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Use of Otoacoustic Emissions to Assess the Efficacy of a Pharmaceutical Otoprotective Agent

Dawn Konrad-Martin PhD, Garnett P McMillan PhD, Lynne Marshall PhD, Judi A Lapsley Miller PhD, Gayla L Poling PhD

Benefits and Limitations to the Use of OAEs
Otoacoustic emissions (OAEs) are byproducts of the outer hair cell (OHC)-based nonlinear cochlear processing that takes place in healthy, mammalian ears. They provide an indirect, noninvasive measure of the OHC electro-mechanical response that enables the auditory system to encode a large range of stimulus levels, discriminate small differences in sound frequencies and detect low-level sounds. Environmental exposures that damage OHCs make cochlear processing more linear, and are associated with abnormal loudness sensation, impaired frequency selectivity, increased pure-tone thresholds and reduced or absent OAEs. These relationships motivate the use of OAEs to identify damage from environmental exposures (e.g., noise) and assess the efficacy with which otoprotectants mitigate the damage.

OAEs are generally considered more sensitive to changes in cochlear function than hearing threshold measures. Evidence shows that distortion-product otoacoustic emissions (DPOAEs) and transient-evoked otoacoustic emissions (TEOAEs) change following noise exposure even when pure-tone thresholds measured contemporaneously remain stable (e.g., Engdahl et al., 1996; Marshall et al., 2009; Seixas et al., 2005). This is consistent with histological results obtained in chinchillas that
indicate up to 30% of the outer hair cells that would respond at a given cochlear location can be damaged before producing an ABR threshold shift (Bohne and Clark, 1982). When shifts in OAE level and hearing thresholds from noise do co-occur, the OAE changes can take place at (Marshall et al., 2001) or below (Helleman and Dreschler, 2012) the frequencies that show a hearing loss. Corresponding changes across the two measures are more often found for temporary (hearing) threshold shift (TTS) than for permanent (hearing) threshold shift (PTS) (Marshall et al., 2001). Additionally, for TTS, the time course of OAE and audiometric changes appears to be similar (humans: Sutton et al., 1994; Marshall et al., 2001; animals: Kujawa and Liberman, 2009). Within a clinical trial, OAE measures are therefore expected to be a sensitive indicator of cochlear damage involving the OHC system and protection achieved from a drug therapy. Finally, OAE testing causes no discomfort to and requires minimal compliance from the test subject, and involves minimal time and cost to perform.

There are limitations and caveats of their use. Limitations include that OAEs are influenced by factors unrelated to cochlear function (e.g., round-trip middle ear transmission, strength of efferent feedback to the middle ear and cochlea, individual- and frequency specific- variations in cochlear reflectance), so protocols must be designed carefully. For example, the fact that OAEs are sensitive to changes in middle ear function means that a test to identify any conductive involvement (e.g., tympanometry) must be included in the protocol so that any OAE changes can be interpreted. Certain patient populations (e.g., children, patients with certain infectious diseases, patients receiving chemotherapy, etc.) are prone to fluctuating middle-ear pressure and conductive loss from otitis media, which can make OAE testing (and hearing monitoring in general) problematic. To this end, documentation of extensive history of middle ear problems is warranted in a clinical trial in which OAE outcomes are incorporated.

OAE results are subject to variability due to limitations of current calibration methods, poor probe fitting techniques, analysis techniques, and any exposure to damaging agents not explicitly being monitored (e.g., use of power tools, personal music players, etc.) during the time between tests. All evoked OAEs arise from a mixture of distortion and reflection emission sources, which can render them challenging to interpret and difficult to relate to underlying basilar membrane processing, particularly when current clinical protocols are used. For example, so called, “mixed”-source DPOAEs may decrease in level following damage, but are also frequently found to become larger (Helleman and Dreschler, 2012). Evidence suggests that basal components may “fill in” regions of damage unless low stimulus levels are used (Martin et al., 2011). Finally, there is the lack of consensus about which OAE measurement protocols are best, and how to define clinically meaningful changes in the measures.

**Pros and Cons of Specific OAE Protocols**
Ultimately, an OAE protocol in a clinical trial should depend on the clinical or research question being investigated and the population being tested. Additionally, a protocol should be theoretically sound, based on known patterns of damage, involve minimal time, generate valid results in the majority of individuals tested, and be accurate and repeatable (Konrad-Martin et al., 2012). In the meantime, the choice of OAE protocols is limited for those who use clinical OAE systems, which provide a narrow range of well-researched test protocols for DPOAEs or TEOAEs, and sometimes both.

DPOAEs and TEOAEs are the OAE types most commonly used clinically in part because they were historically easier to measure than stimulus-frequency OAEs (SFOAEs). SFOAEs are considered the most frequency-specific and the simplest in terms of source generation, particularly when elicited at low stimulus levels; however, recent evidence suggests that evoked OAEs of all types are less frequency-specific and more complex in their generation than formally believed (Shera and Guinan, 1999; Martin et al., 2011). When obtained at low stimulus levels rather than the usual high-level clinical system default settings, an individual TEOAE frequency component appears to arise as a single source reflection emission comparable to an SFOAE (Kalluri and Shera, 2007). One drawback is that many clinical patients will not have TEOAEs at low levels, potentially limiting their utility for tracking functional changes. The broadband TEOAE stimulus makes the measure attractive for rapid testing of a wide range of frequencies, at least until swept tone algorithms for DPOAEs and SFOAEs become clinically available. However, DPOAEs remain favored for making high-frequency measures (above 4 kHz) because current clinical systems extract TEOAEs in a way that removes high-frequency response components.

In a comparison of DPOAE levels, response growth functions, and group delays in a population of adults exposed to an ototoxin, thresholds and group delays identified changes more often than did DPOAE level obtained with moderate-level stimuli (Katbamna et al., 1999). In noise-exposed populations, lower overall primary levels with greater L1-L2 separation done in fine stimulus frequency step-sizes increased the sensitivity of DPOAEs to detect post-exposure changes (Delb et al., 1999; Engdahl and Kemp, 1996; Sutton et al., 1994).

Based on current models of OAE generation, certain OAE protocols may provide a more direct measure of certain aspects of the cochlear mechanical response than others. Phase gradient delays of low-level reflection emissions can be used to estimate frequency tuning (Shera et al., 2002) and their thresholds and levels may provide an indication of the gain of the cochlear amplifier; distortion emission thresholds, response growth and maximum amplitudes provide an indication of the strength and form of the basilar membrane nonlinearity (Shera and Guinan, 1999). The use of canned protocols and analysis programs available on clinical equipment has effectively limited these potentially powerful measures to the domain of research.

Active areas of research include comparing the sensitivity (to cochlear insult) and retest-reliability of emerging OAE protocols and analyses, and substantive improvements in OAE measurement system capabilities. The protocols, analyses and
calibration techniques available with most clinical systems, though well-researched, generally have not caught up with the state of the science. Because of this and due to physical limitations of current systems, clinical OAE measurements are reliable at measurement frequencies up to only 6 to 8 kHz. Still, even basic, moderate-level DPOAEs and TEOAEs are able to separate normal from impaired ears quite well (Gorga et al., 1997; Hussain et al., 1999), and can indicate early changes in cochlear function from noise and ototoxins. Further, most clinical systems allow some control over stimulus levels and frequency step sizes.

Specific Recommendations
Due to the lack of consensus about how to measure and interpret changes in OAEs clinically, it could be argued that they are not well suited as a primary outcome measure in a clinical trial to determine the efficacy of an otoprotective agent. However, having data related to cochlear function that were obtained using a sensitive measure free from confounding changes in cognitive processes of attention and memory would clearly add value to results of a clinical trial. Their use should be seriously considered if time and measurement conditions permit.

Statistical Considerations. The standard clinical trial design for evaluating drug efficacy is suitable for use with OAE outcome data. Briefly, baseline OAE measurements are taken, subjects are randomized to one or more active treatment groups and placebo, and are followed through and immediately after exposure. Statistical tests of treatment efficacy are based on contrasts of the follow-up measurements. Adjustment for baseline OAE response is possible using one of several approaches (Fitzmaurice et al., 2004). In contrast to standard clinical trial design, it is standard clinical practice to compare changes in OAEs to shift reference standards established in a healthy, homeostatic population. We do not recommend this approach in clinical trials, since the goal of such trials is to evaluate the efficacy of a new therapy on changes in cochlear function as opposed to identifying alarming changes with reference to a standard population. In addition to standard concerns with longitudinal studies, OAE outcomes introduce some further challenges. In particular, multiple stimulus frequencies and test levels are likely to be used, generating complex multivariate outcomes. Careful consideration of the statistical model is necessary, with guidance from an experienced statistician recommended, to enhance the accuracy of the statistical tests. Finally, it is not unusual for OAEs to fall below noise after exposure. Such measurements will appear as missing, which can seriously bias outcomes if the probability of falling below the noise floor is associated with any treatment effects. In fact, it is reasonable to expect that this is a common occurrence. One approach is to use censored data models (e.g. ‘survival analysis’) for these trials; another is to set such responses to the noise floor or system distortion level. Such approaches should be considered carefully on a case-by-case basis.

Because the tester’s retest reliability is critical to successful serial OAE measurements, it is also recommended that each tester or group of testers assess (using a statistically
sound method) and document their test-retest reliability for the specific protocol to be used in the clinical trial.

**Testing Procedures.** The twin goals are first to determine valid baseline measures with further characterization of test-retest repeatability (considering noise and distortion generated by the equipment, middle ear function, patient and test environment, probe placement, etc.). The typical moderate- or high-level clinical protocols available with most standard OAE measurement equipment can be used to obtain a gross assessment of cochlear function over a broad range of frequencies. Minimal additional test considerations include the use of a lower-level frequency sweep (e.g., 45 dB SPL), perhaps with fine frequency step measurements, as well as multiple levels measured at up to a few vulnerable frequencies. For this more detailed coverage of the frequency and/or level space, a narrower test frequency region should be targeted based on the mechanism and pattern of damage expected from the exposure. The approach of using a targeted region of testing near the highest frequency that elicits a 6-10 dB SNR DPOAE response appears to be useful for monitoring cisplatin ototoxicity among cancer patients in whom cochlear damage begins at the high frequency coding base and proceeds apically (Ress et al., 1999; Reavis et al., 2008; Dille et al., 2010). In an industrial noise setting, more detailed OAE measures may be fruitful in the 2 to 6 kHz range.

**References**


http://hearing.health.mil/EducationAdvocacy/Newsletters.aspx