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Incidence and disease burden of chemotherapy-induced peripheral neuropathy in a population-based cohort

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Abstract

OBJECTIVE—To assess disease burden of chemotherapy-induced peripheral neuropathy (CIPN), which is a common dose-limiting side-effect of neurotoxic chemotherapy. Late effects of CIPN may increase with improved cancer survival.

METHODS—Olmsted County, Minnesota residents receiving neurotoxic chemotherapy were identified and CIPN was ascertained via text searches of polyneuropathy symptoms in the medical record. Clinical records were queried to collect data on baseline characteristics, risk factors, signs and symptoms of CIPN, medications, impairments, and ICD-9 diagnostic codes for all subjects.

RESULTS—A total of 509 individuals with incident exposure to an inclusive list of neurotoxic chemotherapy agents between 2006 and 2008 were identified. 268 (52.7%) of these individuals were determined to have CIPN. The median time from incident exposure to first documented symptoms was 71 days. Patients with CIPN received a neuropathy ICD-9 diagnosis in only 37 instances (13.8%). Pain symptoms and use of pain medications were observed more often in patients with CIPN. 5-year survival was greater in those with CIPN (55.2%) versus those without (36.1%). Those with CIPN surviving greater than 5 years (n=145) continued to have substantial impairments and were more likely to be prescribed opioids than those without CIPN (OR 2.0, 1.06–3.69).

CONCLUSIONS—Results from our population-based study are consistent with previous reports of high incidence of CIPN in the first two years following incident exposure to neurotoxic chemotherapeutic agents, and its association with significant pain symptomatology and accompanied long-term opioid use. Increased survival following exposure to neurotoxic chemotherapy and its long-term disease burden necessitates further study of among survivors.

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common complications of chemotherapy¹. The acute symptoms of CIPN often results in cessation of chemotherapy, which may impact overall cancer survival. Several classes of

chemotherapeutic agents are neurotoxic, in particular the platinum-based compounds, taxanes, vinca alkaloids, thalidomide-derivatives, and proteasome inhibitors. While these different medications cause CIPN via different pathomechanisms, most result in a sensory-predominant syndrome, often with significant pain. Notably, newer classes of chemotherapeutics (including molecular targeted chemotherapeutics such as ado-trastumab emtasine, brentuximab vedotin and the various check point inhibitors) continue to be associated with CIPN.

With increasing cancer survivorship, the long term disease burden of CIPN is gaining more attention. The National Cancer Institute estimated a 23% decrease in cancer mortality between 1990 and 2012 and an estimated 19 million cancer survivors that will be living in the United States by 2024. Long-term studies on cancer survivors have revealed significant difficulties with activities of daily living and impaired physical and psychological health²⁻⁵. Improved quality of life in cancer survivors is therefore an important consideration as these demographic shifts occur.

Approaches to studying the impact of CIPN have largely focused on single chemotherapeutic agents at tertiary centers; population approaches are lacking. We now report a retrospective population-based study designed to evaluate the prevalence and long term disease burden of CIPN among cancer patients in Olmsted County, Minnesota. Patients exposed to neurotoxic chemotherapy were categorized as developing CIPN (CIPN (+)) or not (CIPN (-)) and compared for baseline risk factors, survival, and long-term impairment.

METHODS

Standard protocol approvals, registrations, and patient consents were obtained. The institutional review boards of both Mayo Clinic and Olmsted Medical Center approved this study.

Patients with incident exposure to chemotherapy agents living in Olmsted County, Minnesota were identified within the study period (2006–2008). The date of the first administered dose and the neurotoxic properties of each of the agents were determined in order to identify those patients exposed to at least one of 28 chemotherapeutic agents associated with the development of peripheral neuropathy as determined by review of a drug reference manual (Micromedex) (Supplemental Table 1). Patients who received a chemotherapy agent not listed on Supplementary Table 1 were not analyzed further.

Ordinal likelihood of distal symmetric polyneuropathy among those exposed to neurotoxic chemotherapy was established using 2005 American Academy of Neurology (AAN) criteria for clinical research⁶. The AAN criteria incorporate data on neuropathic symptoms, ankle reflexes, distal sensation, distal weakness/atrophy, and nerve conduction studies, which allows the scoring of polyneuropathy likelihood from “+” (neuropathic symptoms with decreased distal sensation) to “++++” (abnormal nerve conduction studies with a combination of neuropathic signs and symptoms) (Supplemental Table 2)⁶. In our study, we were able to electronically search for specific words corresponding to these neuropathy attributes within any Mayo Clinic clinical note created between the first day of

chemotherapy and 12/31/2015 (Supplemental Table 3). Clinical notes that were identified by the electronic search were subsequently manually verified and used to score likelihood of polyneuropathy. Evidence of polyneuropathy was additionally obtained from nerve conduction study and electromyography (EMG) reports, when available. CIPN (+) subjects were defined as patients that received neurotoxic chemotherapy and subsequently developed neuropathic signs and/or symptoms of distal symmetric polyneuropathy using AAN criteria (scored as at least +: neuropathic symptoms with decreased distal sensation observed in at least one note in the clinical record). CIPN (–) subjects were defined as having received neurotoxic chemotherapy, but exhibited no reported subsequent neuropathic signs or symptoms.

The Rochester Epidemiology Project (REP) database is an NIH-funded resource that comprehensively links all the medical records of 95% of residents in Olmsted County, MN.⁷ The REP was queried for incident dates of the following ICD-9-CM diagnoses in order to compare baseline characteristics and risk factors among CIPN (+) and CIPN (–) subjects: tobacco use, alcoholism, pulmonary disease, diabetes mellitus, peripheral vascular disease, renal disease, hyperlipidemia, hypercholesterolemia, hypertension, multiple myeloma, obesity, neuropathy, age, gender, height and weight values taken closest to incident chemotherapy date. CIPN (+) and CIPN (–) subjects were also compared for the presence of surrogate markers of impairment that were reported after chemotherapy exposure, such as medication use and self-reported impairment reported on standardized questionnaires (completed during clinical visits), which included activities of daily living (ADL), limb weakness, numbness, fall tendency, pain, stair climbing difficulty, use of a gait aid, work disability, and living arrangements. Five year survival was obtained via the REP for analysis of the impact of CIPN on survival and late effects. Surrogate markers of impairment and medications that were documented 4.5–6 years after neurotoxic chemotherapy exposure were quantified for those living > 5 years and compared between CIPN (+) and CIPN (–) subjects.

All analyses were performed with JMP Pro 9.0.3 software (SAS Institute, Cary, NC). Multivariate logistic regression models were used to calculate odds ratio (OR) and 95% confidence intervals between CIPN and surrogate markers of impairment.

RESULTS

Of the 809 patients receiving chemotherapy between 2006 and 2008, 509 individuals had incident exposure to at least one of 28 putative neurotoxic chemotherapy agents. Electronic text string searches followed by manual chart review were performed using AAN criteria for identifying distal symmetric polyneuropathy. 268 (52.7%) cases were determined to have CIPN (CIPN (+) subjects), while 241 (47.3%) did not (designated as CIPN (–) subjects). Nerve conduction studies or EMG reports were available for 34 CIPN (+) subjects, and when abnormal (15/34) predicted axonal pathology. Subjects were evaluated by a neurologist in a minority of instances (114 CIPN (+) subjects and 72 CIPN (–) subjects). Within CIPN (+) subjects, ordinal likelihood of polyneuropathy (from + to +++) based on AAN criteria was (+) in 220 patients (82.1%), (++) in 36 (13.4%), (+++) in three (1.1%), and (+++++) in nine (3.4%) (Figure 1). CIPN was common in the major categories of

neurotoxic chemotherapeutic agents, with >50% of patients developing CIPN when exposed to taxanes (60%), vinca alkaloids (56%), platinum compounds (54%), proteasome inhibitors (89%), or thalidomide-derivatives (71%) (Table 1). Exposure to multiple agents was common, with many subjects receiving either two (28.4%), three (7.8%), or more (2.2%) neurotoxic chemotherapeutics. The neurotoxic chemotherapy list was designed to enhance sensitivity, and some agents included are very rarely associated with neuropathy. Reflecting this, merely 8 CIPN (+) cases (6 with gemcitabine and 2 with cytarabine) were identified that were only exposed to these chemotherapeutics rarely associated with CIPN (Supplementary Table 1). The ability of diagnostic coding to determine CIPN was assessed and of the 268 CIPN (+) subjects, based on the criteria stipulated above, only 37 (13.8%) had an ICD-9-CM diagnosis of polyneuropathy (Supplemental Table 4).

Timing from incident neurotoxic chemotherapy exposure to CIPN symptom onset was assessed (Figure 2). Twenty four CIPN (+) subjects (8.9%) had a prior recorded history of peripheral neuropathy (identified via either electronic term searches or ICD-9-CM coding), which were excluded from this analysis. Of these, eight had a previous diagnosis of diabetic neuropathy, three had preexisting polyneuropathy as a result of previous chemotherapy, and 13 had diagnoses of polyneuropathy without identified cause. Notably, these 13 individuals with unidentified cause of PN appeared to have a higher overall likelihood of CIPN per AAN criteria, with (+) in eight patients (61.5%), (++) in three (23.1%), (+++) in one (7.7%) and (+++++) in one (7.7%). Among the remaining 244 CIPN (+) subjects, the median interval from incident chemotherapy exposure to symptom onset was 71 days (IQR 28.5–122). Approximately 81% (n=197) of CIPN (+) subjects had documented symptom onset within six months of incident chemotherapy exposure, with 88% (n=214) having reported symptoms within one year of initiation of treatment.

CIPN risk factors and its impact on daily life were assessed. No statistically significant differences were observed in baseline putative risk factors between CIPN (+) and CIPN (–) subjects (Table 2). Patient-provided data on impairments of daily living was available for CIPN (+) and CIPN (–) subjects (Table 3); additionally, complete medication lists for all patients were available for all subjects (Table 4). CIPN (+) subjects were significantly more likely to report difficulty with numbness and shooting pains (OR 4.56, 95% CI 2.76–7.54), general pain (OR 1.55, 95% CI 1.06–2.26) than those without CIPN. Self-reported impairments related to weakness (climbing stairs, walking, weakness) were not different between CIPN (+) and CIPN (–) subjects, supporting the notion that most CIPN impairments are sensory-predominant. CIPN (+) subjects were also more likely to be prescribed serotonin/norepinephrine reuptake inhibitors (OR 2.87, 95% CI 1.45–5.66) or alpha-2-delta receptor antagonists (OR 1.83, 95% CI 1.16–2.90) for the management of pain. Opioids were the most commonly utilized analgesics during the study period, used at similar high rates among CIPN (+) (95%) and CIPN (–) (92%) subjects, although it was not determined whether this was short term or chronic opioid therapy (< 90 day).

Survival times and late effects on impairment in activities of daily living were compared between all CIPN (+) and CIPN (–) subjects. Kaplan Meier survival plots were analyzed to compare survival time for CIPN (+) and CIPN (–) subjects. Five-year survival for those with CIPN (54.1%) was greater than those without CIPN (37.3%) ($p<0.0001$) (Figure 3). One

hundred forty five CIPN (+) subjects and 90 CIPN (–) subjects had five year survival from the date of incident exposure to chemotherapy. We compared the CIPN (+) and CIPN (–) subjects for differences in quality of life based on self-reported ability to perform activities of daily living, and while there were trends of increased impairments in CIPN (+) subjects, no attributes reached statistical significance (Supplementary Table 5). CIPN (+) subjects surviving at least 5 years following incident chemotherapy were significantly more likely to be prescribed opioid analgesics (OR 2.0, 95% CI 1.06–3.69) or SNRIs (OR 4.7, 95% CI 1.04–21.2) (Table 5).

DISCUSSION

Overall, our study supports the assertion that CIPN is a large problem that impacts both the acute and chronic timeframes. We report the development of CIPN in over half of patients receiving neurotoxic chemotherapy in a longitudinal population-based cohort, which is consistent with other epidemiological studies⁸. Overall, this number represents approximately 1/3 of all patients treated with chemotherapy for cancer (including neurotoxic and non-neurotoxic regimens). Most patients reported neuropathic symptoms within 6 months of chemotherapy initiation and it presented with predominantly sensory symptoms, including pain. While cancer itself is often associated with pain (as evidenced by the high opioid use in control patients), subjects with CIPN reported more difficulty with their pain, and were more likely to be prescribed non-opioid based pain therapies. Furthermore, 5-year follow-up in this cohort revealed that this group of 5-year CIPN survivors was more likely to be prescribed opioid and SNRI medications, which suggests long-term pain in CIPN survivors.

Unique to this study is the population-based approach that included all neurotoxic chemotherapeutic agents and cancer subtypes. Given that medical records were available to be searched, from the only medical providers in Olmsted County, we had access to all of the medications that patients likely received during the follow-up period.

The observation of a 5-year survival benefit in patients with CIPN is intriguing. While it is theoretically possible that developing CIPN may correlate with a chemotherapeutic agent's overall potency for killing cancer, there are other more likely explanations for this finding. Since CIPN is usually a dose-related phenomenon, patients who had relatively rapid disease progression after starting neurotoxic chemotherapy would have had lower total doses of the neurotoxic chemotherapy and shorter survivals. Correspondingly, patients who responded well to the neurotoxic chemotherapy would have received higher cumulative doses and have more trouble with CIPN; these patients also would have live longer than patients who had rapid disease progression and lower doses of neurotoxic chemotherapy. A similar phenomenon was recently reported⁹. Alternatively, in patients with aggressive cancers (and poor survival), there may be less self-reporting of neuropathic symptoms and/or that their care providers are less likely to document them. It is difficult to answer this question within our study as few patients received detailed neurological examinations during the study period. This possible underreporting of early CIPN due to cancer severity and opioid use would also lead to an underestimate of the CIPN incidence in this study.

The current study did not identify statistically significant risk factors for CIPN that have been reported previously, namely diabetes mellitus¹⁰ and age¹¹. This may be because these risk factors have not been clarified with all neurotoxic chemotherapy agents. For example, the data regarding obesity/diabetes mellitus and oxaliplatin neuropathy are conflicting^{12–16}, regardless of fairly uniform findings of increased CIPN risk in obese/diabetic patients receiving paclitaxel^{17, 18}. Furthermore, an underestimation of CIPN incidence due to incomplete reporting may have also decreased our power to detect these risk factors.

We also observed increased opioid and SNRI prescriptions in the cohort of patients with CIPN that survived 5 years, which likely represents increase challenges with pain related to this phenomenon. We have previously reported substantial opioid use for polyneuropathy of all causes within the Olmsted County cohort^{19, 20}. The inability to identify significant differences in self-reported impairments in this smaller 5-year survivor cohort may be due to being underpowered at this later time-point, and a larger cohort study may be required to answer this definitively. Such trends among those surviving longer following neurotoxic chemotherapy exposure indicates significant long term impairment and disease burden continuing as long as 5 years after treatment initiation.

Additionally, this study highlights the challenges of performing large retrospective population-based studies in patients with cancer. We aggressively pursued CIPN diagnoses via string searches of clinical notes within the electronic health records, which were then manually verified. With this approach, we identified over ½ of patients developed CIPN. If this had been a prospective study with clinician assessment of neuropathy, the incidence would likely be higher. Conversely, if we had focused on ICD9-CM coding for our assignment of CIPN, we would have severely underestimated the frequency of CIPN in our cohort at ~14%. We also discovered discrepancies between the ICD9-CM coding and the clinical notes (34 CIPN(–) patients received ICD9-CM neuropathy codes), which provides further evidence of their limitations. Such shortcomings, consistent with previous literature on billing code accuracy for a variety of diseases^{21–24}, indicate the need for further improvements in reporting accuracy in order to identify the cause and more effectively manage CIPN.

In light of increased life expectancy following cancer diagnosis and chemotherapy, further study on the long- term impact of CIPN are needed to understand impacts on quality of life, including the impact years after completion of treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Staff NP, Grisold A, Grisold W, Windebank AJ. Chemotherapy-induced peripheral neuropathy: A current review. *Ann Neurol*. 2017 Jun; 81(6):772–81. [PubMed: 28486769]
2. Bao T, Basal C, Seluzicki C, Li SQ, Seidman AD, Mao JJ. Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: prevalence, risk factors, and fall risk. *Breast Cancer Res Treat*. 2016 Sep; 159(2):327–33. [PubMed: 27510185]
3. Zanzville NR, Nudelman KN, Smith DJ, et al. Evaluating the impact of chemotherapy-induced peripheral neuropathy symptoms (CIPN-sx) on perceived ability to work in breast cancer survivors during the first year post-treatment. *Support Care Cancer*. 2016 Nov; 24(11):4779–89. [PubMed: 27470258]
4. Kneis S, Wehrle A, Freyler K, et al. Balance impairments and neuromuscular changes in breast cancer patients with chemotherapy-induced peripheral neuropathy. *Clin Neurophysiol*. 2016 Feb; 127(2):1481–90. [PubMed: 26350407]
5. Tofthagen C, Overcash J, Kip K. Falls in persons with chemotherapy-induced peripheral neuropathy. *Support Care Cancer*. 2012 Mar; 20(3):583–9. [PubMed: 21380613]
6. England JD, Gronseth GS, Franklin G, et al. Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2005 Jan 25; 64(2):199–207. [PubMed: 15668414]
7. St Sauver JL, Grossardt BR, Yawn BP, et al. Data resource profile: the Rochester Epidemiology Project (REP) medical records-linkage system. *Int J Epidemiol*. 2012 Dec; 41(6):1614–24. [PubMed: 23159830]
8. Seretny M, Currie GL, Sena ES, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain*. 2014 Dec; 155(12):2461–70. [PubMed: 25261162]
9. Goldstein D, Von Hoff DD, Moore M, et al. Development of peripheral neuropathy and its association with survival during treatment with nab-paclitaxel plus gemcitabine for patients with metastatic adenocarcinoma of the pancreas: A subset analysis from a randomised phase III trial (MPACT). *Eur J Cancer*. 2016 Jan; 52:85–91. [PubMed: 26655559]
10. Johnson C, Pankratz VS, Velazquez AI, et al. Candidate pathway-based genetic association study of platinum and platinum-taxane related toxicity in a cohort of primary lung cancer patients. *J Neurol Sci*. 2015 Feb 15; 349(1–2):124–8. [PubMed: 25586538]
11. Raphael MJ, Fischer HD, Fung K, et al. Neurotoxicity Outcomes in a Population-based Cohort of Elderly Patients Treated With Adjuvant Oxaliplatin for Colorectal Cancer. *Clin Colorectal Cancer*. 2017 Mar 24.
12. Ramanathan RK, Rothenberg ML, de Gramont A, et al. Incidence and evolution of oxaliplatin-induced peripheral sensory neuropathy in diabetic patients with colorectal cancer: a pooled analysis of three phase III studies. *Ann Oncol*. 2010 Apr; 21(4):754–8. [PubMed: 19887466]
13. Uwah AN, Ackler J, Leighton JC Jr, Pomerantz S, Tester W. The effect of diabetes on oxaliplatin-induced peripheral neuropathy. *Clin Colorectal Cancer*. 2012 Dec; 11(4):275–9. [PubMed: 22682776]
14. Vincenzi B, Frezza AM, Schiavon G, et al. Identification of clinical predictive factors of oxaliplatin-induced chronic peripheral neuropathy in colorectal cancer patients treated with adjuvant Folfox IV. *Support Care Cancer*. 2013 May; 21(5):1313–9. [PubMed: 23196819]
15. Ottaiano A, Nappi A, Tafuto S, et al. Diabetes and Body Mass Index Are Associated with Neuropathy and Prognosis in Colon Cancer Patients Treated with Capecitabine and Oxaliplatin Adjuvant Chemotherapy. *Oncology*. 2016; 90(1):36–42. [PubMed: 26731722]
16. Shahriari-Ahmadi A, Fahimi A, Payandeh M, Sadeghi M. Prevalence of Oxaliplatin-induced Chronic Neuropathy and Influencing Factors in Patients with Colorectal Cancer in Iran. *Asian Pacific journal of cancer prevention: APJCP*. 2015; 16(17):7603–6. [PubMed: 26625769]
17. Hershman DL, Till C, Wright JD, et al. Comorbidities and Risk of Chemotherapy-Induced Peripheral Neuropathy Among Participants 65 Years or Older in Southwest Oncology Group Clinical Trials. *J Clin Oncol*. 2016 Sep 01; 34(25):3014–22. [PubMed: 27325863]

18. Schneider BP, Zhao F, Wang M, et al. Neuropathy is not associated with clinical outcomes in patients receiving adjuvant taxane-containing therapy for operable breast cancer. *J Clin Oncol*. 2012 Sep 01; 30(25):3051–7. [PubMed: 22851566]
19. Hoffman EM, Watson JC, St Sauver J, Staff NP, Klein CJ. Association of Long-term Opioid Therapy With Functional Status, Adverse Outcomes, and Mortality Among Patients With Polyneuropathy. *JAMA Neurol*. 2017 Jul 01; 74(7):773–9. [PubMed: 28531306]
20. Hoffman EM, Staff NP, Robb JM, St Sauver JL, Dyck PJ, Klein CJ. Impairments and comorbidities of polyneuropathy revealed by population-based analyses. *Neurology*. 2015 Apr 21; 84(16):1644–51. [PubMed: 25832668]
21. Hsia DC, Krushat WM, Fagan AB, Tebbutt JA, Kusserow RP. Accuracy of diagnostic coding for Medicare patients under the prospective-payment system. *N Engl J Med*. 1988 Feb 11; 318(6):352–5. [PubMed: 3123929]
22. Campos-Outcalt DE. Accuracy of ICD-9-CM codes in identifying reportable communicable diseases. *Qual Assur Util Rev*. 1990 Aug; 5(3):86–9. [PubMed: 2136670]
23. Torgersen T, Rosseland LA, Malt UF. Coding guidelines for ICD-9 section on mental disorders and reliability of chart clinical diagnoses. *Acta Psychiatr Scand*. 1990 Jan; 81(1):62–7. [PubMed: 2330831]
24. O'Malley KJ, Cook KF, Price MD, Wildes KR, Hurdle JF, Ashton CM. Measuring diagnoses: ICD code accuracy. *Health Serv Res*. 2005 Oct; 40(5 Pt 2):1620–39. [PubMed: 16178999]

Figure 1.
Flowchart of epidemiological study of chemotherapy-induced peripheral neuropathy (CIPN) in Olmsted County, Minnesota (2006–2008).

Figure 2.
Time-to-event curve demonstrating time from incident neurotoxic chemotherapy exposure to onset of signs or symptoms of CIPN.

Figure 3. Kaplan-Meier survival curve demonstrating improved 5-year survival among subjects that developed CIPN ($p < 0.0001$).

Table 1

Distribution of patients exposed to neurotoxic chemotherapy agents.

	Chemotherapeutic Agent	# exposed to agent	# with CIPN (%)
Vinca alkaloid	vincristine	70	43 (61)
	vinblastine	19	7 (37)
	vinorelbine	6	3 (50)
Thalidomide-derivative	lenalidomide	10	7 (70)
	thalidomide	3	2 (67)
Taxane	paclitaxel	136	88 (65)
	docetaxel	18	5 (28)
Proteasome inhibitor	bortezomib	8	7 (88)
Platinum-based agent	carboplatin	116	57 (49)
	cisplatin	88	36 (41)
	oxaliplatin	68	54 (79)
Microtubule destabilizer	ado-trastuzumab emtasine	11	8 (73)

Table 2

Baseline characteristics and putative neuropathy risk factors in CIPN (+) and CIPN (–) subjects. No statistical differences were observed. SD – Standard Deviation.

	CIPN (+) (n=268)	CIPN (–) (n=241)
Mean age in years ± (SD)	58.1 ± 16.4	58.0 ± 18.6
Height (inches) ± (SD)	65.7 ± 4.8	65.2 ± 6.6
Weight (pounds) ± (SD)	178.8 ± 48.7	163.7 ± 47.3
	n (%)	n (%)
Male	115 (42.9)	118 (38.6)
Female	153 (57.1)	123 (51.0)
Caucasian/White	249 (92.9)	227 (94.2)
Tobacco	82 (34.0)	79 (29.5)
Alcohol	10 (4.2)	18 (6.7)
Pulmonary Disease	56 (23.2)	59 (22.0)
Diabetes	87 (36.1)	97 (36.2)
PVD	57 (23.7)	59 (22.0)
Renal Disease	106 (44.0)	112 (41.8)
HLPD/HCLS	121 (50.2)	142 (53.0)
HTN	123 (51.0)	138 (51.5)
MM	25 (10.4)	18 (6.7)
Obesity	63 (26.1)	70 (26.1)

Table 3

Self-reported impairments in CIPN (+) and CIPN (–) subjects (* - $p < 0.05$). OR – Odds Ratio. CI – Confidence Interval.

Self-reported impairment	CIPN (+) (n = 259) n (%)	CIPN (–) (n=190) n (%)	OR	95% CI
Numbness and shooting pains	100 (38.6)	23 (12.1)	4.56	2.76 to 7.54 *
Difficulty with pain	147 (56.8)	87 (45.8)	1.55	1.06 to 2.26 *
Difficulty climbing stairs without stopping to rest	176 (68.0)	114 (60.0)	1.41	0.95 to 2.08
Use of an assistive device	84 (32.4)	53 (27.9)	1.24	0.82 to 1.86
Difficulty climbing stairs	93 (35.9)	58 (30.5)	1.27	0.85 to 1.90
Difficulty with housekeeping	69 (26.6)	44 (23.2)	1.20	0.77 to 1.86
Difficulty preparing meals	52 (20.1)	36 (18.9)	1.07	0.66 to 1.72
Tendency to fall easily	29 (11.2)	18 (9.5)	1.20	0.64 to 2.24
Difficulty walking independently	62 (23.9)	46 (24.2)	0.98	0.63 to 1.52
Work Disabled	39 (15.1)	29 (15.3)	0.98	0.58 to 1.65
Difficulty with transportation	38 (14.7)	30 (15.8)	0.91	0.54 to 1.54
Living out of home	14 (5.4)	9 (4.7)	1.14	0.48 to 2.71
Difficulty bathing	33 (12.7)	29 (15.3)	0.81	0.47 to 1.38
Difficulty dressing	28 (10.8)	25 (13.2)	0.80	0.45 to 1.42
Difficulty getting in and out of bed	20 (7.7)	21 (11.1)	0.67	0.35 to 1.28
Difficulty using the toilet	15 (5.8)	16 (8.4)	0.66	0.32 to 1.38
Difficulty feeding self	9 (3.5)	10 (5.3)	0.64	0.25 to 1.62
Weakness in arms and legs	3 (1.2)	2 (1.1)	1.10	0.18 to 6.65

Table 4

Prescribed medications in CIPN (+) and CIPN (–) subjects (* - $p < 0.05$).

Analgesic	CIPN (+) (n=268) n (%)	CIPN (–) (n=241) n (%)	OR	95% CI
Serotonin/norepinephrine reuptake inhibitors (venlafaxine, desvenlafaxine, duloxetine, minipran)	35 (13.1)	12 (5.0)	2.87	1.45 to 5.66 *
Alpha-2-delta antagonist (gabapentin, pregabalin)	62 (23.1)	34 (14.1)	1.83	1.16 to 2.90 *
Topical Analgesic (amitriptyline+ketamine, capsaicin, lidocaine)	45 (16.8)	27 (11.2)	1.60	0.96 to 2.67
Opioid analgesics (codeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone, propoxyphene, tapentadol, tramadol)	261 (97.4)	227 (94.2)	2.30	0.91 to 5.80
Tricyclic Antidepressants (imipramine, doxepin, amitriptyline, nortriptyline, protriptyline)	25 (9.3)	14 (5.8)	1.67	0.85 to 3.29

Table 5

Prescribed medications in CIPN (+) and CIPN (–) subjects that survived at least 5 years (* - $p < 0.05$). SNRI – serotonin norepinephrine reuptake inhibitor. TCA – tricyclic antidepressant. See Table 4 for list of drugs.

Analgesic	CIPN (+) (n=145) n (%)	CIPN (–) (n=90) n (%)	OR	95% CI
Opioid Analgesic	48 (33.1)	18 (20.0)	2.0	1.06 to 3.69 *
SNRI	14 (9.7)	2 (2.2)	4.7	1.04 to 21.2 *
TCA	10 (6.9)	3 (3.3)	2.1	0.58 to 8.03
Alpha-2-delta antagonist	14 (9.7)	5 (5.6)	1.8	0.63 to 5.2
Topical Analgesic	4 (2.8)	0 (0.0)	5.8	0.31 to 108