Comprehensive review

Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis

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1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a disabling pain condition resulting from chemotherapy for cancer. Severe acute CIPN may require chemotherapy dose reduction or cessation. There is no effective CIPN prevention strategy; treatment of established chronic CIPN is limited, and the prevalence of CIPN is not known. Here we used a systematic review to identify studies reporting the prevalence of CIPN. We searched Embase, Medline, CAB Abstracts, CINAHL, PubMed central, Cochrane Library, and Web of Knowledge for relevant references and used random-effects meta-regression to estimate overall prevalence. We assessed study quality using the CONSORT and STROBE guidelines, and we report findings according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance. We provide a qualitative summary of factors reported to alter the risk of CIPN. We included 31 studies with data from 4179 patients in our analysis. CIPN prevalence was 68.1% (57.7–78.4) when measured in the first month after chemotherapy, 60.0% (36.4–81.6) at 3 months and 30.0% (6.4–53.5) at 6 months or more. Different chemotherapy drugs were associated with differences in CIPN prevalence, and there was some evidence of publication bias. Genetic risk factors were reported in 4 studies. Clinical risk factors, identified in 4 of 31 studies, included neuropathy at baseline, smoking, abnormal creatinine clearance, and specific sensory changes during chemotherapy. Although CIPN prevalence decreases with time, at 6 months 30% of patients continue to suffer from CIPN. Routine CIPN surveillance during post-chemotherapy follow-up is needed. A number of genetic and clinical risk factors were identified that require further study.

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appropriate resource allocation and research planning, and to inform patient decisions about treatment. Understanding risk factors (including genetic risk factors) for CIPN may guide future research and treatment.

Previous reviews of CIPN have combined narrative review with expert opinion, with potential risk of bias [15,28,29]. Here we present what we believe to be the first systematic review and meta-analysis of the incidence and prevalence of CIPN. We also aimed to assess the influence of potential publication bias on our estimation of CIPN measures, and to seek empirical evidence of the impact of study design factors.

2. Methods

2.1. Search strategy

We searched Embase, Medline, CAB Abstracts, CINAHL, PubMed central, Cochrane Library and Web of Knowledge in July 2013 for English-language references. Searches were not limited by date restrictions. Search terms were free text and included; [“Chemotherapy Induced Peripheral Neuropathy” OR “Chemotherapy Induced Neurotoxicity” OR “Chemotherapy Induced Neurotoxicity Syndromes” OR “CIPN” OR “Oxaliplatin Induced Peripheral Neuropathy” OR “Bortezomib Induced Peripheral Neuropathy” OR “Paclitaxel Induced Peripheral Neuropathy” OR “Taxane Induced Peripheral Neuropathy” OR “Cisplatin Induced Peripheral Neuropathy” OR “Vincristine Induced Peripheral Neuropathy” OR “Thalidomide Induced Peripheral Neuropathy” OR “Platinum Induced Peripheral Neuropathy” OR “Carboplatin Induced Peripheral Neuropathy” OR “Docetaxel Induced Peripheral Neuropathy” OR “Proteasome Inhibitor Induced Peripheral Neuropathy” OR “Neurotoxic Chemotherapy Induced Peripheral Neuropathy” OR “Cancer Neuro-pathic Pain” OR “Chemotherapy Induced Neuropathic Pain”] [Search 1] AND [“Prevalence” OR “Epidemiology” OR “Occurrence” OR “Burden”] [Search 2] AND [“Predictors” OR “Risk Factors”] [Search 3]. The search strategy was adapted for each database (see supplementary text A). We also hand searched reference lists of relevant studies and systematic reviews of CIPN prevention trials, and searched the databases of National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN). Our review followed an a priori protocol according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [43]. The review protocol was registered on the PROSPERO website before data extraction (registration no. CRD42013005524) [11].

2.2. Inclusion and exclusion criteria and study selection

We included prospective observational studies of adult cancer patients receiving chemotherapy of any type. Our definition of observational studies included cohort studies in which patients were prospectively identified and followed up using relevant predefined outcomes of interest. We also included control group data from randomized controlled trials (RCTs) of CIPN prevention in which details of the patients who developed CIPN were reported. Studies were excluded if they described animal models of CIPN, were investigating CIPN treatment or prevention, included pediatric populations, or investigated other causes of neuropathy in cancer patients (e.g., pre-existing neuropathy such as diabetic neuropathy or other cancer related causes of neuropathy such as post-mastectomy).

Two investigators (M.S. and S.R.) independently read and selected from all the retrieved references and abstracts. Discrepancies between the reviewers’ selections were resolved by discussion. Full texts of potentially eligible studies were retrieved (Fig. 1).

2.3. Data extraction and quality assessment

We extracted data to a bespoke form, recording the prevalence or incidence of CIPN, and any reported risk factors or predictors of CIPN. We included all relevant outcomes determined after the end of chemotherapy, noting the time (in relation to the end of chemotherapy) at which these were assessed. Where information was incomplete we contacted authors by email. Two investigators (M.S. and S.R.) extracted data, which were then entered into the study database. Discrepancies were resolved by discussion and agreement with a third reviewer (M.F.).

We assessed study quality according to the PRISMA guidelines [43]. We evaluated risk of bias in individual studies using the following criteria: investigator blinding of any type, presence of a control group, use of externally validated instruments for CIPN assessment, clear description of statistical methods used to identify CIPN predictors, and description of longitudinal follow up. Adherence of each study to relevant reporting criteria (STROBE or CONSORT) was assessed [26,61]. We assessed the risk of bias for our summary estimate by seeking evidence of publication bias, selective outcome reporting bias (if a published protocol of the included study was available), reporting of a sample size calculation, and whether the study reported participants lost to follow-up.

2.4. Data synthesis and analysis

Our primary outcome was the prevalence of CIPN. We used random effects meta-regression to quantify heterogeneity and its potential sources. We hypothesized that chemotherapy type and the time of CIPN assessment would explain a large proportion of the observed heterogeneity. Therefore, we included chemotherapy type, last time point of CIPN assessment, and measures of study quality as independent variables in our regression model. We also planned for assessment of risk factors for CIPN across studies. We assessed publication bias using funnel plots, Egger’s test, and trim and fill [22]. We appraised studies using STROBE criteria for observational studies and CONSORT criteria for trials. Where a criterion was partially met, we considered, for the purposes of this analysis, that it was completely met, for ease of calculation. In open label studies (Table 1), we modified the CONSORT criteria by not considering the point for blinding, to account for the design of these studies. STATA 13.1 was used for statistical analyses.

3. Results

3.1. Studies included

We identified 4128 potentially relevant studies, and examined the full text of 138. A total of 31 studies (involving 4179 patients) [4-9,13,14,18,21,24-27,32-38,39,45-48,52,53,60,63-65] met our inclusion criteria. A total of 30 studies reported the incidence of CIPN (new CIPN cases divided by the population at risk). One study reported CIPN prevalence (all CIPN cases divided by population at risk) [26]. Because CIPN might have occurred, and resolved, between study assessments, we calculated the prevalence of CIPN at the time of each assessment [59].

3.2. Study characteristics

Of the 31 studies included, 15 were prospective cohort studies, 10 were RCTs, 5 were nonrandomized controlled trials, and 1 was a cross-sectional cohort study. All nonrandomized controlled trials were open labeled and not blinded. Eight of 10 RCTs (80%) reported investigator blinding of some type. Blinded assessment of outcome was reported in 3 of 14 prospective cohort studies. One prospective
195 cohort study also sought to validate genetic risk factor results in a
196 control group. Nine of 10 RCTs (90%) described a sample size calcu-
197 lation. Of all included studies, 22 (71%) reported study participant
dropout, giving reasons. In all, 14 of 31 study authors (45%) dis-
closed funders and/or whether they had a conflict of interest.

199 Adherence of studies to reporting guidelines is summarized in
200 Table 1. Of 31 studies, 26 (83.9%) used an assessment tool validated
202 for CIPN. All studies reporting CIPN risk factors described methods
203 used to identify these predictors.

3.3. CIPN incidence and prevalence

205 Of 4179 patients, 1960 developed
206 CIPN (aggregate prevalence

207 48%). CIPN prevalence was 68.1% (57.7–78.4) within the first
208 month of the end of chemotherapy, 60.0% (36.4–81.6) at 3 months,
209 and 30.0% (6.4–53.5) at 6 months or later (Table 2). There was con-
210 siderable heterogeneity in the estimates from different studies

211 (I² = 98.2, P < .001). The time of assessment accounted for 36% of
212 the observed heterogeneity (adjusted R² = 0.365, P < .001). An over-
213 view of the individual incidence reported in included studies is
214 shown in Table 1. We did not include the cumulative dose (CD)

215 of chemotherapy (actual dose received) in our meta-regression
216 because standard and maximally tolerated doses would differ sub-
217 stantially from drug to drug (study-specific CD shown in Table 1).

218 As expected, there was co-linearity between the cancer type and
219 the chemotherapy used; because we reasoned that it is more likely
220 that CIPN prevalence would be related to drug than to cancer type,
221 we considered only chemotherapy type in our regression model

222 (Table 3). The type of chemotherapy used accounted for 32% of
223 the observed heterogeneity in our sample (adjusted R² = 0.315,
224 P < .04).

225 Methods used to assess the presence or grade of CIPN were too
226 diverse to include in the meta-regression. Of the 31 included stud-
227 ies, 8 defined CIPN according to the National Cancer Institute Com-
228 mon Toxicity Criteria (NCI-CTC), 1 study used the European
229 Organisation for Research and Treatment of Cancer (EORTC) Qual-
230 ity of Life Questionnaire 30 (QLQ – 30) combined with neurological
231 examination, 1 used in-depth neurophysiological examination

232 (NPS), 1 used a standard neurological examination, and 1 used
233 the Total Neuropathy Score (TNSc). The remaining 18 studies used

234 a combination of 2 or more of the above, and 1 study used skin

235 biopsy (Table 3). To investigate any impact of neurophysiological

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Please cite this article in press as: Seretny M et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic
237 review and meta-analysis. PAIN (2014), http://dx.doi.org/10.1016/j.pain.2014.09.020
for publication bias, although Egger’s test did not suggest asymmetry in the funnel plot at a confidence level of $P = .05$ (95% CI of intercept –0.64 to 7.8); trim and fill analysis did impute 14 theoretical missing studies. These 2 approaches to assess for publication bias are known to have different sensitivities [58].

3.4. CIPN risk factors

Eight of the included studies assessed risk factors for CIPN (Table 4) [8,9,21,26,33,34,48,65]. Four genome-wide association studies (GWAS), totaling 2671 patients, sought single nucleotide polymorphisms (SNPs) associated with CIPN [9,33,48,65]. All GWAS used validation datasets and conducted genotyping blinded to clinical status. These reported polymorphisms associated with a range of proteins, including voltage-gated sodium channels, Schwann cell function–related proteins, receptors for cell surface collagen, receptors involved in neuronal apoptosis, neuronal crest cell development, and an enzyme involved in pyruvate metabolism.

Four studies (701 patients) used statistical modeling to report clinical risk factors for CIPN [8,21,26,34]. Two of these studies included 50 patients or fewer. No study used a separate data set to validate candidate risk factors. Reported clinical risk factors for CIPN included baseline neuropathy, a history of smoking, decreased creatinine clearance, and specific sensory changes during chemotherapy treatment, including cold allodynia (pain in response to a nonpainful cold stimulus) and cold hyperalgesia (exaggerated pain in response to a painful cold stimulus, 20°C).

4. Discussion

4.1. CIPN prevalence

This systematic review and meta-regression suggests a high overall prevalence of CIPN, maximum within the first month after treatment, and falling over time. Approximately one-third of patients can expect to have chronic CIPN 6 months or more after the end of chemotherapy; this has a significant negative impact on long-term quality of life for which effective treatment is needed.

The lack of uniformity in CIPN assessment methods make between-study comparisons difficult. Authors used 5 assessment methods (NCI-CTC, TNSc, EORTC QLQ-C30, neuro-physiological examination, which included nerve conduction studies and/or quantitative sensory testing, and neurological examination) alone or in combination. Of these, only the EORTC QLQ-C30 and quantitative sensory testing component of neurophysiological examination explicitly assess pain as a symptom of CIPN. It is known that although CIPN most frequently presents with pain, motor and other sensory symptoms may also be present [40]. Use of combinations of CIPN and pain assessment tools has been suggested as a.
strategy to improve detection and quantification of pain in CIPN [67]. There have been recent attempts to standardize CIPN assessment and reporting, and we encourage investigators to consider these when developing study protocols [15,16].

Three of the 5 largest studies in our sample did not include the mildest grades of CIPN [9,24,45]. The prevalence of CIPN is therefore likely to be higher than reported here. Early detection of mild CIPN might become important if effective prevention or management strategies become available. A lower incidence in these larger studies is an alternative explanation for the funnel plot asymmetry detected by trim and fill analysis [58].

Current clinical guidelines support use of NPS methods in the diagnosis of suspected CIPN [19,56]. Studies using this approach reported a higher prevalence of CIPN, but whether this is a clinically significant problem is not clear.

We found significant heterogeneity between studies. In meta-analyses aimed at providing a best estimate of, for instance, drug efficacy, significant heterogeneity usually limits the usefulness of pooled data. In contrast, because the etiology and epidemiology of CIPN are so poorly understood, we believe that investigating the sources of heterogeneity is important. Specifically, it might provide insight into the impact of length of assessment and chemotherapy type on the incidence and prevalence of CIPN. Furthermore, as expected, a substantial proportion of the heterogeneity that we observed was accounted for by chemotherapy type, which was related to the cancer type. Although the primary interest of many clinicians will be the prevalence of CIPN for specific chemotherapeutics, CIPN treatment decisions are routinely based on data from treatment trials that have recruited patients irrespective of the chemotherapy that they were prescribed [57].

### 4.2. Risk factors for CIPN

Four studies used multivariate statistical modeling to identify clinical risk factors for CIPN [8,21,26,34]. Despite using valid statistical approaches, these studies did not verify identified risk factors in new population datasets. Consequently, their results are probably affected by the statistical biases underpinning these types of predictive calculations [3,42]. To our knowledge, these are the only studies that describe baseline neuropathy, smoking, and decreased creatinine clearance as risk factors for CIPN. In contrast, description of sensory changes during chemotherapy treatment, including increased pain and nerve hyperexcitability, have previously been documented as predictors of CIPN [20,42]. The postulated mechanisms underpinning these sensory phenomena include axonal hyperexcitability and nociceptor sensitization. These processes may be important in CIPN development, and, to some degree, they fit with the mechanisms described in other neuropathic conditions related to systemic diseases, including human immunodeficiency virus (HIV) and multiple sclerosis [42,64]. There is ongoing debate about the relative importance of etiology in determining the underlying mechanisms of neuropathic pain [19,56,62].

Four studies reported genetic risk factors for CIPN. The functions of the identified genes fit with the postulated pathophysiological mechanisms underpinning CIPN [50]. The recent comprehensive review by Cavaletti et al. discusses these mechanisms in detail. All 4 included studies were, to some degree, affected by the universal limitations influencing pharmacogenetic studies: inadequate sample size, CIPN assessment tools, and use and size of a replication cohort. Despite these possible limitations, the potential clinical usefulness of pharmacogenetic studies in CIPN has recently been...
### Table 3
Studies stratified by drug type.

<table>
<thead>
<tr>
<th>Study type (CONSORT/STROBE)</th>
<th>Main cancer class</th>
<th>CIPN severity report (count by grade if given)</th>
<th>CIPN assessment time points</th>
<th>CIPN assessment method(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin: 72.3% (95% CI = 59.7–86.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antonacopoulou (2009)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argyriou (2007) [8]</td>
<td>Colorectal</td>
<td>Grade I (6/16)</td>
<td>Baseline</td>
<td>TNSc</td>
</tr>
<tr>
<td>Argyriou (2012)</td>
<td>Colorectal</td>
<td>Grade I (38/125)</td>
<td>Baseline</td>
<td>TNSc</td>
</tr>
<tr>
<td>Argyriou (2013)</td>
<td>Colorectal</td>
<td>Grade I (82/169)</td>
<td>Baseline</td>
<td>TNSc</td>
</tr>
<tr>
<td>Argyriou (2013)</td>
<td>Colorectal</td>
<td>Grade I (62/169)</td>
<td>Baseline</td>
<td>TNSc</td>
</tr>
<tr>
<td>Argyriou (2013)</td>
<td>Colorectal</td>
<td>Grade I (6/16)</td>
<td>Baseline</td>
<td>TNSc</td>
</tr>
<tr>
<td>Attal (2009)</td>
<td>Colorectal</td>
<td>Grade I (62/169)</td>
<td>Baseline</td>
<td>TNSc</td>
</tr>
<tr>
<td>Antic (2002)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cascinu (1995)</td>
<td>Gastrointestinal</td>
<td>Grade I (3/16)</td>
<td>Baseline</td>
<td>TNSc</td>
</tr>
<tr>
<td>Gandara (1995)</td>
<td>Ovarian and lung</td>
<td>Only grade 3 reported</td>
<td>Baseline</td>
<td>TNSc</td>
</tr>
<tr>
<td>Kemp (1996)</td>
<td>Gynecological</td>
<td>Grade I (31/81)</td>
<td>Baseline</td>
<td>TNSc</td>
</tr>
<tr>
<td>Pace (2003)</td>
<td>Multiple solid</td>
<td>Grade I (5/5)</td>
<td>Baseline</td>
<td>TNSc</td>
</tr>
<tr>
<td>Pace (2010)</td>
<td>Multiple solid</td>
<td>Only grade 3 reported</td>
<td>Baseline</td>
<td>TNSc</td>
</tr>
<tr>
<td>Planting (1999)</td>
<td>Multiple solid</td>
<td>Grade I (5/5)</td>
<td>Baseline</td>
<td>TNSc</td>
</tr>
<tr>
<td>Van der Hoop (1999)</td>
<td>Gynecological</td>
<td>Mean vibration threshold</td>
<td>Baseline</td>
<td>TNSc</td>
</tr>
</tbody>
</table>
described [10]. As suggested by Postma et al. adherence of future studies to standardized study design and methods will likely aid the advance of personalized oncology, possibly having an impact on CIPN prevalence in the future.

### 4.3. Limitations of this review

It is possible that we have omitted relevant studies despite our detailed search strategy, and we specifically excluded non-English language studies. Multivariate meta-regression would have allowed us to investigate interactions between various factors, but there are too few studies for this approach to be reliable. Because we expected there to be a broad range of CIPN assessment methods used, we did not plan to explore their impact. Our analysis of the impact of NPS as a component of the assessment of CIPN is post hoc and therefore should be interpreted with caution. We did not specifically seek out assessments for pain in CIPN in included studies and therefore

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**Table 3 (continued)**

<table>
<thead>
<tr>
<th>Study type/CONSORT/STROBE</th>
<th>Main cancer class</th>
<th>CIPN severity report (count by grade if given)</th>
<th>CIPN assessment time points</th>
<th>CIPN assessment method(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Schlippe (2001)</td>
<td>Prospective cohort Testicular</td>
<td>Grade I (4/5) Grade II (1/3)</td>
<td>Unclear if at baseline Every 6 wk for first 6 mo after chemotherapy Thereafter every 2 mo for median of 4 y (range 2–8 y)</td>
<td>NPS</td>
</tr>
<tr>
<td>Cisplatin and paclitaxel: 73% (95% CI = 36.2–109.7)</td>
<td>Argyriou (2007) Prospective cohort Multiple solid Mild (2/9) Moderate (6/9) Severe (1/9)</td>
<td>% Severity with cumulative dose</td>
<td>Baseline Cycle 3, 6 3 mo after chemo end Baseline Daily during cycle 1 Cycle 2, 3, 4 Chemo end</td>
<td>NPS</td>
</tr>
<tr>
<td>Kawakami (2012) Prospective cohort Lung</td>
<td></td>
<td></td>
<td></td>
<td>NCI-CTC</td>
</tr>
<tr>
<td>Cisplatin and vincristine: 20.1% (95% CI = –26.2 to 66.5)</td>
<td>Gledenning (2010) Cross-sectional cohort Testicular</td>
<td>Only grade ≥3 reported</td>
<td>Recruited patients at least 5 y post-treatment Assessed once for this prevalence study</td>
<td>(EORTC) QLQ-C30 NES</td>
</tr>
<tr>
<td>Paclitaxel: 70.8% (95% CI = 43.5–98.1)</td>
<td>Argyriou (2006) Prospective cohort Breast</td>
<td>Reported by age group only</td>
<td>Baseline Cycles 3, 6 3 mo after chemo end Unclear if at baseline Cycles 4, 6 Within 1 mo of chemo end Baseline 1 mo after chemo end</td>
<td>PNS</td>
</tr>
<tr>
<td>Baldwin (2012) Prospective cohort Breast</td>
<td>Only grade ≥2 reported</td>
<td></td>
<td></td>
<td>NCI-CTC</td>
</tr>
<tr>
<td>Ghoreishi (2012) RCT Breast</td>
<td>Mild (10/16) Moderate (5/16) Severe (1/16)</td>
<td></td>
<td></td>
<td>TNSc</td>
</tr>
<tr>
<td>Pace (2007) Prospective cohort Breast</td>
<td>Mean neurotoxicity scores reported</td>
<td></td>
<td>Baseline After 12 wk of chemo After 24 wk of chemo</td>
<td>NPS</td>
</tr>
<tr>
<td>Vincristine: 19.6% (95% CI = –26.6 to 65.9)</td>
<td>Johnson (2011) RCT Multiple myeloma</td>
<td>Grade I 31.8% Grade II 11% Grade III 3.6%</td>
<td>Unclear if at baseline At each cycle For 6 months after chemo end for induction (ie, 36 wk from start of induction therapy)</td>
<td>NCI-CTC</td>
</tr>
<tr>
<td>Thalidomide: 63.5% (95% CI = 29.3–97.8)</td>
<td>Johnson (2011) RCT Multiple myeloma</td>
<td>Grade details not reported</td>
<td>Unclear if at baseline At each cycle For 6 mo after end of chemo for induction (ie, 36 weeks from start of induction therapy)</td>
<td>NCI-CTC</td>
</tr>
<tr>
<td>Plasmati (2002) Prospective cohort Multiple myeloma</td>
<td>Grade I (12/24) Grade II (6/24) Subclinical (6/24)</td>
<td></td>
<td></td>
<td>NCI-CTC</td>
</tr>
<tr>
<td>Bortezomib: 46.7% (95% CI = 0.3–93.1)</td>
<td>Dimopoulos (2011) RCT Multiple myeloma</td>
<td>Grade I NR Grade II (64/159) Grade III (45/159) Grade IV (1/159)</td>
<td>Unclear if at baseline Every 3 wk until 1 mo after last chemo dose Longer follow-up but no denominator data</td>
<td>NCI-CTC</td>
</tr>
<tr>
<td>Bortezomib and thalidomide: 96.2% (95% CI = 49.7–143)</td>
<td>Chaudhary (2008) Prospective cohort Multiple myeloma</td>
<td>Grade ≥2 reported</td>
<td>Baseline Cycles 2, 4, 6, 8 End of chemo Note skin biopsy at baseline and end of chemo only</td>
<td>TNSc, NPS Skin biopsy</td>
</tr>
</tbody>
</table>

Abbreviations: Chemo, chemotherapy; CIPN, chemotherapy-induced peripheral neuropathy; EORTC, European Organization for Research and Treatment of Cancer; CI, confidence interval; NCT-CTC, National Cancer Institute Common Toxicity Criteria; NES, neurological examination; NPS, neuropathological examination (quantitative sensory testing and/or nerve conduction studies); NR, not reported; PNS, Modified peripheral neuropathy score; RCT, randomized controlled trial; TNSc, total neuropathy score.

* Abstract only available.

+ Authors report both acute and chronic CIPN grade counts, only acute given here.

* Raw data obtained from author or reported in paper, allowing counts reported in single study to be split by chemotherapy type.
4.4. Strengths of this review

Our meta-analysis quantifies CIPN prevalence across most chemotherapy and cancer types. This allows our prevalence measures to be used by clinicians when deciding between chemotherapy types and regimens. It is also useful for planning future CIPN treatment studies. In addition, these findings may be useful for both resource allocation and research planning. Our pooled prevalence also allows direct estimation of economic costs of CIPN resulting from the chemotherapeutics and cancer types included in our review [51].

In this first meta-analysis investigating epidemiological measures of CIPN, we highlight the effect of the time of assessment, after chemotherapy cessation, on CIPN prevalence. This has implications for surveillance of CIPN at follow up, clinical care planning, and patient expectations. Specifically, our results may contribute to explaining the risks of developing CIPN, and its likely natural history, to patients at consent for chemotherapy. In broad terms, around two-thirds of patients will suffer from CIPN in the first month after chemotherapy, but in only one-half of these will CIPN have resolved by six months. Finally, we have confirmed the urgent need for a standardized approach to the diagnosis of CIPN, reiterating ongoing efforts such as those of the chemotherapy-induced peripheral neuropathy outcome measures standardization study (CI-PERINOMS) group [67].

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2014.09.020.

Acknowledgements

The authors thank Marshall Dozier, Librarian, University of Edinburgh, for her help explaining techniques regarding systematic review search strategies. M.S. is funded by the Wellcome Trust, through the Scottish Translational Medicine and Therapeutics Initiative (STMTI). G.C. is funded by the National Centre for the Replacement, Exmination and Reduction of Animals in Research (NC3Rs). E.S. is supported by the Seventh Framework Programme (STMTI). G.C. is funded by the National Centre for the Replacement, Exmination and Reduction of Animals in Research (NC3Rs). M.M.L. is funded by the Seventh Framework Programme and the NC3Rs. S.R. is supported by the Melville Trust. R.G. is a NHS consultant and honorary lecturer at the University of Edinburgh. L.C. is a reader at the University of Edinburgh and honorary NHS consultant. M.F. holds the St Columba’s Hospice Chair of Palliative Medicine at the University of Edinburgh. Funders were not involved in any part of the design, execution, or interpretation of this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

References


Table 4

CIPN risk factors.

<table>
<thead>
<tr>
<th>Study</th>
<th>Category of risk factor reported</th>
<th>Data source of study</th>
<th>Sample size of study (N)</th>
<th>Risk factor details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argyriou (2013)</td>
<td>Genetic</td>
<td>Prospective cohort</td>
<td>210</td>
<td>SNC4A-rs2302237 OR = 2.65 (1.15–6) SCN10A-rs1263292 OR = 0.39 (0.17–0.88)</td>
</tr>
<tr>
<td>Attal (2009)</td>
<td>Clinical</td>
<td>Prospective cohort</td>
<td>18</td>
<td>Cold allodynia OR = 3.9 (1.8–81) Cold hyperalgesia OR = 3.9 (1.0–1.20)</td>
</tr>
<tr>
<td>Baldwin (2012)</td>
<td>Genetic</td>
<td>Prospective cohort</td>
<td>855</td>
<td>FGD4-rs10771973 OR = 1.57 (1.30–1.91)</td>
</tr>
<tr>
<td>Dimopoulos (2011)</td>
<td>Clinical</td>
<td>RCT</td>
<td>340</td>
<td>Baseline neuropathy HR = 1.79 (p &lt; 0.01)</td>
</tr>
<tr>
<td>Glendenning (2010)</td>
<td>Clinical and treatment-related</td>
<td>Cross-sectional cohort</td>
<td>293</td>
<td>Cisplatin dose increase OR = 1.91 (1.61–2.26) Carboplatin dose increase OR = 1.26 (1.04–1.52) Age at follow-up OR = 1.06 (1.04–1.08)</td>
</tr>
<tr>
<td>Johnson (2011)</td>
<td>Genetic</td>
<td>RCT</td>
<td>970 + 550</td>
<td>ABCA1-rs363717 OR = 0.71 (0.52–0.98) ICAM1-rs1799689 OR = 0.67 (0.44–1.03) PPARD-rs2076169 OR = 0.60 (0.38–0.95) SERPINB2-rs6163 OR = 0.70 (0.52–0.95) SLC12A6-rs7164902 OR = 0.60 (0.44–0.80)</td>
</tr>
<tr>
<td>Kawakami (2012)</td>
<td>Clinical</td>
<td>Prospective cohort</td>
<td>50</td>
<td>Smoking history pack-years HR = 1.03 (1.0–1.05) Decreased creatinine clearance HR = 0.96 (0.92–0.99)</td>
</tr>
<tr>
<td>Won (2012)</td>
<td>Genetic</td>
<td>Prospective cohort</td>
<td>96</td>
<td>TAC1-rs10486003 FOX1-rs2338 ITGA1-rs830884 ACYP2-rs843748 DLEU7-rs797519</td>
</tr>
</tbody>
</table>

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; HR, hazard ratio (95% confidence interval or significance level); OR, odds ratio (95% confidence interval); RCT, randomized controlled trial; SNP, single nucleotide polymorphism.

Note that Jonson et al. reported ORs for both populations included in their analysis. Only 1 set of ORs is reported here. All effect sizes reported here are directly from the cited studies.

* SNP association with CIPN grade ≥ 2 only.
† Won et al. reported the overall predictive accuracy of the multiple logistic regression model yielding the 5 positive single nucleotide polymorphisms (SNPs), 72.8% (65.8–79.9), as opposed to ORs for individual SNPs.

are unable to quantify prevalence of painful CIPN explicitly in our analysis.

Conflict of interest statement

Marta Seretny, Gillian Currie, Emily Sena, Malcolm MacLeod, Robin Grant, and Marie Fallon declare no conflicts of interest. Lesley Colvin serves as an editor for the British Journal of Anaesthesia.


