Review Article

Patient-Reported Measures of Hearing Loss and Tinnitus in Pediatric Cancer and Hematopoietic Stem Cell Transplantation: A Systematic Review

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Purpose: We identified studies that described use of any patient-reported outcome scale for hearing loss or tinnitus among children and adolescents and young adults (AYAs) with cancer or hematopoietic stem cell transplantation (HSCT) recipients.

Method: In this systematic review, we performed electronic searches of OvidSP MEDLINE, EMBASE, and PsycINFO to August 2015. We included studies if they used any patient-reported scale of hearing loss or tinnitus among children and AYAs with cancer or HSCT recipients. Only English language publications were included. Two reviewers identified studies and abstracted data.

Results: There were 953 studies screened; 6 met eligibility criteria. All studies administered hearing patient-reported outcomes only once, after therapy completion. None of

the studies described the psychometric properties of the hearing-specific component. Three instruments (among 6 studies) were used: Health Utilities Index (Barr et al., 2000; Fu et al., 2006; Kennedy et al., 2014), Hearing Measurement Scales (Einar-Jon et al., 2011; Einarsson et al., 2011), and the Tinnitus Questionnaire for Auditory Brainstem Implant (Soussi & Otto, 1994). All had limitations, precluding routine use for hearing assessment in this population.

Conclusions: We identified few studies that included hearing patient-reported measures for children and AYA cancer and HSCT patients. None are ideal to take forward into future studies. Future work should focus on the creation of a new psychometrically sound instrument for hearing outcomes in this population.

Some children and adolescents who receive chemotherapy or who undergo hematopoietic stem cell transplantation (HSCT) are at risk of hearing loss

and tinnitus (Sung et al., 2003). Hearing loss is associated with platinum chemotherapy and cranial irradiation in addition to ototoxic supportive care medications, such as loop diuretics and aminoglycosides. Hearing loss is detectable in 20%–60% of childhood cancer survivors who received platinum-based treatment (Hudson et al., 2013). It has educational, vocational, and social consequences that may vary by age of onset (Bertolini et al., 2004; Brock et al., 2012; Langer, am Zehnhoff-Dinnesen, Radtke, Meitert, & Zolk, 2013; Travis et al., 2014). Tinnitus, which may interfere with sleep, daily function, and quality of life (Sprauten et al., 2012), is another important hearing outcome that is common following platinum chemotherapy.

In addition to objective measures of hearing, such as conventional and high frequency audiometry and otoacoustic emission evaluation, patient-reported measures of hearing are important. Patient-reported outcomes (PROs) evaluate symptoms, signs, or functioning from the patient perspective. Several groups have endorsed the importance of PROs in understanding and improving health in a wide

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variety of contexts (U.S. Department of Health Human Services Food and Drug Administration, Center for Drug Evaluation Research, Center for Biologics Evaluation Research, & Center for Devices and Radiological Health, 2009). PROs are important as an adjunct to objective measures to evaluate the impact of the symptom from the patient's perspective, to document how hearing loss influences usual patient activities, and to understand how symptoms affect quality of life (Basch, 2014). Further, tinnitus is only evaluable by patient report, as objective measures are not available.

It is important to place PROs in the context of different types of outcomes, as articulated by the International Classification of Impairments, Disabilities and Handicaps, developed by the World Health Organization (1980). In this system, the effect of disease on persons was classified as impairment (abnormality of psychology, physiology, structure, or function), disability (restricted ability to perform an activity), and handicap (limitation or prevention of a role due to impairment or disability). These dimensions may be determined through PROs, proxy report, or objective measurements. For example, hearing loss may be objectively measured by using audiometry, proxy report by parents, or self-report by patients. In the same way, listening disability may be measured through proxy report or patient report, as may orientation handicaps. This review is focused on PROs related to hearing and includes impairment, disability, and handicap.

The incorporation of PROs for hearing outcomes is important in clinical trials designed to test otoprotectants or to evaluate interventions with potentially different effects on hearing. However, it is not known whether reliable and valid PROs of hearing outcomes are available in pediatric cancer. It is particularly relevant to measure hearing PROs in adolescents and young adults (AYAs), in addition to children, because this population is at risk for germ cell tumor and osteosarcoma, which are commonly treated with platinum agents (Birch et al., 2002; Bleyer & Barr, 2009). Further, there is a lack of available instrumentation to measure PROs, in general, across the AYA age spectrum because most instruments have been validated in children or adults separately but rarely across the AYA continuum (Taylor et al., 2015).

The objective of this systematic review was to identify studies that described use of any patient-reported scale of hearing loss or tinnitus among children and AYA cancer patients or HSCT recipients to guide instrument selection for future clinical trials in this population.

Method

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations for reporting (Moher, Liberati, Tetzlaff, Altman, & Group, 2009). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, published in 2009 and developed by an international group of experienced authors and methodologists to enhance the

clarity and transparency of systematic reviews, consists of a checklist and a flow diagram.

Data Sources and Searches

We performed electronic searches of OvidSP MEDLINE (1946–), EMBASE (1947–), PsycINFO (1806–), and EBSCOHost CINAHL (1981–) up to August 2015. The search strategy included Medical Subject Heading (MeSH) or CINAHL terms and text words that identified pediatric, adolescent, or young adult patients with cancer and HSCT recipients combined with hearing loss and tinnitus terms (Supplemental Appendix 1 contains the full search strategy).

Study Selection

Inclusion and exclusion criteria were defined a priori. Studies were included if they used any patient-reported scale of hearing loss or tinnitus among children and AYAs (up to age 30) with cancer or recipients of HSCT. Exclusion criteria were as follows: (1) median or mean age of patients > 30 years at time of hearing evaluation; (2) more than 50% of patients did not have cancer or undergo HSCT; (3) hearing measure not self-reported (only parent or clinician reported); (4) instrument not a scale; (5) only evaluated physiological measures of hearing (including audiometry and otoacoustic emissions); (6) non-English publication; (7) publication not full text; (8) case reports and reviews; and (9) duplicate publication.

Two reviewers (first author and eighth author) independently evaluated the titles and abstracts of publications identified by the search strategy, and any potentially relevant publication was retrieved in full. Final inclusion of studies into the systematic review was by agreement of both reviewers. Agreement of study inclusion between the two reviewers was evaluated by using the kappa statistic, and agreement was defined as slight (.00–.20), fair (.21–.40), moderate (.41–.60), substantial (.61–.80), or almost perfect (.81–1.00; Landis & Koch, 1977).

Data Abstraction and Methodological Approach

Two reviewers (first author and eighth author) abstracted all data in duplicate, and any discrepancies were resolved by consensus. Study level variables of interest were year of publication, dates on which patients were diagnosed, country of study population, language of hearing instrument administration, name of instrument used to measure hearing loss or tinnitus, recall period for hearing symptoms, how measure was completed, age of participants, study eligibility, and number of participants. We also abstracted who completed the PRO measure, in addition to the participant; whether administration was on or off therapy; the number of hearing assessments performed; and whether any evaluation of psychometric properties, namely, reliability, validity or responsiveness, was reported in the manuscript or referred to in another publication. In terms of the actual measures, we recorded the number of questions

related to hearing symptoms and the number of hearing domains captured.

Assessment of Study Quality and Statistical Methods

Two reviewers assessed study quality, and any discrepancies were resolved by consensus. Study quality was assessed by using a modified version of an instrument previously developed to describe quality in studies of prognosis (Hayden, Cote, & Bombardier, 2006). This quality assessment instrument examines four potential sources of bias: study participation, study attrition, confounding variables, and measurement of outcomes. Relevant to this systematic review, we abstracted data on bias related to study participation and measurement of outcomes; they were rated as having low, medium, or high risk of bias for each study (Hayden et al., 2006). The systematic review analysis was descriptive.

Results

The flow of study identification and selection is illustrated as Figure 1. There were 953 studies identified by the search strategy, of which 73 were retrieved for full evaluation. Six met eligibility criteria and were included in the systematic review (Barr et al., 2000; Einar-Jon et al., 2011; Einarsson et al., 2011; Fu et al., 2006; Kennedy et al., 2014; Soussi & Otto, 1994). Agreement of study inclusion between the two reviewers was $\kappa = 1.00$.

Characteristics of these studies are illustrated in Table 1. None of the studies were at low risk of bias for study participation or measurement of outcomes. Three of the studies used the Health Utilities Index (Barr et al., 2000; Fu et al., 2006; Kennedy et al., 2014), two used the Hearing Measurement Scale (Einar-Jon et al., 2011; Einarsson et al., 2011), and one used the Tinnitus Questionnaire for Auditory Brainstem Implant (Soussi & Otto, 1994). Language of administration included English, Spanish, Swedish, and Icelandic. All the studies had a small number of participants who were known to self-report hearing PROs, with the largest study including 51 self-reporting participants. All studies administered the questionnaire to participants who had completed therapy, and all studies only administered the questionnaire once.

None of the studies specifically stated that the hearing reported aspect of the questionnaire (if a multidomain instrument) or the questionnaire itself (if the instrument focused on hearing) was previously shown to be reliable, valid, or responsive in children or AYA patients. None were explicitly designed to evaluate psychometric properties related to hearing.

Table 2 summarizes the three instruments used in the studies. The number of hearing questions ranged from five to 44. Two of the instruments (Hearing Measurement Scale and Health Utilities Index) return hearing-specific summary scores, whereas the Tinnitus Questionnaire for Auditory Brainstem Implant does not return an overall score. With respect to face validity and from a hearing-specific perspective, none of the questionnaires appeared ideal based upon the number of questions, relevance, and wording for

Figure 1. Flow diagram of study identification and selection. Flow of studies identified from the search strategy and reasons for exclusion.

Table 1. Characteristics of included studies.

Author and year of publication	Language administered	Name of instrument	How completed	Participant age	Patients enrolled	Number enrolled	Timing	Number of assessments	Psychometric evaluation	Participant bias	Analysis bias
Kennedy et al., 2014	NA	Health Utilities Index	In person	Age distribution not shown for those who self-reported	Radiation for medulloblastoma	NA	Off therapy	Once	None mentioned	Moderate risk	Moderate risk
Einarsson et al., 2011	Swedish	Hearing Measurement Scale	In person	Median 27.5 years (range 17.7–33.9) for hearing impaired and 23.5 (range 15.5–30.4) for normal hearing	Platinum	15	Off therapy	Once	None mentioned	High risk	High risk
Einar-Jon et al., 2011	Icelandic	Hearing Measurement Scale	In person	Median 14.1 years (range 11.1–30.1)	Platinum	15	Off therapy	Once	None mentioned	High risk	Moderate risk
Fu (Fu et al., 2006)	Spanish	Health Utilities Index	In person	Age distribution not shown for those who self-reported	Any cancer	NA	Off therapy	Once	None mentioned	High risk	High risk
Barr et al., 2000	English	Health Utilities Index	Mail	Age distribution not shown for those who self-reported	Advanced stage Wilms' tumor and neuroblastoma	51	Off therapy	Once	None mentioned	Moderate risk	Moderate risk
Soussi & Otto, 1994	English	Tinnitus Questionnaire for Auditory Brainstem Implant	NA	Median 29 years (range 18–63)	Auditory brainstem implant in bilateral acoustic neurofibromas	16	Off therapy	Once	None mentioned	High risk	High risk

Note. NA = not available.

Table 2. Characteristics of included hearing loss and tinnitus instruments.

Name of instrument	Number of questions	Number of levels	Number of domains	Instrument description
Hearing Measurement Scale (Einar-Jon et al., 2011; Einarsson et al., 2011)	44	5	7	Items rated <i>always</i> to <i>never</i> ; questions weighted based upon importance; summary scores are HMS total, HMS disability, and HMS handicap
Health Utilities Index (Barr et al., 2000; Fu et al., 2006; Kennedy et al., 2014)	5	2	1	Algorithm-converted responses to questions to attribute levels for HUI2 and HUI3 that were then used to generate single-attribute utility scores; no tinnitus domain
Tinnitus Questionnaire for Auditory Brainstem Implant (Soussi & Otto, 1994)	19	Variable	1	Does not return an overall score

Note. HMS = Hearing Measurement Scale; HUI = Health Utilities Index.

children and AYA cancer or HSCT patients. For example, “Difficulty hearing conversation at work” would have little relevance to children.

Discussion

In this systematic review, we identified only six studies that explicitly measured hearing-specific PROs in children and AYAs with cancer or HSCT recipients. Note that none of the studies described that the hearing-specific instrument was psychometrically evaluated within this population such that it could be used confidently in future clinical trials (Reeve et al., 2013). The studies all included a small number of participants and were all at moderate or high risk of bias. Thus, we have demonstrated a gap in the literature related to PROs of hearing outcomes for children and AYA patients.

In addressing this gap, two possible directions are possible. First, one could choose to adapt and validate, for pediatric patients, one of the three identified instruments or, indeed, other hearing-related instruments that have been developed outside of cancer or in older patients. Instruments developed outside of cancer may have similar or dissimilar relevance, depending on whether hearing outcomes and tinnitus are expected to be different in cancer and HSCT patients. In the same way, instruments developed for older adults and elderly populations may not be relevant without adaptation, particularly from a social and developmental perspective (Varni & Limbers, 2009). Second, one could choose to develop a new hearing loss and tinnitus PRO measure. The three identified instruments could contribute to item generation if this approach was chosen.

Based upon the small number of identified studies, little appears to be known about the prevalence and importance of tinnitus in children and AYA populations from the patient perspective. As hearing symptoms are central to the acute and survivorship experience after cisplatin chemotherapy, this gap substantially limits the evaluation of treatments and otoprotectants. Descriptive studies of the prevalence and impact of tinnitus are urgently needed in

pediatric populations, given the known impact in older populations (Henry et al., 2015).

The strengths of this systematic review include the inclusion of AYA patients and the rigorous methods utilized. However, there are several limitations. First, we restricted publications to the English language. Many of the identified articles administered the hearing PRO instrument in languages other than English, and it is possible that other studies exist in non-English publications. Second, where hearing was one domain within a multidomain instrument, such as the Health Utilities Index, our search could have missed such articles. Nonetheless, the search should not have missed instruments designed to capture hearing end points.

In summary, we have shown that few studies include hearing PROs for pediatric and AYA cancer or HSCT patients. None of the identified instruments are ideal to take forward into future studies in which hearing outcomes are relevant. Future work should focus on the creation of a new psychometrically sound instrument for hearing outcomes in this population.

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The first, second, third, and eighth authors conceptualized and designed the study; the first and eighth authors collected and analyzed the data and wrote the manuscript; and all authors critically revised the manuscript for important content. All authors approved the final version of the manuscript. The seventh author is a consultant for Decibel Therapeutics.

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