A TINNITUS MODEL USING McKENDRIK EQUATION

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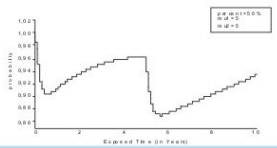
INTRODUCTION Tinnitus is characterized by the perception of sound or noise in the absence of any internal or external acoustical stimulation. It affects about 15 to 20 % of population, causing a several amount of distress for 20 % of these patients. It is of general agreement that there are many subtypes of tinnitus and, because of this, pathophysiology and treatment results may differ amongst different tinnitus populations. Many mathematical models have been proposed for epidemiological analysis, one of them being the McKendrik equation. We propose a mathematical model using the McKendrik equation to preview tinnitus onset on a specific population and its response to specific therapeutic methods

MATHEMATICAL BACKGROUND We suppose that there is a tinnitus disease rate($\lambda(x)$) in $L_1[0;X]$, depending on the age(x); on an empirical basis, we may say that $\lambda(x) = ax^2$ and we suppose that the medical cure rate($\mu(t)$) belongs to $L_1[0; T]$. Although this model may be seen in the light of McKendrick's equations, in this present study we suppose that there is a new sudden clinical event (acute noise trauma, sudden hearing loss, f.ex.) at a specific time t_0 in [0; T], when ρ is the probability that accounts for how long it will take to the onset of tinnitus after the event. Consequently, we may have:

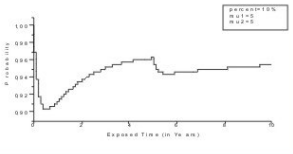
$$\frac{\partial p_1(x,t)}{\partial x} + \frac{\partial p_1(x,t)}{\partial t} = -\lambda(x)\, p_1(x,t) - \rho\ \ p_1(x,t_0)$$
$$\frac{\partial p_2(x,t)}{\partial x} + \frac{\partial p_2(x,t)}{\partial t} = -\mu(t)\, p_2(x,t)$$
$$p_1(x,0) = \lambda(x)\, \exp\left(-\int \lambda(x)\, dx\right)$$
$$p_2(x,0) = 0$$
$$p_1(0,t) = \mu(t) \int_{x=0}^{x=\infty} p_2(x,t)\, dx$$
$$p_2(0,t) = \int_{x=0}^{x=\infty} (\lambda(x)\, p_1(x,t) + \rho\ \ p_1(x,t_0))\, dx$$
$$P_1(t) = \int_{x=0}^{x=\infty} p_1(x,t)\, dx$$

Where t_0 time of accident and $P_1(t)$ probability of health (no tinnitus onset) and $P_2(t)$ probability of tinnitus worsening. Considering the equations, the following graphics arise:

Probability of Health-Instant model



Probability of Health-instant model

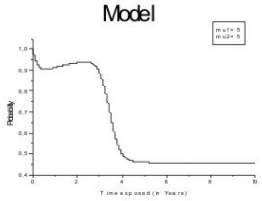


The left graphic shows tinnitus incidence variation with no treatment after a new clinical event in year 5: there is spontaneous recovery, but the healthy population never reach the original level. In the right graphic, with treatment, recovery is better.

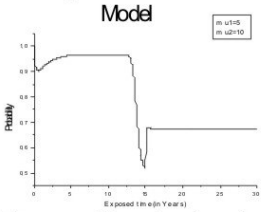
We may suppose now that the noise level is accumulative with maximum in t0 and g(t) is in $L_1[0; T]$; within the previous framework in addition to neural models of pattern formation, we can propose that

$$\frac{\partial p_1(x,t)}{\partial x} + \frac{\partial p_1(x,t)}{\partial t} = -\lambda(x)\, p_1(x,t) - \int_{t=0}^{t=T} g(t-t_0)\, p_1(x,t)\, dt$$
$$\frac{\partial p_2(x,t)}{\partial x} + \frac{\partial p_2(x,t)}{\partial t} = -\mu(t)\, p_2(x,t)$$
$$p_1(x,0) = \lambda(x)\, \exp\left(-\int \lambda(x)\, dx\right)$$
$$p_2(x,0) = 0$$
$$p_1(0,t) = \mu(t) \int_{x=0}^{x=\infty} p_2(x,t)\, dx$$
$$p_2(0,t) = \int_{x=0}^{x=\infty} \left(\lambda(x)\, p_1(x,t) + \int_{t=0}^{t=T} g(t-t_0)\, p_1(x,t)\, dt\right) dx$$
$$P_1(t) = \int_{x=0}^{x=\infty} p_1(x,t)\, dx$$

Probability of Health- Cumulative Model



Probability of Health- Cumulative Model



In the left graphic, the cumulative rate of disease with no treatment and in the left with treatment .

DISCUSSION The instantaneous model graphics show that, in a chronic symptom like tinnitus, acute clinical events may lead to enhancement of symptoms, which may improve with prompt onset of therapeutic strategies. Similar facts happen in the cumulative model and the McKendrik equations may be a helpful tool to preview many tinnitus features. Experimental confirmation is needed to establish its value and may be a powerful aid in planning therapeutic strategies in a given population.

CONCLUSION The McKendrik is a possible helpful model for tinnitus epidemiology and therapeutic strategies planning. Experimental confirmation is needed to verify these results.

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ANALYSIS OF THE CORRELATION BETWEEN THE TINNITUS HANDICAP INVENTORY AND A VISUAL-ANALOG SCALE IN TINNITUS PATIENTS

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INTRODUCTION Tinnitus is characterized by the perception of sound or noise in the absence of any internal or external acoustical stimulation. Tinnitus treatment is still a great challenge and some of the difficulties are brought about by the lack of consensual measurement methods. One of the most applied methods is the visual-analog scale (VAS), which is widely used in chronic pain's evaluation. With the aid of a specific ruler, tinnitus is rated from 1 to 10, according to intensity and annoyance (figure 1). It's an easy applied method for most of the tinnitus patients, although the overall evaluation may be too superficial and influenced by cultural, intellectual and psychological aspects. Back in 1996, Newman et al developed the Tinnitus Handicap Inventory (THI), after the observation and critics to other methods, like the Tinnitus Handicap/Support Questionnaire, Tinnitus Effect Questionnaire, Tinnitus Severity Questionnaire and Tinnitus Reaction Questionnaire. According to the authors, THI is expected to:
- be resumed, suitable for daily clinical practice.
- be easy to apply and interpret.
- cover many tinnitus aspects related to patients' quality of life.
- be reliable and valid.

Tinnitus patients' clinical data were used in THI's development, such as functional, emotional and catastrophical reactions to tinnitus. THI is, nowadays, one of the most widely used tinnitus questionnaires and its brazilian portuguese version was validated in 2005. Our purpose is to evaluate the correlation between VAS and THI scores in tinnitus patients.

MATERIAL AND METHOD 43 patients with tinnitus as the main complaint who presented at OTOSUL between January 2005 and January 2006 were selected. Exclusion criteria were external and middle ear diseases and temporomandibular joint disease. Tonal-vocal audiometry (AMPLAID A177 PLUS) and immitance audiometry (AMPLAID 750) were performed in every patient, and those with conductive and mixed hearing losses and tympanograms type A-s, A-d, C and B were excluded. Patients were asked to fulfill the THI (Tinnitus Handicap Inventory) questionnaire in its brazilian portuguese validated version and to rate their tinnitus (intensity and annoyance) according to a VAS scale in a specific ruler (figure 1). The correlation between THI and VAS was analyzed by the Spearman coefficient.

RESULTS Clinical and demographical data are exposed on table 1. According to the Spearman coefficient, there was correlation between THI and VAS (r_s= 0,564; p= 0,0001; n= 53). This means that, the higher it was the VAS score, the higher it was the expected THI score (direct correlation, graphic 1).

N=43	AVERAGE	SD (+/-)
AGE	62,85 yrs	10,3 yrs
GENDER	M 30,33 % F-69,77 %	-x-
TIME OF TINNITUS	7,45 yrs	9,55 yrs
PERIODICITY	Continuous 74,42% Intermitent– 35,58%	-x-
TYPE	Creak – 62,84% Whistle – 28,56 % Others – 8,60 %	-x-
AETIOLOGY (PROBABLE)	Presbicusys – 35,8 % Noise induced – 11,3 % Metabolic – 7,5 % Others – 3,8 % Multiple – 24,6 % Idiopathic – 17 %	-x-
TYPE OF HEARING LOSS	Descendent – 81,1 % Drop – 7,5 % Ascendent – 7,5 % Others – 3,9 %	-x-
VAS score	6,7	2,5
THI score	53,4	24,45

Table 1 – Clinical and demographical data

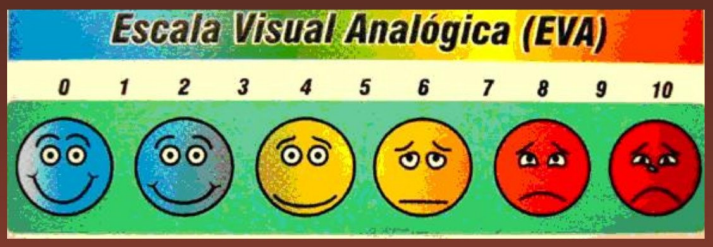
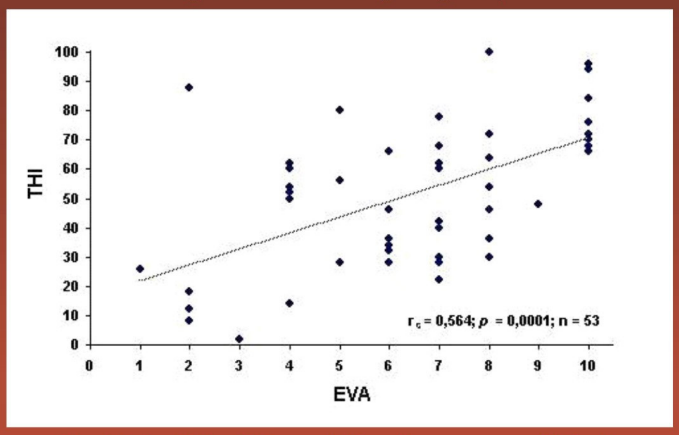


Figure 1 – VAS scale (portuguese)



Graphic 1 – THI x VAS correlation (Spearman coefficient)

DISCUSSION One of the most critical aspects of tinnitus studies is the measurement method employed. In the search for the ideal measurement method, many questionnaires have been proposed, as well as audiometric tinnitus matching and masking levels. The THI is one of the most widely used questionnaires, but in Brazil most of the published studies in tinnitus were done with the VAS. In the last years, there is a tendency in Brazil to use the THI. The correlation of both methods scores' in our data, enhances the reliability of VAS, which is, in our opinion, more easy to apply in the majority of the Brazilian population. THI, however, is, in our opinion, more complete, remarkably in daily life and psychological aspects of tinnitus. Considering those facts, we now apply both methods in our tinnitus clinical trials.

CONCLUSION: There is correlation between Tinnitus Handicap Inventory and Visual-Analog Scores in tinnitus evaluation.

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TINNITUS TREATMENT WITH MEMANTINE

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INTRODUCTION Tinnitus is characterized by the perception of sound or noise in the absence of any internal or external acoustical stimulation. There is increasing evidence that functional changes both in the cochlea and in the central nervous system are involved in the pathophysiology of the different forms of tinnitus. Research has focused on the glutamatergic system, because glutamate is the main excitatory neurotransmitter both in the cochlea and in the central auditory pathways. It has been suggested that increased release of glutamate may be involved in the generation and maintenance of tinnitus by causing "excitotoxicity", in which conditions such as noise exposure may lead to excessive release of glutamate at the synaptic cleft between the inner hair cell and the terminal fibers of the auditory nerve, leading to overexpression of NMDA synaptic receptors. Overexpression of NMDA receptors also makes neurons more sensitive to increased glutamate transmission, which may perpetuate the "vicious cycle" of excitotoxicity. Ten years ago modulation of glutamatergic transmission by topic administration of the nonselective glutamate receptor antagonist caroverine to the inner ear has been proposed for tinnitus treatment. However, the systemic use of nonselective glutamate receptor blockers such as caroverine is limited by severe neurological and psychiatrical side effects. Topical application of selective NMDA antagonists has shown promise in animal studies and in a recent pilot study in humans, but long-term drug application to the cochlea represents still an unsolved problem. An alternative may be provided by systemic application of selective NMDA blockers, such as acamprosate, flupirtine or memantine . The systemic application of the NMDA antagonist memantine has proven efficacy in CNS disorders such as Parkinson's and Alzheimer`s disease. In a recent animal study which studied the effect of memantine on salicylate and quinine-induced tinnitus in rats, beneficial effects on tinnitus-related behavior have been observed, even if they failed to reach statistical significance.

MATERIAL AND METHOD 60 patients were selected at OTOSUL between January 2005 and January 2006, excluding cases with TMJ disorders, external and middle ear diseases. They were randomized into 2 groups of 30, subsequentially taking memantine and placebo (double-blind cross-over design), with a 30 days wash-out period. The group that started with memantine was called Group M and the group that started with placebo, Group P. Tinnitus was analyzed with the brazilian portuguese version of THI (Tinnitus Handicap Inventory), fullfilled for three times by the patients: before taking any drug, in the beggining of the wash-out period and at the end of treatment. THI changes were analyzed by Students, Mann-Whitney and Wilcoxon tests, as well as the side effects. Delta THI was defined by the formula Delta THI = ending THI – starting THI (ending THI=THI at the end of memantine or placebo, starting THI = THI at the beginning of trial). We also performed an ANOVA with the factors time (THI scores before and after treatment), treatment group (memantine or placebo) and treatment order (memantine first, placebo first). This study had the approval of the Ethical Medical Comettee of the Valença Medical School. Memantine`s therapeutical scheme adopted was: Week 1, 5 mg by morning; Week 2, 5 mg by morning and 5 mg by night; Week 3, 5 mg by morning and 10 mg by night; Week 4 till end 10 mg by morning and 10 mg by night.

RESULTS Out of the 60 patients selected, 53 started the trial, with predominance of females (66 %). The most common tinnitus aetiologies in the sample were presbyacusis (58,5 %), methabolic disease (22,6 %) and noise induced hearing losses (20,8%). 43 patients completed the trial. We considered significant, according to previous THI studies, changes in the scores of 10 points or more (up and down). Table 1 show THI scores evolution in treatment with memantine, placebo and general. Evolution was classified as worsening (absolute THI delta 10), steady (absolute delta between –10 and 10) and improvement (absolute delta -10).

	Memantine		Placebo		General	
THI evolution	n	%	n	%	n	%
Worsening (THI >_ 10)	9	20.9	6	14.0	6	14.0
Steady (-10 to 10)	18	41.9	17	39.5	15	34.9
Improvement (THI ≤ -10)	16	37.2	20	46.5	22	51.1

Table 1 – THI Evolution

	Delta THI (MA)	Delta%THI (MA)
Memantine in Group M	5,0	8,7 %
Placebo in Group M	- 13,1	- 24,1 %
Placebo in Group P	- 8,7	- 8,2 %
Memantine in Group P	- 9,7	- 5,7 %

Table 2 – Delta THI of memantine and placebo according to the starting treatment (MA=mean average)

Table 2 shows the Delta THI of memantine or placebo according to the starting drug. The incidence of side effects for memantine was 9,4 %. Dizziness was the most common as also arterial hypertension, insomnia and stomach ache. The ANOVA revealed a significant time effect (p = 0,006) with a reduction of the THI score, regardless of the type and order of treatment. There was no significant time-treatment interaction (p = 0,57) indicating that there was no significant difference between memantine or placebo treatment, but there was a significant interaction between time, treatment and order (p = 0,042), which could indicate a potential carry-over effect.

DISCUSSION This placebo-controlled cross-over study did not show a significant difference between memantine and placebo treatment on tinnitus severity as assessed with the THI. The negative finding of our study together with results from recent studies in animals and humans raise the question of whether systemic treatment with NMDA receptor antagonists in general can be judged as an appropriate strategy in the treatment of chronic tinnitus. Mechanisms mediated by NMDA receptor activation are probably critical for the induction of plastic synaptic changes on a cochlear and central level, and they might be involved in the development of tinnitus. However, in patients with chronic tinnitus, such neuroplastic changes might already be fixed, and NMDA antagonists might not be useful anymore. Support for this notion comes from studies in chronic pain syndromes but, in line with our results, these studies did not demonstrate significant effects of memantine on pain perception. It might be that the concentration of memantine in the cochlea and in the brain is too low to reduce NMDA-receptor-mediated synaptic excitability in chronic tinnitus or that chronic tinnitus is additionally maintained by mechanisms independent from the NMDA-receptor activation. However it seems unlikely that a higher dosage of memantine would have been tolerated. Earlier studies using higher dosages up to 50 mg reported a high percentage of side effects without an increase in efficacy. Furthermore it has been repeatedly stressed that negative findings in pharmacologic studies may be due to the existence of many forms of tinnitus with differing pathophysiology. Thus it might be possible that increased glutamatergic activity and excitotoxicity play a more important role in more acute forms of tinnitus and memantine might be more efficient in those patients. Interestingly, there was a significant interaction between treatment effect and treatment order with a more pronounced placebo effect in the group that started with memantine. One might therefore speculate whether this could represent a delayed carry-over effect of memantine treatment. In order to further clarify whether memantine might exert delayed effects on tinnitus, further studies with longer treatment periods will be necessary.

CONCLUSION This clinical trial`s results don`t provide sufficient data to recommend memantine as a therapeutic alternative for tinnitus, but a possible late effect of the drug should be evaluated in further studies.

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