Article:
Stark, D orcid.org/0000-0002-6172-733X, Rosenberg, AR, Johnston, D et al. (5 more authors) (2016) Patient-reported measures of hearing loss and tinnitus in pediatric cancer and hematopoietic stem cell transplantation: A systematic review. Journal of Speech, Language, and Hearing Research, 59 (5). pp. 1247-1252. ISSN 1092-4388

https://doi.org/10.1044/2016_JSLHR-H-15-0363

TITLE: Patient-reported measures of hearing loss and tinnitus in pediatric cancer and hematopoietic stem cell transplantation: a systematic review

RUNNING TITLE: Hearing loss patient-reported outcomes in children

AUTHORS: Daniel Stark MD, PhD[1], Abby R. Rosenberg MD[2], Donna Johnston MD[3], Kristin Knight MS[4], Lizzie Caperon MSc[5] Elizabeth Uleryk MLS[6]; A. Lindsay Frazier MD, MSc[7] and Lillian Sung MD, PhD[8]

AFFILIATIONS: (1) Section of Oncology and Cancer Research, Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK; (2) Hematology/Oncology, Seattle Children's Hospital, Seattle, US; (3) Division of Paediatric Haematology/Oncology, Children's Hospital of Eastern Ontario, Ottawa, Canada; (4) Pediatric Audiology, Oregon Health and Science University, Portland, US; (5) Scholarly Communications and Researcher Skills, University of Leeds, Leeds, UK; (6) E.M. Uleryk Consulting, Toronto, Canada; (7) Dana-Farber/Boston Children's Cancer Center, Boston, US; (8) Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, Canada

KEYWORDS: hearing loss, tinnitus, patient-reported outcome, children, cancer, hematopoietic stem cell transplantation

WORD COUNT: Abstract: 199; Manuscript: 1,395; Tables 2; Figures 1; Appendix 1

RESEARCH SUPPORT: None

PREVIOUS PUBLICATION: This research has not been previously published in abstract form or presented at a meeting.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTERESTS:

The authors declare no potential conflicts of interest.

*ADDRESS FOR CORRESPONDENCE:

Lillian Sung MD, PhD

Division of Haematology/Oncology, the Hospital for Sick Children

555 University Avenue, Toronto, Ontario, Canada, M5G1X8

Phone: 416-813-5287; Fax: 416-813-5979; Email: lillian.sung@sickkids.ca

ABSTRACT

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

Methods: In this systematic review, we performed electronic searches of OvidSP MEDLINE, EMBASE and PsycINFO to August 2015. Studies were included 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; six 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 six studies) were used: Health Utilities Index, Hearing Measurement Scales and the Tinnitus Questionnaire for Auditory Brainstem Implant. 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.

INTRODUCTION

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 as examples. 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 is another important hearing outcome which is common following platinum chemotherapy. It is important because it interferes greatly with sleep, daily function and quality of life.(Sprauten et al., 2012)

In addition to objective measures of hearing such as conventional and high frequency audiometry and oto-acoustic emission evaluation, patient-reported measures of hearing are important. Patient-reported outcomes (PROs) evaluate symptoms, signs, or functioning from the patient perspective. They 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 impacts on 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 (ICIDH) developed by the World Health Organization. In this system, the effect of

Commented [LS1]: **International Classification of Impairments, Disabilities, and Handicaps'**

WORLD HEALTH ORGANIZATION
GENEVA
1980

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 measured through PROs, proxy-reported or objectively measured. For example, hearing loss may be objectively measured using audiometry, proxy-reported by parents or self-reported by patients. Similarly listening disability may be measured through proxy-report or patient report, as may be orientation handicaps. This review is focused on PROs related to hearing and included impairment, disability and handicap.

The incorporation of PROs for hearing outcomes is important in clinical trials designed to test oto-protectants 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 since 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 since 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 in order to guide instrument selection for future clinical trials in this population.

METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for reporting.(Moher, Liberati, Tetzlaff, Altman, & Group, 2009) The PRISMA statement was published in 2009 and it consists of a checklist and a flow diagram. The statement was developed to enhance the clarity and transparency of systematic reviews and was developed by an international group of experienced authors and methodologists.

Data Sources and Searches

We performed electronic searches of OvidSP MEDLINE (1946-), EMBASE (1947-), PsycINFO (1806-) and EBSCOHost CINAHL (1981-) and up to August 2015. The search strategy included Medical Subject Heading (MeSH) or CINAHL terms and text words which identified pediatric, adolescent or young adult patients with cancer and HSCT recipients combined with hearing loss and tinnitus terms (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, adolescents or young adults (up to age 30) with cancer or recipients of HSCT. Exclusion criteria were as follows: (1) Median or mean age of patients > age 30 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 oto-acoustic emissions); (6) Non-English publication; (7) Publication not full text; (8) Case reports and reviews; and (9) Duplicate publication.

Two reviewers (DS and LS) 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 using the kappa statistic and agreement was defined as slight (0.00-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80) or almost perfect (0.81-1.00).(Landis & Koch, 1977)

Data Abstraction and Methodological Approach

Two reviewers (DS and LS) abstracted all data in duplicate and any discrepancies were resolved by consensus. Study level variables of interest were year of publication, dates in 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 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 (ABI).(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-report 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 multi-domain instrument) or the questionnaire itself (if 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 5 to 44. Two of the instruments (Hearing Measurement Scale and Health Utilities Index) return hearing-specific summary scores whereas the Tinnitus Questionnaire for ABI 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 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 which explicitly measured

hearing-specific PROs in children and AYAs with cancer or HSCT recipients. More importantly, 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. Consequently, 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. Similarly, 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. Likely, 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 oto-protectants. 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. Interestingly, 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 multi-domain 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 endpoints.

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.

AUTHORSHIP AND AUTHOR DISCLOSURES

Contribution: DS, DJ, AR and LS conceptualized and designed the study; DS and LS collected and analyzed the data and wrote the manuscript; and all authors critically revised the manuscript for important content. All authors approve the final version of the manuscript.

The authors declare no competing financial interests. Authors have no financial relationships relevant to this article to disclose

ACKNOWLEDGMENTS

None

REFERENCES

Barr, R. D., Chalmers, D., De Pauw, S., Furlong, W., Weitzman, S., & Feeny, D. (2000). Health-related quality of life in survivors of Wilms' tumor and advanced neuroblastoma: aA cross-sectional study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 18(18), 3280-3287.

Basch, E. (2014). The rationale for collecting patient-reported symptoms during routine chemotherapy. American Society of Clinical Oncology educational book / ASCO. American Society of Clinical Oncology. Meeting, 161-165.

Bertolini, P., Lassalle, M., Mercier, G., Raquin, M. A., Izzi, G., Corradini, N., et al. (2004). Platinum compound-related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. Journal of pediatric hematology/oncology, 26(10), 649-655.

Birch, J. M., Alston, R. D., Kelsey, A. M., Quinn, M. J., Babb, P., & McNally, R. J. (2002). Classification and incidence of cancers in adolescents and young adults in England 1979-1997. British Journal of Cancer, 87(11), 1267-1274.

Bleyer, A., & Barr, R. (2009). Cancer in young adults 20 to 39 years of age: overview. Seminars in Oncology, 36(3), 194-206.

Brock, P. R., Knight, K. R., Freyer, D. R., Campbell, K. C., Steyger, P. S., Blakley, B. W., et al. (2012). Platinum-induced ototoxicity in children: a consensus review on mechanisms, predisposition, and protection, including a new International Society of Pediatric Oncology Boston ototoxicity scale. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 30(19), 2408-2417.

Einar-Jon, E., Trausti, O., Asgeir, H., Christian, M., Thomas, W., Mans, M., et al. (2011). Hearing impairment after platinum-based chemotherapy in childhood. Pediatric Blood & Cancer, 56(4), 631-637.

Einarsson, E. J., Petersen, H., Wiebe, T., Fransson, P. A., Magnusson, M., & Moell, C. (2011). Severe difficulties with word recognition in noise after platinum chemotherapy in childhood, and improvements with open-fitting hearing-aids. International journal of audiology, 50(10), 642-651.

Fu, L., Talsma, D., Baez, F., Bonilla, M., Moreno, B., Ah-Chu, M., et al. (2006). Measurement of health-related quality of life in survivors of cancer in childhood in Central America: feasibility, reliability, and validity. Journal of pediatric hematology/oncology, 28(6), 331-341.

Hayden, J. A., Cote, P., & Bombardier, C. (2006). Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine, 144(6), 427-437.

Henry, J. A., Griest, S., Thielman, E., McMillan, G., Kaelin, C., & Carlson, K. F. (2015). Tinnitus Functional Index: Development, validation, outcomes research, and clinical application. Hearing Research.

Hudson, M. M., Ness, K. K., Gurney, J. G., Mulrooney, D. A., Chemaitilly, W., Krull, K. R., et al. (2013). Clinical ascertainment of health outcomes among adults treated for childhood cancer. The Journal of the Americal Medical Association, 309(22), 2371-2381.

Kennedy, C., Bull, K., Chevignard, M., Culliford, D., Dorr, H. G., Doz, F., et al. (2014). Quality of survival and growth in children and young adults in the PNET4 European controlled trial of hyperfractionated versus conventional radiation

therapy for standard-risk medulloblastoma. International journal of radiation oncology, biology, physics, 88(2), 292-300.

Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. Biometrics, 33, 159-174.

Langer, T., am Zehnhoff-Dinnesen, A., Radtke, S., Meitert, J., & Zolk, O. (2013). Understanding platinum-induced ototoxicity. Trends in pharmacological sciences, 34(8), 458-469.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Group, Prisma. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine, 6(7), e1000097.

Reeve, B. B., Wyrwich, K. W., Wu, A. W., Velikova, G., Terwee, C. B., Snyder, C. F., et al. (2013). ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Quality of Life Research, 22(8), 1889-1905.

Soussi, T., & Otto, S. R. (1994). Effects of electrical brainstem stimulation on tinnitus. Acta oto-laryngologica, 114(2), 135-140.

Sprauten, M., Darrah, T. H., Peterson, D. R., Campbell, M. E., Hannigan, R. E., Cvancarova, M., et al. (2012). Impact of long-term serum platinum concentrations on neuro- and ototoxicity in Cisplatin-treated survivors of testicular cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 30(3), 300-307.

Sung, L., Dupuis, L. L., Bliss, B., Taddio, A., Abdolell, M., Allen, U., et al. (2003). Randomized controlled trial of once- versus thrice-daily tobramycin in febrile

neutropenic children undergoing stem cell transplantation. Journal of the National Cancer Institute, 95(24), 1869-1877.

Taylor, R. M., Fern, L. A., Solanki, A., Hooker, L., Carluccio, A., Pye, J., et al. (2015). Development and validation of the BRIGHTLIGHT Survey, a patient-reported experience measure for young people with cancer. Health Quality of Life Outcomes, 13(1), 107.

Travis, L. B., Fossa, S. D., Sesso, H. D., Frisina, R. D., Herrmann, D. N., Beard, C. J., et al. (2014). Chemotherapy-induced peripheral neurotoxicity and ototoxicity: new paradigms for translational genomics. Journal of the National Cancer Institute, 106(5).

Varni, J. W., & Limbers, C. A. (2009). The PedsQL 4.0 Generic Core Scales Young Adult Version: feasibility, reliability and validity in a university student population. Journal of health psychology, 14(4), 611-622.

Figure Legend:

Figure 1: Flow Diagram of Study Identification and Selection. Flow of studies identified from the search strategy and reasons for exclusion

Supplemental Material Descriptions:

Supplemental Appendix 1: Search Strategies