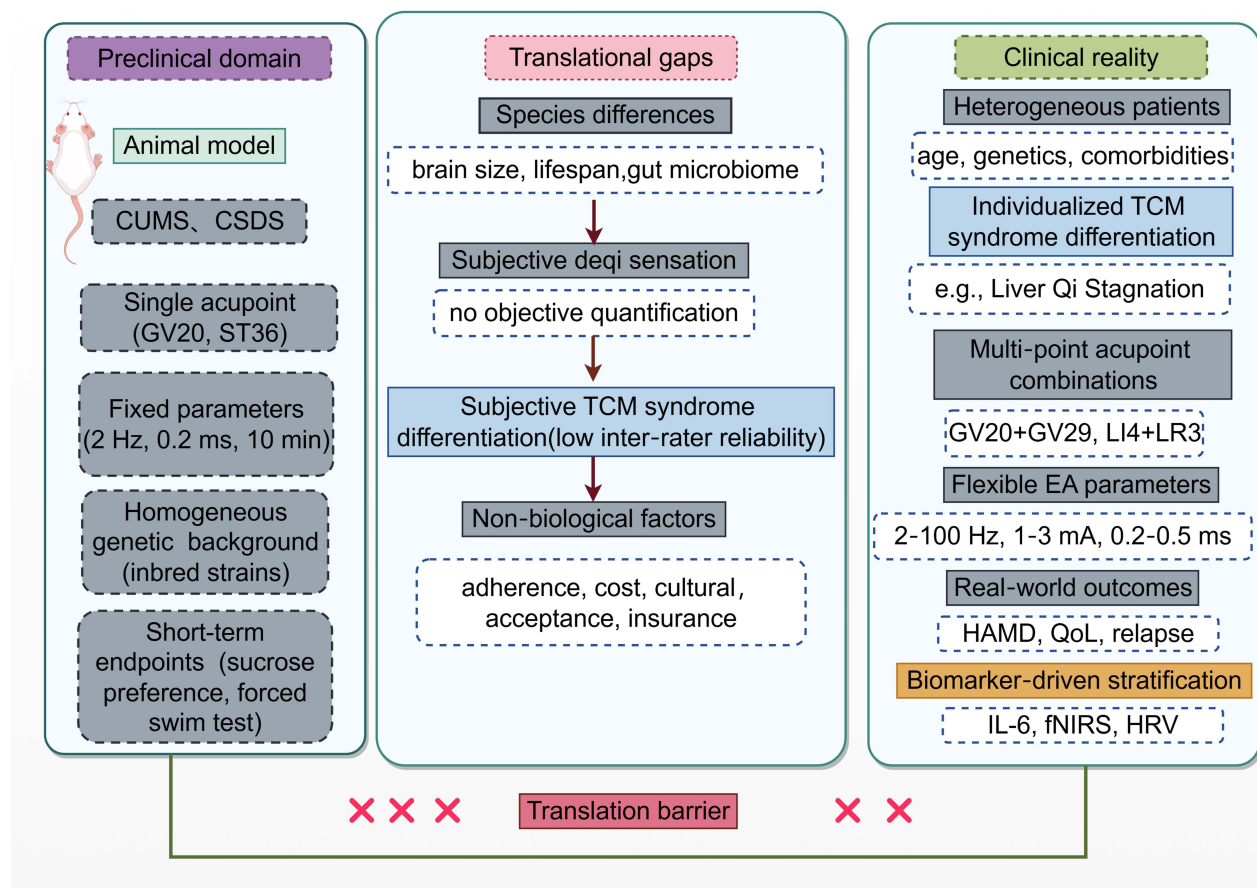
Systemic factors such as therapist characteristics, patient compliance, cultural acceptance, and healthcare accessibility also influence the effect size and scalability of EA for treating depression.<sup>37</sup> Within modern healthcare systems, professional barriers between psychiatry, acupuncture departments, and neuroscience research impede the formation of multidisciplinary teams needed to integrate mechanism understanding, clinical experience, and operational techniques.<sup>93</sup> Neuroscience mechanism discoveries struggle to translate into clinical guidelines, while acupuncture practice lacks channels to connect with modern biology, creating a disconnect between research and application that forms a systemic bottleneck constraining therapeutic development. Additionally, patient-level and healthcare system factors are equally critical yet often overlooked. Patient cognition and acceptance are influenced by cultural background, trust in traditional medicine, and potential concerns about “electrical stimulation,” directly impacting treatment willingness. Treatment adherence faces practical challenges: electroacupuncture requires regular clinic visits, imposing significantly higher time, transportation costs, and lifestyle disruptions than oral medications, compromising treatment integrity—a factor already evident in clinical trial designs for chronic pain.<sup>23</sup> Ultimately, health economics, particularly insurance coverage, directly determines therapy accessibility. Without reimbursement, even biologically effective mechanisms will benefit only a limited population. This translation gap between preclinical models and clinical practice is illustrated in [Figure 2](#).

Therefore, future research must transcend purely biological exploration and systematically incorporate cognitive, adherence, and policy factors to comprehensively evaluate real-world outcomes and develop feasible implementation pathways. As highlighted in a review of acupuncture for Parkinson's disease, while acknowledging its potential, efforts must focus on standardizing protocols and conducting comparative effectiveness studies—which inherently require detailed investigation of non-biological factors such as treatment parameters and course duration.<sup>75</sup>

## Mechanism-Driven Precision Translation Pathways From Efficacy Validation to Mechanistic Research

Further advancement of the EA evidence system hinges on establishing a verifiable mechanism chain rather than repeatedly validating its overall efficacy. Future clinical trial designs for EA in treating depression should prioritize the following three directions.

First, biomarker-based patient stratification and enrichment strategies are key to enhancing trial sensitivity.<sup>94</sup> Given the high heterogeneity of depression in etiology, pathophysiology, and treatment response, integrating multiple biomarkers to define biologically meaningful endophenotypes represents a core pathway for identifying populations with potential superior response to EA. For instance, combining neuroimaging metrics, electrophysiological features (eg., frontal alpha asymmetry),<sup>95</sup> peripheral blood biomarkers (eg., inflammatory cytokines IL-1 $\beta$  and IL-6),<sup>17</sup> and objective behavioral data from wearable devices (eg., sleep parameters)<sup>13</sup> can distinguish subtypes characterized by abnormal neural modulation, heightened inflammatory responses, or disrupted sleep rhythms. Implementing enrichment enrollment designs based on these insights holds promise for significantly enhancing statistical power and clinical translation value.



**Figure 2** Translational gaps between preclinical EA research and clinical practice. Left: preclinical models (rodent, single acupoint, fixed parameters). Middle: gaps (species differences, undefined dose, subjective deqi, TCM syndrome variability in blue, sham challenges, non-biological factors). Right: clinical practice (patient heterogeneity, individualized TCM in blue, multi-point combos, flexible parameters, biomarker stratification in Orange). Dark red solid arrows: translation barriers. Color coding: blue = TCM; orange = biomarkers; gray = methodological/preclinical.

Secondly, the dose–response relationship of EA stimulation must be clarified expeditiously. Comparing therapeutic effects across different frequency, intensity, waveform, and treatment duration combinations will establish optimal parameter protocols for subsequent large-scale trials. Existing studies, such as Torres SF et al on chronic pain<sup>23</sup> and Zhou JH et al on perimenopausal depression,<sup>21</sup> provide reference design paradigms. These demonstrate that systematically evaluating the impact of parameter combinations on specific symptom dimensions or biological pathways is crucial to avoid underestimating efficacy due to suboptimal stimulation parameters. Finally, confirmatory trials require further methodological reinforcement. For control designs, prioritizing controls with higher blinding efficacy—such as penetrating sham acupuncture or non-point superficial needling<sup>95</sup>—is essential to more effectively distinguish specific therapeutic effects. Regarding outcome assessment, limitations of single subjective scales must be overcome by systematically incorporating objective endpoints directly linked to hypothesized mechanisms. Examples include cortical activation patterns measured via functional near-infrared spectroscopy<sup>34</sup> and digitally captured behavioral phenotypes from wearable devices, encompassing activity levels and sleep rhythms.<sup>96</sup> Only through rigorous controlled trials combined with multidimensional objective assessments can higher-level evidence with greater credibility be generated, thereby substantially bridging the gap between basic research and clinical practice.

## Pattern Differentiation and Biological Phenotype Mapping

In the precision translation of EA for treating depression, systematically integrating traditional Chinese medicine pattern differentiation with modern biological phenotypes is the key scientific question determining whether it can establish

differentiated theoretical advantages and clinical competitiveness. Before proceeding, it is important to clarify that the mapping between TCM syndromes and biological endophenotypes described below remains primarily hypothesis-driven rather than empirically validated. While some correlational clues exist in the literature, systematic prospective validation is lacking. Therefore, this section should be viewed as a conceptual framework and a research agenda to guide future studies, rather than a set of established facts. Traditional Chinese medicine pattern differentiation has long demonstrated strong individualized therapeutic capabilities in clinical practice. However, its interpretability and generalizability within modern evidence-based medicine systems remain constrained by the absence of quantifiable, biologically verifiable correspondences. Conversely, while the concept of endophenotypes proposed by modern psychiatry offers high measurability at the biological level, it often fails to directly inform specific intervention strategies. Therefore, establishing a mapping framework between “syndrome differentiation and biological endophenotypes” represents not only a methodological integration effort but also a core breakthrough propelling EA from empirical medicine toward mechanism-driven precision medicine.

Operationally, future clinical studies can utilize TCM syndrome differentiation as a pre-registered stratification variable—rather than a post-hoc subgroup analysis indicator—combined with multimodal biomarkers for patient enrichment and stratification.<sup>97</sup> Specifically, different syndrome patterns may correspond to relatively stable, reproducible biological feature patterns.<sup>98</sup> For instance, liver qi stagnation-related patterns characterized by emotional imbalance and heightened stress responses may manifest as prefrontal-limbic system dysfunction, increased frontal alpha asymmetry, and hypothalamic-pituitary-adrenal axis abnormalities,<sup>99–101</sup> Syndrome patterns associated with qi deficiency or spleen deficiency, characterized by low mood with fatigue and diminished interest, may be more closely linked to weakened autonomic function, reduced heart rate variability, and abnormalities in energy metabolism-related indicators;<sup>102,103</sup> whereas patterns accompanied by sleep disturbances and physical discomfort may exhibit features such as circadian rhythm disruption, elevated inflammatory factors, and abnormal sleep architecture.<sup>104</sup> Although these correlations require validation in prospective studies, this hypothesis-driven mapping framework provides a testable pathway for biologically anchoring syndrome differentiation.

Building upon this, the “precision” of EA treatment extends beyond individualized selection of parameters or acupoints to encompass mechanism-specific matching for particular biological phenotypes. For instance, if a syndrome pattern group exhibits pronounced inflammatory activation at baseline, electroacupuncture protocols primarily targeting anti-inflammatory pathways should be prioritized. Conversely, if another pattern predominantly involves neural network dysregulation or autonomic imbalance, stimulation parameters and point combinations favoring neuromodulation or circadian rhythm restoration should be selected. Through this “syndrome pattern-phenotype-mechanism-intervention parameter” combination, electroacupuncture intervention strategies can evolve from empirical syndrome differentiation and treatment to biologically grounded, mechanism-directed prescriptions. Clarifying the correspondence between syndrome differentiation and phenotypes also holds significant reverse translation value. On one hand, modern statistical and machine learning methods can be applied to reverse-engineer the most predictive syndrome pattern feature combinations from multimodal data, thereby enhancing the consistency and reproducibility of syndrome differentiation. On the other hand, if a specific syndrome pattern consistently correlates with similar biological endophenotypes and treatment response patterns across different studies and populations, that syndrome pattern itself can be regarded as a clinically meaningful “functional biological subtype,” providing empirical support for the modern interpretation of TCM theory.

Thus, the correspondence between syndrome differentiation and biological endophenotypes provides an actionable framework for patient stratification and mechanism matching in EA precision treatment. It also lays a scientific foundation for standardizing, quantifying, and internationally disseminating the TCM syndrome differentiation system within the modern psychiatric context. Integrating this mapping relationship into clinical trial design and real-world studies represents a crucial pathway for achieving differentiated breakthroughs and high-quality translation in EA treatment for depression. To transform the above hypothesis-driven framework into an empirically grounded basis, we propose the following methodological approaches. First, prospective cohort studies with predefined syndrome stratification should be conducted, using TCM syndrome differentiation as a stratification variable. By enrolling patients representing major depression syndromes and collecting standardized biospecimens and clinical outcomes, researchers can test the associations between specific syndrome patterns, biomarker profiles, and differential responses to EA. Second, multimodal data clustering (eg., hierarchical clustering, latent profile analysis) can be applied to multidimensional biological data – including neuroimaging metrics, inflammatory cytokines, hormone levels, and heart rate variability – to identify data-driven clusters, which are then cross-validated with

syndrome labels to examine whether syndromes correspond to biologically meaningful subgroups. Third, supervised learning algorithms (eg., random forest, support vector machines) can be trained to classify syndrome patterns based on multimodal biomarkers, with external validation in independent cohorts. Predictive models can further evaluate whether syndrome-informed biomarkers predict EA treatment response. Fourth, iterative refinement through reverse translation involves back-translating human findings into animal models with construct validity for specific endophenotypes (eg., inflammatory depression, stress-induced anhedonia). If EA with specific parameters shows superior efficacy in a given endophenotype model, and that endophenotype maps to a particular TCM syndrome in humans, cross-species consistency would strengthen the validity of the mapping. Implementing these strategies requires multidisciplinary collaboration. We acknowledge that the proposed mapping remains largely conceptual at this stage, and the above validation strategies represent a necessary next step toward precision EA.

To translate subjective TCM pattern differentiation (eg., Liver Qi Stagnation) into objective biological endophenotypes, we propose a five-step methodological workflow. First, standardized syndrome diagnosis is performed using a validated semi-structured questionnaire (eg., the TCM Depression Syndrome Scale), with consensus reached by two independent TCM practitioners. Second, multimodal biomarker data are collected from patients stratified by syndrome, including neuroimaging (fNIRS, fMRI), peripheral blood inflammatory cytokines (IL-6, TNF- $\alpha$ , IL-1 $\beta$ , CRP), neuroendocrine markers (cortisol, ACTH), electrophysiological measures (EEG, heart rate variability), and multi-omics profiles. Third, unsupervised machine learning is applied for feature selection and dimensionality reduction to identify biomarkers most strongly associated with each syndrome label. Fourth, supervised classifiers (eg., random forest, support vector machines) are trained on the selected features to predict syndrome patterns, and cross-validation together with external validation in an independent cohort yields a biomarker signature for each syndrome (eg., Liver Qi Stagnation characterized by increased frontal alpha asymmetry, elevated IL-6, and reduced heart rate variability). Fifth, reverse mapping validation is performed in a separate prospective cohort to test the concordance between predicted and clinically diagnosed syndromes, as well as the ability of the biomarker signature to predict differential response to EA treatment. This workflow transforms the theoretical mapping into an empirically testable and reproducible process. The resulting syndrome-specific biomarker signatures can directly guide patient stratification and precision EA parameter selection. To further reduce inter-practitioner variability and enhance scalability, future implementation should incorporate a standardized TCM syndrome diagnostic scale (eg., the TCM Depression Syndrome Scale) supplemented by an AI-assisted diagnostic tool based on natural language processing or pattern recognition of clinical features.

To further translate this theory into actionable clinical research hypotheses, this paper constructs a potential mapping framework between common TCM syndromes in depression and modern biological endophenotypes based on existing evidence, proposing corresponding precision intervention strategies ((As shown in [Table 4](#)).

## Development of Standardized and Intelligent Neuromodulation Technologies

Standardization and intelligence represent key technical pathways for reducing parameter heterogeneity, enhancing research reproducibility, and achieving biologically informed dosage prescriptions. Currently, significant variations exist in electroacupuncture stimulation parameters—including frequency, intensity, and waveform—limiting the comparability of research findings and the reliability of efficacy assessments. Existing studies indicate that different parameter combinations can induce distinctly different neurophysiological responses. For instance, Armstrong K et al found that low-frequency EA (2.5 Hz) significantly improved heart rate variability and enhanced parasympathetic activity, whereas mid-frequency stimulation (15 Hz) did not exhibit similar effects.<sup>105</sup> Additionally, Zhan G et al demonstrated that EA modulates EEG microstates, whose alterations serve as objective biomarkers of neuromodulation effects.<sup>106</sup> Therefore, it is necessary to establish standardized recommendations for EA stimulation parameters based on measurable neurophysiological responses. This should integrate evidence from EEG and HRV to define recommended parameter ranges for different therapeutic objectives. Concurrently, research and development of quantitative EA devices should be advanced to achieve precise output and comprehensive recording of stimulation parameters. This will facilitate a shift from experience-driven to data-driven approaches and provide technical support for studying reproducibility and efficacy analysis.<sup>107</sup>

**Table 4** Potential Mapping Framework Between TCM Syndrome Differentiation, Biological Endophenotypes, and Precision EA Strategies

TCM Syndrome	Clinical Features	Biological Endophenotypes	Intervention Strategy & Mechanism Focus
Liver Qi Stagnation	Depressed mood, intense anxiety, chest and rib discomfort, sensitivity to stress	Stress-Circuit Dysregulation-Stress-Circuit Dysfunction Type: 1. Hyperactive HPA Axis Response 2. Abnormal Frontal-Amygdala Circuit Connectivity 3. Asymmetric Frontal Alpha Waves	Focus on Emotional Circuit Regulation: Acupoint Selection: Primarily along the Liver Meridian and Governor Vessel (eg., Tai Chong LR3, Bai Hui GV20) Parameters: Require exploration of specific frequencies for HPA axis desensitization Mechanistic Goal: Restore prefrontal inhibitory control over the limbic system
Heart-Spleen Deficiency / Qi Deficiency	Lethargy, fatigue, loss of appetite, lack of interest	Metabolic-Autonomic Type: 1. Energy metabolism impairment (ATP/mitochondrial function) 2. Autonomic nervous system dysfunction (HRV) 3. Insufficient activation of the reward circuit (striatum)	Enhancing Metabolism and Rhythm:Acupoint Selection: Primarily along the Stomach Meridian of Foot-Yangming and Spleen Meridian of Foot-Taiyin (eg., Zusanli ST36, Sanyinjiao SP6).Parameters: Stimulation mode designed to enhance vagal tone.Mechanism Objective: Elevate heart rate variability (HRV) and optimize brain energy metabolism.
Heart-Kidney Imbalance / Yin Deficiency	Severe insomnia, restlessness, hot flashes and night sweats, cognitive decline	Inflammation-Circadian Rhythm Disorder Pattern: 1. Neuroinflammation activation (IL-1 $\beta$ , IL-6, TNF- $\alpha$ ). 2. Abnormal circadian rhythm gene expression. 3. Fragmented sleep architecture.	Anti-inflammatory Focus with Rhythm Reshaping:Acupoint Selection: Primarily Shao Yin meridians (eg., Shenmen HT7, Taixi KI3).Parameters: Prefer low frequencies (eg., 2 Hz) to maximize anti-inflammatory effects.Mechanistic Targets: Suppress M1 polarization of microglia, regulate sleep homeostasis

From a medium-to-long-term development perspective, closed-loop EA systems represent a key direction for intelligent neuromodulation, but their realization depends on breakthroughs in two fundamental scientific challenges: state recognition and intervention response modeling. Currently, EA therapy predominantly operates in open-loop mode with fixed parameters, whereas precision neuromodulation is progressively shifting toward adaptive closed-loop systems.<sup>108</sup> Closed-loop systems can monitor signals reflecting emotional and neural states—such as specific EEG rhythms or heart rate variability—in real time and dynamically adjust stimulation parameters accordingly. For instance, abnormal theta wave activity associated with depression can be automatically addressed by applying specific-frequency stimulation to normalize neural oscillations. Real-time heart rate variability feedback can optimize autonomic nervous system balance.<sup>105</sup> This state-dependent modulation approach holds promise for upgrading EA therapy from static intervention to dynamic personalized treatment. Current research frameworks integrating brain imaging, neuromodulation, and artificial intelligence have established the theoretical foundation for constructing intelligent neuromodulation systems.<sup>109</sup>

Furthermore, integrating smartphone applications with wearable devices enables continuous passive collection of behavioral, vocal, sleep, and physiological metrics (eg., heart rate variability and skin conductance response), overcoming limitations in temporal resolution and subjectivity inherent to traditional questionnaire assessments.<sup>110</sup> These high-temporal-resolution digital phenotypic data can objectively map symptom trajectories, identify treatment-responsive subgroups, and deepen understanding of EA's mechanism of action. Clear and standardized reporting of multimodal data collection and analysis workflows is critical for ensuring research reproducibility and advancing clinical translation.<sup>107</sup>

## Establishing an Integrated Clinical Practice and Evidence Generation System

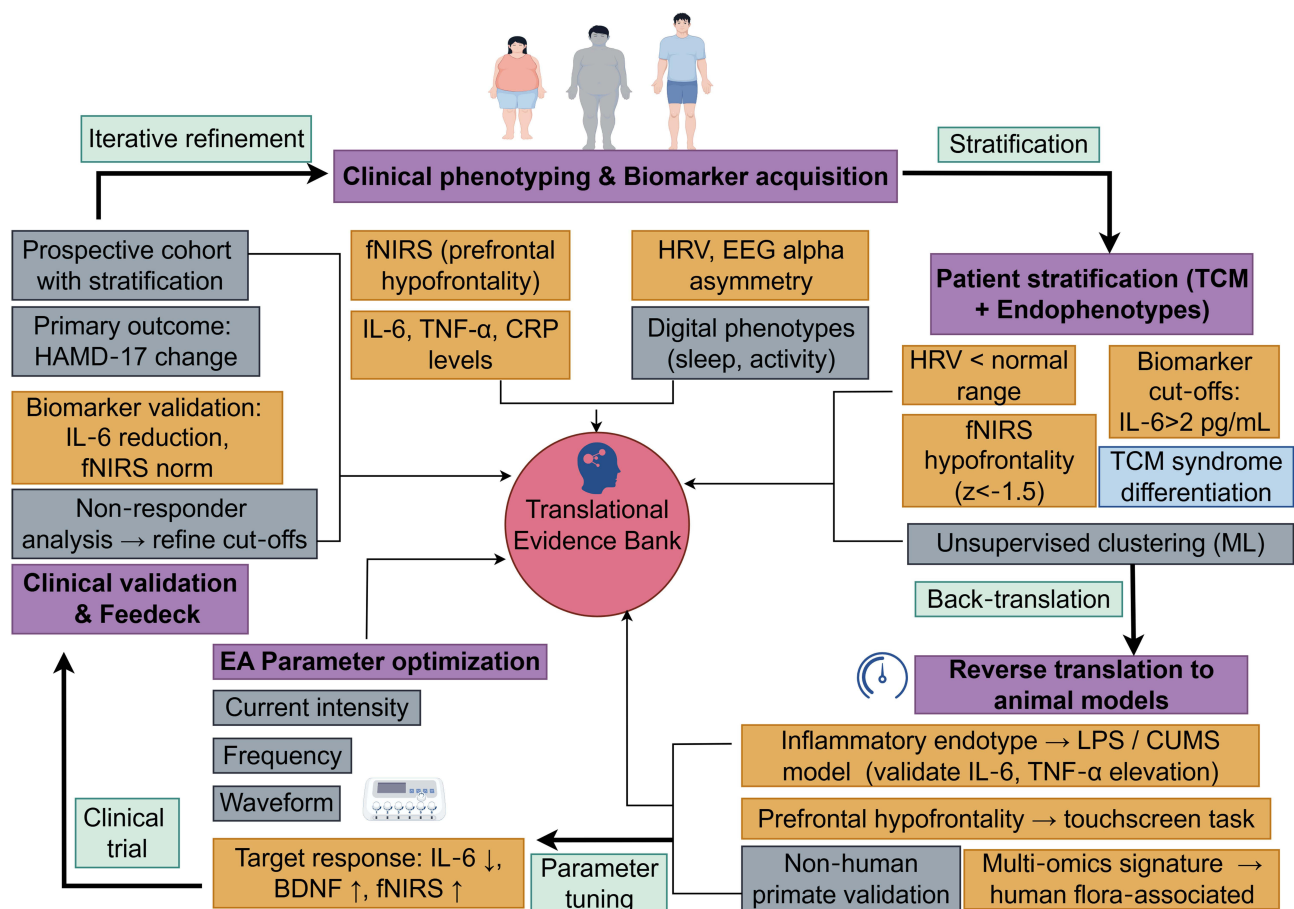
Establishing an integrated clinical practice and evidence generation system is central to bridging the gap between electroacupuncture research and clinical application for depression treatment. This system relies on forming multidisciplinary teams comprising psychiatrists, acupuncturists, neuroscientists, and methodological experts to jointly develop and implement standardized integrated treatment pathways. Existing research indicates that EA combined with pharmacotherapy can more effectively improve depressive symptoms and cognitive function in the short term and is associated with enhanced cortical activation.<sup>34</sup> Multidisciplinary collaboration facilitates the optimization of such combined protocols and ensures the standardization of intervention elements (eg., timing of intervention, stimulation

parameters, and treatment duration) and assessment tools (eg., HAMD-17 scale), thereby enhancing treatment consistency and research reproducibility.<sup>96</sup> Simultaneously, establishing national or international registries for EA treatment of depression patients is crucial. These registries should prospectively collect real-world data, including patient baseline characteristics, detailed stimulation parameters, combined treatment regimens, efficacy metrics, and adverse events. Such data can address the external validity limitations of randomized controlled trials, providing a more accurate reflection of clinical practice outcomes. Drawing on research paradigms from other disease domains,<sup>22,111,112</sup> registries can support comparative efficacy studies—such as evaluating differences between various parameter combinations or acupoint selections—and further validate the potential advantages of combining EA with antidepressant medications.<sup>113</sup>

## Shifting Basic Research Toward Clinical Relevance and Establishing a Reverse Translation Feedback Loop

Enhancing the clinical relevance of basic research on EA treatment for depression requires a strategic shift in research paradigms toward mechanism-driven approaches focused on overcoming translation barriers. First, complex animal models better reflecting the heterogeneity of human depression should be developed. The widely used CUMS model primarily simulates a single stress dimension.<sup>61,79</sup> Future studies should construct “double-hit” models integrating early-life and adult stress, or endophenotypic models targeting specific neural circuit abnormalities. This would better simulate patient subtypes and comorbid conditions (eg., depression with chronic pain), providing a more reliable predictive platform for precision translation targeting specific populations.<sup>78</sup> Second, advanced neurotechnologies should be employed to elucidate the neural mechanisms underlying clinically effective acupoint combinations. For instance, the mechanism of action for the widely used Hegu-Tai Chong combination—clinically proven to possess antidepressant effects<sup>64</sup>—remains to be clarified at the circuit level. Future research should employ multi-channel neural recording and optogenetics to observe and manipulate the effects of acupoint stimulation on emotion-related brain regions (eg., prefrontal cortex, hippocampus, amygdala) in real-time within complex animal models. This approach will reveal the synergistic mechanisms of acupoint combinations at the neural circuit level, providing direct theoretical support for optimizing clinical protocols.<sup>114</sup> Finally, targeted translational research projects should be established to directly address cross-species extrapolation challenges. For instance, parallel studies in animal models and depression patients could employ identical electroacupuncture parameters while measuring consistent biomarker panels—including brain-derived neurotrophic factor, inflammatory markers, and neuroimaging indices.<sup>115</sup> By systematically comparing the consistency of dynamic responses across these indicators in different species, biomarkers bridging basic research and clinical studies can be identified—such as astrocytic alterations reversible by electroacupuncture in both chronic stress models and patients.<sup>79</sup> This validation pathway based on cross-species consistency holds promise for accelerating the translation of laboratory discoveries into clinical validation.

To make the proposed mechanism-driven precision translation framework actionable, it is necessary to specify how clinical data inform the selection of animal models during the reverse translation phase. We propose that the entry points into the closed loop are defined by biomarker-based stratification dimensions derived from clinical studies. First, neuroimaging biomarkers (eg., fNIRS) can serve as direct entry points. If a clinical study identifies a patient subgroup with attenuated prefrontal cortex activation during an affective task, this feature can be back-translated to guide the selection of animal models exhibiting similar prefrontal hypofunction, such as reverse-translated rodent touchscreen behavioral tasks. If resting-state fMRI reveals abnormal default mode network connectivity, chronic stress-induced rodent models with analogous circuit-level dysconnectivity can be prioritized. Second, peripheral inflammatory biomarkers offer another well-defined entry point. If clinical findings show elevated pro-inflammatory cytokines (IL-6, TNF- $\alpha$ , IL-1 $\beta$ ) in a subset of depressed patients, these individuals may respond better to EA protocols targeting anti-inflammatory pathways. Accordingly, we suggest that reverse translation should select animal models that recapitulate the inflammatory endophenotype, for example, lipopolysaccharide (LPS)-induced models or chronic unpredictable mild stress (CUMS) models, with spontaneously depressive-like non-human primates serving as an advanced validation platform. The validation criterion we propose is cross-species consistency: if EA with specific parameters suppresses inflammatory markers in both the clinically defined inflammatory subgroup and the corresponding animal model, the reverse translation loop can be considered empirically supported. Third, multi-omics biomarkers (metabolomic, proteomic, transcriptomic) can also serve as entry points. If a clinical multi-omics analysis



**Figure 3** Operational closed-loop precision translation framework. The framework comprises five nodes arranged in a closed loop. Bold arrows indicate the main closed-loop flow of the precision translation pathway, connecting the nodes in the following order: Node 1 (Phenotyping) → Node 2 (Stratification) → Node 3 (Reverse translation) → Node 4 (Parameter optimization) → Node 5 (Clinical validation) → back to Node 1. Thin arrows point from each node to the central Translational Evidence Bank, representing the deposition of evidence generated at each step (e.g., biomarker data, stratification criteria, animal model validation, optimized parameters, clinical outcomes) for knowledge accumulation and iterative refinement. Node 1 collects measurable biomarkers including fNIRS, IL-6, HRV, and digital data. Node 2 integrates TCM syndromes (blue) with biomarker cut-offs (Orange). Node 3 selects corresponding animal models such as LPS/CUMS for inflammation, touchscreen tasks for prefrontal dysfunction, and multi-omics models. Node 4 tunes EA parameters (frequency 2-100 Hz, current 1-3 mA, pulse width 0.2-0.5 ms, waveform) to achieve targeted biomarker responses (IL-6 reduction, BDNF increase). Node 5 evaluates outcomes using HAMD-17, biomarker changes, and non-responder analysis. Color coding follows the same scheme as in Figure 2.

identifies a conserved metabolic pathway associated with treatment response, this finding can be back-translated using a human flora-associated animal model. Transcriptomic signatures may guide the development of corresponding genetically modified animal models.

In summary, the entry points for closed-loop reverse translation are operationally defined by measurable biomarker dimensions across neuroimaging, inflammatory, and multi-omics domains, each linked to specific animal model selection strategies. This operational framework ensures that reverse translation becomes a hypothesis-driven, empirically testable process. The mechanism-driven EA precision conversion framework is illustrated in Figure 3.

## Conclusion

Research on EA for treating depression is transitioning from traditional efficacy validation to a critical phase of mechanism-driven precision translation. However, the existing evidence base remains significantly constrained: current supporting evidence primarily derives from animal studies and small-sample clinical trials, whose results exhibit uncertain generalizability across species, study designs. Furthermore, distinct neuro-regulatory patterns may underlie different mental illnesses—and even within the same diagnostic category—rendering stable, consistent clinical effects difficult to achieve with a single intervention. Against this backdrop, the translational impasse of EA does not stem from

insufficient underlying mechanisms but rather manifests in multiple “disconnects” between preclinical mechanism discovery and clinical application. These include risks of mechanism extrapolation due to species differences, simplified experimental protocols failing to reflect the clinical complexity of acupoint combinations and individualized syndrome differentiation, lack of clear biological definitions and quantitative standards for therapeutic “doses”, and absence of reliable bridging biomarkers linking molecular mechanisms to subjective symptom improvement.

To address these challenges, this paper proposes a “mechanism-driven precision translation pathway” as a conceptual solution. This pathway emphasizes a verifiable mechanism chain as its core, enabling biologically anchored intervention strategies by systematically mapping TCM syndrome differentiation to modern biological phenotypes; enhancing controllability and reproducibility of stimulation parameters through standardized and intelligent neuromodulation technologies; and strengthening external validity and generalizability of research findings via multidisciplinary research and clinical practice systems. It should be noted that so-called “precision EA” remains primarily in the conceptual development and exploratory phase, with its feasibility and clinical value still contingent upon further validation through high-quality prospective studies.

Overall, future EA research in depression should shift from empirical exploration centered on symptom improvement toward problem-driven research designs oriented toward translational challenges. Through systematic optimization addressing disease heterogeneity, mechanism verifiability, and objective outcome measures, EA may gradually evolve from an empirically based adjunctive intervention into a precision neuromodulation strategy with defined mechanisms, optimizable parameters, and predictable efficacy. This progression will ultimately generate high-quality evidence-based data sufficient to support its clinical positioning.

Beyond scientific rigor, the widespread adoption of a standardized, mechanism-driven EA framework carries substantial economic and public health implications. By reducing inter-study heterogeneity and improving treatment reproducibility, such a framework would minimize wasteful duplication of research efforts and accelerate the generation of actionable evidence. From a health economics perspective, a precisely targetable EA could shorten treatment duration, lower the burden of polypharmacy, and reduce costly adverse events associated with long-term antidepressant use. On a population level, establishing EA as a reimbursable, evidence-based intervention for depression would expand treatment options, particularly in regions where access to psychiatric care is limited. We therefore call upon researchers, clinical societies, and health policy makers to prioritize the development of standardized EA protocols, integrate them into clinical practice guidelines, and invest in implementation science to translate this framework into real-world public health gains.

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## Disclosure

The authors report no conflicts of interest in this work.

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