Incidence, Prevalence and Predictors of Chemotherapy Induced Peripheral Neuropathy

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Comprehensive review

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

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ABSTRACT

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.

1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a disabling side effect of several commonly used antineoplastic agents. The development of CIPN may require chemotherapy dose reduction or cessation, which can increase cancer-related morbidity and mortality [17,31]. CIPN is a predominantly sensory neuropathy that may be accompanied by motor and autonomic changes [62]. Similar to other neuropathic pain conditions, pain in CIPN can be stimulus dependent or independent [66]. The pathophysiology of CIPN is poorly understood, and treatments to prevent CIPN are inadequate. Meta-analyses of clinical trials for CIPN prevention report inconclusive results [1,49]. Treatment options for established CIPN are also limited. Clinical trials of antiepileptic or antidepressant agents to treat other neuropathic pain conditions have generally been negative [30,41,54,55]. Only 1 recent, double-blind, randomized controlled trial showed improvement in CIPN symptoms after 5 weeks of treatment with duloxetine [57].

Understanding of the epidemiology of CIPN is also limited [37]. Previous studies have largely focussed on individual chemotherapeutic agents, with reported CIPN incidence rates ranging from 19% to more than 85% [23]. Annually 165,544 patients survive cancer in the United Kingdom, and more than 1 million in the United States [12,44]. It is therefore important to provide a more precise measure of the prevalence of CIPN to allow

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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 Neuropathic 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 interests. 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 (eg, 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 [2,61]. 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) [4–9,13,14,18,21,24–27,32–36,38,39,45–48,52,53,60,63–65] 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

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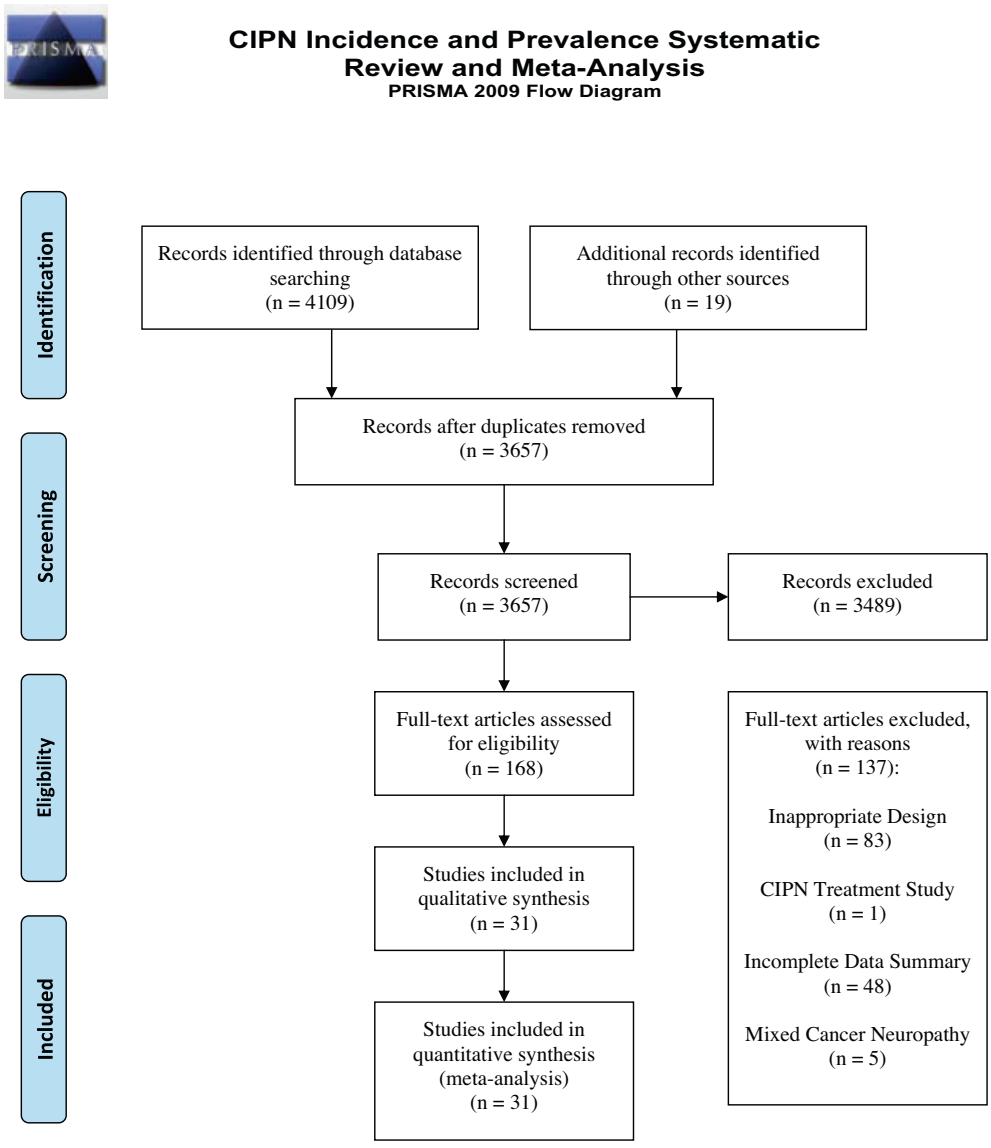

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram.

cohort study also sought to validate genetic risk factor results in a control group. Nine of 10 RCTs (90%) described a sample size calculation. Of all included studies, 22 (71%) reported study participant dropout, giving reasons. In all, 14 of 31 study authors (45%) disclosed funders and/or whether they had a conflict of interest. Adherence of studies to reporting guidelines is summarized in Table 1. Of 31 studies, 26 (83.9%) used an assessment tool validated for CIPN. All studies reporting CIPN risk factors described methods used to identify these predictors.

3.3. CIPN incidence and prevalence

Q5 Of 4179 patients, 1960 developed CIPN (aggregate prevalence 48%). CIPN prevalence was 68.1% (57.7–78.4) within the first month of the end of chemotherapy, 60.0% (36.4–81.6) at 3 months, and 30.0% (6.4–53.5) at 6 months or later (Table 2). There was considerable heterogeneity in the estimates from different studies ($I^2 = 98.2$, $P < .001$). The time of assessment accounted for 36% of the observed heterogeneity (adjusted $R^2 = 0.365$, $P < .001$). An overview of the individual incidence reported in included studies is shown in Table 1. We did not include the cumulative dose (CD) of chemotherapy (actual dose received) in our meta-regression because standard and maximally tolerated doses would differ substantially from drug to drug (study-specific CD shown in Table 1). As expected, there was co-linearity between the cancer type and the chemotherapy used; because we reasoned that it is more likely that CIPN prevalence would be related to drug than to cancer type, we considered only chemotherapy type in our regression model (Table 3). The type of chemotherapy used accounted for 32% of the observed heterogeneity in our sample (adjusted $R^2 = 0.315$, $P < .04$).

Methods used to assess the presence or grade of CIPN were too diverse to include in the meta-regression. Of the 31 included studies, 8 defined CIPN according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), 1 study used the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire 30 (QLQ – 30) combined with neurological examination, 1 used in-depth neurophysiological examination (NPS), 1 used a standard neurological examination, and 1 used the Total Neuropathy Score (TNSc). The remaining 18 studies used a combination of 2 or more of the above, and 1 study used skin biopsy (Table 3). To investigate any impact of neurophysiological

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Table 1
Overview of included studies.

First author (year)	Study type and quality (CONSORT/STROBE score)	Incidence (95% CI)	Main cancer class (chemotherapy)	Dose (mg/m^2) (mean or cumulative)
Antonacopoulou (2009)*	Prospective cohort	58.8% (42.2–75.3)	Colorectal (oxaliplatin)	–
Argyriou (2006)	Prospective cohort (18/22)	61.5% (35.1–87.9)	Breast (paclitaxel)	1980
		42.8% (16.9–68.7)	Lung (cisplatin)	720
Argyriou (2007) [8]	Prospective cohort (19/22)	64% (45.2–82.8)	Colorectal (oxaliplatin)	1740
Argyriou (2007)	Prospective cohort (19/22)	69.2% (44.1–94.3)	Multiple solid (cisplatin and paclitaxel)	126·7
Argyriou (2012)	Prospective cohort (19/22)	83.3% (77.3–89.3)	Colorectal (oxaliplatin)	1646
Argyriou (2013)	Prospective cohort (20/22)	84.5% (79.4–89.5)	Colorectal (oxaliplatin)	1651
Attal (2009)	Prospective cohort (19/22)	66.6% (44.8–88.4)	Colorectal (oxaliplatin)	1278
Baldwin (2012)	Prospective cohort (20/22)	67.2% (64.1–70.3)	Breast (paclitaxel)	–
Cascinu (1995)	RCT (18/25)	64% (45.2–82.8)	Gastrointestinal (cisplatin)	–
Cascinu (2002)	RCT (16/25)	78.9% (60.6–97.3)	Colorectal (oxaliplatin)	783
Chaudhary (2008)†	Prospective cohort (13/22)	96.2% (89.2–103)	Multiple myeloma (bortezomib and thalidomide)	36
Dimopoulos (2011)	RCT (21/25)	46.7% (41.4–52.1)	Multiple myeloma (bortezomib)	38·4
Gandara (1995)‡	RCT (18/25)	12.1% (5.6–18·5)	Ovarian and lung (cisplatin)	379
Ghoreishi (2012)	RCT (19/25)	59.2% (40.7–77.8)	Breast (paclitaxel)	–
Glendenning (2010)†	Cross sectional cohort (21/22)	20.1% (15.5–24.7)	Testicular (cisplatin and vincristine)	400
Gobran (2013)	RCT (13/25)	70% (53.6–86.4)	Colorectal (oxaliplatin)	763
Ishibashi (2010)	RCT (20/25)	93.7% (81.9–105)	Colorectal (oxaliplatin)	72·8
Johnson (2011)	RCT (23/25)	32.1% (29.1–34.9)	Multiple myeloma (thalidomide)	–
		19.6% (16.3–22.9)	(Vincristine)	–
Kawakami (2012)†	Prospective cohort (14/22)	76% (64.1–87.8)	Lung (cisplatin and paclitaxel)	–
Kemp (1996)	RCT (19/25)	67·5% (59.2–75.8)	Gynecological (cisplatin)	–
Krishnan (2005)	Prospective cohort (16/22)	50% (25.5–74.5)	Colorectal (oxaliplatin)	1200
Lin (2006)	Randomised trial (15/24)	90% (71.4–108)	Colorectal (oxaliplatin)	1200
Milla (2009)	Randomised trial (11/24)	92.8% (79.3–106)	Colorectal (oxaliplatin)	772
Pace (2003)	Randomised trial (11/24)	85.7% (67.4–104)	Multiple solid (cisplatin)	420
Pace (2007)	Prospective cohort (14/22)	92.8% (79.4–106)	Breast (paclitaxel)	1744
Pace (2010)	RCT (19/25)	41.6% (21.9–61.4)	Multiple solid (cisplatin)	450
Planting (1999)	Randomised trial (13/24)	13.5% (2.5–24.5)	Multiple solid (cisplatin)	401
Plasmati (2002)	Prospective cohort (15/22)	96% (88.3–103)	Multiple myeloma (thalidomide)	18
Van der Hoop (1999)	RCT (12/25)	41.6% (13.7–69.5)	Gynecological (cisplatin)	416
Von Schlippe (2001)	Prospective cohort (9/22)	17.2% (3.4–30.9)	Testicular (cisplatin)	–
Won (2012)	Prospective cohort (16/22)	40.6% (30.8–50.4)	Colorectal (oxaliplatin)	935

Abbreviation: RCT, randomized controlled trial (note that randomised trials, as opposed to RCTs, did not have blinding or placebo).
– Cumulative or average dose not reported. Reported cumulative dose refers to actual dose received.
* Abstract only available; STROBE assessment not possible. Where upper 95% confidence intervals exceeded 100, only 100% were recorded, as this is clinically interpretable.
† Study pooled incidence across chemotherapy types included.
‡ Study pooled incidence across cancer types.

assessment on the reported prevalence of CIPN, we conducted a post hoc sensitivity analysis. In all, 17 studies (449 patients) used NPS to assess for CIPN; 16 of these used NPS in combination with another assessment method. In these 17 studies, CIPN prevalence was higher; 73.3% (58.6–87.3) within 1 month of chemotherapy cessation, 70.1% (41.8–98.4) at 3 months, and 39.9% (3.9–76.0) at 6 months or more.

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

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Table 2
Comparison of prevalence related to time of CIPN assessment.

Time of assessment (after cessation of chemotherapy)	Prevalence (95% CI)	Studies included	Total no. of patients in group
⩽1 mo	68.1% (57.7–78.4)	Antonacopolou 2009 Argyriou 2007 Argyriou 2012 Argyriou 2013 Baldwin 2012 Cascinu 1995 Cascinu 2002 Chaudhry 2008 Dimopoulos 2011* Gandara 1995 Ghoreishi 2012 Gobran 2013* Ishibashi 2010 Kawakami 2012 Krishnan 2005* Lin 2006 Milla 2009* Pace 2003 Pace 2007* Pace 2010 Van Der Hoop 1999 Won 2012	2085
3 mo	60.0% (36.4–81.6)†	Argyriou 2006 Argyriou 2007 Kemp 1996 Planting 1999 Plasmati 2007	234
⩾6 mo	30.0% (6.4–53.5)†	Johnson 2011‡ Attal 2009 Glendenning 2010 Von Schlippe 2001	1860

Abbreviations: CI, confidence interval; CIPN, chemotherapy-induced peripheral neuropathy.
* Studies included longer-term CIPN follow up but did not provide enough details at these later time points to allow use of data in the meta-regression.
† Wide confidence interval likely due to small number of studies assessing CIPN beyond this time point.
‡ Study considered CIPN only after induction therapy and not during maintenance.

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

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Table 3
Studies stratified by drug type.

	Study type (CONSORT/STROBE)	Main cancer class	CIPN severity report (count by grade if given)	CIPN assessment time points	CIPN assessment method(s)
Oxaliplatin: 72.3% (95% CI = 59.7–86.8)					
Antonacopoulou (2009)*	Prospective cohort	Colorectal	NR	Unclear	TNSc
Argyriou (2007) [8]	Prospective cohort	Colorectal	Grade I (6/16) Grade II (8/16) Grade III (2/16)	Baseline Cycles 4, 8, 12	TNSc NPS NCI-CTC
Argyriou (2012)	Prospective cohort	Colorectal	Grade I (38/125) Grade II (46/125) Grade III (41/125)	Baseline Cycles 3, 6 (FOLFOX) Cycles 4, 8 (XELOX)	TNSc NPS NCI-CTC
Argyriou (2013)†	Prospective cohort	Colorectal	Grade I (62/169) Grade II (46/169) Grade III (61/169)	Baseline Cycle 6, 12 (FOLFOX) Cycles 4, 8 (XELOX)	TNSc NCI-CTC
Attal (2009)	Prospective cohort	Colorectal	Sensory symptom counts described as means/individual	Baseline Cycle 3, 6, 9 12 ± 2 mo after chemo end	NCI-CTC NPS (EORTC) QLQ-C30
Cascinu (2002)	RCT	Colorectal	Grade I (4/15) Grade II (6/15) Grade III (4/15) Grade IV (1/15)	Baseline Cycles 4, 8, 12 Within 2 wk of chemo end	NCI-CTC NPS
Gobran (2013)	RCT	Colorectal	Grade I (7/21) Grade II (0/21) Grade III (14/21) Grade IV (0/21)	Unclear if at baseline At each chemo cycle until end of chemo (variable no. of cycles) Longer follow-up for those with CIPN (but denominator unclear)	NCI-CTC
Ishibashi (2010)	RCT	Colorectal	Grade I (15/15) Grade II (1/15) Grade III (0/15) Grade IV (0/15)	Baseline At each chemo cycle until end of chemo	NCI-CTC
Krishnan (2005)	Prospective cohort	Colorectal	NR	No baseline Within 1 mo of chemo end only reported assessment	NCI-CTC NPS TNSc
Lin (2006)	Controlled trial	Colorectal	Grade I (1/9) Grade II (5/9) Grade III (3/9) Grade IV (0/9)	Baseline Cycles 4, 8, 12 Within 2 wk of end of chemo	NCI-CTC NPS
Milla (2009)	Controlled trial	Colorectal	Grade I (0/13) Grade II (9/13) Grade III (4/13)	Baseline Cycles 5, 9, 12 (Some followed up longer but denominator unclear)	NCI-CTC NES
Won (2012)	Prospective cohort	Colorectal	NR	Unclear if at baseline At each chemo cycle until end of chemo (variable no. of cycles)	NCI-CTC NES
Cisplatin: 42.2% (95% CI = 21.3–63.1)					
Argyriou (2006)†	Prospective cohort	Lung	Reported by age group only	Baseline Cycles 3, 6 3 mo after chemo end	PNS NPS
Cascinu (1995)	RCT	Gastrointestinal	Grade I (3/16) Grade II (10/16) Grade III (2/16) Grade IV (1/16)	Baseline After 9 and 15 wk of therapy Within 1 wk after end of chemo	NCI-CTC NPS
Gandara (1995)	RCT	Ovarian and lung	Only grade ⩾3 reported	Unclear if at baseline At each cycle until chemo end (variable no. of cycles) Study stopped early after interim analysis due to high toxicity in intervention group	NCI-CTC
Kemp (1996)	RCT	Gynecological	Grade I (31/81) Grade II (35/81) Grade III (15/81)	Baseline Cycles 4, 5, 6 Monthly after chemo for 3 mo	NCI-CTC NES
Pace (2003)	Controlled trial	Multiple solid	Grade I (6/12) Grade II (4/12) Grade III & IV (2/12)	Baseline After 6 cycles	TNSc NES
Pace (2010)	RCT	Multiple solid	Only grade ⩾3 reported	Baseline Every cycle for 3 cycles 1 mo after chemo end	TNSc NPS
Planting (1999)	Controlled trial	Multiple solid	Grade I (5/5)	Baseline Cycle 3, 6 3 mo after chemo end (Longer follow-up but no denominator info)	NCI-CTC NES
Van der Hoop (1999)	Controlled trial	Gynecological	Mean vibration threshold	Baseline Cycles 2, 4, 6 End of chemo	NES

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Table 3 (*continued*)

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

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, neurophysiological 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.

§

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 4
CIPN risk factors.

Study	Category of risk factor reported	Data source of study	Sample size of study (N)	Risk factor details
Argyriou (2013)	Genetic	Prospective cohort	200	SNC4A-rs2302237 OR = 2.65 (1.15–6) SCN10A-rs1263292 OR = 0.39 (0.17–0.88)
Attal (2009)	Clinical	Prospective cohort	18	Cold allodynia OR = 39 (1.8–817) Cold hyperalgesia OR = 3.9 (1.0–1.20)
Baldwin (2012)	Genetic	Prospective cohort	855	FGD4-rs10771973 HR = 1.57 (1.30–1.91)
Dimopoulos (2011)	Clinical	RCT	340	Baseline neuropathy HR = 1.79 ($p < 0.01$)
Glendenning (2010)	Clinical and treatment-related	Cross-sectional cohort	293	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)
Johnson (2011)*	Genetic	RCT	970 + 550	ABCA1-rs363717 OR = 0.71 (0.52–0.98) ICAM1-rs1799969 OR = 0.67 (0.44–1.03) PPARD-rs2076169 OR = 0.60 (0.38–095) SERPINB2-rs6103 OR = 0.70 (0.52–0.95) SLC12A6-rs7164902 OR = 0.60 (0.44–0.80)
Kawakami (2012)	Clinical	Prospective cohort	50	Smoking history pack-years HR = 1.03 (1.0–1.05) Decreased creatinine clearance HR = 0.96 (0.92–0.99)
Won (2012)†	Genetic	Prospective cohort	96	TAC1-rs10486003 FOXC1-rs2338 ITGA1-rs830884 ACYP2-rs843748 DLEU7-rs797519

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 $\geqslant 2$ 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 out analysis.

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, reaffirming ongoing efforts such as those of the chemotherapy-induced peripheral neuropathy outcome measures standardization study (CI-PERINOMS) group [67].

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.

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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.

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