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REVIEW

Pathophysiological Insights and Multimodal Interventions in Chronic Tinnitus, Anxiety, and Sleep Disorders

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Abstract: Chronic subjective tinnitus (CST) is frequently accompanied by anxiety and sleep disturbances, together forming a self-reinforcing cycle that significantly impairs patients' quality of life and complicates clinical management. This narrative review aims to elucidate the shared pathophysiological mechanisms underlying these interrelated conditions and to evaluate current multidisciplinary therapeutic strategies. Relevant literature was identified through a targeted search of PubMed, Scopus, and Web of Science databases, focusing on recent clinical and translational studies addressing the neurobiology and treatment of CST, anxiety, and sleep disorders. Emerging evidence highlights the involvement of maladaptive auditory-limbic network connectivity, neurotransmitter imbalances (eg, GABA, glutamate, serotonin), dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, autonomic dysfunction, and disruption of circadian and sleep–wake regulatory pathways in the persistence and mutual reinforcement of these symptoms. Multimodal interventions—including cognitive behavioral therapy, sound therapy, pharmacotherapy, neuromodulation techniques, and targeted sleep interventions—have demonstrated synergistic benefits, particularly when tailored to individual neurobiological profiles. From a clinical perspective, recognizing the bidirectional interactions among tinnitus, affective dysregulation, and sleep impairment is essential for developing effective, integrative treatment frameworks. This review underscores the necessity of personalized, mechanism-informed therapeutic approaches and outlines key directions for future research.

Keywords: chronic tinnitus, anxiety, sleep disturbance, cognitive behavioral therapy, neuromodulation

Introduction

Chronic subjective tinnitus (CST), characterized by the persistent perception of sound in the absence of an identifiable external source, affects an estimated 10–15% of the global adult population, with a substantial proportion experiencing significant functional impairment.[1] Beyond the auditory perception itself, a considerable body of literature has underscored the high prevalence of psychiatric and behavioral comorbidities in tinnitus patients, most notably anxiety disorders and sleep disturbances.[2,3] These conditions often coexist and interact synergistically, contributing to a self-reinforcing pathological cycle that exacerbates symptom severity, diminishes quality of life, and complicates therapeutic management.[4]

Mounting clinical and neurobiological evidence suggests that the interplay between tinnitus, anxiety, and sleep disturbance is not incidental but underpinned by shared pathophysiological mechanisms.[5] Tinnitus may elicit maladaptive emotional responses such as hypervigilance, catastrophizing, and autonomic hyperarousal, which facilitate the development of anxiety symptoms and disrupt sleep continuity.[6] In turn, anxiety can heighten the attentional salience and cortical representation of tinnitus-related signals, while chronic sleep impairment is known to compromise affective regulation, exacerbate sensory hypersensitivity, and potentiate the perception of tinnitus.[5] The resultant loop—wherein each

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condition aggravates the others—constitutes a complex neurobehavioral phenotype marked by cortical dysrhythmia and heightened central gain.

Neuroimaging and neurophysiological studies have revealed altered functional and structural connectivity between the auditory cortex and key limbic and paralimbic regions, including the amygdala, anterior cingulate cortex, and hippocampus.[7,8] Additionally, dysregulation of neurotransmitter systems—particularly GABAergic inhibition, glutamatergic excitation, and serotonergic modulation—has been implicated in the amplification of tinnitus-related distress and sleep dysfunction.[9] Concomitant perturbations in hypothalamic-pituitary-adrenal (HPA) axis activity and autonomic nervous system tone further suggest the involvement of systemic stress-response networks in perpetuating this symptom triad.[10] Importantly, disruptions in sleep–wake regulatory circuits, including the suprachiasmatic nucleus–pineal axis and melatonin signaling pathways, may also contribute to the chronicity and refractoriness of tinnitus in susceptible individuals.[11]

Given the multifaceted nature of CST and its associated comorbidities, unimodal interventions frequently yield suboptimal outcomes. Increasingly, multidisciplinary treatment (MDT) frameworks have been advocated, incorporating cognitive-behavioral therapy (CBT), sound and habituation therapies, pharmacological agents targeting affective and sleep regulation, neuromodulatory techniques (eg, repetitive transcranial magnetic stimulation [rTMS], transcranial direct current stimulation [tDCS]), mindfulness-based approaches, and behavioral sleep interventions.[12] These integrative strategies aim to address the underlying neurobiological and psychological mechanisms, promote adaptive coping, and disrupt the cyclical reinforcement among tinnitus, anxiety, and sleep dysfunction.

Despite growing interest in the associations between tinnitus, anxiety, and sleep disturbances, most existing studies have examined these conditions in isolation, with limited attention to their shared neurobiological mechanisms or their complex bidirectional interactions. This gap in the literature has hindered the development of integrated treatment strategies that can effectively address the full spectrum of symptoms experienced by affected individuals. To bridge this gap, the present narrative review synthesizes current evidence on the overlapping neurophysiological and neuroendocrine mechanisms underlying this triad, discusses existing and emerging multidisciplinary therapeutic approaches, and proposes a conceptual framework to guide personalized, mechanism-informed clinical management and future research.

Methods

This narrative review was conducted to synthesize recent findings on the neurobiological mechanisms and multidisciplinary interventions associated with chronic tinnitus, anxiety, and sleep disturbances. A literature search was performed using three major electronic databases: PubMed, Scopus, and Web of Science. The search covered publications from January 2015 to March 2025 to ensure inclusion of both foundational and contemporary studies.

Search terms included combinations of the following keywords: “chronic tinnitus”, “anxiety”, “sleep disturbance”, “insomnia”, “neurobiology”, “neurophysiology”, “cognitive behavioral therapy”, “neuromodulation”, and “multidisciplinary treatment”. Boolean operators (AND/OR) were used to refine the search.

Studies were included if they were peer-reviewed articles in English that explored the pathophysiological mechanisms, clinical associations, or therapeutic interventions related to any or all of the three conditions. Both clinical and translational studies were considered. Editorials, conference abstracts, and non-English publications were excluded.

Although the review was narrative in nature and not conducted according to PRISMA guidelines, we applied a structured approach to screen the literature and select relevant studies based on relevance, methodological quality, and clinical applicability.

The Interplay Between Tinnitus, Anxiety, and Sleep Disturbances

The clinical co-occurrence of CST, anxiety, and sleep disturbances is well-documented, yet their interplay extends beyond mere epidemiological association. A growing body of neuropsychological and neurophysiological research supports the existence of a bidirectional and mutually reinforcing relationship among these conditions, characterized by shared neural substrates, dysregulated emotional processing, and maladaptive cognitive-affective feedback loops.[13] This section delineates the primary pathways through which tinnitus contributes to anxiety, how anxiety exacerbates tinnitus perception, and the bidirectional relationship between sleep disturbances and both phenomena (Figure 1).

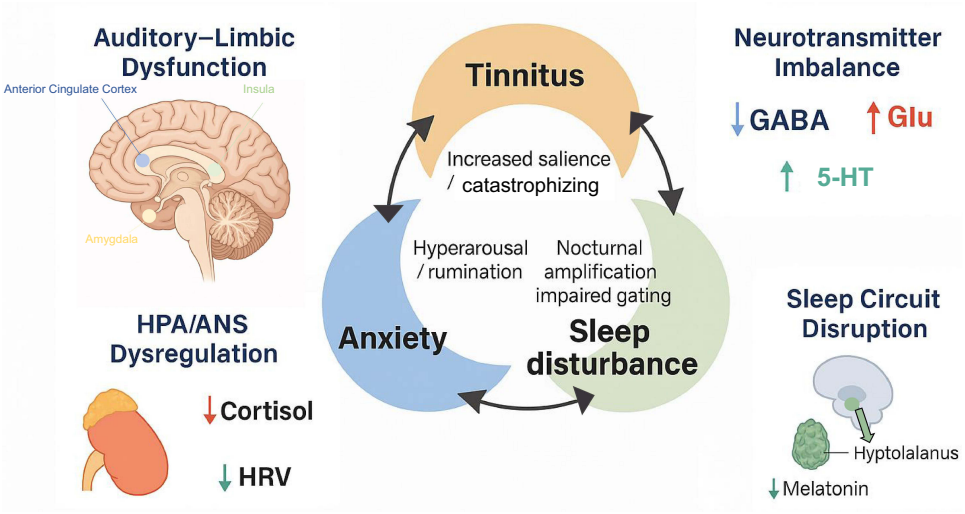

Figure 1 Neurobiological Mechanisms Linking Tinnitus, Anxiety, and Sleep Disturbance. Schematic representation of the reciprocal interactions among tinnitus, anxiety, and sleep disturbance, forming a maladaptive feedback loop. Tinnitus heightens emotional vigilance and distress, triggering anxiety; anxiety induces hyperarousal and rumination, leading to sleep disruption; in turn, poor sleep amplifies tinnitus perception by impairing sensory gating and cortical inhibition. Four neurobiological mechanisms underlie this triad: auditory–limbic dysfunction, HPA axis and autonomic nervous system (ANS) dysregulation, neurotransmitter imbalance, and disrupted sleep regulation circuits.
Abbreviations: HPA, Hypothalamic–Pituitary–Adrenal axis; ANS, Autonomic Nervous System; HRV, Heart Rate Variability; GABA, Gamma-Aminobutyric Acid; Glu, Glutamate; 5-HT, 5-Hydroxytryptamine; ↓, Decreased; ↑, Increased.

Tinnitus-Induced Anxiety and Hypervigilance

CST is not merely an auditory phenomenon but a multidimensional experience, frequently accompanied by profound emotional distress. Tinnitus-induced anxiety is mediated by maladaptive appraisal mechanisms, wherein the persistent perception of sound is interpreted as threatening or uncontrollable, leading to catastrophizing and hypervigilance.[14] Studies utilizing validated instruments such as the Tinnitus Catastrophizing Scale (TCS) and the Tinnitus Handicap Inventory (THI) have demonstrated strong correlations between catastrophic thinking, attentional bias, and anxiety severity.[15]

Neurobiologically, tinnitus-related distress involves heightened functional connectivity between the auditory cortex and limbic/paralimbic structures, including the amygdala, anterior cingulate cortex (ACC), insula, and orbitofrontal cortex.[16] Resting-state fMRI studies have shown that individuals with distressing tinnitus exhibit aberrant activity within the default mode network (DMN) and salience network, implicating impaired emotional salience attribution and failure of habituation.[17] Furthermore, task-based EEG analyses indicate increased theta and gamma band activity in frontotemporal and cingulo-opercular regions, reflecting hypervigilance and sustained attention to the tinnitus percept.[18]

This neural hyper-responsivity is compounded by increased sympathetic arousal and dysregulation of the HPA axis, with elevated cortisol levels observed in tinnitus patients experiencing anxiety.[19] The result is a state of chronic physiological arousal and emotional sensitization that reinforces both the perception of tinnitus and the associated anxiety.

Anxiety-Aggravated Tinnitus Perception

Emerging evidence suggests that anxiety not only coexists with tinnitus but actively contributes to its perceptual and affective amplification through neuroplastic and neuromodulatory mechanisms.[20] Functional neuroimaging has revealed that patients with comorbid anxiety display enhanced activation in the anterior insula and dorsomedial prefrontal cortex —regions implicated in interoception, emotional appraisal, and anticipatory threat processing.[21] These areas are involved in top-down modulation of auditory perception and may facilitate heightened awareness and negative valence attribution to tinnitus signals.[22]

Anxiety alters thalamocortical and corticolimbic communication, increasing excitatory neurotransmission while suppressing GABAergic inhibition in auditory and emotional circuits.[23] This shift contributes to central gain

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enhancement and decreased sensory gating, both of which have been observed in tinnitus sufferers with high anxiety levels.[24] Animal models further support this mechanism, with stress-induced neuroplasticity in the medial geniculate body and auditory cortex shown to increase tinnitus-like behaviors.[25]

Moreover, longitudinal studies have shown that baseline anxiety levels predict the persistence and worsening of tinnitus-related distress over time, even when auditory thresholds remain stable, emphasizing the role of affective circuits over pure sensory input.[26] These findings underscore the importance of addressing anxiety not merely as a secondary symptom, but as a driver of tinnitus chronification and central sensitization.

Sleep Disturbances as Both Cause and Consequence

Sleep dysfunction is among the most frequently reported complaints in individuals with tinnitus, with up to 70% of patients experiencing insomnia symptoms.[27] Recent polysomnographic and actigraphic studies have demonstrated that tinnitus patients exhibit prolonged sleep latency, reduced sleep efficiency, increased nocturnal awakenings, and diminished slow-wave activity.[28,29] These alterations are often independent of hearing loss severity, suggesting a central mechanism.

From a mechanistic standpoint, tinnitus-related sleep disturbance is attributed to an inability to disengage from internally generated auditory stimuli in the absence of external sound masking during night-time.[30] This phenomenon is exacerbated by hyperarousal states driven by amygdala overactivation and autonomic dysregulation. Simultaneously, sleep deprivation has been shown to elevate cortical excitability and reduce inhibition in auditory regions, further increasing the salience and intrusiveness of tinnitus.[31] Neuroendocrine findings reveal altered melatonin secretion patterns in patients with tinnitus-associated insomnia, implicating circadian rhythm disruption as both a consequence and contributor.[32]

Importantly, insomnia has also been identified as an independent risk factor for emotional dysregulation and increased tinnitus severity, with poor sleep quality mediating the relationship between stress and tinnitus-related distress.[27] Cognitive models posit that anticipatory anxiety about sleep failure can intensify tinnitus perception at night, promoting a feedback loop that maintains and escalates the symptom triad.

Neurobiological Mechanisms

Dysfunctional Auditory-Limbic System Connectivity

A core hypothesis in tinnitus pathophysiology posits that persistent auditory phantom perception results from maladaptive neuroplastic changes within central auditory pathways and their coupling with limbic circuits.[33] Functional MRI and magnetoencephalography (MEG) studies have demonstrated increased resting-state functional connectivity between the primary and secondary auditory cortices (eg, Heschl's gyrus, planum temporale) and emotion-processing regions including the amygdala, ACC, insula, and orbitofrontal cortex.[34–36]

Notably, tinnitus patients with significant affective comorbidities show hyperactivation in the anterior insula and ACC, consistent with enhanced interoceptive salience attribution and sustained autonomic arousal.[37] DTI-based studies further report microstructural abnormalities along the uncinate fasciculus and cingulum bundle, key white matter tracts linking auditory and limbic regions.[38,39] Graph-theoretical metrics reveal increased network centrality and reduced modularity in tinnitus-relevant subnetworks, supporting the concept of overintegration between auditory processing and emotional reactivity.[40]

This dysfunction underlies the failure of perceptual habituation and reinforces tinnitus-related distress, even in the absence of overt hearing loss. Such findings support the limbic-cortical dysregulation model,[41] which posits that a "gating failure" between subcortical and limbic structures contributes to tinnitus persistence.

Neurotransmitter Imbalances

GABA is the principal inhibitory neurotransmitter in the mammalian brain and plays a crucial role in regulating neural excitability and sensory gating across auditory and limbic circuits.[42] In CST, a consistent reduction in GABAergic tone has been demonstrated across both animal and human studies.[43] Electrophysiological recordings from tinnitus models

show decreased GABA-mediated inhibition in the dorsal cochlear nucleus, inferior colliculus, and auditory cortex, leading to increased spontaneous firing and neural synchrony—neurophysiological hallmarks of tinnitus-related central gain enhancement.[43]

Magnetic resonance spectroscopy (MRS) studies in humans further support these findings, revealing reduced GABA concentrations in the primary auditory cortex, ACC, and medial prefrontal cortex in tinnitus patients, especially those with high levels of emotional distress or insomnia.[44] This reduction in inhibitory neurotransmission may underlie not only the persistence of the phantom percept but also the failure to habituate and disengage from tinnitus, particularly during quiet nighttime conditions.[45]

Serotonin (5-HT) modulates a wide range of functions relevant to tinnitus, including emotional regulation, sensory gating, and sleep homeostasis.[46] Evidence from positron emission tomography (PET) and post-mortem studies indicates reduced serotonergic transmission and decreased serotonin transporter (SERT) binding in tinnitus patients, particularly within the dorsal raphe nuclei, ACC, and limbic structures.[47,48] This serotonergic deficit is analogous to neurochemical patterns seen in mood and anxiety disorders and may contribute to the heightened emotional reactivity and impaired stress resilience observed in tinnitus sufferers.

Furthermore, serotonin interacts functionally with both GABA and glutamate systems, facilitating inhibitory tone and restraining excitatory overdrive.[49,50] Serotonin depletion may thus exacerbate GABAergic deficits and potentiate glutamatergic plasticity in tinnitus-related networks.[51] Clinically, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have shown inconsistent efficacy in reducing tinnitus loudness, but may provide benefit in reducing associated anxiety and improving sleep, particularly in patients with prominent affective symptoms.[52]

Dysregulation of HPA Axis and Autonomic Nervous System

The persistence and exacerbation of CST are not solely mediated by auditory and emotional circuits, but also by dysregulation of systemic stress-response systems—namely, the HPA axis and the autonomic nervous system (ANS).[53] These systems function in close coordination to maintain homeostasis in the face of internal and external stressors. In individuals with tinnitus, particularly those with comorbid anxiety and sleep disturbance, chronic activation of the HPA axis and sympathetic dominance within the ANS create a pathophysiological milieu that promotes heightened arousal, emotional dysregulation, and impaired sleep initiation and maintenance.[54]

The HPA axis represents the central hormonal pathway for coordinating neuroendocrine responses to psychological stress.[55] Under acute stress, hypothalamic release of corticotropin-releasing hormone (CRH) stimulates the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which in turn drives cortisol release from the adrenal cortex.[56] In healthy systems, this axis is self-limiting via negative feedback. However, in CST, this regulatory feedback loop appears disrupted.[55]

Multiple studies have demonstrated elevated basal cortisol levels, flattened diurnal cortisol rhythms, and altered cortisol awakening responses (CAR) in tinnitus patients, especially those reporting high tinnitus-related distress, generalized anxiety, or comorbid insomnia.[57] Salivary cortisol and hair cortisol concentrations have emerged as robust biomarkers of chronic HPA activation, and both correlate positively with subjective tinnitus handicap scores.[58]

At the neural level, hyperactivity of the paraventricular nucleus (PVN) of the hypothalamus—an HPA axis regulator—has been observed via advanced functional imaging in tinnitus sufferers under stress-inducing paradigms.[55] This hyperactivity may result in persistent glucocorticoid exposure, which can impair hippocampal feedback inhibition, promote amygdala sensitization, and disrupt sleep–wake regulatory mechanisms, thereby closing the loop between stress, arousal, and sleep dysfunction.[59]

In parallel to HPA axis hyperactivity, CST patients often exhibit signs of autonomic nervous system dysregulation, characterized by increased sympathetic nervous system (SNS) activity and reduced parasympathetic (vagal) tone.[60] This imbalance contributes to the somatic manifestations of anxiety (eg, palpitations, muscle tension) and creates a physiological state of hyperarousal, which is incompatible with sleep initiation and maintenance.[61]

Several studies utilizing heart rate variability (HRV) analysis—a validated index of autonomic function—have reported decreased high-frequency (HF) power and increased low-frequency (LF) to HF ratios in tinnitus patients with

high anxiety and poor sleep quality, consistent with vagal withdrawal and sympathetic predominance.[62] Reduced HRV has also been linked to increased cortical excitability and reduced sensory filtering, mechanisms relevant to the central gain theory of tinnitus.[63]

Furthermore, emerging evidence suggests bidirectional interactions between the ANS and auditory-limbic circuits. For example, the nucleus tractus solitarius (NTS), a brainstem center integrating baroreceptor and visceral afferent signals, projects to both the amygdala and hypothalamus, enabling stress signals to modulate auditory salience and emotional reactivity.[64] Chronic autonomic dysregulation may thereby sensitize auditory perception via heightened interoceptive awareness and reinforce distress-related processing of the tinnitus percept.[65]

Together, HPA axis overactivation and autonomic imbalance form the physiological substrate of sustained hyperarousal, which perpetuates both tinnitus-related emotional distress and sleep disruption. The continuous activation of these systems prevents cognitive-emotional disengagement from tinnitus at night, contributing to prolonged sleep latency, frequent nocturnal awakenings, and non-restorative sleep—symptoms commonly reported by affected individuals. These sleep deficits, in turn, impair top-down inhibitory control over the limbic system, further exacerbating tinnitus salience and anxiety, creating a reciprocally reinforcing loop.

This perspective aligns with the allostatic load model, wherein chronic exposure to stress-related neuroendocrine activity exerts cumulative wear on regulatory systems, predisposing individuals to multi-system dysregulation.[66] Tinnitus, in this model, becomes not only a symptom but also a driver of allostatic overload, particularly when coexisting with psychological and sleep-related disturbances.

In addition to classical neuroendocrine dysregulation, recent studies have begun to explore the role of systemic calcium homeostasis in anxiety-related sleep disturbances. One cross-sectional study in patients with generalized anxiety disorder found that elevated parathyroid hormone (PTH) levels and decreased serum vitamin D were significantly associated with higher insomnia severity and anxiety symptoms.[67] These findings suggest that calcium signaling, possibly through its effects on neuronal excitability and autonomic regulation, may contribute to the maintenance of hyperarousal states that disrupt sleep continuity. Given that calcium channels also modulate synaptic transmission and circadian rhythm-related gene expression, disturbances in calcium homeostasis may represent a novel mechanistic contributor to the tinnitus–anxiety–sleep triad.[68,69] Future studies integrating neurochemical, neuroendocrine, and mineral metabolism markers may yield a more comprehensive model of pathophysiological interactions.

Sleep Regulation Circuits Involved

The regulation of sleep and circadian rhythms is orchestrated by a distributed neural system centered on the hypothalamus, particularly the suprachiasmatic nucleus (SCN)—the principal circadian pacemaker—and the ventrolateral preoptic nucleus (VLPO), which promotes sleep onset via GABAergic inhibition of arousal centers.[70] The SCN receives photic input from intrinsically photosensitive retinal ganglion cells and modulates melatonin secretion through a multisynaptic pathway culminating in the pineal gland.[71] This SCN–pineal axis governs the timing of sleep propensity and synchronizes endogenous circadian rhythms with the external light–dark cycle.[72]

In tinnitus patients, this axis appears to be functionally compromised. Polysomnographic and actigraphic data consistently demonstrate prolonged sleep latency, reduced sleep efficiency, fragmented slow-wave sleep, and increased wake after sleep onset (WASO).[73] Functional imaging studies have revealed altered SCN connectivity with thalamic, limbic, and cortical regions in tinnitus patients with comorbid insomnia, suggesting impaired circadian signaling beyond melatonin alone.[74] Concurrently, reduced nocturnal melatonin levels have been observed in both plasma and saliva, and are inversely correlated with tinnitus-related distress and subjective sleep quality.[75]

Melatonin plays a dual role in both circadian regulation and neurophysiological stabilization. In addition to modulating sleep–wake cycles, melatonin exerts GABAergic facilitation, anti-inflammatory, and neuroprotective effects, which may modulate auditory-limbic hyperactivity.[76,77] Exogenous melatonin administration has shown modest efficacy in improving tinnitus-associated insomnia in clinical trials, particularly in individuals with delayed sleep phase or anxiety comorbidity.[78] Importantly, these effects appear more pronounced in subjective measures of distress and sleep initiation than in objective tinnitus loudness, supporting a neuromodulatory rather than auditory-suppressive mechanism.

At a systems level, the interaction between sleep–wake circuits and limbic arousal systems is crucial to understanding the perpetuation of the tinnitus–anxiety–sleep disturbance triad.[7] The ascending arousal system, involving the locus coeruleus, dorsal raphe, and basal forebrain, is functionally overactive in tinnitus patients, contributing to nocturnal hyperarousal and sleep fragmentation.[79] These arousal-promoting nuclei receive reciprocal projections from limbic regions and are sensitive to stress, creating a bidirectional loop whereby emotional dysregulation interferes with sleep architecture and, in turn, sleep deprivation exacerbates emotional and sensory dyscontrol.[80]

Furthermore, recent models posit that insomnia may act as a sensory amplifier, increasing thalamocortical responsivity to internally generated stimuli such as tinnitus.[81] Sleep deprivation has been shown to reduce inhibitory thalamic gating and enhance cortical excitability in auditory and salience networks.[82] This neurophysiological environment favors the intrusiveness of the tinnitus percept and impairs habituation, thereby sustaining a vicious cycle of hypervigilance, emotional reactivity, and sleep disruption.[83]

Multidisciplinary Interventions

Given the multidimensional pathophysiology of chronic subjective tinnitus—encompassing perceptual, emotional, and arousal domains—monotherapies targeting a single symptom cluster have shown limited efficacy.[84] The frequent co-occurrence of tinnitus with affective dysregulation and insomnia underscores the need for a multimodal therapeutic framework capable of addressing shared transdiagnostic mechanisms.[85] Recent integrative models advocate for multidisciplinary interventions (MDIs), combining cognitive-behavioral, auditory, pharmacologic, neuromodulatory, and sleep-targeted strategies to achieve synergistic and durable symptom control. These approaches are increasingly informed by network-level neuroscience, biomarker-guided patient stratification, and transdiagnostic treatment design. In this section, we delineate the principal components of MDI paradigms, critically examining their theoretical underpinnings, clinical implementation, and evolving innovations in the management of tinnitus with comorbid anxiety and sleep disturbance (Table 1).

Cognitive Behavioral Therapy (CBT) and CBT for Insomnia (CBT-I)

CBT, including its sleep-specific derivative CBT-I, constitutes a central psychotherapeutic modality for managing tinnitus-associated functional impairment, particularly in individuals exhibiting significant affective dysregulation and hyperarousal-mediated sleep fragmentation.[86] Rather than targeting the acoustic characteristics of tinnitus, CBT intervenes on cognitive-affective processing loops that perpetuate symptom intrusiveness, distress reactivity, and dysfunctional attentional allocation.[87]

Standard CBT protocols for tinnitus emphasize cognitive restructuring of tinnitus-related maladaptive beliefs, attentional disengagement techniques to disrupt selective auditory monitoring, and graded behavioral exposure to reduce tinnitus-related avoidance patterns.[88] CBT-I, frequently co-administered in tinnitus populations with comorbid insomnia, incorporates empirically derived behavioral interventions—such as sleep restriction therapy, stimulus control, and circadian resynchronization—aimed at restoring homeostatic and chronobiological sleep regulation.[89]

From a mechanistic perspective, CBT exerts therapeutic effects by attenuating negative appraisal bias, modulating prefrontal-limbic circuitry associated with threat salience, and restoring top-down inhibitory control over internally generated perceptual phenomena.[90] Neuroimaging evidence suggests that CBT may normalize hyperactivity within the anterior cingulate cortex and medial prefrontal areas, regions implicated in tinnitus-related distress processing.[91] In the context of CBT-I, successful interventions have been linked to enhanced parasympathetic tone and reduced nocturnal cortisol reactivity, suggesting systemic regulation of the hyperarousal phenotype frequently observed in tinnitus-insomnia comorbidity.[92]

Randomized controlled trials and meta-analyses consistently demonstrate the efficacy of CBT in reducing tinnitus-related distress, improving sleep quality, and enhancing emotional resilience, with effect sizes ranging from moderate to large across various clinical subgroups.[93,94] Importantly, outcomes are independent of changes in tinnitus loudness, underscoring the relevance of perceptual modulation rather than acoustic suppression.[95] CBT-I, when administered adjunctively, has shown additive benefits in sleep continuity, latency, and subjective sleep quality, with downstream

Table 1 Summary of Multidisciplinary Interventions for Tinnitus with Comorbid Anxiety and Sleep Disturbance

Intervention Modality	Core Targets	Representative Methods	Evidence Summary	Mechanistic Rationale	Limitations
Cognitive Behavioral Therapy (CBT) and CBT-I	Cognitive distortions, hypervigilance, sleep misregulation	Cognitive restructuring, sleep restriction, attention retraining	Effective in reducing distress and insomnia; durable across follow-up (Established)	Targets cognitive-affective loops sustaining tinnitus distress and hyperarousal; improves top-down inhibitory control and sleep regulation.	Requires patient engagement; effect size reduced in severe depression or cognitive rigidity; therapist availability may limit access.
Sound Therapy & Tinnitus Retraining Therapy (TRT)	Perceptual salience, habituation, auditory-limbic coupling	Broadband noise, notched music, directive counseling	Modest effects on loudness and distress; enhanced with counseling (Established)	Reduces perceptual contrast and promotes habituation via decreased auditory-limbic coupling; modulates central gain and cortical plasticity.	Limited effect on tinnitus loudness; requires prolonged and consistent use; mechanisms still debated; not effective for all subtypes.
Pharmacological and Neuromodulatory Therapies	Neurochemical imbalance, hyperarousal, distress regulation	SSRIs, GABAergic agents, melatonin, NMDA antagonists	Mixed efficacy; promising in selected phenotypes with comorbidity (Adjunctive /Mixed evidence)	Modulates neurotransmission and stress reactivity; enhances inhibitory tone or attenuates excitatory overdrive in vulnerable neural networks.	Heterogeneous response profiles; side effects; lack of tinnitus-specific indication; long-term effects poorly characterized.
Neuromodulation Techniques (rTMS, tDCS)	Cortical hyperexcitability, network dysrhythmia	1 Hz rTMS to auditory cortex, anodal tDCS over DLPFC	Short-term benefit in subsets; response variability high (Emerging / Experimental)	Recalibrates dysfunctional network excitability and oscillatory patterns; engages plasticity in auditory and prefrontal circuits.	Response variability; lack of standardized protocols; limited durability; mechanism of action not fully elucidated.
Integrated and Precision-Based Care Models	Multidomain symptom profiles, biomarker-driven stratification	Multimodal assessment, digital therapeutics, closed-loop systems	Emerging models; need validation and real-world scalability (Experimental)	Combines multimodal insights (neuroimaging, psychometrics, digital phenotyping) for personalized, adaptive, and scalable intervention.	Still under development; requires infrastructure and interdisciplinary coordination; lacks validation in large-scale trials.

Notes: Evidence Labels: Established – supported by multiple randomized controlled trials or clinical guidelines; Adjunctive / Mixed evidence – promising findings from limited or heterogeneous studies, often used as adjuncts; Experimental – early-phase or investigational interventions with limited clinical validation.

Abbreviations: CBT, Cognitive Behavioral Therapy; CBT-I, Cognitive Behavioral Therapy for Insomnia; TRT, Tinnitus Retraining Therapy; SSRIs, Selective Serotonin Reuptake Inhibitors; GABA, Gamma-Aminobutyric Acid; NMDA, N-Methyl-D-Aspartate; rTMS, Repetitive Transcranial Magnetic Stimulation; tDCS, Transcranial Direct Current Stimulation; DLPFC, Dorsolateral Prefrontal Cortex.

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improvements in tinnitus intrusiveness.[86] Long-term durability of CBT-related gains has been demonstrated in 6- to 24-month follow-up studies.[96]

Recent innovations focus on transdiagnostic CBT models targeting shared psychopathological mechanisms—such as intolerance of uncertainty, metacognitive rigidity, and attentional dyscontrol—across tinnitus, anxiety, and insomnia phenotypes.[97] Furthermore, digital and hybrid delivery platforms, including internet-based CBT (iCBT) with asynchronous therapist guidance, have demonstrated non-inferiority to conventional formats in both efficacy and adherence.[98] Ongoing research into precision-matched CBT protocols, informed by ecological momentary assessment, psychometric clustering, and neurobehavioral biomarkers, aims to stratify patients into response-relevant subgroups.[99,100]

Finally, integration with adjunctive modalities—such as mindfulness-based interventions, neurofeedback, and vagal tone–enhancing biofeedback—represents an emerging frontier in optimizing CBT outcomes in treatment-refractory cases.[101] These developments reflect a paradigm shift toward mechanism-driven, personalized CBT approaches that move beyond symptom management toward transdiagnostic regulatory recalibration.

Sound Therapy and Tinnitus Retraining Therapy (TRT)

Sound-based interventions represent a core pillar within multidisciplinary tinnitus management, particularly for individuals exhibiting elevated tinnitus perceptual salience without profound hearing loss.[102] These interventions aim not at masking the percept per se, but at modulating the perceptual–attentional interface, decreasing auditory-limbic coupling, and facilitating habituation.[103] Among these, Tinnitus Retraining Therapy (TRT)—which combines directive counseling with sound enrichment—has gained prominence as a structured, mechanism-informed approach rooted in neurophysiological models of tinnitus processing.[104]

TRT conceptualizes tinnitus as a conditioned stimulus acquiring aversive salience through associative learning and attentional reinforcement.[105] The therapeutic goal is to disrupt this link by decoupling tinnitus from negative emotional valence and autonomic hyperreactivity.[106] The counseling component targets cognitive restructuring and reattribution of tinnitus meaning, whereas the sound therapy component employs continuous low-level broadband noise to reduce contrast between tinnitus and ambient auditory input.[107] This is theorized to attenuate thalamocortical gain and promote downregulation of aberrant auditory-limbic connectivity over time.

Sound therapy can be delivered via various modalities, including wearable sound generators, customized notched music, or hearing aids with integrated noise enrichment.[108] Emerging protocols are increasingly incorporating spectrally tailored sound stimuli, such as amplitude-modulated tones or frequency-specific neuromodulatory signals, to enhance cortical desynchronization or induce lateral inhibition within tonotopically organized auditory areas.[109] Recent EEG and MEG studies have demonstrated that such stimuli can reduce tinnitus-related gamma oscillatory activity and normalize auditory evoked potentials, suggesting neuroplastic changes in central auditory gain regulation.[110]

While the evidence base for TRT and sound enrichment is heterogeneous, several controlled trials and meta-analyses suggest that combined approaches yield superior outcomes to sound-only or counseling-only strategies, particularly in patients with moderate to severe tinnitus-related distress.[111] Notably, sound therapy has also been associated with improvements in sleep latency and nocturnal tinnitus awareness, potentially via reduction in contrast-enhanced salience during quiet environments.[112]

Recent innovations include the development of bimodal auditory-somatosensory stimulation paradigms, such as the pairing of acoustic input with transcutaneous electrical stimulation of the tongue or cervical nerve branches.[113] These approaches aim to induce spike-timing-dependent plasticity in dorsal cochlear nucleus circuits, and early-phase trials report reductions in tinnitus severity with persistent post-treatment effects. Other neuromodulatory enhancements include real-time adaptive sound delivery using machine learning algorithms that respond to electrodermal or EEG biomarkers of tinnitus distress.[114]

Pharmacological and Neuromodulator Therapies

While behavioral and sound-based interventions form the cornerstone of tinnitus management, pharmacological and neuromodulatory approaches are increasingly explored as adjunctive or second-line options, particularly for individuals with refractory symptoms, heightened limbic activation, or pronounced sleep dysregulation.[115] These interventions target

the neurochemical and electrophysiological substrates underlying the tinnitus–anxiety–insomnia triad, including excitatory–inhibitory imbalance, aberrant thalamocortical oscillations, and stress-induced dysregulation of arousal systems.

Pharmacologically, no agent has received regulatory approval specifically for tinnitus treatment; however, several drug classes have demonstrated symptom-modulatory effects in targeted subgroups. GABAergic agents, such as clonazepam or gabapentinoids, have shown transient reductions in tinnitus perceptual intensity, likely via enhanced central inhibition and anxiolytic effects.[116] Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), may alleviate tinnitus-related distress and insomnia when comorbid depression or anxiety is prominent, though controlled trials report mixed outcomes on tinnitus loudness.[117] Melatonin, a chronobiotic and antioxidant with GABA-potentiating properties, has demonstrated modest improvements in sleep onset latency and tinnitus-related nighttime awareness, with favorable tolerability profiles.[118] Emerging interest surrounds the use of NMDA receptor antagonists (eg, esketamine, memantine) and neuroinflammation-modulating agents (eg, N-acetylcysteine, minocycline), although robust clinical data are lacking.[119]

Neuromodulatory strategies seek to alter dysfunctional cortical or brainstem network activity via exogenous stimulation.[120] Transcranial magnetic stimulation (TMS), particularly low-frequency (1 Hz) repetitive TMS over the auditory cortex, has been the most studied modality, with some trials demonstrating short-term reductions in tinnitus perception and associated distress.[121] However, variability in target localization, stimulation protocols, and patient phenotype has limited its standardization and long-term utility.[122] More recently, theta-burst stimulation (TBS) protocols have been investigated for their potential to induce longer-lasting neuroplastic changes through synaptic depotentiation.[123]

Transcranial direct current stimulation (tDCS) has also garnered interest, with anodal stimulation over the dorsolateral prefrontal cortex or temporoparietal junction shown to modulate tinnitus-related affective salience and attention networks.[124] Meta-analytic data suggest that while tDCS may yield small-to-moderate improvements in tinnitus severity, individual responsiveness varies, necessitating further biomarker-driven targeting strategies.[125]

At the interface of neuromodulation and behavioral therapy, closed-loop neurofeedback—where patients are trained to self-regulate EEG-defined neural signatures of tinnitus distress (eg, alpha/theta ratios, gamma activity)—represents an emerging precision tool. Early-phase trials suggest that neurofeedback may enhance attentional disengagement and reduce distress reactivity, particularly when integrated into cognitive-behavioral frameworks.[126]

Finally, novel bimodal stimulation paradigms combining auditory input with peripheral somatosensory or vagal nerve stimulation have shown early efficacy in reducing tinnitus loudness and improving sleep architecture.[127] Mechanistically, these approaches exploit spike-timing-dependent plasticity and cross-modal network recalibration, and are currently being evaluated in large-scale, sham-controlled trials.[128]

Integrated and Precision-Based Care Models

The clinical heterogeneity of chronic tinnitus, particularly in patients with co-occurring anxiety and sleep disturbance, necessitates a departure from one-size-fits-all management and the adoption of integrated, precision-based care models.[129] These models emphasize the synergistic integration of behavioral, auditory, neurophysiological, and pharmacologic interventions, guided by individual symptom profiles, neurobiological signatures, and treatment response trajectories. Such an approach aligns with current paradigms in systems neuroscience and personalized medicine, wherein tinnitus is conceptualized not merely as an auditory phenomenon but as a dynamic network disorder with modular therapeutic entry points.[130]

Integrated care models typically involve coordinated input from audiologists, psychologists, sleep medicine specialists, neurologists, and in some cases, psychiatrists or neurophysiologists.[131] Multidisciplinary tinnitus clinics have begun to implement tiered intervention pathways, in which patients are stratified based on clinical phenotype—such as distress-dominant, sleep-impairment–dominant, or neurocognitive-avoidant subtypes—and allocated to appropriate intervention sequences. For example, a patient presenting with high sleep reactivity and delayed sleep onset may benefit initially from CBT-I and melatonin supplementation, followed by sound therapy and tinnitus-focused CBT as arousal levels normalize.

Precision care models further extend this logic by incorporating biomarker-informed decision-making. Advances in neuroimaging, neurophysiological recording (eg, EEG, HRV), and digital phenotyping (eg, ecological momentary assessments) are increasingly used to identify neural or behavioral markers predictive of treatment responsiveness.[132] For instance, heightened frontotemporal connectivity or elevated gamma-band activity may inform the choice of neuromodulation targets, while actigraphy-derived sleep fragmentation indices may guide behavioral sequencing and sleep hygiene prioritization.[133,134]

Recent studies have also explored algorithmic and machine learning–based frameworks to optimize treatment matching and response prediction.[114] Multimodal data—integrating psychometrics, cortical activity patterns, autonomic markers, and real-time self-report—can be used to model individual treatment trajectories and adapt interventions in a dynamically responsive manner.[135] Additionally, digital health platforms delivering internet-based CBT, remote sound therapy calibration, and wearable neuromodulation interfaces are facilitating the operationalization of integrated care at scale, particularly in resource-limited or geographically dispersed populations.[136]

Challenges and Future Directions

Despite significant advances in mechanistic understanding and therapeutic diversification, the clinical management of tinnitus—particularly in patients with co-occurring anxiety and sleep dysfunction—remains constrained by critical conceptual and translational gaps.

Lack of Biologically Informed Subtypes

A primary limitation is the lack of biologically informed subtyping frameworks. Current treatment selection is largely symptom-driven, with minimal integration of objective markers of neural network dysfunction or stress-related neurophysiology. Emerging evidence from functional neuroimaging, EEG-based connectivity analysis, and autonomic profiling points toward distinct mechanistic phenotypes—such as limbic-salience dominant, hyperarousal-prone, or sleep-fragile subtypes—but these remain underdeveloped in both research stratification and clinical algorithms.

Methodological Inconsistencies and Outcome Heterogeneity

Methodological heterogeneity further impedes progress. The continued reliance on subjective, unidimensional outcome metrics—often divorced from physiological endpoints—hinders cross-study comparability, limits mechanistic inference, and restricts biomarker validation. There is a critical need for standardized, multi-domain outcome frameworks that concurrently assess perceptual, affective, and regulatory dimensions of tinnitus burden.

Treatment Durability and Long-Term Effectiveness

Moreover, the long-term efficacy of current interventions is suboptimal. While behavioral, acoustic, and neuromodulatory modalities may yield transient reductions in distress or intrusiveness, sustained remission is rare, and relapse under stress exposure remains common. This highlights the insufficiency of symptomatic suppression in the absence of durable modulation of trait-level dysfunctions, such as affective reactivity, attentional rigidity, and sleep architecture instability.

Toward Biomarker-Guided Personalized Interventions

These challenges underscore the need for a personalized medicine framework in tinnitus care. Recent studies have identified neurobiological and physiological markers—such as altered limbic-auditory connectivity, HRV, salivary cortisol, and GABA/glutamate balance—that may help delineate mechanistic subtypes. Stratifying patients based on dominant traits (eg, affective hyperreactivity, autonomic dysregulation, or circadian vulnerability) could guide tailored interventions, such as CBT, neuromodulation, or behavioral sleep therapy. Moreover, variability in treatment response remains a major clinical hurdle. Incorporating biomarker-informed feedback loops and adaptive treatment models may enable dynamic intervention adjustment and improve long-term outcomes.

Clinical Translation Barriers

Future research must prioritize the development of precision-stratified intervention models, leveraging multimodal biomarkers for individualized treatment matching. In parallel, the integration of closed-loop neuromodulation, adaptive digital therapeutics, and real-time behavioral state monitoring holds promise for enhancing treatment responsiveness and long-term regulatory recalibration. Bridging the gap between mechanistic neuroscience and scalable clinical implementation will be essential for advancing tinnitus care toward a precision neuropsychiatric paradigm.

However, translating these insights into routine clinical practice remains fraught with challenges. Multidisciplinary intervention strategies—though conceptually compelling—require coordinated infrastructure across audiology, psychiatry, neurology, and behavioral sleep medicine. Such integration is rarely achievable in standard outpatient care, particularly in community or under-resourced healthcare settings where siloed service delivery predominates.

Cultural and regional factors further complicate clinical translation. Patients' perceptions of tinnitus, mental health, and behavioral interventions are shaped by cultural beliefs and social norms, which can influence treatment engagement and adherence. In some settings, psychological therapies such as CBT may be stigmatized or underutilized, while in others, there may be a strong preference for traditional or pharmacological approaches. The acceptability of mindfulness-based interventions, neuromodulation, or digital therapeutics also varies cross-culturally, necessitating adaptation to local values, language, and health literacy levels. Moreover, disparities in healthcare delivery systems—such as differences in referral pathways, interdisciplinary collaboration, and service reimbursement—pose additional obstacles to the standardized adoption of integrative care models across global contexts. Addressing these barriers will require not only the technical validation of interventions but also cultural tailoring, cross-cultural research frameworks, and implementation strategies informed by local healthcare realities.

Economic and System-Level Constraints

In parallel with clinical feasibility, economic and resource considerations represent a critical but often overlooked dimension in the implementation of multidisciplinary care for tinnitus and its comorbidities. Interventions such as rTMS and cognitive behavioral therapy, while demonstrating clinical efficacy, are associated with high direct costs and often require multiple sessions delivered by trained specialists. This poses a significant burden for healthcare systems, particularly in low- and middle-income regions, where such resources are scarce or unevenly distributed.

Furthermore, insurance reimbursement for behavioral and neuromodulatory therapies remains inconsistent across jurisdictions, limiting access for socioeconomically disadvantaged populations. From a patient perspective, out-of-pocket costs, travel burdens, and time commitments can all negatively impact adherence and long-term engagement.

While formal cost-effectiveness analyses are still limited in this domain, emerging data suggest that digital CBT and remote-delivered mindfulness-based therapies may offer more scalable and cost-efficient alternatives. Future research should prioritize economic evaluations of intervention combinations, and health policy frameworks must consider reimbursement models and resource reallocation strategies to support equitable, sustainable implementation of multidisciplinary tinnitus care.

Conclusion

Chronic subjective tinnitus, particularly when accompanied by anxiety and sleep disturbances, represents a multidimensional neurobehavioral condition underpinned by aberrant auditory-limbic connectivity, neurochemical imbalance, stress system dysregulation, and circadian disruption. These interlocking mechanisms contribute to symptom chronicity, perceptual amplification, and therapeutic resistance. Monomodal interventions, though partially effective, often fail to achieve lasting relief due to their limited engagement with this complex pathophysiological architecture.

This review highlights the rationale for adopting multidisciplinary and mechanism-informed treatment models, integrating cognitive-behavioral interventions, sound-based therapies, pharmacological modulation, and neuromodulation techniques. When tailored to individual neuropsychological and physiological profiles, such integrated approaches hold promise for enhancing treatment efficacy and durability.

Nonetheless, critical challenges persist—including the absence of biologically grounded subtyping, methodological inconsistencies across trials, and limited scalability of complex interventions. Future progress will depend on the advancement

of precision medicine strategies, the development of biomarker-guided therapeutic frameworks, and the implementation of closed-loop, adaptive treatment systems that dynamically respond to individual neural and behavioral states.

Ultimately, the convergence of systems neuroscience, digital health, and transdiagnostic clinical frameworks offers a transformative opportunity to reconceptualize tinnitus management—not merely as symptom suppression, but as personalized modulation of maladaptive brain–behavior circuits.

Data Sharing Statement

Data will not be made available as no new data was generated in this paper.

Author Contributions

All authors agreed on the journal to which the article will be submitted, reviewed and agreed on all versions of the article before submission, during revision, and the final version accepted for publication. All authors agreed to take responsibility and be accountable for the contents of the article and any changes introduced at proofing stage. The contributions of the different authors are as stated: Can Jiang contributed to conceptualization, methodology, writing – original draft, visualization, and project administration. Zaiqiao Ding contributed to methodology, investigation, data curation, and writing – review and editing. Tingrui Zan was involved in investigation, and writing – review and editing. Wenxia Liao contributed to writing – review and editing, resources and supervision. Hongyan Li was responsible for conceptualization, writing – original draft, and writing – review and editing. Shu Huang contributed to supervision and writing – review and editing. Xiao Yang was responsible for conceptualization, supervision, writing – review and editing.

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