DEVELOPMENT AND CLINICAL TRIALS OF PSYCHO-AUDIOLOGICAL MODULE (PAM) AS AN INTERVENTION FOR PATIENTS WITH TINNITUS

by

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LIST OF ABREVIATIONS

ACT	Acceptance and Commitment Therapy
BEST	*Borang Evaluasi Soal selidik Tinnitus*
BSER	Brainstem Evoked Response
CBT	Cognitive Behavioral Therapy
DASS	Depression, anxiety and stress scale
dB	Decibel
dB(A)	Decibel with 'A' weighted
dBSL	Decibel Sensation Level
FDA	Food and Drug Administration
GP	General practitioner
HL	Hearing level
HSNZ	Hospital Sultanah Nur Zahirah
HUSM	Hospital Universiti Sains Malaysia
Hz	Hertz
IHC	Inner hair cell
IIR	Investigator Initiated Research
JEPem	JawatankuasaEtikaPenyelidikanManusia USM
KKM	Kementerian Kesihatan Malaysia
LDL	Loudness discomfort level
LOCF	Last observation carried forward
MML	Minimum masking level
NMRR	National Medical Research Register
OAE	Otoacoustic emission
OHC	Outer hair cell
OR	Odd Ratio
ORL	Otorhinolaryngology
PAM	Psycho-Audiological Module
PTA	Pure tone audiometry
PTM	Progressive tinnitus management
RCI	Reliable clinical index
RI	Residual inhibition
SL	Sensation level
SOAE	Spontaneous otoacoustic emission
TCT	Tinnitus coping technique
THI	Tinnitus handicap inventory
TRT	Tinnitus retraining therapy
UK	United Kingdom
US	United State of America
USMKK	University Sains Malaysia Kampus Kesihatan
VAS	Visual analog scale

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PEMBANGUNAN DAN PERCUBAAN KLINIKAL MODUL PSIKO-AUDIOLOGICAL (PAM) SEBAGAI SATU INTERVENSI UNTUK PESAKIT DENGAN TINNITUS

ABSTRAK

Tinitus adalah simptom yang biasa berlaku di kalangan pesakit yang mengalami masalah berkaitan telinga dan ia boleh menjadi serius jika tidak dirawat. Fokus utama kajian ini adalah untuk membangunkan satu intervensi baru yang dikenali sebagai Modul Psiko-Audiologikal (PAM), untuk mengendalikan masalah tinitus. Kajian ini dilaksanakan dalam tiga fasa: Fasa I adalah mengenai pengurusan semasa masalah tinitus oleh pakar ORL, audiologis dan pegawai perubatan di Malaysia, fasa II adalah pembangunan dan pengesahan PAM dan fasa III menilai keberkesanan PAM dalam merawat pesakit dengan tinnitus (dibandingkan dengan penopeng jalur lebar, BBM).

Fasa I, melibatkan pengagihan 212 borang soal selidik ke 16 buah hospital di seluruh Malaysia. Kadar respon yang baik diperolehi (51.8%), membolehkan analisis terperinci terhadap hasil kajian dapat dijalankan. Analisis mendapati penilaian *pure tone audiometry* dan *tympanometry* adalah penilaian rutin yang dilakukan di klinik-klinik ORL dan Audiologi ke atas pesakit dengan tinitus. Pemberian ubatan dan pemasangan alat bantu pendengaran adalah rawatan yang biasa ditawarkan kepada pesakit. Walau bagaimanapun, majoriti daripada responden tidak berpuas hati dengan pengurusan yang dijalankan pada masa sekarang dan mereka menantikan satu garis panduan yang standard untuk menguruskan pesakit dengan tinitus dengan cara yang lebih berkesan.

Pembangunan PAM dalam fasa II adalah berdasarkan kajian ilmiah dan perbincangan di kalangan pakar-pakar yang berkenaan termasuk ahli psikologi klinikal. Ia terdiri

daripada empat bahagian yang tertentu dengan tujuan untuk membimbing pesakit dengan tinitus dalam proses untuk mengurangkan gangguan tinitus. PAM yang baru dibangunkan kemudian telah disahkan oleh pakar-pakar dan pesakit dengan tinnitus.

Fasa III merupakan percubaan klinikal untuk menjustifikasikan keberkesanan intervensi PAM untuk merawat pesakit dengan tinitus. Ia dijalankan keatas 28 orang peserta dengan masalah tinitus. Perubahan antara sebelum dan selepas intervensi (2 minggu, 3 bulan dan 6 bulan) dinilai dengan menggunakan borang Evaluasi Borang Soal selidik Tinitus (BEST), borang Bahasa Malaysia *Depression, Anxiety and Stress Scale* 21 (BM *DASS* 21) dan penilaian psikoakoustik tinitus. Analisis penemuan mendapati kedua-dua intervensi didapati berkesan, tetapi intervensi PAM lebih berkesan dalam mengurangkan keterukan tinnitus dengan *effect size* yang besar (r = 0.531) berbanding dengan intervensi kawalan (BBM, n = 28) (r = 0.370). Selain itu, keberkesanan intervensi PAM adalah lebih jelas dengan melihat jumlah peserta dengan *clinical significant reduction* yang ketara dalam keterukan tahap tinitus. Pada minggu ke 2 selepas intervensi, 32% peserta menunjukkan *clinical significant reduction* dan bilangan ini meningkat kepada 64% pada lawatan susulan 6 bulan. Intervensi PAM juga berkesan dalam mengurangkan gejala psikologi. Ini dapat dilihat dalam lawatan susulan 6 bulan, bilangan peserta dengan *clinical significant reduction* adalah sehingga 32%. Di sudut lain, tiada perubahan ketara dapat dilihat pada kekuatan tinnitus dan tahap *minimum masking level (MML)* dalam kumpulan PAM. Disebabkan prestasinya yang unggul, intervensi PAM perlu digunakan dalam persekitaran klinikal untuk menguruskan pesakit tinitus dengan teratur.

DEVELOPMENT AND CLINICAL TRIALS OF PSYCHO-AUDIOLOGICAL MODULE (PAM) AN AS INTERVENTION FOR PATIENTS WITH TINNITUS

ABSTRACT

Tinnitus is a common symptom among otological patients and serious if untreated. The main focus of the present study was to develop a new intervention, known as Psycho-Audiological Module (PAM), for treating tinnitus. This study had three consecutive phases: Phase I was about determining the current tinnitus management by ORL specialists, audiologists and medical officers in Malaysia, Phase II was about the development and validation of PAM and the effectiveness of PAM intervention in treating patients with tinnitus (relative to broadband masker intervention, BBM) was studied in Phase III.

In Phase I, 212 validated questionnaires were sent to 16 hospitals. A good response rate was obtained (51.8%) enabling detailed analysis of the survey outcomes. It was found that pure tone audiometry and tympanometry were the routine assessments performed in most ORL and audiology clinics for patients with tinnitus. Pharmacotherapy and hearing aid fitting were the most common treatments offered to the patients. Nevertheless, the majority of respondents were not satisfied with their current practice and they looked forward to have one standard guideline for managing patients with tinnitus in a more effective manner.

In Phase II, the PAM was developed based on extensive literature review and discussions among the relevant experts including a clinical psychologist. It consists of four specific parts with the general aim to guide patients with tinnitus in the habituation

process. The newly developed PAM was then validated by the experts and patients with tinnitus.

In Phase III, a clinical trial to justify the effectiveness of PAM intervention to treat patients with tinnitus was carried out in 28 participants with complaint of tinnitus. The changes between pre- and post-intervention (2 weeks, 3 months and 6 months) sessions were assessed by *Borang Evaluasi Soal selidik Tinnitus (BEST)*, Bahasa Malaysia Depression, Anxiety and Stress Scale 21 (BM DASS 21) and tinnitus psychoacoustic measures. While both interventions were found to be effective, the PAM intervention was superior in reducing tinnitus severity with a large effect size (r=0.531) relative to the control group (BBM, n=28) (r = 0.370). Furthermore, the effectiveness of PAM intervention was more evident by looking at the number of participants with clinical significant reduction in the perceived tinnitus severity. At 2 weeks after intervention, 32% of participants revealed clinical significant reduction and the number increased to 64% at 6 months follow-up. The PAM intervention was also effective in reducing perceived psychological symptoms. At 6 months follow-up, the number of participants with clinical significant reduction could be as high as 32%. On the other hand, no significant changes were seen in tinnitus loudness and minimum masking level in the PAM group. Due to its superior performance, PAM intervention should be used in clinical setting for managing patients with tinnitus in a structured manner.

CHAPTER 1

INTRODUCTION

1.1 Research Background

Tinnitus is a perception of sound that originates in the head without any external sound stimulation(McFadden, 1982). It is perceived as a meaningless sound either tonal or complex sound (Jastreboff, 1990); typically described as ringing, humming, hissing, whistling and buzzing sounds. Tinnitus is a symptom of wide range of different underlying pathology, commonly associated with ear pathology such as noise induced hearing loss, aging, middle ear diseases, ototoxic medications and vestibular schwannoma (Møller, 2003; Baguley *et al.*, 2006; Herraiz *et al.*, 2006; Roberts *et al.*, 2010; Kim *et al.*, 2011). It also occurs among people with other medical illnesses such as arthritis, hypertension, arteriosclerosis, vascular diseases, temporomandibular disorders and emotional disorders (Dobie, 2004; Zöger *et al.*, 2006; Fujii *et al.*, 2011; Hilgenberg *et al.*, 2012).

The absolute mechanism of tinnitus is controversial, as a conclusion, Pfister (1999) has suggested that tinnitus could be originated anywhere between the peripheral ear and central auditory pathways, commonly associated with sensorineural hearing loss. In other opinion, tinnitus is contributed by an abnormal activity in the central auditory nervous system or in the brain (Jastreboff, 1990; Møller, 2003). Until now, no test could identify the regions that trigger the tinnitus accurately (Henry *et al.*, 2005a). However, treatments to treat the effect of tinnitus have been developed actively and applied to most tinnitus sufferers.

Regardless of its vague mechanism, the impact of tinnitus persistence can be tremendous to the sufferers. McKenna *et al.* (1991) reported that 45% of tinnitus

patients with otological problems needed psychological treatments. On the other hand, Sindhusake *et al.* (2003) reported that 67% of individuals with tinnitus had described tinnitus as mildly to extremely annoying. Untreated tinnitus could affect individual lifestyle, general health and emotional status including depression and anxiety. This happens because tinnitus has been perceived as a threat, continually intrusive and becomes difficult to cope with it (Halford and Anderson, 1991; Vesterager, 1997; Hiller and Goebel, 1999; Hallam *et al.*, 2004; Zöger *et al.*, 2006). Moreover, Tyler and Baker (1983) reported that the common difficulties faced by tinnitus sufferers were sleep problems, disturbance or persistence of tinnitus, speech understanding and feeling of despair and frustration.

There are many treatment options that have been studied in reducing tinnitus loudness or tinnitus annoying (Hoare *et al.*, 2011). There are sound enrichments (Smith *et al.*, 1991; Sweetow, 2013), anti-depressant medications (Vernon and Meikle, 2003b; Langguth *et al.*, 2009), tinnitus retraining therapy (TRT) (Phillips and McFerran, 2010),relaxation therapy (Weber *et al.*, 2002), information or counselling (Henry *et al.*, 2009) and cognitive behavioral therapy (CBT) (Henry and Wilson, 2001; Andersson, 2002; Andersson and Kaldo, 2006; Kaldo *et al.*, 2008). For those with permanent hearing loss, the use of hearing aids (Moffat *et al.*, 2009; Searchfield *et al.*, 2010; McNeill *et al.*, 2012) and/or cochlear implants (Punte et al., 2011; Olze et al., 2012) can be useful. The above-mentioned treatments have different levels of effectiveness to different sufferers. Moreover, for patients with severe distress, they need further referral to mental health professionals.

Subjective tinnitus is the main scope of this study, it is idiopathic in nature. Finding a cure to treat this type of tinnitus is endless, individuals with tinnitus should learn to understand their condition and change their negative perception

towards tinnitus. This could be achieved through psychological intervention, most reported in literature is CBT. This technique, which was adapted from chronic pain management, has produced successful management for patients with tinnitus (Sweetow and Sabes, 2010; Hesser *et al.*, 2011; Arch *et al.*, 2012; Hesser *et al.*, 2012).

1.2 Problem Statement

In regard to tinnitus, not many studies have been conducted involving Malaysian population. More studies are therefore warranted to study the important aspects of tinnitus among patients and practitioners in Malaysia. For example, little is known regarding how tinnitus patients are managed by practitioners in Malaysia. Proper assessment and management by clinical practitioners are indeed important to improve the quality of life of tinnitus sufferers. According to the first prevalence study on patients with tinnitus in Malaysia, 33% of patients with ear problems had tinnitus (Cheu Lih (2004). In the national ear and hearing disorder survey, which was conducted in year 2005 by Ministry of Health, Malaysia, the prevalence of tinnitus among respondents (aged 18 years and above) was 26.4% with 50% of them had unilateral tinnitus and 35% had bilateral tinnitus (Health, 2007).These data further support the importance of proper management of tinnitus as it is a prevalent symptom. By unveiling how tinnitus patients are treated (or not treated), important information could be gathered that would improve the existing clinical services in Malaysia.

As yet, more studies are required in searching for an effective treatment for tinnitus. Commonly, patients with tinnitus are treated with devices (hearing aids, tinnitus masker, laser therapy or sound enrichment) but not all of them require or

would get benefit from those devices. Moreover, these devices have to be purchased and their cost can be troublesome to the patients.

Audiologists are clinical professionals who are trained particularly in giving counseling and practicing aural rehabilitation for hearing impaired patients. They are also trained in assessing and managing tinnitus cases but limited to audiological perspective. As mentioned before, the psychological management such as CBT is one of the promising treatments for patients with tinnitus. Since CBT can only be performed by qualified mental health professionals, it is "prohibited" for audiologists to perform CBT without undergoing a formal training and certification in psychology. On the other hand, psychologists or clinical psychologists who are audiologically literate in treating tinnitus are also limited.

By considering these issues, there is a clear need to have a new mode of treatment with some psychological elements. This innovative treatment module should be valid and can be conveniently conducted by audiologists for managing patients with tinnitus in a better manner. Consequently, the present study brings forward a new intervention method, known as Psycho-Audiological Module (PAM) that combines psychological and audiological elements with the aim to reduce the effects of tinnitus on the patients' daily life. Accordingly, this study was conducted to determine the efficacy of PAM intervention (relative to the conventional treatment) in reducing tinnitus annoyance in patients from three aspects; tinnitus severity (e.g. the effect of tinnitus on daily life), psychological impacts (e.g. depression) and psychoacoustic (e.g. tinnitus loudness).

1.3 Research Objectives

1.3.1 General Objective

- To determine the effectiveness of Psycho-Audiological Module (PAM) as a new intervention tool for tinnitus

1.3.2 Specific Objectives

i. To determine the current management of tinnitus by otorhinolaryngology (ORL) specialists, audiologists and medical officers in ORL clinics in Malaysia,

ii. To develop the content of PAM in Malay version,

iii. To determine the validity of PAM by means of content validity index and face validity,

iv. To compare the perceived tinnitus severity scores, perceived psychological symptoms and tinnitus psychoacoustic measurements before and after PAM implementation (within group comparisons),

v. To compare the perceived tinnitus severity scores and tinnitus psychoacoustic measurements between PAM and control groups (broadband masking, BBM) (between group comparisons), and,

vi. To determine the clinical significance of both PAM and BBM interventions by means of effect size and reliable change index (RCI).

1.4 Study Benefits

The present study has several benefits. The development of an evidence-based and research-tested module of intervention for tinnitus could facilitate

audiologists or other related professionals in managing patients with tinnitus consistently and effectively. Moreover, this intervention module could be used as the reference material for improving audiology practice, encouraging more audiologists to get involved in the psychological intervention, increasing the level of confidence among audiologists in managing tinnitus cases and guiding other related professionals when treating patients with tinnitus.

1.5 Research Design

In order to answer all the research objectives, this study was carried out in three consecutive phases (Figure 1.1). Each phase is further described by specific chapters.In Phase I, a cross-sectional survey study was conducted to determine the current management of patients with tinnitus by ORL specialists, audiologists and medical officers (working in ORL departments) in Malaysia. Particularly, it was of interest to acquire information on the referral pathways for patients with complaint of tinnitus, assessments, treatments, outcome measures that are commonly practiced in the clinics and so on. Moreover, it was also of interest to determine the practitioners' satisfaction towards their current practices. The detailed methodology for this survey study is described in Chapter 3. Chapter 4 of the study shows the survey results, while the detailed discussions are provided in Chapter 5.

In Phase II that employed a validation study design, the content of PAM was developed and validated accordingly. The content of PAM was developed based on clinical discussions and relevant literatures. As mentioned earlier, PAM would consist of audiological and appropriate psychological elements. When the content of PAM was finalized, it then underwent validation processes. The detailed

methodology for this validation study is provided in Chapter 6. The related results and discussions are described in Chapter 7 and Chapter 8, respectively.

The effectiveness of the validated PAM in treating tinnitus was determined in Phase III. In this phase that employed a randomized control trial design, the performance of PAM in reducing tinnitus distress in tinnitus patients was compared with the conventional tinnitus treatment (broadband masking, BBM). Chapter 9 provides the detailed methodology of this study. The related results are described in Chapter 10 and the detailed discussions are shown in Chapter 11.

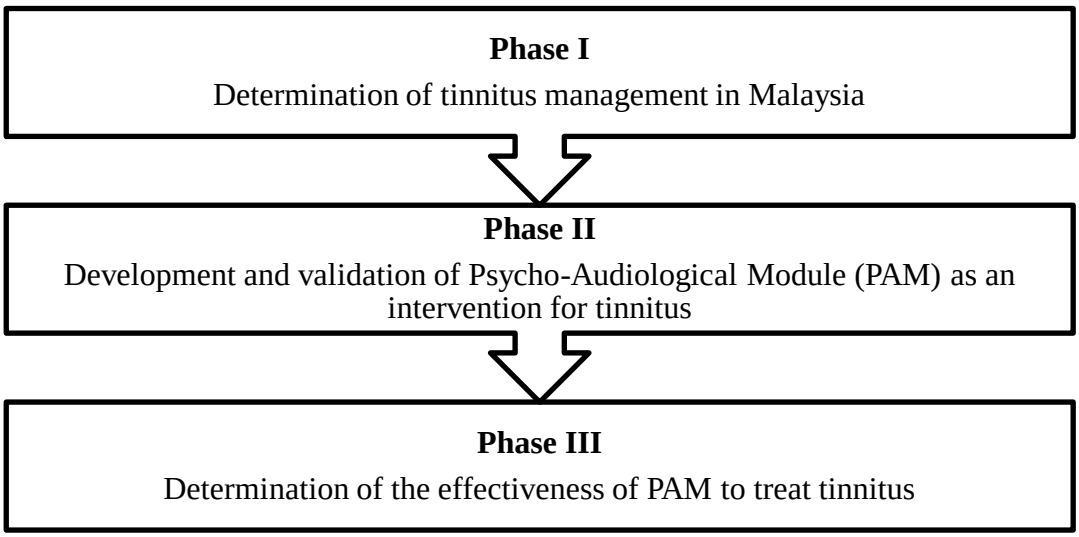

Figure 1.1: The three consecutive phases of the study

CHAPTER 2

LITERATURE REVIEW

2.1 Definition

The word tinnitus came from Latin verb '*tinnire*' meaning 'to ring, or tinkle' (Stevenson and Waite, 2011). It was described since 850s by El-Razi in his book (Stephens, 2000). In general, tinnitus is defined as '*the conscious expression of a sound that originates in an involuntary manner in the head of its owner, or may appear to him to do so*' by McFadden (1982) quoted by Jastreboff and Hazell (1993). This definition includes auditory hallucination of schizophrenia and variety of somatosounds such as palatal myoclonus, spontaneous otoacoustic emission and bruits of vascular origin. Pawell J. Jastreboff (1995) defined tinnitus as a phantom auditory perception or *'The perception of sound that results exclusively from activity within the nervous system without any corresponding mechanical, vibratory activity within the cochlea, and not related to external stimulation of any kind'* (Jastreboff, 2004).

2.2 Description of Tinnitus

Perception of tinnitus can occur either without pathology or with pathology. A study by Heller and Bergman (1953) found that 94% of individuals with apparently normal hearing would experience tinnitus in quiet room or room with ambient noise of less than 35 decibel (dB). This suggests that almost all people have tinnitus but it is barely audible because it is masked by the environment noise. In some cases, it may become audible suddenly with temporary hearing loss for few a seconds to not more than five minutes (Dauman and Tyler, 1992). Nicolas-Puel *et al.*

(2006) found that in 36.6% of cases, the tinnitus had appeared spontaneously without identifiable causes, and 34.8% was due to ear pathology. In tinnitus with pathology, it can last more than five minutes or more than once a week (Kaltenbach, 2011).

There are two categories of tinnitus; subjective and objective tinnitus. Subjective tinnitus is a perception of sound without external sound stimulation and audible to the patient only. It is a symptom of different underlying pathophysiologic processes. The causes could be otologic, neurologic, infectious, or drug-related. Otologic causes of tinnitus include noise-induced hearing loss, presbycusis, otosclerosis, Meniere's disease, sudden sensorineural hearing loss and impacted wax (Herraiz *et al.*, 2006; Zagólski, 2006; Chan, 2009; Han *et al.*, 2009). Neurologic etiologies of tinnitus include head injury, whiplash, multiple sclerosis and cerebellopontine-angle tumors (most often vestibular schwannoma) (Levine, 1999; Folmer and Griest, 2003; Baguley *et al.*, 2006).

Tinnitus may also arise as a result of infectious sources such as otitis media, otitis externa, Lyme disease, meningitis, or syphilis (Sindhusake *et al.*, 2003; Kim *et al.*, 2011; Nondahl *et al.*, 2011). Drugs that possibly contributed to the occurrence of tinnitus were salicylates, non-steroidal anti-inflammatory medication, aminoglycoside antibiotics, loop diuretics, and chemotherapy agents (Cazals, 2000; Reiter *et al.*, 2011). However, similar to most cases caused by drug consumption, tinnitus was reversible when drug consumption was stop or reduced in doses.

Objective tinnitus is a real noise that could be perceived by the patients and the examiner. The most reported sound is pulsatile tinnitus. Pulsatile tinnitus is a sound from turbulence of blood flow that is transmitted to the inner ear. In some cases, it could also be a subjective type of tinnitus. It can be caused by arterial

lesions, venous lesions or skull base, temporal and petrous bone lesion. In a study by Waldvogel *et al.* (1998), 42% of subjects with pulsatile tinnitus were classified as objective tinnitus, the majority of them presented with vascular pathology.

Pulsatile tinnitus is an uncommon symptom and requires a thorough otological evaluation if present. In an imaging study of 74 patients with pulsatile tinnitus, brain computed tomography revealed that pulsatile tinnitus had strong relation with the presence of vascular tumors, vascular malformations, and congenital or acquired vasculopathies (Sonmez *et al.*, 2007). Highly vascularized tumors of the temporal bone, venous anomalies and vascular stenosis could also be the cause of pulsatile tinnitus (Hofmann *et al.*, 2013).

Majority of patients has perceived tinnitus as ringing, whistling, hissing and buzzing. As reported by Sindhusake *et al.* (2003), the majority of subjects tested had ringing and buzzing types of tinnitus. Nicolas-Puel *et al.* (2006) found that 77.9% of subjects reported their tinnitus as whistling sound and 11.6% as buzzing sound. Different with recent study by Martines *et al.* (2010), tinnitus was reported as pure tones in 66.99% of their subjects and 27.88% reported tinnitus as narrow band noises.

According to Dobie (2004), the quality of tinnitus has no relation to specific diagnostic value. Its characteristic is related to the sound patterns stored in the auditory memory via the limbic system and is associated with the emotional states. Except for cases with Meniere's disease, the tinnitus is usually reported as high pitched sound (Herraiz *et al.*, 2006). In cases with extra-cochlear lesion, the tinnitus is usually described as pulsatile sounds (Wackym and Friedland, 2004).

2.3 Pathophysiology of Tinnitus

Tinnitus is a symptom of auditory disorders that can be induced by a number of lesions at different locations in the auditory system. There are several hypotheses describing mechanism of tinnitus but none of them have been truly proven yet. The major obstacle in searching for the true generator of tinnitus is inaccessibility of neural structures in life human. In the earliest opinion, spontaneous otoacoustic emission (SOAE) was responsible for tinnitus generation (Wilson, 1980). Penner (1990) studied SOAE among 96 subjects with tinnitus and 4.2% of them had tinnitus caused by SOAE. Penner then suggested that SOAE could be suppressed by using aspirin with appropriate dosage and this was supported by Guitton *et al.* (2003). However, the aspirin only suppressed the SOAE and the perception of tinnitus was not changed. This demonstrates a weak relation between tinnitus and SOAE.

Lesion of outer hair cells (OHCs) and inner hair cells (IHCs) are another theory of tinnitus generation. The loss of hair cell or hair cells function would cause afferent neurons to trigger abnormal auditory sensations at frequency at or near the focus of the lesion. It is called as the 'edge effect' theory (Kemp, 1981; Jastreboff, 1990; Zenner and Ernst, 1993; Eggermont and Roberts, 2004). This effect was further explained by Jastreboff (1990) in his dysfunctional discordant or discordant damage theory.

Dysfunctional of OHCs with intact IHCs has led to decrease or absent of signal to type II auditory nerve fibres leading to temporary loss of inhibition process in the dorsal cochlear nucleus. Each part of basilar membrane with local damage to the OHCs would serve as a source for tinnitus-related neuronal activity (Jastreboff, 2004; Kaltenbach, 2011). This theory explains that tinnitus could occur in individuals with normal hearing because of partial damage to OHCs and intact

IHCs. This partial damage to OHCs might not affect the audiogram but is enough to create imbalanced signal in the dorsal cochlear nucleus. On the other hand, individuals with profound or total hearing loss may not have tinnitus because of the total damage of OHCs and IHCs.

Damage to the peripheral auditory pathways could also lead to abnormal activity in the auditory nerve fibres. These changes would shift the balance of excitatory and inhibitory inputs and alter spontaneous input to the central auditory system (Eggermont and Kenmochi, 1998; Kaltenbach, 2011). Møller (2003) proposed that damages to the nerve would give rise to artificial synapses between individual nerve cells that create an ephaptic (false synapse) transmission between nerve fibers or cross talk leading to the generation of tinnitus.

In some cases, tinnitus is not originated from lesion in the peripheral auditory pathways. As reviewed by Kim HN *et al.* (1999), 22% out of 27 cases with cochlear implant, the tinnitus was not changed after the implantation. For cases with vestibular neurectomy, 11% out of 9 cases reported no changes in tinnitus perception. In a study of Kameda *et al.* (2010), 242 records of patients with unilateral vestibular schwannoma surgery were reviewed. They then found that 70.7% of patients had tinnitus before surgery. After the tumor removal, only 25.2% of the patients reported that their tinnitus had disappeared, 31.6% of them found their tinnitus unchanged and the tinnitus became worse in 9.9% of patients.

In the past 20 years, the functional imaging techniques have been utilized to study tinnitus-relevant neuronal activities in the human brain (Lockwood *et al.*, 1998; Reyes *et al.*, 2002). The imaging techniques can reveal the changes of activity in the central nervous system by measuring the regional cerebral blood flow (rCBF) (Mirz *et al.*, 1999). Mirz *et al.* (2000) examined individuals who were presented

with synthesized aversive sounds (tinnitus-like sounds). Positron Emission Tomography (PET) techniques revealed that the tinnitus-like sounds had activated primary and secondary auditory areas bilaterally, dorsolateral prefrontal attention areas, and structures in the limbic system, which is involved in emotional processing. On the other hand, as reviewed by Weissman and Hirsch (2000), the functional imaging technique is most useful in identifying the source of objective pulsatile tinnitus.

2.4 Prevalence of tinnitus

Epidemiological studies to estimate tinnitus prevalence have been carried out in many countries including Europe and United State (US) since 1960s. In Asian countries, the epidemiological studies on tinnitus prevalence started in 2000s. These studies used different definitions of tinnitus, different phrasing and context of questioning in the questionnaires and different demographic populations. However, the variations in tinnitus questionnaires were not purely related to tinnitus prevalence (Sanchez, 2004).

The national study of hearing conducted in United Kingdom (UK) in 1980s was the longest multi-stage epidemiology study of hearing and its disorder including tinnitus. The prevalence of self-reported tinnitus in this study was 10.1% (Davis and El Rafaie, 2000), and the incidence rate within 10 years of this survey was one person for every 171 individuals (Hall *et al.*, 2013). The prevalence found in this study was not much different from the previous studies as reviewed by Sanchez (2004). Between years 1993 and 2003, the tinnitus prevalence ranged from 3% to 30%. This range was not so difference from the findings in epidemiology studies

conducted in Asian countries. Table 2.1 reveals the summary of epidemiology studies conducted in Asian countries for comparisons.

Table 2.1: Summary of epidemiological studies done in Asian countries

Authors	Year	Subject populations	Tinnitus definition	Prevalence
Fujii et al	2002	Takayama Study Population-based cohort study in Takayama city of Gifu 14 423 adults aged 45 to 79 years old	Have you ever had tinnitus lasting longer than 5 minutes? Do not include when this happened immediately after very loud sounds.	11.9%
Michikawa et al	2006	Kurabuchi study Community-based cross-sectional study in Kurabuchi town, Takasaki City of Gunma Perfecture 1320 adults aged 65 years and above	In the past year, have you experienced any ringing, buzzing or other sounds (tinnitus) in your ears?	18.6%
Chard EM et al	2008-2009	Population-based cross-sectional study in Asiut Egypt 8 484 participants aged 6 years old or more than	N/A	5.17%
Park KH et al	2009-2011	Korean National Health and Nutrition Examination Survey in South Korea 21 893 participants aged more than 12 years old	Within the past year, did you ever hear a sound (buzzing, hissing, ringing, humming, roaring, machinery noise) originating in your ear?	19.7%
Thirunavukkarasu K and Geetha C	2013	Retrospective study by reviewed all patient's file that has visited All India Institute of Speech and Hearing in Mysore, India. Aged 60 years old and above	Complaint of any tinnitus	16.8%

In Malaysia, the national ear and hearing disorder survey carried out in year 2005 was the first ear and hearing epidemiological study in Malaysia. Organized by Ministry of Health, Malaysia, this survey aimed to determine the national prevalence of hearing loss, causes of ear disorders and associated symptoms including tinnitus. The findings revealed that the prevalence of tinnitus among respondents aged 18 years and above was 26.4% with 50% of them had unilateral tinnitus and 35% had bilateral tinnitus. The prevalence increased with the severity of hearing impairment. Among the respondents with presbycusis, 10.7% of them had tinnitus (Health, 2007).

2.5 Factors associated with prevalence of tinnitus

2.5.1 Age

It was estimated that 70% of people with presbycusis had tinnitus (Davis and El Rafaie, 2000), and the prevalence was higher among people aged 55 to 64 years and 65 to 84 years with 14.3% and 14.7%, respectively (Nondahl *et al.*, 2011). Fujii *et al.* (2011) reported that the prevalence of tinnitus among Japanese increased from 4.9% (women) and 9.4% (men) at the age of 45 to 49 years old to 14.5% (women) and 15.5% (men) at the age of 70 to 79 years old. As reported in the UK national study of hearing (Hall *et al.*, 2013), the incidence rate increased steadily with age with higher rate was observed in men and women aged 60 to 69 years old.

The increase in prevalence with age was not always linear throughout the life span. As reported by Sindhusake *et al.* (2003), the tinnitus prevalence was the highest at the age of 60 to 69 years old (32.7%) and then continuously reduced after the age of 70 years old for both men and women (70-79 years, 30.5% and 80+years, 25.4%). In a study of Shargorodsky *et al.* (2010), the tinnitus prevalence was the

highest at the age of 40 to 49 years old (21.7%) and continually reduced until 4.1% at the age of more than 80 years old. The reason for this decrement was not clear but Nondahl *et al.* (2011) assumed that older adults might feel that their tinnitus is less important than their overall general health. On the other hand, since the majority of elderly adults have elevated hearing thresholds, they are more concerned about the hearing loss rather than the tinnitus (Roberts *et al.*, 2010). In this regard, they might be able to cope with tinnitus and would less likely to report it.

2.5.2 Hearing loss

Pathophysiological studies have suggested that tinnitus is generated due to any disorders along auditory pathways and it is evident that hearing loss is strongly correlated with tinnitus, particularly sensorineural hearing loss. Sanchez (2004) reported that the severity of tinnitus was correlated with the degree of hearing difficulty. The associations between high-pitch tinnitus and high-frequency hearing loss have also been reported (Martines *et al.*, 2010; Shargorodsky *et al.*, 2010; Salvago *et al.*, 2012).

Sindhusake *et al.* (2003) carried out a study on elderly community aged 49 years old and above. The audiometric findings showed that the participants with poorer hearing were the ones who mostly reported tinnitus. The number of participants with tinnitus increased as the pure tone average (PTA) increased. Furthermore, when tinnitus and hearing level were analysed with age, they found that the association between tinnitus and hearing loss was greater in younger participants (aged less than 65 years) than the elders (aged above 65 years).

2.5.3 Occupational noise exposure

The occurrence of tinnitus among workers exposed to continuous noise is common. As shown by Nondahl *et al.* (2002a), participants with significant tinnitus were more likely to have history of noise exposure. Ahmed *et al.* (2001) performed a cross-sectional study among workers from two factories in the Eastern Province of Saudi Arabia. They then found that 38.3% of subjects exposed to daily noise above the permissible level of 85 dB(A) had hearing impairment and 10% of them claimed to have tinnitus.

In a study of Palmer *et al.* (2002), questionnaires about history of noise exposure were mailed to 22,194 adults in Great Britain including members of armed services. They then found that the severity of hearing difficulty increased with the increase of duration of working in the noisy working environments and men were more affected than women.

2.5.4 Other factors

Other risk factors associated with tinnitus prevalence that have reported are cardiovascular and cerebrovascular disease, head or neck trauma and injury, hyper- and hypothyroidism, alcohol, anxiety, depression and smoking. (Hoffman and Reed, 2004). Epidemiological studies were performed by Nondahl and his colleagues (2002b; 2010; 2011) in Beaver Dam, Wisconsin aiming at finding the prevalence, incidence and factors associated with tinnitus in adults aged 48 to 92 years. In their second cohort of study (1998-2000), the incidence of tinnitus was 5.7% among 2513 participants (Nondahl *et al.*, 2002b). The factors that were significantly associated with tinnitus were history of head injury (Nondahl *et al.*, 2010; Nondahl *et al.*, 2011), history of cardiovascular disease, history of smoking and history of arthritis

and hearing loss. In their latest cohort study (2005-2008)(Nondahl *et al.*, 2011), apart from hearing loss and hazardous noise exposure, the risk factors for getting tinnitus were associated with history of head injury, depressive symptoms and history of ear infection. Arthritis and medications also gave the risk to tinnitus emergence in this cohort.

2.6 Effect of Tinnitus

Individuals with tinnitus may react differently to their tinnitus, depending on their psychological state and the hearing level (Andersson, 2003; Hiller and Goebel, 2006; Wallhäußer-Franke *et al.*, 2012). Disabling tinnitus could affect lifestyle, general health and emotional status. This happens when tinnitus is perceived as a threat, continually intrusive, or difficult to cope. As stated by Halford and Anderson (1991), the severity of tinnitus was strongly related to the elevated anxiety and depression. Nevertheless, the depressive tendency was lower in elderly aged more than 65 years old and in male population (Andersson and Vretblad, 2000). Tinnitus was described as more discomfort when hearing loss is present.

Moreover, the prevalence of persistent tinnitus was higher among workers with complaints of tiredness and frequent headache for both genders (men and women) (Palmer *et al.*, 2002). Other problems reported by individuals with tinnitus were irritation, sleep difficulties, concentration difficulties, emotional disturbance and depression (Tyler and Baker, 1983; Andersson *et al.*, 1999).

The level of tinnitus annoyance has significant correlations with permanent or continuous tinnitus, increasing tinnitus loudness, poor mask ability, history of sudden hearing loss, craniomandibular disorders and long standing of noise exposure (Hiller and Goebel, 1999; Hoekstra *et al.*, 2014). It is also correlated with

vertigo or dizziness, hyperacusis and history of neurological diseases. In contrast, no clear pattern of the tinnitus-related distress found in cases of vascular disorder, cervical spine dysfunction, acoustic neuroma and Meniere's disease (Hiller and Goebel, 2007).

2.7 Decreased sound tolerance

Tinnitus is frequently associated with sound intolerance or decrease sound tolerance. It is a complex phenomenon, in which the limbic and autonomic nervous systems are involved. Hyperacusis is unusual intolerance to ordinary environmental sounds (Baguley, 2003), occurs with or without hearing loss in individuals with tinnitus (Goldstein and Shulman, 1995). It happens due to an abnormal functioning of the peripheral auditory system (dysfunction of facial nerve innervates the stapedius muscle or dysfunction to the outer hair cells system), as well as the central auditory system (increased sensitivity of neurons in auditory pathways resulting from sound deprivation due to hearing loss or changes in neurotransmitter and neuromodulators) (Baguley, 2003).

Hyperacusis is different from recruitment. The recruitment is an experience commonly associated with cochlear hearing loss and specifically with dysfunction of the outer hair cells: as a sound level is increased, the perceived loudness increases faster than normal and it does not vary with mood as hyperacusis (Baguley, 2003). In hyperacusis, the patient would experience physical discomfort when exposed to certain level of sound and the same sound would not evoke a similar reaction in the average listeners (Jastreboff, 2004).

Among Polish population, 15.2% of 10,349 individuals with constant tinnitus had hyperacusis (Fabijanska *et al.*, 1999). Anari *et al.* (1999) revealed an exclusive

finding in describing symptoms of hyperacusis among patients attending audiology clinic in University Hospital of Go¨teborg, Sweden. They found that 14% of the subjects suffered from hyperacusis as an isolated symptom, and 35% of them were annoyed by the hyperacusis compared to tinnitus. The most common complaint reported by the subjects about the discomfort of sound was pain, particularly for environmental sounds. Fatigue and stress were additional factors that would make their sound hypersensitivity becoming worse.

Phonophobia and misophonia are other phenomena for sound intolerance faced by tinnitus sufferers. Phonophobia is a condition when certain sounds or all sounds (typically environmental sounds) cause fear to the patients. In this regard, they are afraid that the sounds may damage the ear or make the tinnitus worsen. Misophonia is a condition where the patients dislike certain sounds without feeling of fear (Baguley, 2003; Jastreboff, 2004). Both phenomena are abnormal reactions of autonomic and limbic systems resulting from enhanced connections between the auditory and limbic system. The intolerance may be specific to certain sounds with emotional associations.

2.8 Tinnitus evaluation

The major challenge for managing tinnitus is the subjective nature of the symptom. It is difficult to know whether the condition actually exists as claimed. Although tinnitus itself is not dangerous, it could be a sign of potentially dangerous diseases that can become life threatening if left undiagnosed and untreated. By assessing the symptom, at least the clinician could help the patients to manage the symptom and reduce the distress related to tinnitus. Steiger and Hamill (2004) proposed a clinical pathway for tinnitus evaluation and management (Figure 2.1). It

shows the flow of tests, procedures, management options and decisions involved in treating patients with tinnitus. This clinical pathway is one of many pathways suggested by many authors.

Tinnitus evaluation should start with initial contact, this includes detailed history of otologic problems, subjective judgments of patient's tinnitus pitch, tinnitus loudness, annoyance and interference with daily life and subjective sound intolerance including hyperacusis (Steiger and Hamill, 2004; Langguth *et al.*, 2011). Newman *et al.* (2011) listed important elements to explore when dealing with patients with complaints of tinnitus (Table 2.2).

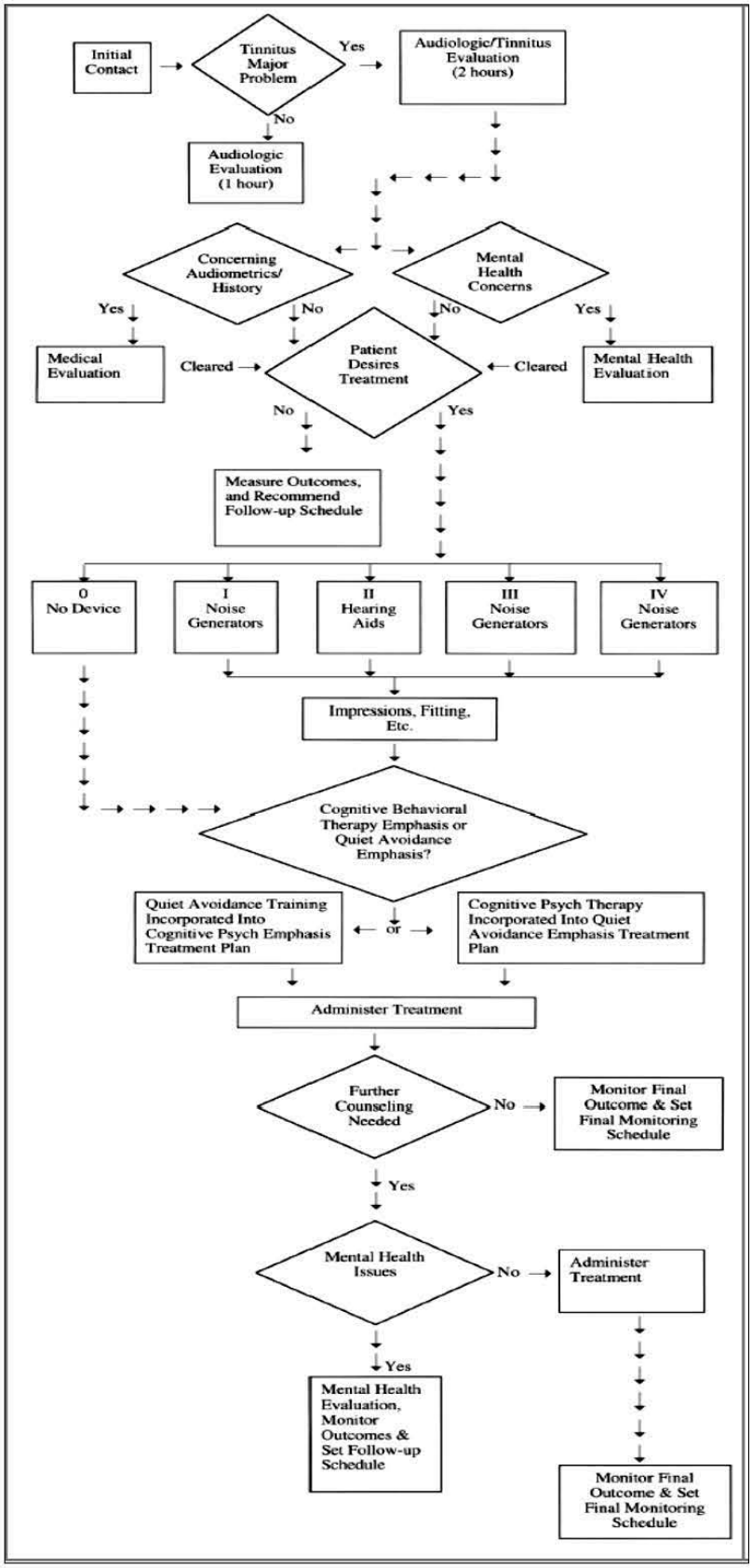

Figure 2.1 The tinnitus clinical pathway as suggested by James R.Steiger and Teri A. Hamill (adapted from Steiger and Hamill (2004))

Table 2.2 Elements to explore when a patient complains of tinnitus (adapted from Newman *et al.* (2011)).

Nature and chief complaint	Location (unilateral or bilateral) Duration Character (pulsatile, intermittent, constant) Quality (ringing, hissing, roaring) Associated vertigo or hearing loss Perceptual characteristics (pitch, loudness)
Medical and surgical history	Noise exposure (occupational, recreational) Head trauma Medications and ototoxic agents Dental problems Exacerbating factors (diet, stress, activity level, smoking, alcohol) Review of systems Prior otologic survey
Psychosocial history	Level of annoyance Sleep disturbance Depression, stress Suicidality
Compensation	Pursuing compensation, disability or other legal action related to tinnitus
Physical examination	Otoscopy Tuning fork examination Test of cranial nerves Oral cavity examination Palpation of temporomandibular joint and inspection of dentition
For pulsatile tinnitus	Assessment for bruits Rate of tinnitus compared to pulse Effect of light digital pressure over internal jugular vein Effect of tuning the head (causing tinnitus of venous origin to subside)

2.8.1 Psychoacoustic measurement for tinnitus

The psychoacoustic testing provides an objective measure to quantify the profiles of tinnitus. The importance of obtaining psychoacoustic information of tinnitus has been highlighted since 1928 by Jones and Knudsen (Henry and Meikle, 2000). Even though the measurement was not strongly related with tinnitus severity (Kajsa-Mia Holgers, 2003), it helps clinician and the patients in many ways.