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The Influence of a Single Therapeutic Dose of Methadone on Selected Auditory Functions in Patients Addicted to Opioids and Undergoing Substitution Therapy – a Preliminary Study

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The main purpose of this research was to determine the influence of a therapeutic dose of an opioid drug (methadone) on selected auditory functions in patients addicted to opioids (recognition ICD-10; F11) and undergoing substitution therapy. Various hearing tests were used in this research – pure tone audiometry, impedance audiometry, otoacoustic emission measurement, and a speech in noise test – in two sessions, before and after methadone intake. It was found that methadone causes an improvement in speech intelligibility when speech is presented in speech-like noise, and slightly decreases hearing thresholds [dB HL]. Methadone consumption has no significant impact on distortion product otoacoustic emissions levels (DPOAE). In summary, a prescribed methadone dose does not worsen the hearing of opioid-dependent subjects.

Keywords: methadone; opioids; speech intelligibility; otoacoustic emissions; hearing threshold.

1. Introduction

Psychoactive substances, such as alcohol or opioids, may affect human cognitive functions, leading to structural and functional changes in the Central Nervous System (CNS) (Yates, 2009; Kalat, 2011; Feit *et al.*, 2014; Gorzelańczyk *et al.*, 2016).

Opioids are a group of substances that affect the three main types of opioid receptors, i.e., μ, κ, δ (NCBI, 2005; Feit *et al.*, 2010). They can activate neurons, mainly through the μ and δ opioid receptors, or inhibit neurons by increasing the membrane potential gradient by the κ receptor (Feit *et al.*, 2010). In the nervous system there are a lot of naturally occurring peptides which interact with opioid receptors (endomorphin, dynorphin, enkephalin, endorphin, orphanin FQ) (NCBI, 2005; Corbett *et al.*, 2006; Feit *et al.*, 2010; Lopez *et al.*, 2012). The natural source of opioids is a milky sap which is extracted from the opium poppy (Papaver somniferum) and used

in morphine production (Corbett *et al.*, 2006; Feit *et al.*, 2010; International Narcotics Control Board, 2013). These substances are substrates for the production of semi-synthetic derivates (e.g. heroin). Opioids can also be synthetic, for example, methadone is a morphine derivate used in the substitution treatment of opioid addicted individuals, and in cancer and non-cancer pain treatment (WHO/UNODC/UNAIDS, 2004; NCBI, 2005).

The administration of the therapeutic doses of methadone during substitution treatment aims to restore patients to normal social functioning. As a synthetic derivate of morphine, methadone has comparable analgesic and antitussive properties to morphine (NCBI, 2005; Yates, 2009). Methadone suppresses the respiratory centre, which can cause respiratory depression (Victor *et al.*, 2005; Corbett *et al.*, 2006; Lopez *et al.*, 2012). It also prolongs the QT interval (analysed on the basis of electrocardiogram results), which can cause abnormal functioning of the cardiovascular system, such as arrhythmia (NCBI, 2005; Benyamin *et al.*, 2008). Methadone mainly influences the opioid receptors located in the CNS and in organs consisting of smooth muscle (NCBI, 2005; Victor *et al.*, 2005; Lopez *et al.*, 2012; Nguyen *et al.*, 2014a). Methadone is administered orally, mainly in liquid form. Despite the fact that it has similar pharmacological properties to morphine, it causes a weaker narcotic effect than morphine (Corbett *et al.*, 2006; Yates, 2009). It is expelled from the body more slowly than morphine, resulting in a later occurrence of the withdrawal symptoms (Yates, 2009).

The largest number of opioid receptors was found in the striatum and in the thalamus (Victor *et al.*, 2005). The majority of sensory information reaches the thalamus (Kalat, 2011), the impulses are then transmitted to the cerebral cortex (Gorzelańczyk, 2011; Kalat, 2011; Feit *et al.*, 2014), from whence they come back to the thalamus (via the striatum). The circulation of information in the cortico-subcortical loops, thanks to a feedback mechanism, allows for the control of mental functions (Laskowska, Gorzelańczyk, 2009; Gorzelańczyk, 2011; Kalat, 2011). According to the model of cortico-subcortical loops, the basal ganglia, which are clusters of gray matter in the brain with connections to the cerebral cortex, control motor, emotional, and cognitive functions (Laskowska, Gorzelańczyk, 2009; Gorzelańczyk, 2011). Five cortico-subcortical loops have been distinguished and, among them, the limbic loop is responsible for behaviour control and the correction of mistakes. This loop consists of the dorsal thalamic nuclei (posterior and medial, Gorzelańczyk, 2011). In this part of the thalamus, the lateral geniculate body nuclei are located (lateral geniculate complex) representing the IV neuron of the auditory pathway (Śliwińska-Kowalska, 2005).

Methadone can influence the functions of the inner ear (Fowler, King, 2008; Schrock *et al.*, 2008; Cianfrone *et al.*, 2011; Lopez *et al.*, 2012; Nguyen *et al.*, 2014a; 2014b). The occurrence of sudden sensorineural opioid associated hearing loss has been described in many papers (OAHL) (Benyamin *et al.*, 2008; Fowler, King, 2008; Schrock *et al.*, 2008; Shaw *et al.*, 2011; Antonopoulos *et al.*, 2012; Lopez *et al.*, 2012; Vorasubin *et al.*, 2013; Nguyen *et al.*, 2014a). Opioids can have a direct negative impact on the functioning of the inner ear and consequently cause hearing loss, which is usually temporary (Nguyen *et al.*, 2014a). In some cases, corticosteroids and drugs that improve blood circulation can reduce hearing loss (Schrock *et al.*, 2008; Nair *et al.*, 2010; Antonopoulos *et al.*, 2012). However, the reversibility of opioid-assisted hearing loss depends on, among other factors, the type of opioid substance used, the length of addiction and/or the general health of the patient (Lopez *et al.*, 2012; Nguyen *et al.*, 2014a; 2014b). Hydrocodone (a pain reliever and a semi-synthetic derivate of morphine), in combination with paracetamol, mainly causes irreversible sensorineural hearing loss (Lopez *et al.*, 2012). There were described cases of fully reversible hearing loss caused by some opioid intakes (Ishiyama *et al.*, 2001; van Gaalen *et al.*, 2009; Christenson, Marjala, 2010; Lopez *et al.*, 2012; Nguyen *et al.*, 2014a). Methadone can affect the vestibulocochlear organ and lead to dizziness (Cianfrone *et al.*, 2011). Furthermore, an overdose may result in temporary hearing loss, usually remitting after 24 hours (Lopez *et al.*, 2012).

Proper hearing requires optimal innervation and blood supply to the cochlea, and especially the inner (IHC) and the outer (OHC) hair cells (Lopez *et al.*, 2012). The cochlea is very active and sensitive to blood pressure changes (Lopez *et al.*, 2012; Wicher, 2014). Oxygen, nutrients, and other substances (including drugs) are transmitted to the hair cells through a complex network of blood vessels. All types of opioid receptors were found in the cochlea and the vestibular apparatus in rats and guinea pigs (Nguyen *et al.*, 2014a; 2014b). In the human cochlear ganglion, the presence of μ opioid receptors was also found (Nguyen *et al.*, 2014a; 2014b).

In the inner ear, the activity of the synapses between the IHCs and dendrites of the nerve cells (the afferent pathway, the first neuron of the auditory pathway) is modified by efferent innervation (Lopez *et al.*, 2012; Wicher, 2014). Glutamate acid is the principal excitatory neurotransmitter in the afferent pathway (Lopez *et al.*, 2012; Wicher, 2014). The excessive release of glutamate and its agonists may result in damage to the cochlear ganglion neurons (Lopez *et al.*, 2012). Neurotransmitters like acetylcholine (ACh), γ-aminobutyric acid (GABA), and encephalin (opioid peptide) occur in the afferent auditory

pathway (Śliwińska-Kowalska, 2005; Lopez *et al.*, 2012). Dopamine is a mediator between the efferent axon terminals and the dendrites of the afferent nerve fibres (Lopez *et al.*, 2012). It should also be noted that dopamine receptors may interact with opioid receptors (Lopez *et al.*, 2012).

In conclusion, there are opioid receptors and endogenous opioid peptides in the inner ear (Al-Mana *et al.*, 2008), therefore it can be assumed that the administration of exogenous opioids may influence the transmission of impulses across synapses in the peripheral auditory system. Opioid substances can affect the function of cortico-subcortical loops (via opioid receptors – the largest number of these receptors was found in the striatum) (Feit *et al.*, 2014; Gorzelańczyk *et al.*, 2016) including their activity in the central part of the auditory system.

Opioid addicted patients take individually adjusted doses of the substitution drug (e.g. methadone) during treatment. The substitution treatment is extended and indefinite. It is unclear, however, how the administration of opioids over many years of substitution treatment affects the auditory system. It can be hypothesised that methadone administration may result in the hearing deterioration of patients, with respect to their hearing thresholds and frequency selectivity (the impact of methadone on the peripheral part of the auditory system). It is possible that the administration of therapeutic doses of methadone significantly changes speech intelligibility in opioid-dependent people, in particular, speech presented with background noise (impact of long-term opioids intake on CNS).

The main purpose of the presented research was to determine the effect of a single, therapeutic dose of methadone on selected functions of the auditory system in subjects addicted to opioids and undergoing substitution therapy. This study aimed to assess the auditory pathway functioning at different stages of sound processing. The study carried out was preliminary. As far as the authors are aware, a study on the effect of substitution therapy used with opioid dependent people on the functioning of the auditory system has not been conducted previously.

2. Material and methods

Subjects with normal hearing, who were under substitution maintenance therapy in the MEDSEVEN clinics in Gdańsk and Bydgoszcz, took part in the experiments. During visits to the clinic (they had to plan their visits due to full-time jobs or living far from the clinic), the patients were given their individual, therapeutic dose of methadone. The shortest period of addiction among the subjects was 2 months, and the longest period took 8 years. All the subjects (21 participants) were diagnosed with opioid dependence (F11.2 in ICD-10). The age of patients was between 20 and 79 years (mean 41.9 years, standard deviation 13.3 years). In further analyses, data acquired from opioid-dependent people (except those who had been taking opioids as part of pain treatment or had thresholds above 30 dB HL) were taken into account.

The patients were divided into groups according to: the age, length of addiction, dose of methadone, length of time of their being under substitution therapy, time between methadone intake and the second session of tests, taking other drugs prescribed by a doctor which have an impact on central nervous system (CNS) (e.g. quetiapine (Ketrel), trazodone (Trittico CR)). The criteria for the group selection and the group sizes are shown in Table 1.

Table 1. Grouping of recruited patients who entered the study due to respective factors.

Factor	Code factor	Description	Group size
Age	< 40	below 40 years of age	10
	≥ 40	40 years of age and more	11
Interval of addiction	long	20 years and more	7
	medium	10–20 years	7
	short	shorter than 10 years	7
Dose of methadone	high	85 mg and more	5
	medium	60–85 mg	9
	small	smaller than 60 mg	7
Treatment time in the substitution therapy	long	40 months and more	6
	medium	20–40 months	7
	short	shorter than 20 months	8
Interval between methadone intake and second test session	$< h$	–	11
	$\geq h$	–	10
Other drugs intake	yes	–	9
	no	–	12

The impact of a therapeutic dose of methadone on selected hearing parameters was determined using the results of four tests:

- pure tone audiometry (PTA);
- tympanometry;
- the distortion products of otoacoustic emissions (DPOAE) measurements;
- a speech intelligibility test in noise, using the Polish Sentence Test (PST).

The impact of methadone on hearing was assessed during two experimental sessions using the abovementioned tests. The first session was conducted prior to methadone intake, and the second one about an hour after. The time interval was defined by clinical observations: subjectively, the strongest effects of methadone start about one hour after the drug intake.

Before testing, patients were informed about the experiment and were asked to sign a consent form stating that their participation in the research was voluntary. An audiological review and a survey were also conducted. Unfortunately, it was not possible to perform an extra session before the experiment proper, because the patients would not agree to such a long study or to come two days before the experiment (for example), in order to avoid the learning effect. After the review and survey, the four tests were performed: PTA, tympanometry, DPOAE measurement, and PST (first session). After this part of the experiment, the subjects were given their therapeutic dose of methadone and after about 60 minutes they took part in the same tests (the second session). All the measurements were performed in a room adapted for hearing tests (the noise level did not exceed 40 dB SPL, within the frequency range of speech sound, according to PN-EN ISO 8253-1).

As a part of PTA, hearing thresholds were determined for all the octave audiometric frequencies (0.125–8 kHz) with 5 dB steps, using the Audiotympanometer Interacoustic Audiotraveller AA222. The same equipment was used to measure tympanograms.

Distortion products of otoacoustic emissions (DPOAEs) were recorded and analysed using a Bio-Logic Scout Sport System ver. 45.00.04. The levels of the tones were $L_1 = 65$ dB SPL, $L_2 = 55$ dB SPL, respectively. The range of frequencies was 0.75–8 kHz.

The speech intelligibility test was performed using the Polish Sentence Test (PST), developed at the Institute of Acoustics, A. Mickiewicz University, Poznań (Ozimek *et al.*, 2008; 2009). The PST enables assessment of the ability to comprehend speech in speech-like noise (babble noise type). The test contains 37 equivalent lists of 13 sentences. Each sentence in each list contains no more than 9 syllables. All the sentences have a semantically neutral context, and each of the 37 lists is phonemically, energetically, and statistically balanced. The PST determines the speech reception threshold (SRT), defined as the signal to noise ratio (in dB or in percentage points), at which the listener repeats 50% of the presented sentences correctly. The obtained results are recurrent. The test makes it possible to assess the real ability of the auditory system to process speech understanding in noise. The PST software was implemented in Matlab. The speech signals were generated using an RME BabyFace sound card and presented monaurally via Sennheiser HD600 headphones. Three different lists were presented to each ear. The listener's task was to repeat all the understood words/sentences, and these repetitions were recorded. Prior to the experiment proper, in order to familiarise people with speech intelligibility measurements and the study procedure, a brief auditory training session was conducted.

In accordance with the procedure, patients did not receive their daily, single doses of methadone before the first session. Sometimes withdrawal symptoms (e.g. shaking hands, dilated pupils, psychomotor agitation) were observed before the methadone intake. For this reason, the experiment was conducted in the early morning and the general instruction was given to the subjects on the day preceding the tests.

3. Results

3.1. Pure tone audiometry

The main objective of this stage of the study was to determine the effect of therapeutic doses of methadone on hearing thresholds. This basic audio test, which is usually carried out prior to any hearing study, was done to establish whether the patients have normal hearing. Hearing thresholds were determined twice, before and after a dosing interval of 45–59 minutes (the "less than one hour") and 60–90 minutes ("one hour or more") in 21 subjects (data acquired from 18 subjects was taken into consideration in the analysis). Analysis of variance (ANOVA) showed that hearing thresholds before and after the dose of methadone was taken are significantly different ($[F(1, 17) = 7.601, p = 0.013]$). The significance level was less to 0.05 ($p < 0.05$) for all the statistical analysis. Analysis of variance revealed that hearing thresholds also depended on the frequency ($[F(5, 85) = 4.570, p = 0.001]$). The results of the Tukey test showed that the difference between the average value of hearing thresholds before and after a dose of the drug is statistically significant for the frequency $f = 250$ Hz $[F(17, 1) = 9.360, p = 0.007]$ and for the frequency $f = 1000$ Hz $[F(17, 1) = 4.620, p = 0.046]$. In turn, for the frequencies 125 and 2000 Hz, significance levels were equal to $p = 0.074$ and 0.062, respectively. This implies that they are on the edge of statistical significance (within the range of 90% of confidence interval). Figure 1 shows the mean

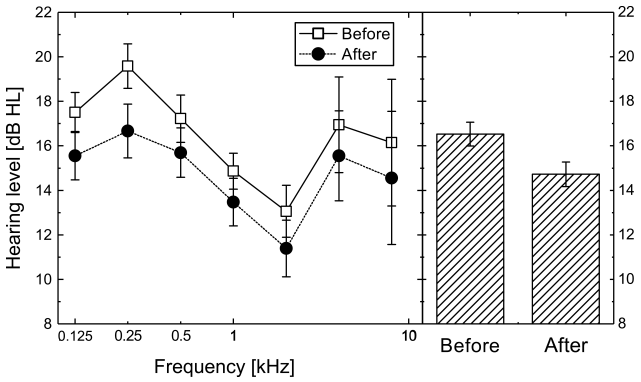

Fig. 1. Mean values of hearing thresholds (and appropriate SEs) before and after the use of methadone (right panel of the figure) and the average audiograms within the octave frequencies; range 0.125–8 kHz (left panel of the figure).

values of hearing thresholds and the average audiograms within the frequency range of 0.125–8 kHz.

In conclusion, it can be generally stated that the mean hearing threshold ($HTL_{0.5,1,2,4}$) for the frequencies 0.5, 1, 2 and 4 kHz for all (eighteen) patients did not exceed 25 dB HL. Figure 1 also shows by how much a therapeutic dose of methadone reduces the hearing thresholds in the analysed frequency range. It has to be noted that this reduction (statistically important) is very small, and the inference that methadone improves pure tone detection in opioid-dependent subjects may be controversial because of the 5 dB step used in PTA performing. Nevertheless, the results obtained in such a small group of analysed opioid-dependent people show positive effect of single, therapeutic dose of methadone.

The difference between the mean hearing threshold after using methadone and the average hearing threshold before the drug administration (Hearing Level Differences, dHL) was calculated. It was found that for the majority of patients the hearing threshold was lower after the drug was taken, as is shown by the negative values of dHL in Fig. 2.

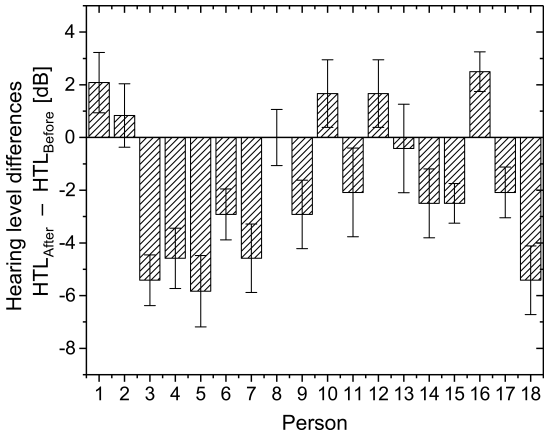

Fig. 2. Mean difference (and appropriate SEs) of the hearing thresholds (dHL) for respective patients.

It was shown that for twelve patients (67%) a reduction in the average hearing threshold (i.e. an improvement in sensitivity to the lowest sound levels) was observed. Furthermore, it was demonstrated that a reduction in the hearing thresholds was observed in patients using low and high doses of methadone (< 60 mg or > 85 mg) [$F(2) = 9.830$, $p < 0001$]. A statistically significant relationship was also noticed between the decrease in hearing thresholds and the shorter time intervals between successive trials ([$F(1) = 4.374$, $p = 0.038$]), and also ingesting additional medication by the patient ([$F(1) = 21.438$, $p < 0.001$]).

3.2. Impedance audiometry

The results obtained from 18 subjects out of 21 patients who participated in the study were analysed. These measurements were treated as a part of general diagnosis of the patients. For each patient a tympanogram of type A was recorded. The obtained results confirmed the proper functioning of the middle ear of each participant (Harris *et al.*, 2005). In the second part of the impedance audiometry, the acoustic reflex thresholds were measured before and after methadone was taken. However, these results were not compared because the reflex thresholds were immeasurable in many cases, and due to the ultimately limited data that had been acquired.

3.3. Distortion product otoacoustic emissions (DPOAE)

Initially (the first session) 17 patients were tested. However, only the results obtained from 12 of them were analysed, for the reasons mentioned in Sec. 2, and due to withdrawal symptoms in some cases. The DPOAE levels, for respective frequency before and after using methadone, were compared. It was shown that the use of the opioid did not significantly affect the changes in the level of DPOAEs [$F(1, 11) = 0.257$, $p = 0.62$] but there is noticeable tendency to boost OAE levels. Figure 3 presents the average values of

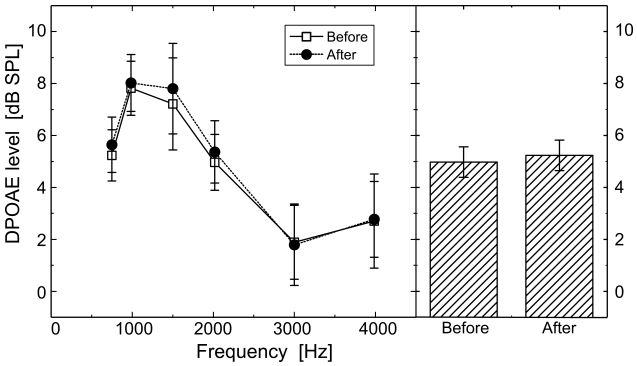

Fig. 3. Mean values of the DPOAE levels (and appropriate SEs) before and after the use of methadone (right panel of the figure) and the average levels within the frequency range 0.75–4 kHz (left panel of the figure).

DPOAE levels before and after drug intake, and also the average values as a function of f_2 frequency.

In the case of one patient, it was found that after a single therapeutic dose of methadone the levels of the DPOAE signals were higher than compared to the values measured before the drug was taken.

3.4. Speech intelligibility against babble noise

Speech Reception Thresholds (SRT) were fully measured in two sessions for 17 patients, but analysis was carried out for just 15 cases (see the inclusion criteria in Sec. 2). Four subjects refused to participate in PST at all, or started but did not finish the test because of withdrawal symptoms. Speech intelligibility measurement is one of the most important and valuable hearing tests, as an audiogram does not say very much about the functioning of the entire auditory system, especially in terms of speech perception. The SRT was determined on the basis of three different lists which were presented to each ear separately. The thresholds of speech intelligibility before and after taking methadone were compared and subjected to an analysis of variance. A statistically significant difference was clearly proved [$F(1, 14) = 19.689$, $p = 0.001$]. This result is shown in Fig. 4.

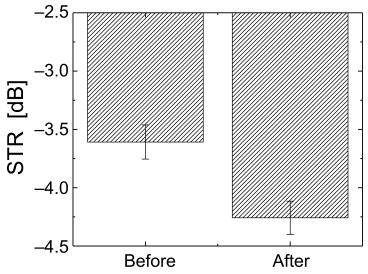

Fig. 4. Mean values of the SRT (and SEs) before and after the use of methadone.

In order to perform further analysis, a relative measure of speech intelligibility was used, which is the SRT differences (dSRT), defined as the difference between the SRT before and after the administration of the methadone. The dSRT value was determined individually for each patient, and the results are shown in Fig. 5. Negative values of the dSRT indicate improvement in speech intelligibility with a noise background after the drug ingestion, which was observed for the vast majority of the patients.

The post hoc analysis demonstrated a significant relationship between the main effect (improving speech intelligibility), and participation time in the substitution treatment program (long-term treated patients), as well as between the main effect and the length of addiction (addicts for 10 years or for over 20 years). Speech intelligibility improvement was statistically significant regardless of the time elapsed since ingestion of the drug.

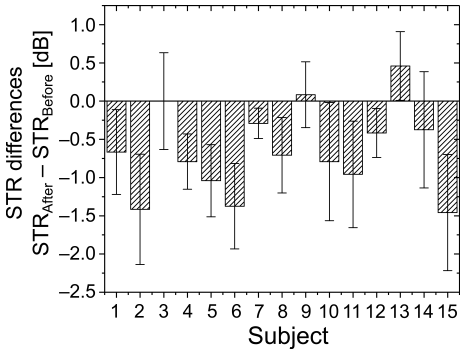

Fig. 5. Mean values of the SRT (and SEs) differences before and after use of the methadone for respective patients.

Another measure of speech intelligibility evaluation is the percentage points (p.p.) of improvement in speech understanding. It has been demonstrated that in the case of the Polish Sentence Test the slope of psychometric function describing speech intelligibility at the SRT point is equal to 25.6%/dB, see Ozimek *et al.* (2008; 2009) for details. Assuming that near to SRT value this relationship is a linear function, it was calculated that, averaged across the participants, the change of SRT of 0.65 dB corresponded to an improvement in speech intelligibility of about 16.6 p.p. On the basis of this relationship, the p.p. change in speech intelligibility for each of the patients was determined. The results are shown in Table 2.

Table 2. The mean values of the changes in the speech reception threshold (dSRT) for individual listeners.

Patient	dSRT [dB]	SE [dB]	Speech intelligibility improvement [p.p.]
1	−0.67	0.55	17.07
2	−1.42	0.72	36.27
3*	0.00	0.63	0.00
4	−0.79	0.36	20.27
5	−1.04	0.47	26.67
6	−1.38	0.56	35.20
7	−0.29	0.20	7.47
8	−0.71	0.49	18.13
9*	0.08	0.43	−2.13
10	−0.79	0.77	20.27
11	−0.96	0.70	24.53
12	−0.42	0.32	10.67
13*	0.46	0.45	−11.73
14	−0.38	0.76	9.60
15	−1.46	0.76	37.33
Mean	−0.65	0.55	16.64

For 80% of patients, speech intelligibility with a background noise was markedly improved. For only two patients did the intelligibility of speech decrease,

and for one patient there was no change in the SRT value after the ingestion of methadone (marked * in the table). According to the data comprised in Table 2, for three patients improvement of speech intelligibility exceeded 30 p.p.

4. Discussion and conclusions

For the purpose of assessing the effect of opioid substance (methadone) on the auditory system in opioid-dependent subjects, four different types of test were performed. These tests, due to the methodology, can be divided to subjective tests (pure tone audiometry and speech intelligibility) and objective tests based on measurements of physical values (distortion product otoacoustic emission measurements and tympanometry).

The starting point for the evaluation of the auditory system is to define hearing thresholds as a function of frequencies, which is realised in pure tone audiometry (PTA). In such studies it is possible to evaluate the whole auditory system, including the decision unit, taking into account the attentional processes. However, it is worth adding that the sounds used in this sort of investigations are not present in everyday life; they are in a sense artificial. For the presented set of experiments, it was necessary to perform PTA, as an indispensable element of the diagnosis of hearing. The second subjective trial was the speech in noise test. It connects to the most important aspects of auditory system functioning, (e.g. the masking effect) with frequency selectivity and the assessment of information contents in the signal (speech sound analysis, speech mode, attention processes) (Moore, 1999). It was thought that this research tool would be the most useful in evaluating the effects of opioids on the auditory system.

Analysis of the results of the most basic hearing test, i.e. PTA, showed that hearing thresholds in the frequency range of 0.125–8 kHz were lower in opioid-dependent subjects one hour after methadone consumption (see Fig. 1). Mean improvement was barely 0.7 dB in the 5 dB steps method. This change (even statistically significant, $p < 0.05$) is very small and does not enable certain inference. The determined changes were higher in people who took part in the second session of the experiment less than one hour after the methadone intake, in comparison to those who had a break of longer than 60 minutes.

Distortion product of otoacoustic emission (DPOAEs) measurements were used for a more detailed evaluation of the impact of methadone on the cochlea. This method (i.e. DPOAE changes) enables changes in cochlear micromechanics to be shown, especially in the function of the outer hair cells (OHCs) (Śliwińska-Kowalska, 2005; Wicher, 2014). The cochlea is a very important element of the auditory pathway, due to the compound mechanobioelectric processes that take place in there (Pankowska *et al.*, 2011). These processes are the main source of action potentials stimulating the appropriate regions of the brain responsible for hearing. It is worth emphasising the role of olivocochlear efferents which are responsible for the feedback between the cochlea and the higher levels of the auditory pathway (Wicher, 2012; 2013; 2014; Wicher, Moore, 2014). Efferent fibres mostly innervate OHCs (Śliwińska-Kowalska, 2005; Wicher, 2014), and they are responsible for otoacoustic emission phenomena. Furthermore, the conclusions contained in other reports (e.g., Benyamin *et al.*, 2008; Fowler, King, 2008; Schrock *et al.*, 2008; Shaw *et al.*, 2011; Antonopoulos *et al.*, 2012; Lopez *et al.*, 2012; Vorasubin *et al.*, 2013; Nguyen *et al.*, 2014a) strongly suggested that DPOAE measurements should be performed. It was expected that the DPOAE levels would be reduced in opioid dependent subjects after methadone intake. The results of this research showed that methadone has no effect on micromechanics of the inner ear. The DPOAE levels were not significantly changed one hour after drug consumption.

To determine a tympanogram, an impedance audiometry investigation is usually applied. However, an impedance audiometry also includes the determination of the acoustic reflex threshold (Śliwińska-Kowalska, 2005). The creation of an acoustic reflex is connected with the activity of the hearing organ (the peripheral part), the upper stages of the auditory pathways (including brain stem), efferent connections, and the facial nerve. In the case of an ipsilateral stimulation, the acoustic reflex also activates the spiral cochlear ganglion, the ventral cochlear nucleus, the nucleus olives upper, and the medial nucleus movement of the facial nerve on the side of stimulus response. However, in the case of contralateral stimulation, in addition to the above-mentioned activity, the acoustic reflex also activates the motor nucleus of the facial nerve on the side opposite to the one where the stimulation is delivered (Gierek, Slaska-Kaspera, 2007). The acoustic reflex arises in both ears, regardless of whether the stimulation is monaural or binaural (Śliwińska-Kowalska, 2005; Wicher, 2014).

The acoustic reflex thresholds were not measurable in both sessions for all frequencies. But it is worth noting that the acoustic reflex involves the activity of three neurons in the auditory pathway. The second and third neuron reaches the crossing of nerve fibres from the right and left ear. The opioid receptors are mainly found in the striatum and the thalamus (NCBI, 2005; Victor *et al.*, 2005; Kalat, 2011), as a portion of the fourth neuron of the auditory pathway. Therefore, the effect of the opioids on the acoustic reflex may be measurable, so the testing of more subjects is required.

Very important conclusions can be drawn from the research on speech intelligibility, when speech is presented with a background noise. The results averaged over all subjects showed a statistically significant reduction in the SRT, by approx. 0.7 dB after the administration of methadone. In four patients the administration of the methadone revealed an STR reduction of 1–1.5 dB, which means a speech intelligibility improvement of 26–38 percentage points (p.p.). However, in the case of five participants, the SRT was lower by about 0.5–1 dB (cf. Table 2). In other cases, improvement in speech intelligibility, understood as a decrease in the SRT value, was not greater than 0.5 dB. Only two participants showed the opposite effect, i.e. an increase in the value of SRT which did not exceed 0.5 dB. If speech intelligibility is expressed in percentage points (p.p.), then three patients showed an improvement in speech intelligibility of 30 p.p., while eight of them showed an increase in speech intelligibility of a few to nearly 30 p.p. However, in two subjects a decrease in speech intelligibility was observed that did not exceed 12 p.p.

A closer analysis of the results obtained by means of subjective methods of research indicates that the administration of a single, therapeutic dose of methadone improves the detection of pure tones (improved sensitivity, lower hearing threshold), and in particular improves speech intelligibility while the speech is presented with a background noise (decrease SRT). The effect of the methadone within the first hour after administration did not markedly improve the sensitivity to pure tones. Speech intelligibility improvement, on the other hand, was more visible for a longer time period (over one hour) after the methadone administration.

The presented results confirmed the hypothesis which posited that opioids significantly affect cognitive function, in particular, speech recognition, which is directly translated to an improvement in speech intelligibility when speech is presented in babble noise. An average SRT of −3.6 dB measured before the methadone was administered to our participants is significantly higher than the SRT value for non-addicted persons with normal hearing which is equal to −6.1 dB (Ozimek *et al.*, 2008; 2009). Similar results were presented by Gorzelańczyk *et al.* (2013) who found that the average SRT value for people addicted to opioids was −3.7 dB. This may indicate a significant, deteriorating effect of long-term treatment by means of psychoactive drugs on speech intelligibility. It is most probable that in addicted people this results from permanent changes to the central nervous system (Feit *et al.*, 2014; Gorzelańczyk *et al.*, 2016), which may result in speech intelligibility deterioration.

The application of the Polish Sentence Test (PST) produced extremely important results and conclusions, because they may directly suggest a lack of side effects with respect to speech intelligibility, in the framework of the implemented program of drug treatment. However, it is difficult to speculate if the PST, as a method, is sufficiently sensitive to clearly show the side effects of the drug(s). On the other hand, the present study showed an improvement in speech intelligibility, on average by 17 p.p. after the methadone was administered. It can be assumed then that a given therapeutic dose of the opioid may improve the functioning of the nervous system in people addicted to opioids. The speech intelligibility thresholds measured before and after administration of the methadone in people addicted to opioids have not been determined so far. However, there are some studies concerned with the effect of therapeutic doses of the drug on eye movements. Their results indicate that for people addicted to opioids, a therapeutic dose of methadone improves their eye movements, which may indicate an improvement in the efficiency of psychomotor and cognitive functions (Feit *et al.*, 2014; Gorzelańczyk *et al.*, 2014; 2016). Therefore, it seems that the methadone reduces the adverse effects of opioid abuse and may have a protective effect on brain functions, e.g. cortico-subcortical loops (Gorzelańczyk *et al.*, 2016).

The presented results regarding the efferent pathway may raise some doubts. The efferent part of the auditory pathway, which reaches the striatum and the thalamus (Wicher, 2014), may mediate the functioning of the auditory system. Opioids have a strong influence on the fourth neuron of the auditory pathway, as shown above. However, they do not have a significant impact on the peripheral part of the auditory system. The DPOAE effect of opioids may not be measurable when the measurement procedure used here is applied. The relationship between these ototoxic drugs and the impaired perception of sounds, especially high frequency ones, is clearly recognised and reported by (Cianfrone *et al.*, 2011), There is, however, a shortage of information concerned with the effects of opioids on the processing of sounds in different frequency ranges.

The results gathered for participants dependent on opioids, before and after taking a therapeutic dose of methadone, showed an improvement in the functioning of the eye movements and reducing the probability of risky behaviour (Feit *et al.*, 2014; Gorzelańczyk *et al.*, 2014; 2016). This may indicate the effectiveness of methadone in people dependent on opioids. It is possible that the central effects of the methadone, by improving the functioning of the cortico-subcortical loop, increases the overall efficiency of cognitive abilities. As a result, a decrease in the thresholds of hearing (a hearing sensitivity improvement) and improved speech intelligibility in people dependent on opioids is observed. However, the complex relationship between the auditory system and the complexity of the five cortico-subcortical loops, as well as the small number of participants were the main constraints leading to a clear assessment of effects of the methadone on the

performance of selected auditory functions. It is therefore possible that a single dose of the drug improves the functioning of the auditory system (i.e. hearing thresholds reduction, speech intelligibility improvement), due to a decrease in withdrawal symptoms and overall improvement in cognitive and psychomotor performance (including attention).

In summary, the results of the studies concerned with opioid-dependent participants undergoing substituting therapy, by using a therapeutic dose of methadone, allow the following conclusions to be drawn:

1) For all the participants tested, the average threshold of hearing (i.e. the average threshold for the frequencies of 0.5, 1, 2, 4 kHz, $HTL_{0.5,1,2,4}$) is within the normal limits and does not exceed 25 dB HL.
2) A therapeutic dose of methadone does not significantly affect the levels of the distortion product of the otoacousic emission signals (DPOAE). However, there is a noticeable tendency of an increase in the level of OAEs an hour after the drug is administered.
3) The speech reception threshold (SRT) in normally hearing, opioid-dependent individuals is significantly higher when compared to that in the non-dependent individuals. This may indicate a connection between being opioid-dependent and a deterioration in the perception of speech sounds and speech intelligibility.
4) A therapeutic dose of methadone administered to patients during treatment improves the sensitivity of hearing and speech intelligibility when speech is presented in babble noise.

It was shown that the administration of a single (therapeutic) dose of methadone does not impair hearing in opioid-dependent patients undergoing substitution therapy. The above presented study is a first attempt at analysing this problem and should be treated as a preliminary one.

In order to fully evaluate the impact of opioids on the functioning of the auditory system, it is necessary to examine a larger number of people addicted to this drug.

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