# Clinical review

*Fortnightly review*

## Tinnitus—investigation and management

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Tinnitus (from the Latin *tinnire*, which means to ring or to tinkle) describes the sensation of any sound perceived in the head or in the ears without an evident external stimulus. Though tinnitus is subjective, for clinical purposes it is subdivided into subjective and objective tinnitus, the latter describing those few incidents in which the sound is detected or potentially detectable by another observer. Tinnitus is a manifestation of malfunction in the processing of auditory signals involving both perceptual and psychological components and should as such be differentiated from auditory hallucinations, which are generally considered to be a symptom of psychiatric or neurological disorders.

The characteristics used to classify tinnitus depend on the purpose of the classification (box 1).[1] Furthermore, distinctions should be made between acute and chronic tinnitus and between chronic tinnitus occurring after an acute tinnitus and chronic tinnitus of insidious onset.[2] Tinnitus is considered to be chronic when is has been present for more than three months without signs of spontaneously resolving.

### Box 1—Classification of tinnitus

- Normal *v* pathological tinnitus
- Type and probable site of underlying disorder
- Acute *v* chronic state
- Self reported or measured psychoacoustic characteristics
- Grade of severity or annoyance

### Summary points

- Tinnitus—a manifestation of malfunction in the processing of auditory signals involving both perceptual and psychological components—is often associated with sensorineural hearing impairment.
- Overall, 10-14% of adults have prolonged spontaneous tinnitus or have tinnitus "always" or "often"
- The effects of tinnitus are primarily psychosocial
- Management consists of a thorough otoaudiological examination to identify the few treatable cases and to convince remaining patients of the non-threatening nature of their problem, and an evaluation of current health state and psychological wellbeing
- Management includes reassurance and solid counselling, prosthetic treatment, and psychological intervention
- Empirical results justify a positive prospect, if not for "cure" then for possibilities of alleviating the consequences of the symptom

### Prevalence

Most people experience tinnitus occasionally, and most experience it in silent soundproofed rooms. The British national study of hearing found that 10% of adults had prolonged spontaneous tinnitus—that is, tinnitus "usually lasting for longer than 5 minutes"; 1% experienced severe annoyance due to tinnitus, and in 0.5% of adults tinnitus severely reduced the ability to lead a normal life. The same study ascertained that 7% of the population in the United Kingdom present to their general practitioners with tinnitus and 2.4% are referred to hospitals.[3] A largescale Swedish study[4] reported somewhat higher figures: for 2.4% of adults "tinnitus plagues me all day," and 14.2% suffered from tinnitus "often" or "always."

### Aetiology

Tinnitus is a symptom of many diseases and may be triggered anywhere along the auditory pathway, but the emergence of persistent annoying tinnitus is considered to have psychological components (see below). The symptom may be associated with any form of sensorineural hearing impairment; difficulty in hearing is the major determinant of tinnitus, followed by aging and exposure to noise.[3] Conductive hearing impairment with tinnitus occurs after middle ear surgery and myringoplasty, and in chronic suppurative otitis media and is a common feature of otosclerosis. Temporary tinnitus may be due to wax in the ear canal, to otitis media or Eustachian tube catarrh, to drug ingestion or toxaemia, or to recent exposure to noise. Causes of objective tinnitus may be divided into vascular or muscular (for an overview see Jackson[5] ) (box 2). In rare cases the onset of persistent unilateral tinnitus may be the first sign of an acoustic neuroma.

It is not exceptional for tinnitus to occur in patients with normal hearing. In a Swedish population study,

### Box 2—Possible causes of tinnitus

- Inner ear pathology associated with hearing impairment (noise induced hearing loss, presbyacusis, Ménière's disease, etc)
- Middle ear pathology often associated with hearing impairment (chronic suppurative otitis media, otosclerosis)
- Wax in the ear canal
- Drug ingestion
- Cardiovascular or neurological disorders
- Emotional response to stimulus furthered by stress, depression, etc

19% of subjects with subjective normal hearing said they suffered from tinnitus "always,"[4] and the British national study found that 7% of adults were annoyed by prolonged spontaneous tinnitus but did not have difficulty hearing.[3] Such data emphasise the role of the brain as the primary site of the perception and experience of tinnitus.

The clinical course of tinnitus is either no change or increasing loudness and decreasing annoyance. Most people learn to tolerate tinnitus, but a few do not; several theories give different explanations for this.

A recent neurophysiological model offers one explanation of tinnitus with implications for both diagnosis and management.[6 7] The theory focuses on tinnitus as a threat, which in some patients evokes strong emotions, such as fear of serious illness and anger, which are easily enhanced by adverse professional intervention. Based on the principles of neural plasticity, the theory says the brain has potential to relearn patterns that will de-emphasise the impact of tinnitus. Treatment is by retraining, with the goal of removing inexpedient emotional responses and eventually the perception of tinnitus itself.

In the theory of habituation, factors such as chronic stress, high levels of arousal, the significance of the sound, or sudden onset and unpredictability of the stimulus may interfere with the process of normal habituation.[8 9] Another model proposes dishabituation (renewed focus on the sound) instead of lack of habituation as the difference between those who complain of tinnitus and those who do not,[10] and a nationwide Swedish questionnaire study found that the most important predictors of discomfort from and adaptation to tinnitus were controllability and degree of maskability by external sounds.[11]

### Box 3—Testing for tinnitus in secondary care

- Full otological examination
- Routine audiological testing with pure tone, reflex, and speech audiometry
- Supplementary *x* ray examination or magnetic resonance scans if acoustic neuroma or neurological disorder is suspected
- Tests to determine characteristics of tinnitus[5 12]:
  Pitch and loudness matching
  Minimum masking level
  Test for residual inhibition
  Loudness discomfort levels

## Investigation

In primary health care, investigation of tinnitus should include an ear, nose, and throat examination; an evaluation of current health state; a thorough history, covering previous ear disease, recent noise exposure, hearing status, and drug intake; and an impression of the psychosociological situation of the patient, with special attention to signs of depression. If tinnitus is persistent or annoying the patient should be referred to an ear, nose, and throat clinic, tinnitus clinic, or audiology department for further examination and counselling (box 3). Although loudness measures and reported severity of tinnitus are poorly correlated, these tests are normally included in tinnitus protocols. Measuring tinnitus is important both for diagnostic reasons and to reassure the patient that the symptom is being carefully assessed.

Annoyance due to tinnitus or its severity is measured or graded by questionnaires, which are available in many forms and lengths. They deal with both the perceptual aspects of the symptom and its individual psychosocial consequences—impact on concentration, hearing, memory, irritability, sleep, and overall psychological wellbeing.[13]

## Management

Tailoring treatment to individual needs is a cornerstone of management: both undertreatment and overtreatment may lock the patient in a vicious circle and produce a "sufferer." Preventing the patient being annoyed by tinnitus begins in primary practice with an explanation of the basic psychological mechanisms involved in the perception of tinnitus and, for most patients, reassurance as to the benign nature of their problem.

Patients seen in clinical settings tend to be those who do not habituate to tinnitus. It is estimated that around 80% of patients referred to tinnitus clinics can be helped simply by relevant examination and reassurance.[5] For those needing more treatment the approach varies among professionals and countries but is usually multidisciplinary. There is no cure for tinnitus in the common sense of the word—no drug has been proved effective in attenuating not to say abolishing tinnitus for an appreciable proportion of patients. Antidepressants or nocturnal sedatives may deal with the effects of tinnitus for highly emotional patients for a short period while the underlying psychological disturbance is being treated.

With a few exceptions, surgery specifically aimed at eliminating tinnitus is obsolete. A detailed overview of pharmacological and surgical approaches is available elsewhere.[2 14]

## Prosthetic treatment

Since the late 1970s prosthetic treatment involving hearing aids, tinnitus maskers, or combination instruments has been widespread in tinnitus management.

Maskers look similar to hearing aids and produce a broad band of noise. The instruments generate an external, constant sound that can be controlled by the patient, allowing the patient to concentrate rather than be distracted by sounds from televisions, etc; they

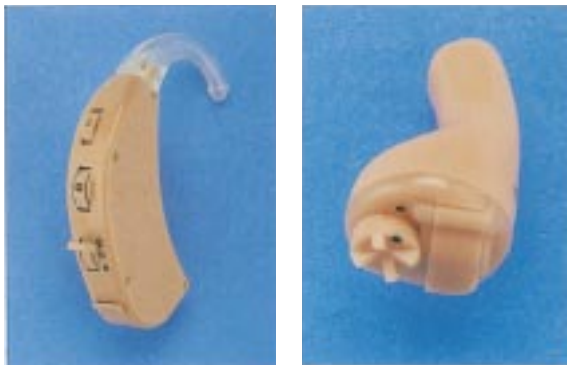

**Fig 1** Maskers can be worn behind or in the ear

divert attention and thereby make tinnitus less troublesome. After therapeutic masking about 10% of patients experience a period of total absence of tinnitus,[15] but because this residual inhibition is unpredictable it should not be overemphasised in counselling.

The neurophysiological approach focusing on behavioural retraining of the associations induced by perception of tinnitus uses devices similar to maskers but calls them tinnitus retraining instruments. According to this theory traditional masking is counterproductive, since for retraining to occur the stimulus has to be perceived during training.[7] In 149 patients given retraining, 96% showed improvement, and in 19.6% tinnitus totally disappeared for an average of 10.5 days.[16]

When a hearing impairment is present, hearing aids should be fitted, as they distract attention away from tinnitus through amplification of ambient sounds and often provide a masking effect. The stress mechanisms involved in the experience of tinnitus cause some patients to attribute hearing problems to tinnitus; for them, improving hearing by means of amplification results in improvement of tinnitus. A thorough interview will reveal whether a hearing problem or tinnitus is the major complaint, and counselling in the use of the hearing aid should be delivered accordingly. Experienced hearing aid users whose hearing aid gives no relief from tinnitus may be provided with combination instruments or with hearing aids and maskers separately.

The percentage of patients who can be helped through instrumentation varies across studies and designs. Thus a multicentre study of 472 patients reported benefit from maskers or combination instruments in 89% of patients and for hearing aids in 69%,[17] while two Swedish controlled studies concluded that masker treatment is not unequivocally superior to placebo and that hearing aids fitted exclusively for hearing purposes did not reduce tinnitus.[18 19] Placebo effect or not, instruments are part of multidisciplinary management. As the basic mechanism of tinnitus becomes understood, patients will be more carefully selected for prosthetic treatment.

## Psychological effects

The effects of tinnitus are primarily psychological, which is not to say that all patients with tinnitus need psychological therapy. Given the nature and the localisation of the symptom anxiety and distress are fully intelligible reactions that are initially best handled by proper medical examination, explanation, and reassurance. A person experiencing tinnitus will need a plausible explanation to counteract adverse and obstructive thoughts. Someone with a positive, non-threatening knowledge about tinnitus is likely to be better prepared than someone who has none.[20] As patients often want to review information or share it with family or friends, some sort of written information is advisable. Several booklets are available and have been analysed in a recent study.[20] Box 4 shows the ten questions patients most often ask.

### Box 4—"Top ten" questions about tinnitus[20]

- Is there a cure for tinnitus?
- What is tinnitus?
- What can trigger tinnitus?
- Is tinnitus dangerous?
- What has research on tinnitus found?
- What are the influences of medicines on tinnitus?
- How is tinnitus associated with hearing loss?
- What treatments are currently available?
- What are the results from different treatments?
- How do psychological factors influence tinnitus?

Patients with tinnitus often report insomnia, concentration difficulties, and emotional problems such as depression, frustration, and irritability. If further intervention is required, a thorough history taking is highly relevant for deciding whether tinnitus is the primary problem or if specific traits of personality or environmental factors, or both, preceded the symptom. Patients may have a long history of depressed moods, sleeping problems, or inexpedient ways of coping in stressed situations; in these cases tinnitus is not the single cause of all problems and should not be treated as such.

The literature contains descriptions of a variety of psychological methods, including cognitive approaches aimed at affecting attitudes, thoughts, and beliefs. In combination with behavioural strategies such as relaxation training and biofeedback these methods form the basis of self control or coping techniques.[21-23] Methodological limitations such as lack of proper controls or small samples often preclude firm conclusions as to whether any treatment effect is due to specific factors, but the therapeutic effect in itself is great in any treatment of tinnitus—patients often express relief when they see a professional who has more than 10 minutes for listening and reassurance.

## Conclusion

Empirical results justify a positive prospect if not for the "cure" of tinnitus then for the possibilities of alleviating the consequences of the symptom. Although patients should not just be told they will have to live with their tinnitus, this is still basically true, and indeed most people with tinnitus do habituate. Patients presenting with tinnitus need a thorough examination of current health state, an otoaudiological examination, and an evaluation of psychological wellbeing, as well as solid counselling based on current knowledge, preferably including some sort of written information.

Patients who are depressed or have psychosocial problems should be identified as such and treated accordingly. When these services are not provided by the general practitioner, patients should be referred to a tinnitus clinic or audiology department.


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## *Lesson of the week*

# Hypokalaemia and hypertension associated with use of liquorice flavoured chewing gum

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**Use of liquorice flavoured chewing gum may induce hypokalaemia and hypertension or oedema**

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Prolonged ingestion of substances containing glycyrrhizinic acid, such as liquorice, is a well known cause of exogenously induced hypermineralocorticoidism. This is characterised by sodium retention, hypokalaemia, hypertension, metabolic alkalosis, and suppression of the renin-aldosterone system.[1] We describe two cases showing that hypokalaemia induced by glycyrrhizinic acid should be considered in patients with hypertension or oedema even if they have not eaten sweets that obviously contain liquorice.

## Case reports

### Case 1

A 21 year old woman presented to her general practitioner with a headache. She ate about 100 g of liquorice daily. She used an oral contraceptive. On earlier occasions her blood pressure had been 110/70 mm Hg. Clinical examination was unremarkable except that her blood pressure was 190/120 mm Hg. She was advised to stop eating liquorice and taking the oral contraceptive. Despite these measures, her blood pressure remained raised even after treatment with a combination of atenolol, lisinopril, hydrochlorothiazide, and amlodipine.

She was referred to our outpatient clinic. Two weeks after the drug treatment had been discontinued her blood pressure was 180/110 mm Hg and plasma concentrations of sodium, potassium, and bicarbonate were 143 mmol/l (normal 136-146 mmol/l), 2.6 mmol/l (3.8-5.0), and 35.9 mmol/l (23-29), respectively. Plasma renin activity was 0.096 ng/(l×s) (normal 0.96-3.61), and plasma aldosterone concentration was 160 pmol/l (normal 320-2000), both being inappropriately low as her 24 hour sodium excretion was 86 mmol.

The clinical picture was compatible with exogenously induced hypermineralocorticoidism, so a more thorough history was taken. This showed that she had replaced her liquorice intake by two packets of Stimorol Sugar Free R (Warner Lambert Confectionary) chewing gum a day. This chewing gum contains 585 mg liquorice in each 15 g packet, and 8-12% of the liquorice consists of glycyrrhizinic acid (manufacturer's information). Her daily intake of glycyrrhizinic acid was calculated to be about 120 mg. Three weeks after she stopped using the gum her blood pressure was 110/80 mm Hg and plasma potassium concentration 5.3 mmol/l.

### Case 2

A 35 year old woman was referred to us with profound hypokalaemia of 2.2 mmol/l. She denied eating liquorice. She used an oral contraceptive. Because she had pretibial oedema she took chlorothiazide 500 mg twice daily. Clinical examination showed that her blood pressure was 140/80 mm Hg and that she had pitting oedema. Plasma potassium and bicarbonate concentrations were 2.2 mmol/l and 30.8 mmol/l, respectively. One week after stopping chlorothiazide

treatment and starting treatment with potassium chloride 600 mg three times a day her electrolyte concentrations were still abnormal: sodium was 146 mmol/1, potassium 2.0 mmol/1, and bicarbonate 37 mmol/1. Two weeks after discontinuation of the diuretic the concentrations had further deteriorated, sodium being 144 mmol/1, potassium 1.5 mmol/1, and bicarbonate 39 mmol/l. She was admitted to the hospital for further analysis and infusion of potassium chloride. Plasma renin activity was 0.036 ng/(l×s) and plasma aldosterone concentration 80 pmol/1 (normal 1.08-4.32 ng/(l×s) and 320-2000 pmol/l, respectively, for a daily sodium excretion of 57 mmol).

The clinical picture was suggestive of exogenous mineralocorticoid administration. She was noted to use chewing gum (BenBits Cool Mint R (Sorbits in Britain); Leaf United Kingdom). This gum is liquorice flavoured and contains 160 mg liquorice, of which 10% is glycyrrhizinic acid, in each 16 g packet. She used about three packets a day (50 mg glycyrrhizinic acid). She was advised to stop using the gum. Intravenous and oral potassium supplementation was able to be stopped after 2 and 15 days, respectively.

Three weeks after she stopped using the chewing gum her oedema had disappeared completely, her blood pressure had fallen to 110/80 mm Hg, and her plasma potassium had risen to 4.2 mmol/1 in association with normalisation of the other electrolyte concentrations.

## Discussion

These two case histories show that low doses of glycyrrhizinic acid in liquorice flavoured chewing gum can raise renal cortisol concentrations, resulting in severe hypokalaemia and hypertension or oedema. Even in the Netherlands, where liquorice is popular and where the mineralocorticoid activity of the extract of *Glycyrrhiza glabra* root was described 50 years ago,[2] the diagnosis was almost overlooked. The box lists products containing considerable amounts of glycyrrhizinic acid.[3-6]

Glycyrrhizinic acid is hydrolysed into glycyrrhetenic acid, which is the active metabolite that inhibits renal 11β-hydroxysteroid dehydrogenase. This enzyme catalyses the inactivation of cortisol to cortisone.[7] Cortisol, unlike cortisone, has the same affinity as mineralocorticoids for the mineralocorticoid receptors of the cells in the cortical collecting ducts.[7] Given this equal receptor affinity and the much higher circulating concentrations of cortisol compared with aldosterone, inhibition of 11β-hydroxysteroid dehydrogenase increases the kidney's exposure to the mineralocorticoid effects of cortisol. A dose-response study of glycyrrhizinic acid in healthy volunteers showed that a significant fall in plasma potassium concentration from 4.3 mmol/l to 3.5 mmol/1 occurred at a dose of 800 mg or more a day.[8] To our knowledge, only two similar cases of hypermineralocorticoidism associated with the use of chewing gum have been described.[9 10] Why some people are susceptible to low doses of glycyrrhizinic acid remains to be elucidated. Oestrogens may react with the mineralocorticoid receptor or inhibit 11β-hydroxysteroid dehydrogenase activity,[11] which may explain why female sex and the use of oral contraceptives can increase the susceptibility to glycyrrhizinic acid.[8] Interestingly, both our patients were women using oral contraceptives, but other predisposing factors may be important as the association has been described in a man.[9] The inhibition of 11β-hydroxysteroid dehydrogenase lasts for two weeks after glycyrrhizinic acid is removed, but suppression of the renin-angiotensin-aldosterone axis may persist for as long as two to four months,[12] as happened in case 1.

In conclusion, the regular use of chewing gum containing small amounts of glycyrrhizinic acid should be considered in history taking, especially in women using oral contraceptives who present with hypokalaemia in combination with hypertension or oedema.

### Products containing considerable amounts of glycyrrhizinic acid

- Confectionery:
  Liquorice sticks, bricks, cakes, toffee, pipes, bars, balls, tubes, Catherine wheels, pastilles, and allsorts
  Torpedos
  Blackcurrant
  Pomfret (Pontefract) cakes
  Servez vous
  Sorbits chewing gum
  Stimorol chewing gum
- Health products:
  Liquirizia naturale
  Liquorice flavoured diet gum
  Throat pearls
  Liquorice flavoured cough mixtures
  Herbal cough mixtures
  Antibron tablets
  Liquorice tea
- All types of liquorice root:
  Russian, Iranian, Chinese, Turkish, Afghan, and unknown origin
- Chewing tobacco
- Alcoholic drinks:
  Belgian beers
  Pastis brands
  Anisettes—raki, ouzo, Pernod

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