The current paper is an attempt at highlighting important strategic indicators, as well as important variables, that the audiology community needs to consider in order to play a more central role in pharmaco-vigilance as part of pharmaco-audiology. Pharmaco-vigilance is an important aspect of pharmacological treatment of disease. In developing countries, where burden of disease is high with resource constraints dictating healthcare priorities; it is important to deliberate on risk/benefit of medications prescribed to treat disease. In the form of a literature review, the author presents current arguments with regards to audiology practice. In audiology, pharmaco-vigilance in the form of ototoxicity monitoring is gaining momentum within the South African research and clinical communities. This ototoxicity monitoring is however non-systematic, non-comprehensive, and does not seem to have a strategic plan behind it. This is fundamentally due to lack of involvement of audiologists in the risk/benefit evaluation of medications during the drug development and monitoring process. The current paper argues for an expanded role of the Audiologist which will ensure collaborative engagement with all relevant stakeholders in order to ensure that both quantity and quality of life are considered during the drug development and monitoring process.

**Keywords:** Benefit, ototoxicity monitoring protocol, pharmaco-audiology, risk, vigilance

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**ABSTRACT**

The current paper is an attempt at highlighting important strategic indicators, as well as important variables, that the audiology community needs to consider in order to play a more central role in pharmaco-vigilance as part of pharmaco-audiology. Pharmaco-vigilance is an important aspect of pharmacological treatment of disease. In developing countries, where burden of disease is high with resource constraints dictating healthcare priorities; it is important to deliberate on risk/benefit of medications prescribed to treat disease. In the form of a literature review, the author presents current arguments with regards to audiology practice. In audiology, pharmaco-vigilance in the form of ototoxicity monitoring is gaining momentum within the South African research and clinical communities. This ototoxicity monitoring is however non-systematic, non-comprehensive, and does not seem to have a strategic plan behind it. This is fundamentally due to lack of involvement of audiologists in the risk/benefit evaluation of medications during the drug development and monitoring process. The current paper argues for an expanded role of the Audiologist which will ensure collaborative engagement with all relevant stakeholders in order to ensure that both quantity and quality of life are considered during the drug development and monitoring process.

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**INTRODUCTION**

Africa has and continues to experience significant health challenges. Within the public health sector, these challenges include well-documented lack of appropriate skills, unfavorable professional-to-patient ratios with obvious incongruence between supply and demand, infrastructural constraints where access to health care services is severely compromised by limited well-functioning public health facilities, general lack of resources for the size of the population requiring health services, challenges with translating knowledge and policies into practice for various reasons including linguistic and cultural diversity quandaries, as well as risk versus benefit assessments predicaments.\[^{1-3}\] Risk: benefit assessments refer to the evaluation of safety signals (medical and/or surgical) within the health care industry. The value of risk: Benefit evaluations in pharmacology have been well documented.\[^{4}\] Due to ototoxicity, these evaluations require increased attention by the audiology community as part of their pharmacovigilance initiatives.\[^{5}\] Ototoxicity is defined as drug-induced hearing loss that presents as a high-frequency hearing loss, which may be accompanied by tinnitus and/or vertigo. It is well established that many drugs (for example, aminoglycoside antibiotics; some chemotherapeutic drugs, etc.), are capable of inducing ototoxicity.\[^{5,6}\] The current paper argues for increased attention to pharmacoaudiology in Africa and the rest of developing countries, with clear roles for the audiologist within the team during the risk and benefit evaluation of treatment methods where ototoxic medications are involved. This paper aims to illustrate that audiologists should not play a peripheral role in the

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process of evaluating risk versus benefit of treatments which are or are potentially ototoxic. Rather, they should be centrally located within the multi-disciplinary and multi-stakeholder team involved in the drug development and evaluation process.

As asserted by Bankaitis and Schountz[7] that no drug is completely safe, and that investigators and the Food and Drug Administration (FDA) are willing to accept more severe side effects from a drug used to treat a life-threatening disease such as HIV infection; it becomes important to adopt a highly vigilant approach toward drug monitoring and risk/benefit evaluations. The drug-induced hearing loss may not qualify as a “more severe side effect,” however, it does require some attention by the research and clinical community as part of the ethical care of patients; over and above clinical care.[5] Literature defines a serious adverse event as any untoward medical occurrence that at any dose can cause any of the following: lead to death of the patient, is life-threatening to the patient, leads to inpatient hospitalization or prolongation of hospitalization, and can result in persistent or significant disability/incapacity.[8-10] Although ototoxicity has not gained recognition of a serious adverse effect, according to this definition, it can be argued to fall under the adverse effects because it is a persistent or significant disability to the individual affected; despite the health-saving benefits that the individual gains from the ototoxic drug itself.

All biologically active substances exhibit some kinds of detrimental and undesirable effects on the body.[4] Although physicians prescribe drugs to prevent or treat disease, those same drugs can be toxic to certain patients. This is particularly true for drugs developed to treat infectious life-threatening diseases such as HIV/AIDS.[7]

In such instances, a new drug developed may obtain early enthusiastic endorsements and approval of its therapeutic value prematurely; only to later then receive condemnations because of its adverse side reactions. This phenomenon has been observed with initial use of some antiretroviral drugs, which have later been found to be ototoxic as well.[5] For example, it is reported that the HIV discovery and biology led to the development of experimental/investigation drugs, which the FDA may have hastily approved for clinical trials involving human participants as an emergency response to sustain life.[5,7]

The Medicines Control Council of South Africa might have engaged or might even be currently partaking in such acts, particularly where communicable diseases are concerned. This has life-sustaining as a goal, and not necessarily the quality of life; which hearing loss can be argued to impact. These are some of the reasons why it becomes important to deliberate on risk versus benefit of treatment drugs, and to establish whose responsibility this task is. Approval of experimental drugs has implications for research into an audiological function, and prescription of drugs with known or unknown ototoxic effects has serious implications for the ethical care of the patient being treated.

**Evaluation of Risk versus Benefit**

The obvious goal in drug research is to recognize the harmful effects of newly developed drugs by laboratory tests before any injury is experienced by human participants,[4,10] and that is what ototoxicity monitoring in audiology is aimed at. Unfortunately experimental methods as well as ototoxicity monitoring protocols have not been standardized; therefore, final analyses are not always entirely dependable and/or generalizable.[5,6,11] More importantly, audiological assessments and monitoring do not always form part of the initial experimental methods where the harmful effects of the drug being developed are being established. It is for this reason that the audiology community needs to directly become involved in the drug development process. This is the process which highlights the critical need to ensure that all drugs used are monitored in terms of their efficacy, as well as analyzed in terms of their negative side effects; and in audiology, this is termed ototoxicity monitoring.[7]

Comparative evaluation of benefits (positive effects-efﬁcacy) and risks (potential harm) of medicines conducted during drug research and development is of paramount importance in pharmacology. This is inclusive of medicines for treatment, prophylaxis, prevention, or diagnosis.[8-10,12] One could argue that the responsibility for this evaluation lies with the manufacturers whose benefit/risk monitoring of medicines should be ongoing, including the postauthorization period. The goal would be to ensure minimization, if elimination is not possible, of safety hazards as well as maximization of treatment benefits.[12] However, long-term quality of life effects of the medicines might not be easily identified without specialized sensitive testing which is often conducted by healthcare professionals, as is in the case of audiologists and ototoxicity, who do not ordinarily form part of the initial drug testing and development phases. It, therefore, becomes critical that such benefit/risk evaluations are comprehensive, inclusive, and ongoing; with the representation of all healthcare professionals.

Standard clinical trials must be performed on any new experimental drugs; with an understanding that exceptions will be made for drugs specifically developed for serious illnesses; as was the case with the AIDS epidemic, in 1987, where the FDA created an exception
to the standard clinical trial procedure to expedite the evaluation process of promising experimental drugs.\[13\] This was the era where the FDA rapidly approved HIV drugs in as little as 3 years, before the completion of all standard clinical trials. Similar scenarios might have been at play for diseases such as multidrug resistant (MDR) and extensively drug-resistant tuberculosis (XDR-TB), and Ebola. FDA definition of a “safe” drug was modified according to the severity of the disease that the drug was developed to treat. This, therefore, raises important implications for pharmacovigilance where ongoing benefit/risk evaluations are conducted.

Benefit/risk evaluation should, at a minimum, be conducted by researchers, physicians/clinicians/audiologists acting on behalf of their patients, the patients themselves, as well as the regulatory authority which decides on whether a drug should be approved or not; whether it should be withdrawn or not’ while making recommendations about the alternative treatment plan or intermediate action.\[4,9‑11\] Numerous challenges can be identified with each of these groups responsible for this benefit/risk evaluation, particularly within the developing country context with unlimited barriers to quality healthcare delivery.

**Influencing Factors to Benefit/Risk Evaluation**

In developing countries such as South Africa, benefit/risk evaluation can be significantly impacted by factors such as nature of the problem, indication for drug use and population under treatment, economic factors, stakeholders with vested interests in the drug, as well as time, data and resources constraints.\[10,14\] First, nature of the problem that determines the time-course of action which usually defines the medical seriousness of the suspected adverse drug reaction and its potential threat to life, can be limiting when it comes to inclusion of important quality of life side effects such as hearing loss and balance disorders, following treatment with ototoxic and/or vestibular toxic drugs. Consequently, quality of life in the benefit/risk evaluation becomes less-prioritized and requires much deliberation in the drug development processes.

Second, indication for drug use and population under treatment also influence the benefit/risk evaluation. Audiologists working in pharmaco-audiology need to be aware of which drugs have a higher acceptable risk and also be aware of all circumstances where there are no reasonable therapeutic alternatives and plan their ototoxicity monitoring and management programs appropriately. Where drugs are given for a life-threatening condition or a self-limiting disease, pretreatment counseling, monitoring and early audiological intervention become key.

Third, economic factors; particularly in low-income countries like South Africa, play a major role in benefit/risk evaluations. Health departments in developing countries might accept medicines with less favorable benefit-risk balance because of affordability when compared to the alternative.\[1,2,10,14\] This is where the lobbyist role of audiologists should become heightened; where pharmaceutical companies are directly engaged with to ensure ethical clinical management of patients where both quantity (prolonging life) and quality of life are taken cognizance of. Economic factors in benefit/risk evaluation are concerned with tradeoffs and weightings where economic efficiency in terms of the difference between benefits and costs is measured; with cost used for a patient who responds equally to different products.\[14\] If the quality of life side effects monitoring such as ototoxicity monitoring did not form part of the drug development process; economic factors might be miscalculated. With ototoxicity, the permanent long term hearing loss brings with it significant economic costs to both the patient and the state if not prevented and/or eliminated. First, loss of employment because of a hearing loss has implications for the economy of the country, and secondly; rehabilitation costs such as fitting of hearing aids and aural habilitation cannot be under-estimated.

Fourth, stakeholders such as patients, physicians, pharmaceutical companies, ethics committees, regulatory authorities, other public health bodies, medical aids, and consumer groups may all have very different perspectives in benefit/risk evaluation of drugs.\[14\] It is therefore important to be aware of who the stakeholders were during the determination of the benefit/risk of a drug. As practising clinicians and audiologists, the patient’s perspective seems the logical site of evidence-base for the objective collection of audiological data for ototo/ vestibular toxicity. In a context like the South African context; sensitivity to influences of linguistic and cultural diversity to clinical management is important. Two patients exposed to the same benefits and risks may view the risk differently, may accept the risk differently, and may also make different decisions around the risk. Influences of linguistic and cultural diversity may compound this level of risk evaluation. Nonetheless, it is important that such risk is clearly communicated to the patients for informed consent; but also because proper pretreatment counseling about side effects of drugs has been shown to improve drug adherence.

Finally, time, data and resources constraints significantly influence benefit/risk evaluation.\[14\] This is particularly
important when the potential major risk is urgent. Since ototoxicity may not be considered a major adverse event, the time urgency may not be taken seriously. However, it is important that sufficient data on comparator drugs or other treatment modalities be obtained as early and as reasonably quickly as possible. That means accurate and sensitive standard ototoxicity monitoring protocols need to be implemented in all clinical sites where ototoxic and potentially ototoxic medications are prescribed.\[5,11\] Systematic, comprehensive, and standardized ototoxicity monitoring programs would facilitate collation of large databases that would allow for easy review of adverse drug reactions. The current status of ototoxicity monitoring in South Africa, which comprises of nonstandard and limited ototoxicity monitoring programs, would negatively influence benefit/risk evaluation of any drug. Besides standardizing the monitoring protocols, the audiology community would also need to address the issue of workforce and equipment constraints that are major contributors to the limited ototoxicity monitoring in developing country contexts.\[11\] Within the South Africa context, where there are limited audiologists to population size, considerations about utilizing trained nonaudiologist screeners to implement ototoxicity monitoring programs need to be made.

**What Audiologists Need to Consider**

For benefit/risk evaluation in ototoxicity, the audiology community needs to carefully engage in scoping the context, benefit evaluation; risk evaluation; benefit-risk evaluation; options analysis; as well as deciding on the available options which are appropriate for the context.

First, as far as scoping the context is concerned, each context needs to establish specifications/descriptions of the drugs and where these are marketed/used within their context.\[14\] This needs to be continuously updated as new drugs become introduced in the market. Establishing indications for use based on factors such as burden of disease as well as the various levels of care within the South African context is crucial. Once indications have been established, identification of one or more alternative therapies or modalities, including surgery, forms part of the important considerations. Finally, scoping the context also includes establishing and providing descriptions of the suspected or established oto/vesotular toxicity problems. Establishing the time of onset, the degree, and the progression of tinnitus, vertigo, hearing loss, or any combination of these is important.

Second, benefit evaluation is another important consideration to be made during benefit-risk evaluation. Although this has not traditionally involved audiologists, it is an important consideration for audiologists to become familiar with. Benefit evaluation involves studies of the incidence or prevalence and natural history of the target disease. It also entails establishing the purpose of treatment (cure, prophylaxis, etc.), and how this influences tolerance for toxicity.\[14\] Essentially, tolerance for toxicity is reported to be low when the drug is to prevent disease in a healthy person, while it is greater if the drug is to prevent serious or fatal complications of existing disease. Furthermore, benefit evaluation involves comparison of information on efficacy and general toleration data to alternatives. These alternatives include other medical treatments; surgical treatment or other interventions; as well as the option of no treatment.\[10,14\]

Third, an area where audiologists should be significantly involved is risk evaluation. Risk evaluation is another consideration where the weight of evidence for the suspected risk (ototoxicity) in terms of incidence and/or prevalence is established. It is also the process where “risk profiles” with their most common reactions for the target treatment as well as similar profiles for alternative drugs are drawn up, and the drugs compared.\[10,14\] This requires proper record keeping as well as the use of standardized protocols which will allow for proper and accurate comparisons. Risk evaluation for ototoxicity would include detailed presentations and analyses of evidence such as audiograms and (distortion products) DP-grams; where extraneous variables such as concomitant treatments (for example in HIV/TB treatments), concomitant noise exposure, and so on, are either eliminated or carefully controlled for.\[15\] Considerations of preventability, predictability and reversibility of ototoxicity also form part of risk evaluation. Strategies such as the use of oto-protectors with the ototoxic medication, adjustments of doses, methods of administration, the frequency of administration, and so on, become key during this process.\[15,16\] Furthermore, this process involves deliberations around alternative therapies as well as no therapy. An important example of an alternative therapy that has been presented as less ototoxic during TB treatment within the South African context is bedaquiline.\[17\] Bedaquiline is the first drug in the first new class of drugs to be developed for the treatment of TB since 1971, and the first to be developed specifically for XDR-TB.\[18\] This is an important milestone in TB treatment as hearing loss is a significant side effect of TB treatment in a large number of affected individuals.

Fourth, all the above-listed considerations allow for benefit-risk evaluation where the purpose and effectiveness of treatment, as well as benefits as related to the seriousness of the target disease, are summarized.
Moreover, dominant risks and their severity, duration and incidence, are also summarized. Finally, taking into account alternative therapies or no treatment, the benefit-risk relationship is also summarized. This process can only be properly performed if appropriate audiological evidence has been collated, analyzed and presented during the benefit-risk relationship establishment. This appropriate evidence should be collected through utilizing sensitive ototoxicity monitoring protocols such as ultra-high frequency audiometry and/or otoacoustic emissions.[19]

Finally, once the risk-benefit relationship has been established, it is important for audiologists to engage in options analysis where a list of all appropriate options for action are determined, where the pros and cons and likely consequences (impact analysis) of each option under consideration are described, and where the manner in which the consequences of the recommended action should be monitored or assessed is suggested.[14] This is the process that is the most challenging for audiologists in developing country contexts where available options are significantly influenced by financial constraints. These available options include maintenance of the status quo where there is no evidence for ototoxicity concern, “watching and waiting” which involves monitoring subsequent experience of ototoxicity if insufficient evidence exists, and additional data is gathered, intensive additional data-gathering/new research which can be clinical or nonclinical involving standardized protocols for data collection in clinical and nonclinical settings, modifications to the drug or its use or amendments to the drug information, restriction of drug availability, suspension of drug license or investigational-status approval, withdrawal of the drug from the market which can be voluntary or mandatory, as well as communication of new or reinforced information to the medical profession or the public about the target drug.[10,14]

**DECISION-MAKING: PRINCIPLES TO CONSIDER WHEN DECIDING ON THE OPTIONS**

Decision-making during benefit-risk evaluation needs to be conducted by a multidisciplinary and/or multi-stakeholder team guided by principles including objectivity, equity, and accountability.[14] Objectivity, first, refers to the objectivity of the evidence base for all relevant sources by a variety of methods (observational, epidemiological, and experimental). Second, it refers to expertise which includes the regulator, the manufacturer, as well as the consumer. The principle of objectivity ensures avoidance of bias and conflict of interest. It calls for scientific decision-making such as the use of algorithms, and it also ensures that decision-making is based on explicit predetermined criteria.[10,14] Coplan et al.[20] assert that the current process of benefit–risk assessment of medicines relies primarily on intuitive expert judgment; and proposes that frameworks for transparent, rational and defensible decision making that benefits patients, drug developers, and decision makers are needed. The audiology community would need to establish and standardize monitoring protocols that can facilitate such objectivity in decision-making.

As far as the principle of equity is concerned, all drugs should be treated fairly. This principle dictates that decision making be transparent, be sensitive, be specific, follow due process, be an open process, and involve consultation with relevant stakeholders; utilizing an appropriate comparator.[20] The principle of accountability highlights that the expected outcomes must be specified or estimated, that criteria should be established for determining and assessing the effectiveness of the actions chosen; and that if action was not complete withdrawal, data must continue to be collected for ongoing monitoring of safety.[14]

**IMMEDIATE PLAN FOR THE DEVELOPING COUNTRY CONTEXT: WHAT AUDIOLOGISTS SHOULD DO**

Audiologists need to make sure that where ototoxic medications are prescribed, pretreatment education, to ensure informed consent, occurs. Despite the fact that there are currently limited alternative options available to the attending physicians within the developing country context, it still remains an ethical obligation to inform the patients of potential side effects in the form of oto/vestibular toxicity. This has the benefit of facilitating early identification of ototoxicity since the patient will be aware, and it also serves as a method of encouraging patients to attend monitoring sessions. Furthermore, pretreatment education about possible side effects has a positive impact on drug adherence as patients will be less likely to default on treatment as a consequence of their experiencing unknown, unexplained, or unanticipated side effects.[21]

Regardless of the fact that typically once drug-induced damage has occurred, the cochlea cannot recover; early identification of ototoxicity is still crucial. Along with primary prevention, early detection of hearing loss is important for providing management options such as the option of adjusting the therapy to potentially less ototoxic regimen (e.g., bedaquiline in MDR-TB), planning audiological management and counseling; and for severe hearing loss, amplification may be the only treatment option; and so on. This is in support
by Konrad-Martin et al.[22] who argue that a vigorous ototoxicity monitoring program also allows for easier facilitation of audiological rehabilitation posttreatment should this become necessary since the audiologist would have developed a working relationship with the patient during the repeated testing sessions.

As far as medical intervention is concerned, audiologists, physicians, and pharmaceutical companies should intensify their efforts toward development of nonototoxic therapeutic agents with systematic trials to ensure that enough evidence is gathered for proper benefit/risk evaluations. Currently, for example, evidence on the ototoxic potential of the newly developed drug, bedaquiline, for the treatment of MDR-TB is required in different contexts. Moreover, increased efforts should also be placed on the development of and the increasing of the evidence-base for otoprotective agents which can serve as a preventative measure where ototoxic medication cannot be avoided. Otoprotective agents in the form of compounds such as angiotensin-converting enzyme magnesium, D-methionine (sulfur-containing compound), and L-N-acetylcysteine should be investigated.[16] Furthermore, restorative care which involves regeneration of hair cells damaged by ototoxic drugs through the use of neurotrophins also requires careful consideration.[23] These strategies are especially important in developing country contexts for strategic long-term financial savings which will be made by eliminating potential litigation costs, amplification devices costs, rehabilitation costs, as well as social grants linked costs because of the economic impact associated with the consequent unemployment of the affected individual.

**Future Directions**

For large sets of data that can be used to establish evidence that is enough for benefit/risk evaluation in ototoxicity monitoring; audiologists need to engage in pharmaco-audiology where pharmacovigilance is prioritized in vulnerable, high-risk populations, such as HIV/AIDS*, tuberculosis*, cancers, malaria*, renal failure, and certain chronic infectious diseases (*major health problems in Africa). In these populations, it is imperative that audiologists set up structured postmarketing surveillance follow-up and ad-hoc case-control studies where ototoxicity is monitored. These are believed to be more “naturalistic” circumstances where the sample is representative of the disease population, without the artificial creation of controlled variables that are not normal in the context. These would also allow for surveillance over longer periods of drug exposure in case the drug’s ototoxicity has a gradual, late and progressive nature of onset and development.

While the above studies will involve medications already on the market, parallel studies on alternative medications, including generic medications, should also be run to allow for the development of options lists for ethical benefit/risk assessments. This is important because establishing benefit/risk without any alternative options can be argued to be an unethical practice while also continuing to prescribe medications with well-established ototoxic effects because there are no alternatives, is not best practice. Concurrently, increased efforts at development of otoprotective agents would aid this process significantly. These efforts should aim at moving studies from animal models to human studies as suggested by Safdarian.[24]

Audiologists’ active and strategic involvement in pharmaco-audiology, through establishing ototoxicity monitoring programs, would facilitate the establishment of evidence in these contexts to demonstrate the important role that the audiologists may have in both the assessment and treatment of all patients with “high risk” conditions. Their active involvement in task teams putting together treatment guidelines, using evidence-base to continuously inform policy, would ensure that this often neglected side effect is also considered in the benefit/risk evaluation processes. Audiologists’ role in lobbying and advocating for their expanded role in FDA processes of drug development, drug approval, and drug monitoring is paramount for useful engagement in benefit-risk assessment for both new drugs and marketed drugs. Involvement in Advisory Panels on benefit, risk and cost management of prescription drugs where the risk of ototoxicity is a reality, as well as providing recommendations on communication and awareness programs for the public on ototoxicity, should form part of the workload for audiologists involved in ototoxicity monitoring.

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There are no conflicts of interest.

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