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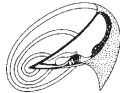
Current practice of ototoxicity management across the United Kingdom (UK)

Devina Maru and Ghada-Al Malky 

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The British Society of Audiology



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Abstract

Objective: Effective management of patients diagnosed with ototoxicity is needed to reduce hearing and balance damage which affects communication and life quality. Despite widespread recommendations to monitor and manage ototoxicity in an early and effective manner, there is limited evidence to support the actual implementation of these recommendations for affected patient groups in healthcare services across the UK with limited publications available. In this study, an online questionnaire analysed the current practice of ototoxicity management and patient pathways across the UK once the diagnosis of ototoxicity was confirmed, targeting Audiologists, ENTs/AVPs and GPs. **Design:** Qualitative Survey Study. **Study sample:** A randomised sample of hearing services in the UK, including audiology departments; GP practices and local health settings were targeted with a total of 134 completed surveys. **Results:** About 72% reported the absence of ototoxicity management protocols within their centre. Results depicted great inconsistency and variation across the UK in ototoxicity management services provided, treatment modification, monitoring and referral pathways. **Conclusion:** Developing and advocating national guidelines are intended not only to inform clinical decision making but to provide minimum standards of care in ototoxicity management and offer greater awareness and education to improve patients' quality of life.

Key Words: Ototoxic agents, ototoxicity management, audiologists, ENTs/AVPs, GPs, aminoglycoside ototoxicity, cisplatin ototoxicity, ototoxicity monitoring, paediatric ototoxicity management, balance management, ototoxicity education

Introduction

Drug ototoxicity is defined as a temporary or permanent drug-induced ear dysfunction resulting in sensorineural hearing loss, tinnitus and/or disequilibrium. One of the basic tenants of medicine is to 'do no harm' (Ruhl et al. 2014); however, clinicians are faced with the challenge of weighing the benefits of combating a life-threatening disease and the risks of developing the ototoxic consequences of the drug. The discovery and use in the 1940s of aminoglycosides, coupled with the clinical findings of drug-induced damage to hearing and vestibular end organs of the inner ear, led to a vast amount of clinical and scientific research into the aetiology and mechanisms of ototoxicity. However, currently there is very limited evidence of actual current practice across the UK for ototoxicity monitoring and the management of patients when diagnosed with this condition.

Although ototoxicity may seem a small price to pay for curing malignancies or severe infections, patients may perceive a hearing loss as a major effect on daily functioning and quality of life

(Theunissen et al. 2014). Hearing loss at speech frequencies up to 4 kHz may result in a deterioration of speech intelligibility. Hearing loss at higher frequencies (>4 kHz) might have an adverse effect on the recognition and appreciation of sounds perceived in nature and music (birds, instruments, melodies) (Theunissen et al. 2014). In addition to the consequences of the physical disability, considering the patient holistically is essential. Ototoxic medications can lead to serious communication, educational, social and psychological difficulties significantly affecting the patient's quality of life (WHO 1997).

An informal consultation was held at the World Health Organisation (WHO) headquarters in Geneva regarding strategies for the prevention, control, and management of deafness and hearing impairment. Concerns regarding the necessity and need for further data regarding ototoxicity were highlighted (WHO 1994). A national standardised ototoxicity management protocol currently does not exist, and this study provides evidence of the inconsistency and variation amongst hospitals across the UK.

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Ototoxicity is a trait shared amongst aminoglycoside and macrolide antibiotics, loop diuretics, salicylates, quinine and platinum-based chemotherapeutic agents to name a few (Yorgason et al. 2006). Ototoxicity is one of the main preventable causes of deafness and an outcome that can perhaps be most directly influenced by healthcare professionals (Mudd 2016).

As most of ototoxic hearing loss is irreversible, the management emphasis tends to be on prevention. Presently, there is no existing therapy which reverses ototoxic damage; however, research continues in trying to develop new innovative ways to minimise ototoxic injury whilst retaining therapeutic efficacy of the agents (Verdel et al. 2008; Tieu and Campbell 2013; Freyer et al. 2017). Multi-drug treatments are becoming the norm in populations at large. This is one of many factors that may increase the risk for ototoxicity. Research has shown that there is a greater chance of continuous extension of damage from ototoxicity in the individual who has started to show early evidence of suffering from ototoxicity, highlighting the importance for active ototoxicity monitoring to detect these early changes and continue to detect and manage further deterioration (Gurney et al. 2007).

Once ototoxicity is confirmed, various possible methods of the management can be employed. Management options include modification to the medication (drug withdrawal, dosage modification, and alternating with non-ototoxic medications to increase exposure-free durations), supporting the hearing function (prescribing hearing aids or cochlear implants), minimising the disability (assistive listening devices, home modifications, speech and language therapy, occupational therapy), balance management (including balance training, vestibular rehabilitation and protection of alternative sources of balance information such as recommending annual ophthalmological examination) and providing counselling (support groups, hearing therapy, and information leaflets). When the patient complains of dizziness or imbalance, permanent vestibular damage has already occurred. Vestibular rehabilitation is recommended to aid an individual in facilitating central compensation. In bilateral vestibular loss, rehabilitation will aid the patient in using other mechanisms to improve balance function. Regarding hearing dysfunction, the American Speech-Language-Hearing Association (ASHA 1994) states that if an ototoxic hearing loss results in communication deficit, the Audiologist is ethically bound to begin, or recommend, aural rehabilitation (e.g. amplification, assistive listening devices, speechreading). Intervention should begin as soon as possible after hearing or balance loss has been identified.

The WHO action programme on Essential Drugs and the Division of Drug Management and Policies provides a vast amount of accessible documentation, which can be utilised as guidelines for educational campaigns to enhance public education and knowledge on ototoxic medication (WHO 1994). Educational materials including posters, brochures and media communication are suggested for schools, health centres, hospitals and other suitable public places in collaboration with non-governmental organisations. It is important to counsel patients regarding the risks of ototoxic medication and to emphasise the importance of prompt reporting of symptoms such as tinnitus, hearing loss, disequilibrium and oscillopsia (i.e. visual disturbance where objects in the visual field start to oscillate).

Professional education extended to healthcare providers with refresher courses was also recommended as a large proportion of hearing impairment worldwide is related to the inappropriate use, monitoring and management of ototoxic drugs. The introduction of regulation and legislation in developing countries was mentioned, as there is no restriction limiting the availability of ototoxic drugs.

WHO encourage physicians to refer to the International Programme on Chemical Safety documents and to ILO General Conference Recommendations No. 177, concerning safety in the use of industrial chemicals at work; in particular the synergistic cochleotoxic effects of noise and solvents, especially toluene (WHO 1994).

Accurate interpretation and effective management is dependent on baseline testing. If for any reason baseline testing cannot be performed it could prove beneficial to ask the patient or a family member about the availability of audiometric records. Frequent monitoring and early identification permits early intervention as appropriate. Long-term audiological follow-up post-treatment evaluations, which can be coordinated with medical follow-up visits are just as important and should always occur, as a delayed hearing loss is possible up to years post drug discontinuation and are important to determine whether hearing loss is stable or progressive. Follow-up testing should occur immediately, and at 3 months, 6 months and 1 year after cessation of treatment (Schell et al. 1989; ASHA 1994; AAA 2009). The management of children differs as they have a greater risk than similarly treated adults (Knight et al. 2005; Al-Malky et al. 2015) and additionally, minimal hearing loss is debilitating for young children acquiring speech and language skills (Bess et al. 1998; Crandell and Smaldino 2000; McFadden and Pittman 2008). This increases the need for early detection and management of ototoxicity in children. Furthermore, parents/carers should be counselled regarding hearing and balance dysfunction in addition to obtaining information from them at baseline testing regarding the child's history of speech and language and motor development. Parents/carers should be made aware of clinical signs and symptoms indicative of cochlear or vestibular dysfunction and advised to report to the physician immediately.

Criteria for ototoxicity have been established and widely cited by ASHA, National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), Brock and others (Mudd 2016). The introduction of Chang and Chinosornvatana and International Society of Paediatric Oncology (SIOP) scales provided scope to update the current criteria classifications. The classifications tend to describe cochleotoxic hearing loss primarily by the results of the audiogram (Crundwell et al. 2016) and are commonly used to simplify and categorise hearing status for clinicians. The variations and inconsistencies amongst the classification systems utilised to report the degree of ototoxicity combined with the lack of standardisation in audiological protocols creates difficulties in accurately characterising ototoxicity in different patient groups (Chang 2011). Grading systems need to be paired with audiological monitoring protocols coupled with the active participation of implementation by the hearing care professional to enable an accurate assessment and grading of ototoxicity (Brock et al. 1991; Chang and Chinosornvatana 2010). Likewise, vestibulotoxicity criteria have not been well established. A battery of vestibular testing for recording vestibulopathy, including caloric testing, vestibular evoked myogenic potentials (VEMPs), video head impulse test (vHIT) and videonystagmography (VNG) in addition to subjective questionnaire-based assessments are currently utilised infrequently (Halmagyi et al. 2012; Ahmed et al. 2016).

Despite recommendations nationally and internationally to monitor and manage ototoxicity in an early and effective manner, there is limited evidence to support the actual implementation of these recommendations for these specific patient groups in healthcare services across the UK and other countries (Phillips and Bell 2001; Melchionda et al. 2013; Kikic and Al-Malky 2014). There is limited research in this area with very few publications

specifically targeting this topic. Therefore, we administered an online questionnaire targeting different types of clinicians across the country. The online questionnaire aims to assess what happens with patients once the diagnosis of hearing loss or vestibular impairment due to ototoxicity is confirmed. Clarification of any grey areas regarding referral pathways, job roles in terms of what aspect of the management the hearing professional deals with, minimal standards of care, as mentioned above, relating to the management options that should be offered and monitoring and follow-up guidelines were areas of main focus within this survey.

Methodology

A qualitative study design was utilised. Clinicians were invited to complete an online questionnaire to explore their current practice in management of their patients when the adverse effect of ototoxicity was confirmed.

Online questionnaire

The online questionnaire was developed utilising the survey tool 'UCL Opinio'. This web-based questionnaire service enabled the creation of the questionnaire, distribution, secure storage of data and reporting facilities. The questionnaire was accessed via a hyperlink that was made available through the invitation cover letter emailed to the participants. The study was approved by the UCL Data Protection and Legal Services.

Prior to the final distribution of the questionnaire across the UK, a pilot of the questionnaire was circulated to four Audiologists, four Ear, Nose and Throat (ENTs)/Audio-vestibular physicians (AVPs) and four General Physicians (GPs). The questionnaire was modified according to their constructive feedback.

Questionnaire design

The questionnaire included 25 questions. The majority of the questions required the selection of an answer in order to proceed to the next question; this ensured the maximum amount of data was collated. Conditional branching (or skip logic) was used to change what question or page a respondent sees next based on how they answer the current question. This created a custom path through the survey that varied based on a respondent's answers. Open-ended questions were sometimes used in order to allow respondents to provide additional qualitative information regarding the various views of the professionals.

Questionnaire structure

The customised questionnaire was developed to collate four separate categories of information.

Demographics section (four questions) covered: The respondent's clinical role; patient group the service is delivered to (e.g. adult, paediatric); regional location (with the option to mention the name of the hospital where they work if happy to do so).

Ototoxic Agent and Monitoring section (five questions) covered: The patient group exposed to the ototoxic agent (e.g. cancer, cystic fibrosis, tuberculosis [TB]) that they manage, name of the ototoxic agents prescribed, whether or not baseline testing is conducted prior to starting the ototoxic agent and whether or not the patient is involved in a clinical trial for otoprotection.

Referral Pathway section (five questions) covered: Source of referral; frequency of visits; onward referrals once ototoxicity was

confirmed; setting of ototoxicity management (e.g. specialised clinic, ad hoc basis); whether follow-ups are offered following cessation of ototoxic medication.

All participants who stated their involvement in the management process of ototoxic patients were subsequently provided with a set of questions regarding the referral pathway. The initial question enquired about the source of referral and the following options were available for selection: GP referral, ward referral, ENT referral, AVP referral, audiology department referral, walk-in-clinic, hospital department referral and other.

Ototoxicity Management section (11 questions) covered: Whether the centre follows an ototoxicity management protocol; and what ototoxic management services the centre currently provides. This included six large categories: modification of medication, improving the hearing function, minimising the disability, balance management, counselling and post-treatment follow-up. Each of these categories had further subdivisions for detail.

The last two open-ended questions of this section enquired about their professional opinion regarding the ototoxicity management process.

Participants

The participants invited to take part in this questionnaire were Audiologists, ENTs, AVPs and GPs practicing in the National Health Service (NHS) or private sectors of healthcare in the UK. The Action on Hearing Loss (AoHL) website provided a list of all hearing services in the UK, including audiology departments based in hospitals and local health settings funded by the NHS and private hearing services. An additional online search was conducted to find a list of GPs across NHS trust websites. Every fifth contact was selected from the search list ensuring a good representation of each region in the UK.

Centres, hospitals, departments and GP practices were contacted directly via telephone where requests were made for an invitation email (containing the questionnaire hyperlink) to be added to their department or practice mailing list of the professionals mentioned above. Audiologists were also accessed through the Phonak professionals mailing list.

Data collection and analysis

The questionnaire was made available via the UCL Opinio hyperlink for 3 months. Subsequent reminder emails were sent prior to the closing date explicating the anonymity of the participation and a hyperlink to the questionnaire. Participants could only access the questionnaire once to prevent duplication of responses and accuracy of the results. Participants were given a unique ID number and all responses were securely and accurately logged online. There were 134 questionnaires used in this analysis of data. A descriptive analysis of the collected data was performed and presented in the results section below.

Results

Results are reported as adjusted relative frequencies (ARF), or relative frequency (RF) of respondents by choice or absolute frequencies (AF). ARF is the percentage of respondents who selected a given option, from the total number of respondents to the given question. RF of respondents by choice is used when respondents can choose all/any of the options that apply in their answer, the percentage frequency of their choices is given. AF is the number of respondents who selected the given option.

Demographics

A total of 134 questionnaires were collated during a 3-month period of making the questionnaire live online. The professional demographics of respondents show 68% were Audiologists, 21% hospital physicians including ENTs and AVPs, 4% GPs and 7% included other hearing professionals such as Speech and Language Therapists (SALT), Teachers of the Deaf, Advanced Nurses, Community Audiology Paediatricians, Educational Audiologists, Advanced Practitioner in ENT and Paediatric Associate Specialists. The respondents who completed the survey provided a good representation of all geographical regions across the UK as demonstrated in Figure 1.

Respondents were asked directly if they were involved in managing or referring patients that have ototoxicity. This was confirmed by 84% of the respondents who then stated that they delivered their service(s) to adult, geriatric (>60 y/o) and paediatric

populations on either a daily (3%), weekly (15%), monthly (20%), annual (19%) or on an ad hoc basis when a patient reports symptom worsening (20%).

Ototoxicity monitoring and baseline recordings

Figure 2 shows the distribution of responses when asked if the majority of patients were monitored for ototoxicity-related hearing or balance problems. Of the respondents, 60% indicated that monitoring was performed for cochleotoxicity alone (hearing loss), 31% confirmed that they did not know whether ototoxicity monitoring was performed or not and only 7% and 1.5%, respectively, indicated that monitoring was performed for both hearing and balance problems or just for balance problems. When asked if baseline assessments were performed to assess hearing and balance function prior to exposure to the ototoxic agents only 16%

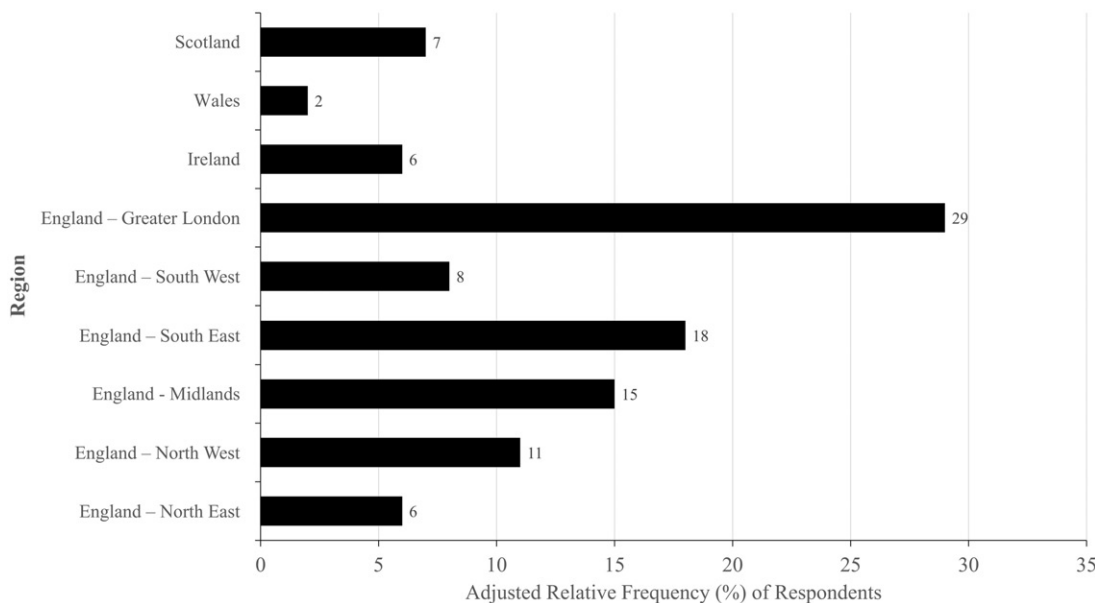


Figure 1. Geographical locations across the UK of survey respondents (N = 134).

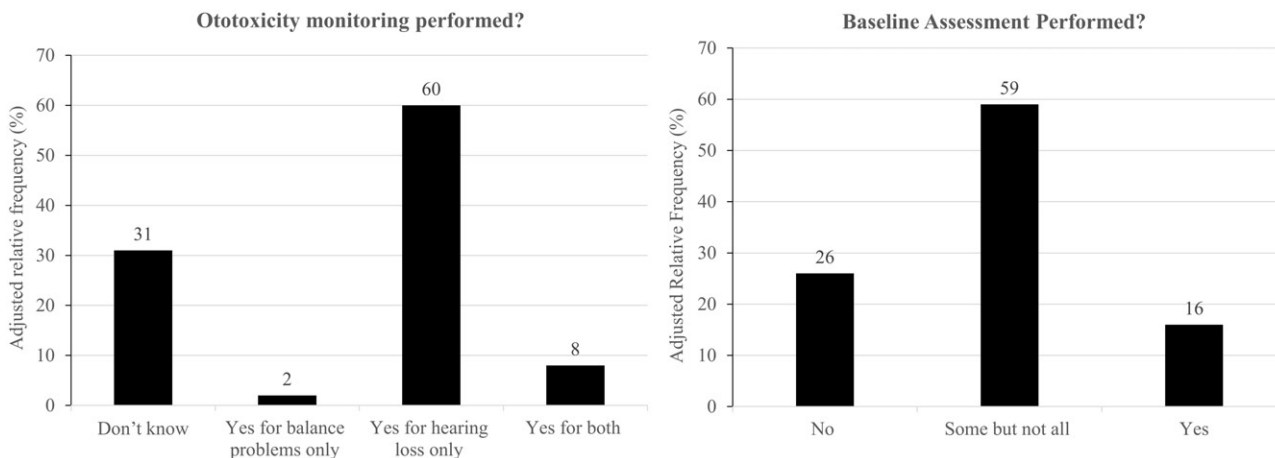


Figure 2. ARF (%) distribution of responses to questions asking if ototoxicity monitoring of hearing and balance function and if baseline assessments were performed.

indicated that it is performed, 26% indicated that no baseline recording is performed and 59% indicated that it is performed for 'some but not all' patients.

Ototoxic agent, patient group mostly exposed

Table 1 illustrates the ARF of patient groups exposed to the ototoxic agent and the patient groups the respondents treat/manage. The commonest group of patients (90%) that were managed by the respondents were those treated for cancer as well as patients with a variety of severe infections. The respondents who selected the

'other' patient category specified the patient groups they treated. These included neonates, Neonatal Intensive Care Unit (NICU) babies, transplant patients, and patients undergoing iron-chelating treatments. When asked to specify the type of ototoxic agents used, 40 respondents specified the ototoxic agents they commonly encounter include: cisplatin, carboplatin, gentamycin, tobramycin, amikacin, benzyl penicillin, macrolides, aspirin, chemotherapy (usually platinum-based), ototoxic ear drops, TB medication, vancomycin, exjade, deferoxamine and furosemide. The majority of the respondents mentioned aminoglycosides (68%) and cisplatin (63%) as the common cause of ototoxicity.

Respondents were questioned whether patients who are on an ototoxic agent are involved in a clinical trial for otoprotection (i.e. clinical trials investigating otoprotective agents to prevent hearing loss, tinnitus and/or balance problems) 46% selected the 'don't know' option, 8% selected 'yes,' whilst 46% selected the 'no' option.

Table 1. ARF (%) showing which patient groups are mostly exposed to ototoxic agents (respondents were allowed to choose multiple options).

<i>Patient group</i>	<i>Adjusted relative frequency (%)</i>
Cancer	90
Acute infection	47
Chronic infection	40
Tuberculosis (TB)	26
Thalassemia	15
Cystic fibrosis	30
Cardiovascular disease	13
Kidney disease	33
Other	10

Referral pathway

Table 2 shows a breakdown of each target group and their responses. The Audiologist's main source of referral was from ENT specialists (67%), closely followed by referral from other hospital departments (56%). For ENT/AVP specialists the main source of referral was from the GPs (71%), followed by hospital departments (62%). The GPs' main source of referral was through ENT specialists (40%) and Audiologists (40%), and the 'other' hearing

Table 2. Absolute frequencies (%) from each target group regarding the patient referral pathway.

<i>Speciality</i>	<i>Source of referral</i>	<i>How they manage the referral</i>	<i>Management outcome</i>
Audiologist (n = 64)	GP: 37.5%	Manage themselves: 31%	Patient discharged: 20%
	Ward: 52%	Refer to GP: 14%	Follow up: 33%
	ENT: 67%	Refer to audiology: 16%	Monitoring continues: 30%
	AVM: 14%	Refer to ENT: 48%	Referral to another service: 14%
	Audiology Department: 23%	Refer to AVM: 14%	Other: 6%
	Walk in clinic: 9%	Refer to other: 17%	
	Hospital Department: 56%		
ENT/AVP (n = 21)	GP: 71%	Manage themselves: 76%	Patient discharged: 14%
	Ward: 38%	Refer to GP: 14%	Follow up: 52%
	ENT: 48%	Refer to audiology: 43%	Monitoring continues: 29%
	AVM: 5%	Refer to ENT: 5%	Referral to another service: 5%
	Audiology Department: 38%	Refer to AVM: 5%	Other: 5%
	Walk in clinic: 62%	Refer to other: 0%	
	Hospital department: 62%		
GP (n = 5)	GP: 20%	Manage themselves: 0%	Patient discharged: 0%
	Ward: 0%	Refer to GP: 20%	Follow up: 40%
	ENT: 40%	Refer to audiology: 60%	Monitoring continues: 20%
	AVM: 20%	Refer to ENT: 20%	Referral to another service: 20%
	Audiology department: 40%	Refer to AVM: 0%	Other: 20%
	Walk in clinic: 20%	Refer to other: 0%	
	Hospital department: 0%		
Other (n = 6)	GP: 17%	Manage themselves: 17%	Patient discharged: 0%
	Ward: 67%	Refer to GP: 0%	Follow up: 50%
	ENT: 17%	Refer to audiology: 50%	Monitoring continues: 33%
	AVM: 0%	Refer to ENT: 17%	Referral to another service: 0%
	Audiology Department: 33%	Refer to AVM: 0%	Other: 0%
	Walk in clinic: 0%	Refer to other: 17%	
	Hospital department: 100%		
Other: 0%			

professionals who completed the survey mentioned their main source of referral is through the hospital departments. In the optional comments section, it was identified that the most common hospital department referrals were from oncology and TB clinics and for those respondents who selected the ‘other referral’ option there was a mention of patients self-referring or referrals from solicitors indicating medico-legal involvement.

Questions regarding how each target group managed the referral demonstrated a mixture of responses. The respondents were given the following options: manage the patients themselves, refer to GP, refer to the audiology service, refer to ENT, refer to AVP and refer to other. Audiologists mainly referred to the ENTs (48%), ENTs mostly managed the patients themselves (76%), while 55% of the GP and ‘other’ groups referred to the audiology services. The respondents who selected the ‘other referral’ option mentioned in the comments section referral to hearing services in the community, visiting teacher services, and sending patients back to the referrer.

Further questioning regarding what happens once the patient has completed their treatment with the ototoxic agent revealed a similar pattern of varied responses from each of the target groups. The options presented for selection were patient discharged and never seen again, follow up, monitoring continues, referral to another service and other (Figure 4(f)). All the target groups had a common trend with the majority selecting ‘follow up’, closely followed by ‘monitoring continues’ and then ‘patient discharged’. In the comments section, it was evident that the number of months each professional followed up and monitored patients differed and a few respondents mentioned they don’t know or are unsure what happens to the patient once the treatment is completed.

Below are few of the open-response comments regarding what determines how many months they follow up or monitor the patient:

‘Dependent on the referrer.’

‘As necessary, no protocol in place.’

‘Follow up as per patient request.’

‘Follow up hearing as per ENT/Oncology/AVP request.’

‘Annually.’

‘3 months.’

‘Package of care for 6 appointments and expand if appropriate.’

‘Only when hearing aids are fitted management monitoring continues otherwise patient is discharged.’

These comments insinuate great variability across the UK and the absence of standards for post-treatment follow up has an impact on the patient’s quality of care as ototoxic hearing and balance problems can develop after cessation of treatment.

Setting for ototoxicity management

The setting where patients with ototoxicity are managed also differs as shown in Figure 3. The larger proportion of the patients are reported to receive treatment within the audiology department (44%) followed by the ENT clinic (28%). Only 8% are treated at bedside within a hospital ward whilst 6% are treated in a community setting such as their GP practice and 5% are treated on an ad hoc basis through walk-in-clinics. The respondents (5%) who selected the ‘other’ option specified the settings where

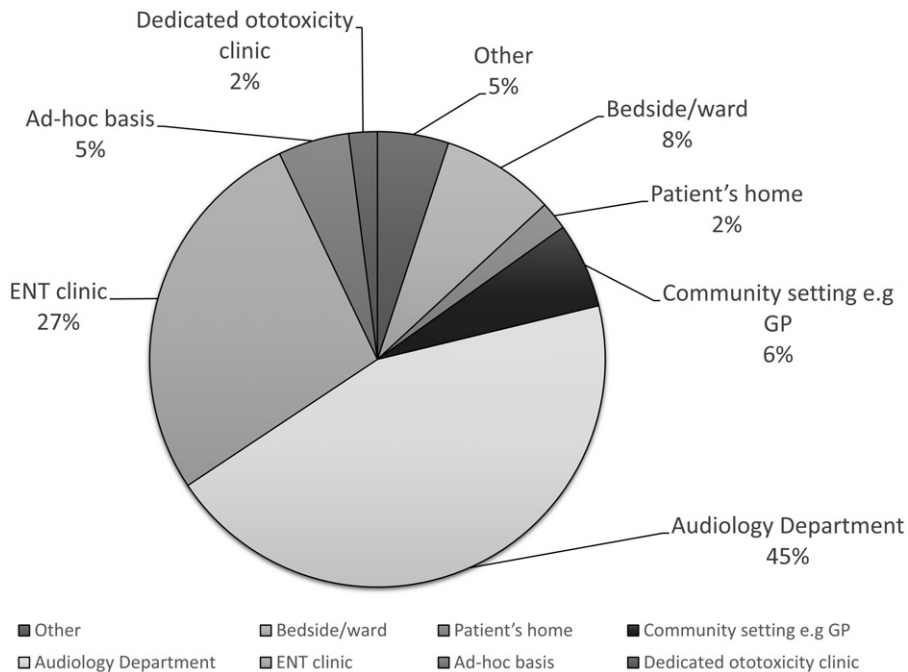


Figure 3. Pie chart illustrating the distribution of the various locations where patients with ototoxicity are generally management.

management takes place. Responses included head and neck cancer clinics, complex otology clinics, cochlear implant clinics, paediatric audiology clinics, oncology clinics, audio-vestibular medicine clinics and through medicolegal claims. Only 2% stated that treatment takes place at a dedicated ototoxicity clinic, which was the same amount as those treated at the patient’s home.

Ototoxicity management protocol

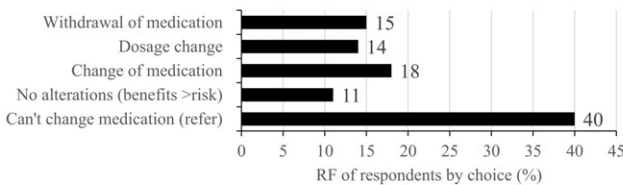
Only 28% of respondents reported an ototoxicity management protocol existed within their centre compared with 72% reporting no protocol exists at all, highlighting the need for UK-wide clinical guidelines for a standardised ototoxicity management protocol.

Ototoxicity management services provided

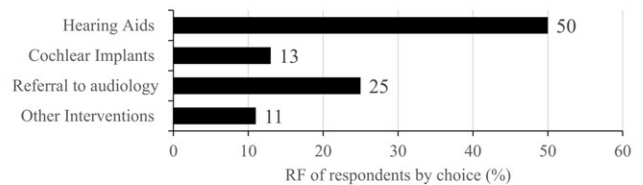
In Figure 4(a)–(f), Ototoxicity Management Services are provided. Respondents were allowed to select as many options of the six main categories of management services (modification of medication, improving hearing function, minimising the disability, balance management, counselling and post-treatment follow-up) which their centre provides for ototoxicity management. In the figure, the number of respondents to each of these questions was presented and showed that only 42–78 (31–58%) actually addressed these questions with the smallest number of responses provided to the ‘balance management’ category. In the ‘modification of medication’ category, 40% indicated that they do not have the authority to change medications and would need to refer the patient to their

managing consultant. This response is probably the response given by the Audiologists and the clinicians not responsible for the overall management of the original condition of these patients. Eleven percent of respondents indicated that they would not alter the ototoxic medication even after damage is confirmed as overall benefit exceeds the risk of ototoxicity but may also be an indication of limited awareness of alternative options or the impact of ototoxicity on patients. Hearing aids provision was the main option offered as a rehabilitation tool to support hearing function with a smaller proportion offering cochlear implantation. Twenty-five percent of the respondents indicated that they would refer their patients to audiology to manage the hearing loss. The respondents were asked to provide more information under the ‘other interventions’ choice and these included: refer for continuing monitoring, for hearing therapy, for balance management and for counselling. For ‘minimising disabilities’, the highest percentage went to providing assistive listening devices but there was an awareness of the need to refer to other services also demonstrated. Regarding the ‘balance management’ category many specified that they would refer their patients to specialised balance clinics for vestibular rehabilitation with some indicating that this is provided by physiotherapists. There were good responses to the ‘counselling’ category with many respondents indicating that they provide a patient centred service where they listen and support patients and provide them with information about hearing loss, hearing aids and referral to audiology and hearing therapy if needed. There were several references to the use of leaflets on ototoxicity provided by charities like NDCS and AoHL. It was encouraging to see that 67% of respondents indicated they would either follow-up or continue to

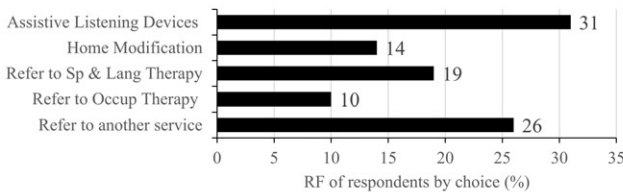
(a) Modification Of Medication (n=66)



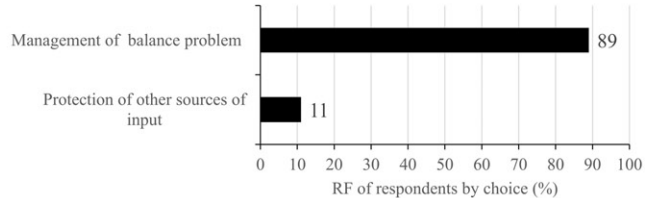
(b) Improving Hearing Function (n=76)



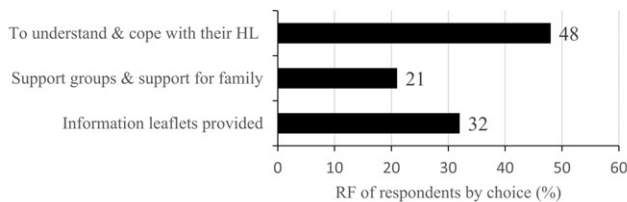
(c) Minimizing Disability (n=59)



(d) Balance Management (n=42)



(e) Counselling (n=55)



(f) Post-treatment Follow-up (n=78)

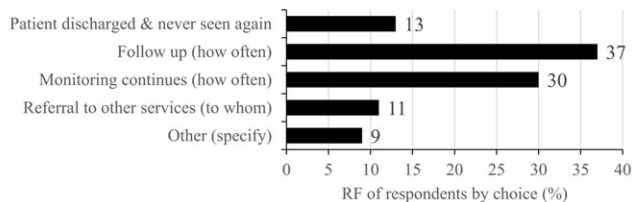


Figure 4. (a–f) Relative frequency (RF) of respondents by choice (%) specifying the different ototoxicity management services that they offer (respondents were asked to choose all the options that applied to their service. n: number of respondents to each question).

monitor their patients for ototoxicity post-treatment (post-treatment follow-up category). There was a significant variability regarding how often and who follows them up with some indicating that this is done at 6 months after treatment and then annually. Many respondents also indicated that frequency is dependent on the patient's symptoms and is driven by the level or severity of these complaints.

Trends of responses to the open-ended questions

The survey ended with two open-ended questions enabling the respondents to have the freedom and space to provide detailed opinions about the way patients are managed for ototoxicity within their departments. The responses clarified the simple yes/no and multiple-choice answers throughout the survey, yielding more accurate information and providing contextualisation, and actionable insight.

Question 24 asked *'What do you believe is the most important part of the ototoxicity management process?'*

A total of 56 respondents provided their opinions to this question and three common themes appeared: prevention, monitoring and counselling. Below are some of the responses of each of the three main themes identified:

'Ensuring you provide them with all the information to help them understand how the medication caused their hearing loss or balance problem and helping them to cope.'

'Management of patient's needs (counselling, hearing amplification and hearing therapy and other onward referrals).'

'Regular monitoring, managing hearing loss or balance or both and counselling the patient.'

'Regular assessment and psychological support for patient and family and best amplification possible (HA or CI).'

'Education and awareness of the team to support the patient journey.'

'Monitoring progress of hearing loss and effectiveness of any intervention.'

'To continue to monitor after completion of treatment and to effectively communicate back to the oncology team any changes in hearing.'

'Monitoring changes in the patient's high frequency hearing as there often can be a slight subtle change in only the high frequencies which would have been missed if only frequencies between 0.25 kHz and 8kHz were tested.'

'Monitoring services (before, during, after), management of patient's needs, in my case, it will be nice to make onward referral for management of hearing/tinnitus difficulties. Counselling is vital.'

Question 25 asked *'What do you feel would be an improvement to the way you manage your ototoxicity patients?'*

A total of 47 respondents answered this question and the main themes identified from the responses were the following: national guidelines and/or a departmental or trust protocol, establishing a proper pathway, training and education, greater awareness amongst staff and improved liaison. Below are some of the responses of each of the three main themes identified:

'Having a well-funded/staffed service and a clear guideline/pathway on managing children with suspected ototoxicity.'

'A departmental protocol that is clear, so everyone can follow the same regulation.'

'Establishing a proper pathway.'

'Greater awareness amongst all staff for all the drugs that can cause ototoxicity and how to approach the pathway for the patient, there is no protocol.'

'Having a protocol as there is not one in our department of what options are available to the patient, how often to see them, no set guidelines so everyone has a different way of managing the ototoxic patient.'

'National guidelines that are enforced and/or at least departmental protocols.'

'Clearer protocol on what to look for, referral and general management to all staff members that may be involved with these kinds of patients.'

'Better knowledge of dosage and associated risk.'

'Greater knowledge and easy access to other medical personnel who are dealing with each patient.'

'Streamlining/better communication between departments.'

'Audiologist and ENT staff training is needed.'

'Training in recognizing ototoxicity.'

'Greater awareness amongst staff of all drugs that can cause ototoxicity.'

Discussion

Over 200 drugs of which some are utilised in the treatment of life-threatening illnesses are unfortunately known to damage ear sensory cells and nerve fibres causing sensorineural hearing loss and vestibular disorders (Walker et al. 1990; Raphael 2002). Responses from 134 respondents with different clinical backgrounds involved in the management of patients exposed to ototoxic medications were analysed. Results from this study confirmed that ototoxicity monitoring was not consistent, with only 60% stating that monitoring for cochleotoxicity alone is conducted and which drastically decreases for monitoring for vestibulotoxicity where only under 10% stated that this was performed in conjunction with monitoring hearing loss or just monitoring balance function alone (Figure 2). There was limited confirmation that baseline testing is performed

(16% said yes and 56% confirmed that it is performed for some but not all patients) which is important to establish patients' hearing and/or balance functions before exposure for them to act as their own controls before and after intake of ototoxic agents (Figure 2). Regarding the presence of ototoxicity management protocols, 72% of the respondents reported that none existed.

The results shown in Table 1 are concordant with current literature that the main ototoxic patient group exposed and agent used were chemotherapeutic agents, such as cisplatin for cancer patients, or from treatment with aminoglycoside antibiotics for patients with infections such as meningitis, encephalitis, TB, patients with cystic fibrosis suffering from repeated chest infections and patients with large wounds (Ton and Parng 2005). Aminoglycosides and cisplatin are known to be potent ototoxicity inducers (Lautermann et al. 2004). Patients with kidney pathology were the next most common patient group exposed to ototoxic agents. This patient group is quite interesting because patients with kidney pathology may commonly be given ototoxic aminoglycosides to combat severe infections, such as post-dialysis peritonitis, are at a higher risk if the ototoxic drug is excreted via the kidney or may be more commonly monitored for ototoxicity because they may have combined kidney and ear pathology related to their treatment with ototoxic drugs. Verdel et al. (2008) conducted a study and found that the ototoxic agents had the ability to influence the ionic homeostasis in the kidney and ear, altering the transport of sodium and/or potassium causing the potential toxic effects in both organs.

Identifying the most commonly identified ototoxic medications and exposed patient groups provides clinicians with a scope of looking at alternative medications that can be utilised for these life-threatening illnesses whilst curing the patient but with minimal ototoxic effects. Knowledge about the patient groups is also valuable for the development of targeted ototoxicity monitoring and management programmes and guidelines that are compatible with each specific patient groups' needs (Table 1). Recent literature represents a successful example of this. For example, a study found that the hearing of 168 cystic fibrosis patients without pre-existing ototoxicity were not affected during a single course of tobramycin (Mulheran et al. 2006), nor did the hearing deteriorate for 19 patients who had serial hearing tests over a median of three courses when taking tobramycin (Scheenstra et al. 2010). This led to clinicians switching the aminoglycoside antibiotic amikacin to tobramycin due to its less ototoxic effects but similar therapeutic efficacy.

In addition, otoprotective agents such as antioxidants show great promise in minimising or preventing ototoxicity (Sha et al. 2001; Yang et al. 2011; Aksoy et al. 2014; Freyer et al. 2017). Despite the absence of a commercially-available medication that can prevent toxic effects to the ear, pioneering research is currently advancing worldwide in an attempt to rebuild, replace or generate cochlear hair cells via gene and stem cell therapy (Matsui et al. 2005; Cotanche and Kaiser 2010). A large percentage of respondents in the survey (46%) selected the 'don't know' option with respect to the question enquiring about patient involvement in an otoprotective clinical trials. This emphasises the need for education and training regarding current trials in ototoxicity prevention that needs to be reinforced not only amongst patients but working professionals too.

Providing greater awareness and education around ototoxicity will be beneficial for informing clinical decision-making. This was also highlighted in the open-ended questions when asked about their opinion of what they felt could be improved with respect to the management process. WHO recommends ototoxicity training

amongst the staff which is led, guided and supported by ENTs in the development and conduct of the training with regular refresher courses to update relevant knowledge. Similarly, the American Academy of Audiology (AAA 2009) Position Statement also mentions the importance of Audiologists taking a lead in staff training as is highlighted by the following quote from this document *'Only the Audiologist is endowed by their professional training with the ability to achieve both objectives of ototoxicity monitoring. The Audiologist thus should take the lead in developing ototoxicity-monitoring programmes, driven by the dual goals, again, of preventing or minimising hearing loss and helping the patient to maintain the most effective hearing communication possible.'*

Ototoxic management should involve a multidisciplinary team (MDT) approach; hence questions enquiring about the setting of management and referral pathways were discussed within the survey. It is vital for every member of the team to have sufficient knowledge regarding ototoxicity to manage and refer the patient appropriately. Petersen and Rogers (2015) proposed an example of the MDT approach involved in the care of a patient with ototoxicity. They proposed an idealised two-tier schema explaining which MDT health professionals and services would be involved during the patient's journey for the management of cochleotoxicity and highlighted which aspects of therapy each professional would address. A team could be comprised of a family GP who is involved in referrals and post-discharge follow-up, an Audiologist to provide information regarding risk, pre-existing hearing loss and to inform, counsel, assess, monitor and support the patient during and after treatment; the medical and nursing personnel involved with prescribing and administering the treatment, acting on the outcomes of monitoring and coordinating post-treatment follow-up; ENTs/AVPs undertaking clinical risk-benefit evaluations; and the pharmacologist with knowledge of drug effects and interactions. Liaison amongst all members within the team is very important to provide unnecessary referrals back and forth, which was seen in the results above (Table 2), and to effectively provide appropriate intervention and management. From the survey, it was evident that there was no clear role of each professional and the responsibility of the patient seemed to shift from one clinician to the other. Referrals seemed to constantly occur back and forth. For example, the results found that an Audiologist would refer to an ENT to manage the patient whilst some ENTs would refer to the Audiologists when ototoxicity was diagnosed while some refer back to the GP. This needs to be clarified in future protocols so that minimal grey areas exist.

A study by Khoza-Shangase and Jina (2013) in South Africa found that GPs do not actively engage in monitoring and management strategies. They discovered that 75% of GPs did not seek audiological assessments for their patients when placed on ototoxic medication. They recommended that a close relationship needs to be established amongst GPs and Audiologists to contribute towards efficacious patient care. GPs should refer for ototoxicity monitoring during the treatment period, which in turn ensures early identification of hearing impairment and consequently serves as preventative measures for ototoxicity, as damage to the auditory system may be prevented or reduced before the patients start complaining and ototoxic effects become irreversible. A similar study in the UK was not found in the literature.

The setting where patients are managed also showed great variation (Figure 3) reinforcing the idea there is a lack of clarity about where and who manages the ototoxic patients reinforcing the need for guidelines and protocols. It was surprising to find that a

small percentage (2%) stated that treatment takes place at a dedicated ototoxicity clinic. It was not clear whether this is because few dedicated services exist or that other clinicians are not aware of them. Nevertheless, this highlights the need for education and knowledge updates amongst professionals regarding what services are available and to ensure facilities are being utilised otherwise it would be a waste of resources and funding. It is also worth noting that many patients requiring ototoxicity monitoring are extremely ill, and any changes in hearing status or vestibulotoxic effects that they experience can be masked by their overall poor medical condition making them non-responsive to audiological testing. Moreover, there may be difficulties in transporting these patients to the audiology departments, especially if they are located at different hospital sites that are common in the UK. These factors necessitate implementing a flexible and compassionate approach to monitoring these patients. The current survey showed that bedside/ward testing was a setting used by a mere 8% of respondents. If bedside testing is the only available method of monitoring these patients, it is certainly preferred to not be testing at all and would offer a much more feasible and comfortable option for them. The current availability of smaller more portable audiological equipment can assist in allowing for bedside testing if the background noise was deemed acceptable.

The WHO proposed the use of a pro-forma of a screening survey of ototoxic damage as a tool to aid in early detection and monitoring for ototoxicity. It was mentioned it would be suitable for GPs (see Annexe 5 of the WHO 1994 report). In this ototoxicity draft model form there were sections to (a) identify the patient's case history (oncology, renal disease, TB, CF etc.); (b) presence of a condition that can affect the metabolism of the ototoxic agent (renal, liver or metabolic diseases); (c) specify details of the drugs taken (type, dose, route of administration and duration of treatment); (d) risk factors to ototoxicity (exposure to noise, other ototoxic drugs, family history etc.); (e) specify before and during/after treatment ear complaints, findings on otoscopic examination, and outcomes of audio-vestibular investigations. Columns representing 'before' and 'after' treatment emphasise the importance of monitoring prior as well as after treatment.

As highlighted earlier, an overwhelming 72% of hearing professionals across the UK indicated no protocol for ototoxicity management existed within their centre, which is clearly reflected by the variation in management and lack of standardisation in their practice. The use of available clinical guidelines will encourage clinicians to evaluate their practice. The use of evidence can shape practice at a clinical level. Knowledge can be disseminated through literature, clinical guidelines and professional society recommendations, which will aid in creating a refined national guideline or protocol for ototoxicity management to ensure patient care is at its optimal level.

A wide range of ototoxicity management services are provided across the UK which include counselling, balance management, improving the hearing function, follow up, minimising the disability and medication alteration (Figure 4).

The medication category (Figure 4(a)) depicts the highest selected option to be 'unable to make changes to the medication themselves' which can be due to the fact there was a skewed high percentage of Audiologists who completed the survey. Despite this, the next highest category was 'changing the medication.' This emphasises the advantage of physicians having access to a wide variety of drugs of the same family therefore enabling a greater choice for therapeutic treatment. They rely on the progressing

scientific knowledge and the most credited clinical trials to aid in balancing the drug effectiveness and safety and undesired ototoxic effects when making decisions about treatment.

Ototoxicity results in sensorineural hearing damage with/without tinnitus and a possible associated labyrinthine disequilibrium symptomatology. At present, there is no cure for permanent ototoxicity; however, hearing aids can ameliorate the hearing loss and enhance the patient's quality of life. The 'improving the hearing function' category (Figure 4(b)) within the survey identifies that many respondents (50%) do provide hearing aids as a form of ototoxicity management, which is reassuring. The ENTs/AVPs usually would refer to an Audiologist regarding recommendations for a suitable hearing aid and that is dependent on the person's lifestyle, listening needs and hearing concerns. Respondents who selected the 'other intervention' elaborated in the comments sections that they provide tinnitus management or hearing therapy, counselling, assistive listening devices or onward referral for more support.

Hearing aids and cochlear implants unfortunately cannot restore normal hearing but can reduce the effects of damage and rehabilitative function. Additionally, assistive listening devices maximise hearing abilities providing auditory communication enhancement. This new technology enhances the sound by reducing the effects of distance, noise and reverberation and transmitting sound directly to the ears or hearing aids. Examples include television listening systems, personal FM systems and amplified telephones. In 2003, the Federal Communications Commission (FCC) in the US requested manufacturers and service providers to construct digital wireless phones that can be easily utilised with hearing aids to minimise interference and to better the technology for hearing impaired people. Currently, most hearing aid manufacturers can effectively allow hearing aids to have compatibility with different devices including mobile phones, TV, radio and others. Moreover, signalling and substitution systems, which convert sound or key strokes into another mode, such as text or flashing lights, are also helpful in improving the patient's quality of life and for safety aspects. These include fire alarms with flashing lights, doorbells with a built-in light system to warn the person someone is at the door, and alarm clocks that can be placed under the pillow with vibratory features. However, education for clinicians needs to be provided about these options and possibly a leaflet/catalogue be made available for them to offer this information to their patients. A discussion about how to purchase the devices during the management and rehabilitation sessions can also be provided by the Audiologists.

Referral to other services such as occupational and speech and language therapists reinforce the multidisciplinary holistic treatment approach. The comments section revealed other services the clinicians referred to included social services, psychology, social workers, education services and Teacher of the Deaf. It was encouraging to see that some proportion of respondents indicated that they manage balance impairment (Figure 4(d)), however, few indicated that they try to protect alternative sources of balance. Balance homeostasis compromises three aspects including vision, proprioception and labyrinthine activity. Yearly ophthalmological examinations and physiotherapy to enhance stability is a useful aspect of balance management that should be employed.

Counselling plays a vital role in the rehabilitative process. The audiology professionals are well equipped to provide more in-depth counselling than just information giving. The first part of the counselling process should entail detailed simplified education about their type and degree of hearing loss and the impact on their

communication abilities. Further details can then be provided about services including support groups for families and themselves and devices available to enhance communicative and listening abilities. The treatment should be tailored to individual needs with goals established and questionnaires to grasp the progress. The healthcare provider should provide various written information leaflets comprising a step-by-step explanation of hearing aid fitting and the rehabilitation process including when follow up occurs and what signs to look out for to identify early deterioration. Additional information about support groups available would also be beneficial for the patient.

Hearing health professionals are beginning to acknowledge the benefits of offering group hearing aid orientation sessions. It enables groups of individuals to work with each other or their family/significant others using and repairing hearing aids, developing listening and communication strategies, and adjusting to amplification whilst providing peer group support. The inclusion of family members and/or significant others throughout the rehabilitation process is strongly recommended (McCarthy and Roeser 2016). They should be able to understand their roles in communication breakdowns and how to enhance and rectify such problems. Clear Speech is an example of a rehabilitative strategy taught to family members. They are taught to use an appropriate rate (speed) and volume of speech to improve communication with people with hearing impairment and how to use communication repair strategies to facilitate smoother conversations effectively. Family members can be taught good communication practices such as limiting background noise when conversing, getting the attention of the listener and not communicating from room to room (McCarthy and Roeser 2016). Respondents to the 'counselling' category (Figure 4(e)) showed that all three aspects of this management were provided to some degree with aiding the patient to understand and cope with hearing loss having the highest response frequency (48%).

ASHA (1994) strongly advocates ototoxicity monitoring post-treatment due to late onset or continued ototoxic effects (Bertolini et al 2004; Fausti et al. 2003). The European Review for Medical and Pharmacological Sciences (2011) stated that reasons for this phenomenon include a slow clearance rate of aminoglycosides and platinum-based drugs in the inner ear which is correlated with functional and morphological changes in different target cells (Imamura and Adams 2003; Roland 2004; van Ruijven et al. 2005), non-pathogenic non-iatrogenic noxae (trauma, noise, infections, circulatory, metabolic or endocrinological disorders), or iatrogenic oto-surgery (AAA 2009).

The results in Figure 4(f) and its associated free text answers revealed that some professionals (13%) would discharge without monitoring post-treatment, whilst others just monitored annually or when the patient reported symptoms, reflecting variability in practice amongst professionals across the UK. The clinicians aiding in the management should adopt more of a proactive approach rather than a reactive approach. The absence of a protocol or national guidelines to follow is affecting the quality of patient care and preventing early detection not just before treatment but also further deterioration post-treatment.

Limitations of this study include an inability to assess response rate or confirm real level of engagement. Estimations regarding the number who deleted the email without giving due consideration toward it, how many read and deleted it due to a lack of interest, on leave, no time or because they believed it to be not relevant to them, is a barrier to all questionnaires. A randomised sample of each

target group was contacted representing each region in the UK. However, when the e-mail was distributed and forwarded internally within their departmental or practice mailing list, it was difficult to keep count of how many clinicians received the survey.

Conclusion

Minimal standards of care are intended not to exclusively inform clinical decision-making, but to provide greater awareness, education and to improve and standardise the management of hearing loss and/or balance problems due to ototoxicity across the UK. The following key issues should be incorporated when advocating national guidelines: referral pathways highlighting what aspect of management each professional deals with, clear audiological protocols for ototoxicity monitoring and follow-up guidelines, clarification on which grading criteria to implement when assessing the severity of the ototoxicity, knowledge of medication alternatives to ototoxic medications for therapeutic treatment for various pathologies, and for the various possible management options for ototoxicity. In addition, training on ototoxicity amongst the staff should be implemented which is led, guided and supported by Audiologists with regular refresher courses to update relevant knowledge. Effective management and aural and/or vestibular rehabilitation is essential to improve the post-treatment quality of life of patients suffering from this condition.

Further research aims to obtain a larger sample size and a secondary survey specifically for patients who suffered from ototoxicity to explore their experience during the management process is planned. Additional exploration regarding opinions about education programmes for the staff would be included to assess the best format, timing and personnel to involve when developing them. Exploration of the general consensus of a preliminary management guideline and to further develop and improve the protocol before final implementation nationwide would constitute the larger aim.

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