Article:
Johnston, DL, Sung, L, Stark, D orcid.org/0000-0002-6172-733X et al. (2 more authors) (2016) A systematic review of patient-reported outcome measures of neuropathy in children, adolescents and young adults. Supportive Care in Cancer, 24 (9). pp. 3723-3728. ISSN 0941-4355

https://doi.org/10.1007/s00520-016-3199-x

A Systematic Review of Patient Reported Outcome Measures of Neuropathy in Children, Adolescents and Young Adults

Donna L. Johnston, MD[1], Lillian Sung, MD, PhD[2], Daniel Stark, MD, PhD[3], A. Lindsay Frazier, MD, MSc[4], Abby R. Rosenberg, MD, MS[5-7]

[1]Division of Paediatric Haematology/Oncology, Children's Hospital of Eastern Ontario, Ottawa, Canada; [2]Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, Canada; [3]Section of Oncology and Cancer Research, Leeds Institute of Molecular Medicine, University of Leeds, UK; [4]Dana-Farber/Childrens Hospital Divisino of Childhood Cancer and Blood Disorders, Boston MA; [5]Cancer and Blood Disorders Center, Seattle Children's Hospital, Seattle, US; [6] Division of Hematology/Oncology, Department of Pediatrics, University of Washington School of Medicine, Seattle, US; Fred Hutchinson Cancer Research Center, Seattle, US

Corresponding Author: Dr Donna Johnston,
Division of Hematology/Oncology, Children's Hospital of Eastern Ontario,
401 Smyth Road,
Ottawa, ON Canada K1H 8L1
Email: djohnston@cheo.on.ca
Phone: 613-737-7600 ext 2210
Fax: 613-738-4828

Purpose: Peripheral neuropathy is an important, yet poorly studied side effect of pediatric cancer treatment. There are many measures of patient reported peripheral neuropathy in adults but very few in children. We aimed to systematically review and summarize reliable and valid patient reported peripheral neuropathy scales used in pediatrics.

Methods: Four major electronic databases (Medline, Embase, EBSCO Host in Cumulative Index to Nursing and Allied Health Literature and PsycINFO) were reviewed for studies that measured peripheral neuropathy in pediatric patients. Studies eligible for inclusion were those that described use of any patient-reported scale of peripheral neuropathy among children, adolesecnts and young adults with any underlying diagnosis (not limited to cancer).

Results: From a total of 765 articles retrieved, 5 met eligibility criteria and were included. One was a neuropathy symptom score used in patients with diabetes, the remaining four were in oncology patients and all were based on the Total Neuropathy Scale. All involved objective assessments conducted by trained professionals; none relied purely on patient-report.

Conclusions: There are no validated instruments that consist solely of a patient reported outcome measure of neuropathy in pediatrics and adolescents. Because the clinical evaluation of neuropathy requires specialized training, it is not generalizable in large studies conducted in many diverse institutions. Future studies should validate adult patient-reported neuropathy scales in pediatric and adolescent populations, or develop novel instruments designed for this population.

Key Words: peripheral neuropathy, pediatrics, systematic review, patient reported

Introduction:

Children who undergo chemotherapy for treatment of their cancer can experience toxicities from their therapy. Chemotherapy induced peripheral neuropathy (CIPN) is an important toxicity of several commonly used pediatric cancer medicines , including vincristine and cisplatin [1]. CIPN may manifest in any of the 3 elements of the peripheral nervous system: sensory, motor or autonomic. Symptoms of CIPN include numbness, tingling, loss of proprioception, pain, weakness, disco-ordination, and change in thermoregulation, blood pressure, and intestinal mobility. These symptoms may be cumulative and progressive and can have both an immediate and long-term impact on overall quality of life and physical function [2-5]. Up to 40% of testicular cancer survivors suffer from persistent long-term CIPN [5] and over one third of ovarian tumor survivors also suffer from persistence of CIPN [4].

Objective measures of CIPN (e.g., nerve conduction studies) are rarely feasible or cost-effective to conduct on large scale studies, and they are often unpleasant to administer. In many clinical studies, the Common Terminology Criteria for Adverse Events (CTCAE) are used to report toxicities, but they have been shown to under-report the incidence of CIPN by up to 40% [6-8]. Comprehensive clinical neurological exams tend to be poorly reproducible, inconsistent or incomplete in their assessment of CIPN [7].

Patient reported outcomes (PROs) measure symptoms and signs from the patient perspective and thus are a measure of the impact of therapies from the patients

perspective. They are an important adjunct to objective measure to determine how the symptom affects the patient's quality of life. Uncertainty regarding available, validated instruments to measure PROs of peripheral neuropathy in children, adolescents and young adults with cancer led us to undertake a systematic review of all patient reported outcome tools to measure peripheral neuropathy in this age range. Adolescents and young adults (AYAs) are a particularly disadvantaged group in terms of understanding of PROs as there are very few instruments that span the AYA age range [9]. Our objectives were to identify studies that describe validated patient-reported scales of peripheral neuropathy in children, adolescents and young adults.

Methods:

Data Sources and Electronic Searches. We utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for this systematic review [10].

A medical librarian developed and executed our electronic searches using the Ovid search platform in the following databases: Medline (1946-), Embase (1947-), EBSCOHost in Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981-) and PsycINFO (1806-) from their inceptions up to August 2015. We used the medical subject headings and text words specific to each database to identify pediatric, adolescent or young adult patients combined with peripheral neuropathy terms. The full search strategy is in Appendix 1.

Study Selection. The inclusion and exclusion criteria were defined *a priori.* Inclusion criteria were studies that used any patient-reported scale of peripheral neuropathy among children, adolescents and young adults with any underlying diagnosis (not limited to cancer). The exclusion criteria were: the study population did not include anyone under the age of 18 years; the neuropathy measure was not patient reported; the study only included clinician reported or objective measures; the study only evaluated physiological measures of neuropathy (e.g. nerve conduction studies, biosthesiometry); the study was a non-English publication; the publication was not full text (e.g. conference proceedings, dissertations); or the study was a case report or review.

Data Abstraction. Two reviewers (DJ and AR) independently identified the titles and abstracts of studies identified by the search strategies. Potentially eligible studies were evaluated at full text. They applied the inclusion and exclusion criteria and final inclusion of studies into the systematic review was by agreement of both reviewers.

The same two reviewers then abstracted all data in duplicate and discrepancies were resolved by consensus. Data were abstracted with a common case report instrument, developed prior to data collection based on study objectives. The variables of interest from the studies were year of publication, study dates, country of study population, languages, name of the tool to measure neuropathy and description of the scale, recall period for neuropathy symptoms, how the PRO was completed, age of participant, medication used in study population, number of participants enrolled, who completed the PRO instrument, timing of assessment, number of assessments, and any psychometric evaluation. We abstracted published data only; no authors were contacted to obtain additional or unreported information.

Data was abstracted and data on bias related to study participation and measurement of outcomes were rated as having low, medium or high risk of bias for each study based on published tools [11]. Discrepancies in bias assessments were resolved by consensus. All included studies were included in qualitative

descriptive analyses.

Results:

From a total of 765 articles retrieved 718 were excluded based on title and abstract. Forty-seven full text articles were screened for full inclusion and exclusion criteria and 42 were excluded; 4 were not conducted with pediatric patients, 17 did not include patient-report, 12 were conference proceedings, and 6 were duplicate articles. A total of 5 full text articles met eligibility criteria and were included [6, 8, 12-14]. Figure 1 demonstrates the flow for article identification and selection.

Details of the 5 included articles of patient reported outcomes of neuropathy in patients under the age of 18 years are in Table 1. Four of the articles utilized a modified form of the Total Neuropathy Score (TNS) in pediatric oncology patients; three of these were published by the same authors. We were unable to determine if there were overlapping patients included in the three studies. The final paper utilized the neuropathy symptom score in pediatric diabetes patients.

Pediatric Modified Total Neuropathy Scale

The three articles utilizing a modified TNS use a scale called the "pediatric modified total neuropathy score" (Ped-mTNS) [6, 12, 14]. This scale uses a scripted questionnaire for sensory symptoms of tingling, numbness or hurt, functional symptoms of buttoning, walking and going up stairs, and autonomic symptoms of dizziness or hot or cold hands or feet. If there is a yes response to any of these neuropathies then they are rated on 0-4 scale. The Ped-mTNS also has 5 clinical testing domains: light touch sensation, pin sensibility, vibration sensibility, strength,

and deep tendon reflexes. The Gilchrist 2013 study on the Ped-mTNS included psychometric properties of the scale in patients aged 5 to 18 years [12]. This study tested test-retest reliability by retesting 10 patients by the same investigator and 10 by another investigator with at least 1 hour between the tests and no new chemotherapy given in this interval. The overall Chronbach alpha was 0.76, the test-retest intra-class coefficient (ICC) was 0.99 (95% CI of 0.96-0.99) and inter-rater ICC was 0.98 (95% CI of 0.95-0.99). Testing of validity showed that the subjects scored significantly worse compared to controls (8.7 to 1.4, $p<0.001$).

Total Neuropathy Score Pediatric Vincristine

One of the four articles utilizing a modified TNS was the total neuropathy score pediatric vincristine (TNS-PV) [8]. This study measured the worst subjective symptom of tingling, numbness or neuropathic pain and rated them on a scale from 0 (no symptoms) to 4. It also measured vibration sensibility, temperature sensibility, strength, tendon reflexes, constipation and hoarseness, also on a 0 to 4 scale by trained evaluators. Neuropathic pain was also measured in this study using the FACES pain scale. The study measured interrater reliability by using the scale on the same patient twice in the same day. The Chronbach alpha for the scale as a whole was 0.84 showing internal consistency reliability. There was strong correlation between the TNS-PV score the total vincristine dose received by the patient.

Neuropathy Symptom Score

The final article was a patient reported outcome in diabetic patients aged 8 to 18 years [13]. The neuropathy symptom score asks patients about burning, numbness, tingling, fatigue, cramping, or pain in the legs, nocturnal exacerbation of signs, and any maneuver that reduced the signs. The scoring included detailed neurologic exam as well as nerve conduction studies. There was no evaluation of reliability, validity or responsiveness of the scale described in the study.

Discussion:

In this systematic review, we identified five articles describing patient reported outcomes of neuropathy in pediatric and adolescent patients. Four of the five described a pediatric modification of the Total Neuropathy Score, and one study evaluated the Neuropathy Symptom Score. The Neuropathy Symptom Score article did not describe any psychometrics of this instrument that was modified for pediatrics, and thus cannot be considered a validated scale for measuring neuropathy in pediatrics.

The total neuropathy scoree has been modified for pediatrics in the Ped-mTNS and the TNS-PV. Both scales have a patient reported component for sensory, functional and autonomic neuropathy symptoms, as well as an objective component that measures strength, deep tendon reflexes, temperature and vibration sensitivity and others. The objective measures require fairly extensive assessment and are not overly conducive to all clinical settings. These tools as well have only been used in very small numbers of patients, and were administered only after professionals received training on measuring the objective component [8] or by a physiotherapist [6, 12, 14].

Based on our findings, an instrument consisting solely of a patient-reported neuropathy instrument has not been developed for pediatric populations. As this is a symptom that is known to impact quality of life in survivors of cancer therapy [2, 7, 15], it is prudent to measure it effectively in the population of patients

experiencing this symptom. Amongst adults, the Gynecologic Oncology Group (GOG) has developed a patient reported outcome measure for neuropathy (the "FACT/GOG-NTX") [16]. This measure is a 4 to 13 item PRO measure describing neuropathy symptoms ranging from numbness, tingling, discomfort, weakness and hearing loss. There are no objective elements in this scale. This may be a promising instrument to evaluate for reliability and validity in a pediatric population as the items appear to be applicable in this age range. If it is not valid and discriminant in the pediatric population, then future work should be undertaken to develop an effective scale for this population. Ultimately, pediatric and adolescent age-appropriate PROs to assess neuropathy may facilitate better understanding of its impact on overall well-being, in turn informing interventions and improving clinical care.

Acknowledgements

The authors would like to thank Lizzie Caperon from the University of Leeds for her assistance with the electronic searches.

Conflict of Interest

The authors have no conflict of interest to declare. The authors have full control of the primary data and agree to allow the journal to review data if requested.

References:

1. Argyriou AA, Bruna J, Marmiroli P, Cavaletti G (2012) Chemotherapy-induced peripheral neurotoxicity: an update. Crit Rev Oncol Hematol 82:51–77.

2. Beijers A, Mols F, Dercksen W, Driessen C, Vreugdenhil G (2014) Chemotherapy-induced peripheral neuropathy and impact on quality of life 6 months after treatment with chemotherapy. J Community Support Oncol. 12:401-406.

3. Brydoy M, Oldenburg J, Klepp O, Bremnes RM, Wist EA, Wentzel-Larsen T, Hauge ER, Dahl O, Fosså SD. (2009) Observational study of prevalence of long-term Raynaud-like phenomena and neurological side effects in testicular cancer survivors. J Natl Cancer Inst. 101:1682-1695.

4. Matei D1, Miller AM, Monahan P, Gershenson D, Zhao Q, Cella D, Champion VL, Williams SD (2009) Chronic physical effects and health care utilization in long-term ovarian germ cell tumor survivors: a Gynecologic Oncology Group study. J Clin Oncol. 27:4142-4149.

5. Fung J, Fossa SD, Williams A, Travis LB (2015) Long term morbidity of testicular cancer treatment. Urol Clin N Am. 42:393-408.

6. Gilchrist LS, Marais L, Tanner L (2014) Comparison of two chemotherapy-induced peripheral neuropathy measurement approaches in children. Support Care Cancer. 22:359-366.

7. Frigeni B, Piatti M, Lanzani F, Alberti P, Villa P, Zanna C, Ceracchi M, Ildebrando M, Cavaletti G. (2011) Chemotherapy-induced peripheral neurotoxicity can be misdiagnosed by the National Cancer Institute Common Toxicity scale. J Peripher Nerv Syst. 16:228-236.

8. Lavoie Smith EM, Li L, Hutchinson RJ, Ho R, Burnette WB, Wells E, Bridges C, Renbarger J (2013) Measuring vincristine-induced peripheral neuropathy in children with acute lymphoblastic leukemia. Cancer Nurs. 36:E49-60.

9. Taylor RM, Fern LA, Solanki A, Hooker L, Carluccio A, Pye J, Jeans D, Frere-Smith T, Gibson F, Barber J, Raine R, Stark D, Feltbower R, Pearce S, Whelan JS (2015) Development and validation of the BRIGHTLIGHT Survey, a patient-reported experience measure for young people with cancer. Health Qual Life Outcomes. 13:107.

10. 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.

11. Hayden JA, Cote, P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med. 144:427-437.

12. Gilchrist LS, Tanner L (2013) The pediatric-modified total neuropathy score: a reliable and valid measure of chemotherapy-induced peripheral neuropathy in children with non-CNS cancers. Support Care Cancer. 21:847-856.

13. Höliner I, Haslinger V, Lütschg J, Müller G, Seick Barbarini D, Fussenegger J, Zanier U, Saely CH, Drexel H, Simma B (2013) Validity of the Neurological Examination in Diagnosing Diabetic Peripheral Neuropathy. Pediatric Neurology 49:171-177.

14. Gilchrist LS, Tanner L, Hooke MC (2009) Measuring Chemotherapy-Induced Peripheral Neuropathy in Children: Development of the Ped-mTNS and Pilot Study Results. Rehabil Oncol. 27:7-15.

15. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, Friedman DL, Marina N, Hobbie W, Kadan-Lottick NS, Schwartz CL, Leisenring W, Robison LL (2006) Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 355:1572-1582.

16. Huang HQ, Brady MF, Cella D, Fleming G (2007) Validation and reduction of FACT/GOG-Ntx subscale for platinum/paclitaxel-induced neurologic symptoms: a gynecologic oncology group study. Int J Gynecol Cancer. 17:387-393.

Figure 1 – Flow diagram of study identification and selection

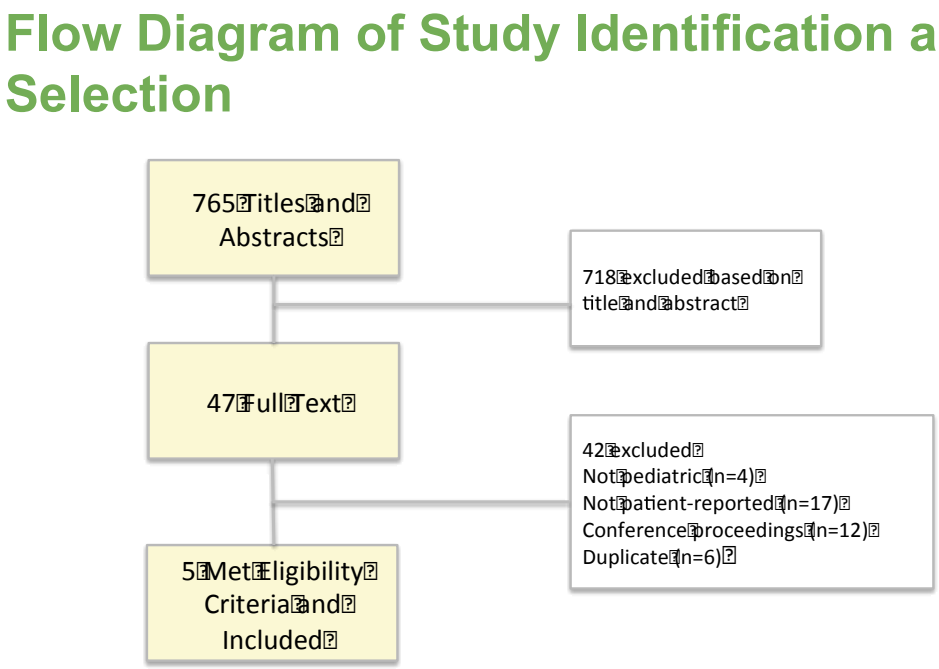

Table 1 – Summary of Patient Reported Outcome Measures of Neuropathy in Pediatrics

Author	Year Pub	Language Administered	Name of Instrument	How Completed	Age Participants	Patients Enrolled	Number participants	Timing	Number Assessments	Psychometric Evaluation	Participant Bias	Analysis Bias
Gilchrist	2014	English	Ped-mTNS	In person	5-18 mean 10.7±3.9	ALL within 2 wk DI, lymphoma, solid non-CNS within 3-4 mos start chemo	66 – 60 completed	ALL within 2 wk DI, lymphoma, solid non-CNS within 3-4 mos start chemo	1 for ped-mTNS, 1 by oncologist for review neuro signs/symptoms	none mentioned	Low	Moderate
Gilchrist	2013	English	Ped-mTNS	In person	9.56±3.1	ALL, Lymphoma, non-CNS solid, VCR or cisplat, 2 wk from end DI or 2 mos after start chemo	66 - 60 completed	ALL, Lymphoma, non-CNS solid, VCR or cisplat, 2 wk from end DI or 2 mos after start chemo	1 but 10 retested by same investigator and 10 by another investigator, 1 hour between tests	Yes	Low	Low
Holiner	2013	English	Neuropathy Symptom Score	In person	13.8±2.5	Diabetes>1 year, insulin >0.5iu/kg/d	39	Diabetes>1 year, insulin >0.5iu/kg/d	1 assessment	none mentioned	Moderate	High
Lavoie-Smith	2013	English	TNS-PV	In person	6.38±4.4	ALL receiving vincristine	65	ALL receiving vincristine	Baseline and day each subsequent VCR, to week 15	Yes	High	Low
Gilchrist	2009	English	Ped-mTNS	In person	10.6±4.7	ALL, lymphoma, non-CNS solid, 30 day from start chemo with VCR or cisplat or stop chemo within 2 months	20	ALL, lymphoma, non-CNS solid, 30 day from start chemo with VCR or cisplat or stop chemo within 2 months	1 assessment	none mentioned	Moderate	Moderate

Appendix 1 – Full Search Strategy

#	Searches	Results
1	exp neoplasms/ or exp antineoplastic agents/	3215865
2	(neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp.	3368734
3	Antineoplastic Combined Chemotherapy Protocol*.mp.	112772
4	(Cisplatin or Induction Chemotherapy or Lymphoma or Neoplasms or Neurotoxicity Syndrome*).ti,ab.	222600
5	Chemotherap*.ti,ab.	273747
6	Neurologic Examination.ti,ab.	2687
7	patient outcome assessment/	1462
8	(prom or (patient* adj2 outcome* adj2 (assessment* or research* or questionnaire*))).ti,ab.	2669
9	Questionnaires/ or (questionnaire* or survey*).ti,ab.	757262
10	instrument*.ti,ab.	179337
11	(scale or scales).ti,ab.	423222
12	self report/ or ((patient* or self) adj2 report*).ti,ab.	175792
13	psychometrics/ or psychometric*.ti,ab.	68053
14	evaluation studies as topic/ or "reproducibility of results"/ or validation studies as topic/ or "Sensitivity and specificity"/	618527
15	Self-Assessment/	10771
16	(((Patient* or self) adj2 (evaluat* or apprais*)) or "self-apprais* or self-evaluat*").ti,ab.	77744
17	(evaluation studies or validation studies).pt.	272094
18	EORTC CIPN-20.mp.	2
19	FACT GOG.mp.	31
20	Total Neuropathy Scale.mp.	2
21	EORTC.mp.	5110
22	nerve conduction stud*.mp.	3578
23	Electric Stimulation.ti,ab.	3512
24	Median Nerve.ti,ab.	7553
25	Neural Conduction.ti,ab.	263
26	Peripheral neuropath*.ti,ab.	14240
27	Precursor Cell Lymphoblastic Leukemia-Lymphoma.mp.	21022
28	Vincristine.ti,ab.	15444
29	(child or child* or "school-child*" or kindergar* or kid or kids).ti,ab.	998308
30	(boy* or girl* or minor or minors* or underag* or juvenil* or youth*).ti,ab.	426853
31	(adoles* or teen* or puber* or pubescen* or prepubescen* or prepuberty*).ti,ab.	213014
32	(pediatrics or pediatric* or paediatric* or peadiatric*).ti,ab.	218983
33	("school-child*" or kindergar* or school* or preschool* or "pre-school*" or highschool* or "school-age" or schoolage*).ti,ab.	206430
34	(youth* or "young adult*" or (young adj2 adult*)).ti,ab.	102594
35	infant/ or infant, newborn/	977407
36	Interviews as Topic/ or interview*.ti,ab.	236956
37	diary/ or (diary or diaries).mp.	15626
38	exp Peripheral Nervous System Diseases/	122177
39	Antineoplastic Combined Chemotherapy Protocols/	112766
40	Cisplatin/	42883
41	Induction Chemotherapy/	1003

42	Lymphoma/	45810
43	Neoplasms/	318069
44	Precursor Cell Lymphoblastic Leukemia-Lymphoma/	21020
45	Vincristine/	21046
46	Antineoplastic Agents/	209750
47	Neurotoxicity Syndromes/	3598
48	Hemoglobin A, Glycosylated/	25011
49	Electric Stimulation/	107792
50	Median Nerve/	8636
51	Neural Conduction/	26297
52	Neurologic Examination/	24934
53	1 or 2 or 3 or 4 or 5 or 27 or 28 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 [Concept 1 - Cancer/Clinical terms]	4100079
54	26 or 38 [Concept 2 - Peripheral Neuropathy terms]	127856
55	29 or 30 or 31 or 32 or 33 or 34 or 35 [Concept 3 - Age limits]	2226039
56	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 49 or 50 or 51 or 52 or 36 or 37 [Concept 4 - Instrument terms]	2363726
57	53 and 54 and 55 and 56	560
58	limit 57 to (english language and humans)	494
59	Measuring vincristine-induced peripheral neuropathy in children with acute lymphoblastic leukemia.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1
60	58 and 59	1
61	(The pediatric modified total neuropathy score: a reliable and valid measure of chemotherapy induced peripheral neuropathy in children with non CNS cancers).m_titl.	1
62	58 and 61	1
63	Validity of the neurological examination in diagnosing diabetic peripheral neuropathy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1
64	58 and 63	1