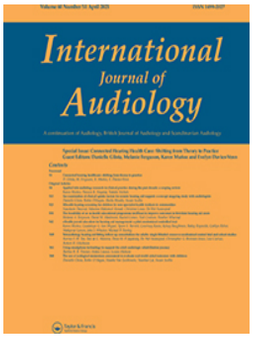

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ORIGINAL ARTICLE

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Association of beta blocker use and hearing ability in adults: a cross-sectional study

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ABSTRACT

Objectives: To investigate the potential association between beta blocker use and hearing ability in adults and to discern whether this effect is dose-dependent.

Design: Cross-sectional analyses. Multiple linear regression was performed with hearing ability as the dependent variable and beta blocker use as the independent variable. The independent variable was classified into three dose categories for secondary analysis. Adjustments were made for age, gender, educational level, and tobacco smoking status.

Study sample: 1636 adults, 75 of whom reported being on beta blockers, from the internet-based Netherlands Longitudinal Study on Hearing (NL-SH).

Results: No significant association was found between beta blocker use and hearing ability in noise. In the adjusted regressions, beta blocker use changed the speech reception threshold in noise (SRT) by −0.04 dB signal-to-noise ratio (SNR) (95%CI [−0.67 to 0.58], $p = 0.890$). Medium dose beta blocker use changed SRT by −0.42 dB SNR (95%CI [−1.38 to 0.71], $p = 0.433$), while a high dose changed it by −0.26 dB SNR (95%CI [−1.74 to 1.4], $p = 0.767$).

Conclusions: No evidence was found for beta blocker-induced changes in hearing ability. Future studies on this topic should favour case-control and cohort study designs, while focussing on a hypertensive population to minimise confounding by indication.

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Hearing; ototoxicity; beta blockers; medication; adverse effects

Introduction

Over 460 million adults worldwide have impaired hearing (WHO 2019). Throughout life, hearing deteriorates as age increases, but many other risk factors may influence the development of hearing loss (Goderie et al. 2020; Van Eyken, Van Camp, and Van Laer 2007). Several potential causes have been identified, including noise exposure, tobacco smoking, genetic factors, certain medical conditions, and certain medications (Besser et al. 2018; Cianfrone et al. 2011; Goderie et al. 2020; Kiely et al. 2012; Momi et al. 2015). Toxicity to the ear, known as ototoxicity, is well established for certain medications, such as cisplatin and aminoglycosides (Ganesan et al. 2018). However, ototoxicity is so poorly studied for many medications that it has been referred to as a "hidden menace" (Bisht and Bist 2011; Rohra, Memon, and Khan 2008).

Ototoxicity can manifest in many ways, ranging from hearing impairment to tinnitus (Bisht and Bist 2011). Because of the complex nature of the ear as well as the multiplicity of medication effects and widespread off-target action, the development of hearing impairment is a suspected adverse effect in a number of medications (Cianfrone et al. 2011; Ganesan et al. 2018). It is therefore of interest to healthcare providers to develop a higher awareness of established ototoxicity of widely prescribed drugs, particularly those for chronic use.

With the chronic and prevalent nature of cardiovascular disease (WHO. 2017), it is unsurprising that beta blockers continue to be widely prescribed for numerous cardiovascular indications (Frishman 2008). While they are speculated for having ototoxic effects (Cianfrone et al. 2011), challenges remain in clinical practice for identifying and monitoring medication ototoxicity (Ganesan et al. 2018).

Beta blockers were designed for cardiovascular use and the majority are specific to the beta1 adrenergic receptors (ARs), predominantly located in the heart. However, beta receptors in other parts of the body can cause off-target effects, which brings us to wonder about downstream effects if beta receptors are present in the ear. For example, respiratory exacerbations can be provoked by beta blockers' unintended activity on beta2 receptors in the lungs (Malerba et al. 2015; Sirak, Jelic, and Le Jemtel 2004). Although most beta blockers target beta1, non-specific beta blockers can bind to beta2 as well. For instance, carvedilol blocks both beta1 and beta2 in addition to alpha ARs (Messerli and Grossman 2004), thus opening the potential to more off-target effects. Most pertinent to the current study, Fauser, Schimanski, and Wangemann (2004) demonstrated that beta1

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Table 1. Dose cut-offs of reported beta blockers used for dose categorisation.

	Low dose (mg)	Medium dose (mg)	High dose (mg)
Bisoprolol	≤1.25	>1.25 and ≤ 2.5	>2.5
Nebivolol	<15	≥15 and ≤27.5	>27.5
Atenolol	<50	≥50 and <75	≥75
Propranolol	<50	≥50 and <100	≥100
Metoprolol	≤50	> 50 and <150	≥150
Sotalol	<160	≥160 and ≤200	> 200

ARs are present in inner ear epithelial cells, neuronal cells involved in auditory transmission, as well as in hair cells in both the inner and outer ear. In a histochemical study, Khan et al. (2007) showed that alpha, beta1 and beta2 ARs are present in the Organ of Corti and the spiral ganglion of rats. This raises the question about whether beta blockers, even when selective for beta1, may have unintended effects in the ear. Schimanski, Scofield, and Wangemann (2001) found the presence of beta2 receptors in nonstrial tissues in the cochlear lateral wall in gerbils. If beta ARs are present in the auditory system, there is reason to believe that specific and/or non-specific beta blockers may contribute to hearing impairment.

The above studies give reason to investigate the potential ototoxic effect of beta blockers. In fact, beta blockers can be found on lists of ototoxic medications according to clinicians' expert opinions (Cianfrone et al. 2011), and certain beta blockers have documented incidents of being associated with hearing impairment or hearing loss (Faldt 1984). The strongest evidence for beta blockade-induced hearing loss is a cross-sectional study of 125 participants demonstrating a significant association between carvedilol usage and hearing loss (Al-Ghamdi et al. 2017). However, this association is yet to be confirmed by other studies.

In this study, we investigate the association between beta blocker use and hearing ability in an adult population. Hearing ability is measured as speech recognition in noise, which is more representative of hearing performance in daily life than pure-tone audiometry (Houtgast and Festen 2008). The secondary research aim is to investigate the association between the dosage of beta blockers and hearing ability in the same population. The hypothesis is that beta blocker use is associated with worse hearing ability in noise and that this relationship is dose-related.

Materials and methods

Study design

This observational cross-sectional study uses data from the Netherlands Longitudinal Study on Hearing (NL-SH). This ongoing prospective web-based cohort (NL-SH) was set up in 2006 to examine the relationship between hearing ability and several aspects of life in adults. Its data has also been used to investigate the development of deterioration of hearing over time. The major portals for recruitment are the online Dutch National Hearing Test (NHT; www.hoortest.nl) and the study website (www.nlsh.nl) where people can take the hearing test. After being presented with the test results, people are asked if they would like to take part in the research. Participants must be between the ages of 18–70 years to enrol. Online measurements take place every five years. At each time point, participants complete an online hearing test, followed by questionnaires on demographics, lifestyle, and psycho-social health. The NL-SH is led by the Amsterdam University Medical Centre and approved by its medical ethical committee. The current study uses baseline data of a selected sample of the NL-SH.

Study sample

Adult, non-hearing-aid users from the NL-SH were included if they completed the online hearing test and filled out the medication information section of the questionnaire. Participants were excluded from the current study if they reported having a cochlear implant. This resulted in 1636 participants whose baseline data was collected between November 2006 and February 2013. For the secondary question regarding beta blocker dosage, participants not reporting beta blocker usage were excluded.

Dependent variable: speech recognition in noise

Speech recognition in noise was measured using the online Dutch National Hearing Test (NHT), of which the reliability and validity have been established (Smits, Merkus, and Houtgast 2006). Participants listened to a series of 23 digit triplets (e.g. 5-2-4) with a fixed background noise, while using their keyboard or mouse to indicate the triplets heard. The test difficulty adapted to their answers, with the relative sound intensity of the triplets increasing or decreasing by two decibels if the answer was incorrect or correct, respectively. The speech reception threshold in noise (SRT) was calculated by the average signal-to-noise ratio (SNR) of the last twenty responses and represents the SNR where the participant recognises 50% of the digit triplets correctly (Smits, Merkus, and Houtgast 2006). While innovative, this digits-in-noise test correlates highly ($r = 0.96$) with the standard speech-in-noise sentences test as used in the laboratory and clinical practice (Smits, Theo Goverts, and Festen 2013).

Independent variable: beta blocker use and dose

For the primary question, beta blocker use was dichotomised into beta blocker use or non-use. Up to 10 medications could be self-reported in the questionnaire with information including medication name, dose, frequency, and duration of usage in the last 28 days. The question was taken from the Treatment Inventory of Costs in Patients with psychiatric disorders (Hakkaart-van Roijen 2002) and adapted for the NL-SH to better measure healthcare costs. Medications were then classified based on the second hierarchical level of the Anatomical Therapeutic Classification (ATC) system of the WHO. The six reported beta blockers were then further coded based on their chemical names. For dose analysis, the reported beta blocker doses were classified as low, medium, or high based on our cut-offs for each medication. Due to the lack of established dose categorisation systems, the derivation of these cut-offs was based on typical daily dosing and can be viewed in Table 1. Unreported or incomprehensible dose values were excluded from the dose analysis.

Independent variables: demographics and smoking status

Age, gender, educational level, and tobacco smoking status were tested as possible effect modifiers and as confounders. Educational level was assessed based on responses to highest completed education and categorised into three levels: low, intermediate, and high. Tobacco smoking was dichotomised to either current or former smoker and never smoked.

Table 2. Sample characteristics.

	Total participants ($n = 1636$)		Beta blocker users ($n = 75$)		Beta blocker non-users ($n = 1561$)	
	n	%	*n*	%	*n*	%
Mean age, years (SD)	45.8 (13.0)	–	52.3 (8.8)		45.4 (13.1)	
Sex						
Men	587	35.9	32	42.7	555	35.6
Women	1049	64.1	43	57.3	1006	64.4
Hearing ability						
Hearing Test Score in dB signal-to-noise-ratio (SD)	−5.72 (2.78)	–	−5.36 (2.84)	–	−5.74 (2.77)	–
Educational level[a]						
Low	292	17.8	20	26.7	272	17.4
Intermediate	534	32.6	31	41.3	503	32.3
High	808	49.4	24	32.0	784	50.3
Chronic conditions history in the last 12 months						
Severe heart disease or myocardial infarction[b]	21	1.3	8	10.8	13	0.8
Hypertension[c]	267	16.4	50	66.7	217	14.0
Severe kidney disease[d]	6	0.4	1	1.4	5	0.3
Diabetes[e]	41	2.5	7	9.5	34	2.2
Smoking history [f]						
Current or former smoker	960	58.9	57	76.0	903	58.1
Non-smoker	670	41.1	18	24.0	652	41.9

[a]2 participants had missing data on educational level, both of which were beta blocker non-users.
[b]8 participants had missing data on history of myocardial infarction, 7 of which were beta blocker non-users.
[c]7 participants had missing data on history of hypertension, all of which were beta blocker non-users.
[d]17 participants had missing data on history of kidney disease, 16 of which were beta blocker non-users.
[e]16 participants had missing data on history of diabetes, 15 of which were beta blocker non-users.
[f]6 participants had missing data on smoking history, all of which were beta blocker non-users.

Other variables

The presence of chronic medical conditions was self-reported on the questionnaire with a checkbox list of 27 chronic conditions. This list was based on the official list of Statistics Netherlands used nationally for public health purposes (Mootz and van den Berg 1989). For descriptive purposes, we included information about the presence of four relevant conditions in our dataset: severe heart disease or myocardial infarction, hypertension, severe kidney disease, and diabetes.

Statistical analyses

Analyses were performed using multiple linear regression, with SRT as the dependent variable. Assumptions of multiple linear regression were verified. Standard errors and confidence intervals were derived with bootstrapping as the residuals were non-normally distributed. To examine effect modification, interaction terms were constructed and added to the regression model. Confounding was checked by adding each possible confounder to the regression model in a forward selection procedure. A variable was considered a confounder if its inclusion resulted in a 10% change of the coefficient of the independent variable. Data is presented for both before and after adjustment for effect modification and confounding.

For the secondary research question regarding beta blocker dosage, two dummy variables were constructed for the medium and high dosages and were compared with the group with low dose beta blocker use.

All analyses were done with SPSS version 24.0 (IBM Corp., Armonk, NY) and p-values < 0.05 were considered statistically significant.

Results

Demographic and health characteristics of the study participants are given in Table 2. Among the total sample of 1636 participants, the mean age was 45.8 years, ranging from 18 to 70 years, and there were more women than men ($N = 1049$ and 587, respectively). Almost half (49.4%) of all participants reported a high educational level. Among the four chronic medical conditions included, the most prevalent was hypertension at 16.4%. The presence of hypertensive participants was 66.7% in the beta blocker users group and 14.0% among the non-users.

Table 3. Beta blocker medications used by participants in sample ($n = 75$).

Beta blocking agent	Frequency (*n*)	Percent (%)
Metoprolol	40	53.3
Atenolol	13	17.3
Propranolol	8	10.7
Bisoprolol	8	10.7
Nebivolol	3	4.0
Sotalol	3	4.0

Out of the total 1636 participants, 75 (4.5%) reported beta blocker use. As shown in Table 3, different beta blockers types were reported in different frequencies. The most frequently reported beta blocker was metoprolol, with 40 (53.3%) beta blocker users reporting usage, followed by atenolol with 13 (17.3%) users. As displayed in Table 4, most beta blocker users reported using either a low or medium dose beta blocker (82.6%).

No effect modification was found in the independent variables. Age, gender, history of tobacco smoking, and education level were found to be confounding variables. After adjustment for these confounding variables, the multiple linear regression showed no association between beta blocker use and hearing ability in noise, nor a relationship between beta blocker dosage and hearing ability in noise. Use of beta blockers changed the SRT by −0.04 dB SNR (95%CI [−0.67 to 0.58], $p = 0.890$). In the secondary analysis which investigated the association between beta blocker dose and hearing ability in noise, the adjusted model found that the use of a medium dose beta blocker changed SRT by −0.42 dB SNR (95%CI [−1.38 to 0.71], $p = 0.433$), while a high dose changed it by −0.26 dB SNR (95% CI [−1.74 to 1.4], $p = 0.767$). Details can be found in Table 5.

Table 4. Beta blocker medications dose strengths reported by participants in sample ($n = 63$).

Dose	Frequency (n)	Percent (%)
Low	26	41.3
Medium	26	41.3
High	11	17.5

Twelve participants did not report a valid dose.

Table 5. Summary of multiple linear regression analyses for beta blocker use and speech reception threshold in noise (SRT).

			95% confidence interval			
	Parameter	β	SE	Lower	Upper	p
Primary analysis						
Raw model	Beta blocker use	0.38	0.32	−0.22	0.98	0.24
Adjusted model	Beta blocker use	−0.04	0.32	−0.67	0.58	0.89
Secondary analysis[a]						
Raw model	Beta blocker dose medium	0.08	0.57	−0.93	1.17	0.88
	Beta blocker dose high	0.11	0.95	−1.41	1.85	0.90
Adjusted model	Beta blocker dose medium	−0.42	0.56	−1.38	0.71	0.43
	Beta blocker dose high	−0.26	0.93	−1.74	1.41	0.77

[a]For secondary analysis, two dummy variables were constructed for the medium and high dose groups and compared with the low dose beta blocker users group.

Discussion

Summary of main findings and comparison with other studies

The present study investigated the potential beta blocker induced changes in hearing ability in adults. No statistically significant association was found, implying beta blockers have no effect on hearing ability in noise. Still, other explanations exist for this lack of effect in our study. Upon dose analysis, the vast majority of participants were found to be taking low or medium doses. However, a dose-dependent effect would be better explored as a continuous variable of a single isolated medication. Another factor to consider is that the majority ($N = 64$) of the reported beta blocker use in our study involved beta1-selective agents (metoprolol, bisoprolol, atenolol, and nebivolol). It is possible that any suspected ototoxicity is not class-wide and only present within selective or non-selective beta blockers. This is supported by a cross-sectional study (Al-Ghamdi et al. 2017) in which only the non-selective beta blocker carvedilol was significantly associated with hearing loss, while beta1-selective beta blockers metoprolol and atenolol had no significant association. None of our study participants were taking carvedilol and therefore we could not assess this particular drug's potential impact on hearing ability.

This study enriches the existing literature with a more clinically relevant viewpoint on the relationship between medication use and hearing ability. A previous cross-sectional study using NL-SH data also investigated medication use and hearing ability (Stam et al. 2015) and found no significant relationship between hearing ability and the odds of reporting beta blocker use. In contrast, our study placed beta blocker use as the independent variable in an effort to identify effects of beta blocker use. We also provide an additional dimension by including analyses of beta blocker subclass and dose strength. A previous study on beta-adrenergic medication use and hearing (Mills et al. 1999) combined both beta agonists and beta antagonists, two opposing pharmacological effects. Our study is better positioned to provide clearer results about beta receptor action by focussing on beta antagonists.

Beta blocker-induced ototoxicity is an inherently challenging research topic due to the major potential for "confounding by indication": Grouping participants by medication use also groups them by their diseases requiring the treatment. Our study supports this idea, as shown by the different levels of presence of chronic conditions between beta blocker users and non-users (Table 2). Although hearing impairment has been associated with hypertension and other cardiovascular diseases (Besser et al. 2018; Hong et al. 2015), it is uncertain whether to attribute this association to the disease, the treatments, or other obscuring factors (Kiely et al. 2012). However, other studies are needed to disentangle confounding effects, including those of underlying disease states.

Since hearing impairment develops over time, it is cost-efficient to study this question through a case-control or a retrospective cohort study. A case-control study can control for underlying disease states by matching cases with controls who share the same beta blocker indication, but are treated with non-beta blockers. This is most practical with hypertension because of the various medication options available (James et al. 2014). Conditions such as heart failure would not be conducive to this approach, since the very existence of the condition requires a beta blocker (Yancy et al. 2013). Similarly, a cohort study can also select participants with beta blocker treated hypertension to control for underlying disease states. Although this would only address one of numerous confounders, this approach will minimise "confounding by indication" and be more likely to yield clear conclusions.

Strengths and limitations

One strength of this study is its web-based format. Contrary to popular belief, it has been shown that internet samples are more diverse than paper questionnaires in terms of gender, socio-economic status, geographic region, and age (Gosling et al. 2004). Web-based studies also have the benefit of a widespread geographic reach (Granello and Wheaton 2004). In addition, this study used speech-in-noise testing, a more ecologically valid measurement of everyday hearing tasks than pure-tone audiometry (Houtgast and Festen 2008; Kramer et al. 1996). Our study also benefitted from strong interdisciplinary collaboration between experts in audiology, epidemiology, and pharmacy.

Our study has limitations. Because of its cross-sectional design, we can only hypothesise about causality between a medication class and observed effects. Secondly, the data reported in this study was self-reported, which can introduce response and recall bias. It can be argued, however, that web-based studies have the benefit of being home-based, where participants can readily confirm the accuracy of their reported medications. There may also be concerns that the home-based setting of the hearing test can introduce variability to the results. However, the nature of speech-in-noise testing makes results relatively insensitive to equipment type and ambient noise levels (Culling, Zhao, and Stephens 2005). We also attempted to control for this by providing clear testing instructions.

Another limitation is that only a minority reported beta blocker use, and the duration of therapy was unknown. Future research would benefit from a larger sample size, which would also allow for focussed analyses on groups with narrower age ranges. We would also recommend investigating duration of therapy to explore the possibility of cumulative toxicities. Lastly,

this study was not able to discern the influence of underlying conditions, which requires different study designs.

Implications

While the relationship between beta blocker use and hearing impairment remains unestablished, there is reason to maintain awareness among prescribers for monitoring hearing ability. Since beta blockers are notorious for a wide array of potentially life-threatening adverse effects (Sirak, Jelic, and Le Jemtel 2004; Yancy et al. 2013), hearing impairment is understandably less prioritised. Knowledge and disclosure of ototoxicity may be improved in general prescribing practice (Wium and Gerber 2016), particularly because its detection is complicated by the gradual and highly prevalent nature of hearing loss. From a pharmacovigilance perspective, more reporting of adverse effects in clinical practice can contribute to filling data gaps on an international level. This data can then open doors to larger scale data analyses, including the more cost-effective retrospective studies.

Conclusions

In considering whether beta blockers are a culprit to a patient's hearing disability, this study aimed to find an association between beta blocker use and hearing impairment. This cross-sectional analysis did not find evidence for beta blocker-induced changes in hearing ability. The question of beta blockers and hearing ability is inherently difficult to study, largely because of the confounding underlying disease states. Future research on this question should design studies to minimise this confounder, which is most appropriately done by focussing on hypertensive participants in case-control or cohort designs.

Ethical approval

Subjects gave written informed consent and the study protocol was approved by the Amsterdam University Medical Centre's medical ethics committee.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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