Chapter 63
Tinnitus and Depression

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Keypoints

1. There is an increased prevalence of depressive symptoms in individuals with tinnitus.
2. Affective disorders, together with personality factors, play an important role in creating the distress experienced by many individuals with tinnitus.
3. The co-occurrence of tinnitus and depression may be explained by the involvement of limbic brain structures in the pathophysiology of tinnitus.
4. Tinnitus is associated with neuroendocrine alterations, which are characteristic for depressive disorders.
5. Patients with tinnitus and depression should be efficiently treated.
6. Efficient treatment of co-morbid depressive symptoms has to consider a large variety of possible underlying disorders.

Keywords Tinnitus-related distress • Depression • Psychiatric co-morbidity • Limbic brain areas • Quality of life • Suicide

Abbreviations

DCN	Dorsal cochlear nucleus
PTSD	Post traumatic stress disorder
ICD	International classification of diseases
DSM	Diagnositic and statistical manual of mental disorders

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Introduction

There is abundant evidence of increased prevalence of depressive symptoms in individuals with tinnitus [1–10]. This is especially the case in individuals with disabling tinnitus [2, 3]. Also, high correlations between scores in tinnitus severity measures and depression scales have been reported [6, 9]. Thus, the occurrence of co-morbid depression may explain to some extent why some individuals suffer severely from tinnitus, whereas other individuals are not bothered by their tinnitus. Further studies have shown an additional role for specific personality traits such as anxiety, obsessiveness, neuroticism, or agreeableness [9, 11, 12]. However, it is important to note that all these findings are mainly derived from studies that used self-report questionnaires for the assessment of depressive symptoms, not from structured interviews. This difference is important, since the presence of depressive symptoms does not automatically mean that a patient fulfills diagnostic criteria for a depressive disorder. Depressive symptoms may be indicative of a depressive disorder, but they can also occur in the context of a large variety of other psychiatric disorders, such as bipolar disorders, personality disorders, anxiety disorders, dementia, or addiction, just to name a few. Therefore, further studies using structured interviews will be needed to determine exactly the prevalence of co-morbid psychiatric disorders in tinnitus.

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Depression

Diagnosis of Depression

For non-psychiatrists, detection of depressive symptomatology is obviously difficult. However, the use of simple screening questions may help to identify potential depression. The following two questions have been proposed as a screening method for depression: "During the past month have you often been bothered by feeling down, depressed, or hopeless?"; "During the past month have you often been bothered by little interest or pleasure in doing things?" [13]. If the patient answers with "yes" to one of the questions, depression is likely and further diagnosis by a psychiatrist or psychologist should be initiated. A more detailed screening instrument is the Mini-International Neuropsychiatric Interview [M.I.N.I., [14]]. As mentioned above, depressive symptoms may occur in a variety of psychiatric diseases. The exact differential diagnosis is of importance, since it has important consequences for the therapeutical management. For example, depressive symptoms can occur in the context of a bipolar affective disorder or a posttraumatic stress disorder, which requires completely different therapeutic management than major depression. Thus, when screening questions suggest potential co-morbid depression, a psychiatrist should be involved in further diagnostic assessment and therapeutic management.

The exact diagnostic classification may further depend on the classification system. The most widely used classification systems are the "*Diagnostic and Statistical Manual of Mental Disorders*" of the American Psychiatric Association (DSM-IV) [15] and the "*International Classification of Diseases*" of the WHO (ICD-10) [16]. Classification criteria for major depression (DSM IV) and depressive disorders (ICD 10) are displayed in Tables 63.1 and 63.2.

Interplay Between Tinnitus and Depression

Given the association between tinnitus and depressive symptoms, the question about the nature of the relationship arises. Clinical experience suggests that all kinds of relationships may occur: Depressive symptoms may develop as a reaction to tinnitus. Specific vulnerability factors such as anxious or obsessive personality traits may contribute to the development of such depressive reactions. In other cases, where tinnitus exists for a long time without causing any substantial distress, a depressive episode may lead to decompensation of the tinnitus with subsequent impairment in quality of life. There is also the possibility that tinnitus and depressive symptoms are consequences of a third condition (e.g. traumatic event). Finally, tinnitus and depressive disorders may also co-occur incidentally since both are relative frequent conditions. In clinical practice, differential diagnosis of all relevant factors contributing to tinnitus distress is of importance, since all these factors may represent potential targets for treatment. As an example, let us consider a patient who complains about chronic tinnitus with variations of perceived distress, ranging between severe disturbances to none at all. Psychiatric exploration may reveal a co-morbid seasonal affective disorder or a co-morbid bipolar disorder, which explains the variations in tinnitus distress. In this case, the co-morbid psychiatric condition should be specifically treated with the primary aim of mood stabilization, which in turn will lead to decreased variations of distress and impairment.

Similarities Between the Pathophysiology of Tinnitus and Depression

Pathophysiologic models of tinnitus have claimed the involvement of frontal and limbic brain regions. In his neurophysiological model of tinnitus, Jastreboff hypothesized in detail that the prefrontal cortex may be the brain structure that integrates sensory and emotional aspects of tinnitus and may be involved in the emotional and autonomic reaction to tinnitus [17]. The activation of the non-classical (extralemniscal) ascending auditory pathways in some forms of tinnitus [18] (see Chap. 10) may explain the coactivation of cortical association areas, limbic areas, and the autonomic nervous system [19]. Recent neuroimaging studies (in non-depressed individuals with tinnitus) have confirmed the involvement of the prefrontal cortex, the subgenual frontal cortex, and the amygdalo-hippocampal area in the pathophysiology of tinnitus (for review see [20, 21] or Chap. 17, 18, 19).

Table 63.1 DSM IV criteria of major depression [15]

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood or loss of interest or pleasure: Note: Does not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.
   1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful). Note: In children and adolescents, this can be an irritable mood;
   2. Markedly diminished interest or pleasure in all (or almost all) activities most of the day, nearly every day (as indicated by either a subjective account or observations made by others);
   3. Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month), or change in appetite nearly every day. Note: In children, consider failure to make expected weight gains;
   4. Insomnia or hypersomnia nearly every day;
   5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down);
   6. Fatigue or loss of energy nearly every day;
   7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick);
   8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others);
   9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism).

E. The symptoms are not better accounted for by bereavement (i.e. after the loss of a loved one), the symptoms persist for longer than 2 months, or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Table 63.2 ICD 10 criteria for depressive episode [16]

A. General criteria for depressive episode:
   1. The depressive episode should last for at least 2 weeks.
   2. The episode is not attributable to psychoactive substance use or any organic mental disorder.

B. Presence of at least two of the following symptoms:
   1. Depressed mood to a degree that is definitively abnormal for the individual, present for most of the day and almost every day, largely uninfluenced by environmental circumstances, and sustained for at least 2 weeks.
   2. Marked loss of interest or ability to enjoy activities that were previously pleasurable.
   3. Decreased energy or increased fatigability.

C. An additional symptom or symptoms from the following should be present, to give a total of at least four:
   1. Loss of confidence and self-esteem and feelings of inferiority;
   2. Unreasonable feelings of self-reproaches or excessive and inappropriate guilt;
   3. Recurrent thoughts of death or suicide or any suicidal behavior;
   4. Complaints or evidence of diminished ability to concentrate or think, accompanied by indecisiveness or vacillation;
   5. Change in psychomotor activity, with agitation or inhibition;
   6. Sleep disturbances of any type;
   7. Changes in appetite (decrease or increase) with corresponding weight change;

D. There may or may not be the somatic syndrome.

These brain areas are well known as critical parts of brain networks, functionally altered in individuals with depressive disorders [22, 23]. Thus, imaging data suggest that the neuronal correlates of tinnitus and depression overlap in limbic networks, which provides a possible explanation for the co-occurrence of tinnitus and depressive symptoms.

In this context, an important role for the dorsal cochlear nucleus (DCN) has also been proposed [24]. There is increasing evidence from animal studies that the DCN is an important contributor to tinnitus. There are direct projections from the DCN to brain stem structures such as the locus coeruleus, reticular formation, and raphe nuclei which are the principle sites for synthesis of serotonine and noradrenaline and are implicated in the control of attention and emotional responses. Thus, attentional and emotional disorders, such as anxiety and depression, commonly associated with tinnitus may result from an interplay between these non-auditory brainstem structures and the DCN [24].

Also, serotonergic dysfunction, which is assumed to play an important role in the pathophysiology of depression [25], has been suggested to be involved in

tinnitus [26, 27]. However, evidence for this hypothesis is scarce.

Finally, neuroendocrine alterations such as a hypothalamic–pituitary–adrenal axis dysfunction, which are pathognomonic for stress-related disorders such as depression or posttraumatic stress disorder (PTSD) [28, 29] have been described in tinnitus patients [30, 31], indicating another pathophysiological overlap between tinnitus and affective disorders. Interestingly, a recent study has shown that tinnitus patients differ only slightly from controls in physiological reactivity during stress tests, indicating relatively normal psychophysiological reactivity [32].

Depression

Treatment Options for Depression

There are several reasons why patients with tinnitus and depression should be promptly and efficiently treated. Efficient treatment depends on the exact etiology of co-morbid depressive symptoms to tinnitus. If diagnostic assessment reveals a major depression (see Table 63.1), standard treatment options include antidepressants and psychotherapy. There is a large variety of antidepressants available, which differ in their mechanisms of action and side effects. Also, there are some antidepressants that specifically address specific symptoms of depression. For example, amitriptylin and mirtazapin have sedative effects and are preferentially used in patients with insomnia, whereas venlafaxine, duloxetine, and bupropion exert an activating effect and are preferred in patients who suffer from loss of energy. Thus, the choice of the best antidepressant is complex and depends on previous patient's experience with specific drugs, the predominant symptoms of depression and co-morbidities. Also, cognitive behavioral therapy has been shown to be efficient in the treatment of depression. Further non-pharmacologic treatment options include light therapy, sleep deprivation, aerobic exercise, transcranial magnetic stimulation or electroconvulsive therapy.

Several antidepressants have been investigated for their use in tinnitus [33, 34] (see Chap. 78). Two randomized double-blind placebo-controlled studies investigated the effects of antidepressants in patients with tinnitus and co-morbid depression [35, 36]. The tricyclic nortriptyline significantly reduced depression scores, tinnitus disability scores, and tinnitus loudness relative to placebo [1]. Also the serotonin reuptake inhibitor sertraline was significantly more effective than placebo in reducing tinnitus severity [2]. In both studies, reduction in tinnitus disability scores correlated high with reduction of depression scores, suggesting that antidepressants have beneficial results in depressed tinnitus patients, but that this is mainly due to the antidepressant effect of the drug.

However, induction or worsening of tinnitus has also been reported in the context of treatment with antidepressants, both as a side effect of drugs such as phenelzine, amitriptyline, protriptyline, doxepin, imipramine, fluoxetine, trazadone, bupropion, and venlafaxine. Worsening of tinnitus has also been associated with withdrawal of antidepressants (venlafaxine and sertraline) [37]. Interestingly, transcranial magnetic stimulation of the dorsolateral prefrontal cortex, performed for the treatment of depression, has also been described to induce and worsen tinnitus in rare cases [38]. This suggests that tinnitus can be generated or worsened by modulation of neural activity in the frontal cortex. Thus, the complex interactions between antidepressant treatment and tinnitus may be explained by antidepressant-induced modulation of frontal cortex networks [39], which in turn may result in altered top–down control of activity in the central auditory pathways.

Suicidal Tendency

Depression can become life-threatening by leading to suicidal ideation. The most important risk factor for suicide is depressive disorder, both in tinnitus patients [40–42] and in non-tinnitus patients [43, 44]. Further risk factors include male gender, elder age, and social isolation [3]. In tinnitus patients with depression, suicidal tendencies have to be assessed because a high risk of suicide requires immediate action. This sensitive area can be approached by asking the patient about passive suicidal ideations (for more details, see Chap. 54). It is important to know that asking about suicidal thoughts does not increase the risk of committing suicide.

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