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Medication-induced exacerbation of neuropathy in Charcot Marie Tooth Disease

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Abstract

Toxin or medication-induced worsening of preexisting peripheral neuropathy is a generally accepted but not well-studied phenomenon in humans. Drug-induced exacerbation of Charcot Marie Tooth disease (CMT) neuropathy is a common concern; a list of potential drugs to avoid is maintained by the CMT Association but with limited direct evidence or advice on relative risk. An extensive literature search for reported cases of drug effects in CMT patients found the vast majority concerned excessive vincristine toxicity in patients with undiagnosed demyelinating forms of CMT, many after 1 or 2 doses. The CMT North American database was also queried for all drug-related effects. All but one drug cited as worsening neuropathy was present on a compiled inclusive list. These results and other available evidence were used to develop a revised risk stratified list for CMT patients and clinicians to consult prior to discussing risk to benefit ratios and making treatment decisions.

Keywords: Toxic neuropathy; Vincristine; Chemotherapy; Nucleoside analogs; Hereditary neuropathy; Drug-induced neuropathy

1. Introduction

Despite greatly improved understanding of the pathophysiology and an increasing accuracy in determining the cause of many forms of peripheral neuropathy, the majority of cases continue to have only symptomatic treatments available. In addition, despite these advances, the cause of many cases remains undiscovered. While accounting for only an estimated 2% of neuropathy cases, medication-induced neuropathies are among a minority of potentially reversible causes. Simply stopping the agent is the intervention in most instances, although incomplete or delayed recovery is characteristic of some forms. The field is not static — new medications, which are not initially known to induce neuropathy continue to be approved and associations with toxic neuropathy were found only after widespread use. For example leflunomide was approved in 1998 as a novel class of agent against rheumatoid arthritis. Peripheral neuropathy was not identified as a risk in preclinical or prerelease trials, but after widespread use a review 6 years later uncovered 80 cases of probable drug-induced neuropathy [1]. Older agents with a recognized risk of toxic neuropathy may have escalation of usage because of new applications or broadened indications, for example thalidomide, suramin, and amiodarone. However, there are many more agents suspected of causing peripheral neurotoxicity than have definitive proof. Many have, at best, a tenuous temporal association with the onset of neuropathy and a causative mechanism or laboratory animal model is lacking. It is much more difficult to dissect out potential causes with slowly developing toxicity after extended exposure. For example, Gaist et al., required a large sample size in order to associate idiopathic neuropathy with statin exposure after an earlier smaller negative trial [2].

Existing peripheral neuropathy is a generally accepted risk factor for increased susceptibility to neurotoxic agents

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[3]. Numerous examples have been described, but this issue has not been rigorously studied in humans. Genetic traits are known to affect peripheral nerve vulnerability to toxins. Examples include the slow Wallerian degeneration (Wld^S) trait, which blunts the effects of axotomy and vincristine exposure and defects in murine DNA repair, which enhance the toxic effects of cisplatin [4,5]. Also, certain mitochondrial RNA gene defects predispose to familial aminoglycoside-induced deafness [6]. More immediately pertinent to clinical neurology, however, is whether certain medications are unduly hazardous to patients with hereditary neuropathies, especially Charcot-Marie-Tooth disease (CMT). CMT is a common disorder, affecting approximately 150,000 Americans. Should CMT patients avoid certain medications, even if clearly indicated, because of concerns of neurotoxicity? Also unclear is whether CMT subtypes are differentially sensitive to certain medications—concerns for CMT1A may not apply to less common subtypes. The Charcot-Marie-Tooth Association (CMTA), a nonprofit organization founded in 1983 concerned with patient support, public education, and promotion and support of research into the cause and treatment of CMT, has long maintained an unwavering list of potentially hazardous medications for patients with CMT and treating physicians to consult. This list is extensively accessed by patients and treating physicians and, in some cases, could deter the use of a preferred medication for an unrelated condition because of inordinate perceived risk. The list includes 25 medications and vitamins unsegregated in terms of relative risk. The list is published in a nationally distributed newsletter and on their website (http://www.charcot-marie-tooth.org/med_alert.php). Access to the dedicated medication alert webpage was queried. For the month studied this page was accessed 2012 times, suggesting that it is frequently consulted, presumably primarily by CMT patients and the public. The issue of CMT subtypes is not addressed.

The CMT North American (CMTNA) Database is an extensive collection of recorded clinical details of CMT patients mainly in the United States and Canada. The instrument used is a highly detailed 9-page form that catalogues a multitude of clinical characteristics based on patient information, physician examination findings, clinical course, medication use, genetic testing and family history. The database is designed to enable targeted queries to the information without identification of personal patient data. The goals of this study were threefold: 1) conduct a thorough literature search for reported associations between CMT and peripheral nerve toxicity attributed to specific medications; 2) query the CMTNA Database for all medications taken and attempt to associate with reports of clinical worsening or no clinical effect; and 3) use the obtained information in conjunction with the best available general knowledge of toxic neuropathy to generate a more informative list ranked by probable relative risk to patients with CMT.

2. Methods

2.1. Literature search

A literature search using both Pubmed and Medline was conducted in order to reduce the chance of missing reports. A variety of inclusive search terms were used including CMT, Charcot, Charcot-Marie-Tooth, HMSN, hereditary neuropathy in conjunction with toxic, medication, neurotoxic and each drug from a broad list of medications cited to induce peripheral neuropathy. Reports addressing animal models, in vitro work and human cases without a reasonable clinical, electrodiagnostic or genetic description of CMT were excluded. Additional scrutiny of the referenced cases in a number of articles was also conducted to identify further cases not available in these indices. A broad list of medications was gathered based on a list included in a major text of neurotoxicology supplemented with additional agents included in other recent review sources [5,7–10].

2.2. CMT North American Database

The CMTNA Database, initiated at Wayne State University and currently housed in the department of medical and molecular genetics at Indiana University, is a computerized registry tool derived from a highly detailed, 9-page questionnaire, administered to CMT patients and treating physicians in neuromuscular clinics throughout the United States and Canada. This instrument ascertains abundant clinical information including concomitant medical conditions, clinical and family history, CMT subtype, genetic testing, occupational exposures, symptoms and social history. Additionally, it attempts to document exposures to each medication on the CMTA list as well as all other medications taken, duration of exposure, and perceived neuropathy effect. We queried the database for all medication related fields, which included medication names, exposure duration, effect or lack of effect on the neuropathy, and associated clinical details when provided. In addition, the CMT subtype, genetic test results when available, related medical conditions including diabetes, renal failure, ethanol exposure, possible occupational hazards, and other non-identifying information were queried. Criteria for inclusion were exposure to a medication on either the CMT Association or the composite inclusive toxic medication list. Exposures to any other medications not on the chosen list but reported to worsen neuropathy were also added to the study list.

3. Results

3.1. Literature review

Despite the general acceptance of the concept of medication-induced worsening of CMT, only 26 reports

addressing CMT and toxic medication effects were identified. Twenty-two of the reports address vincristine [11–30]. Two reports of nucleoside analogs, two of cisplatin, and 1 of carboplatin and taxoids were identified and reviewed [31–34].

Vincristine, a widely used vinca alkaloid, is a first-line chemotherapeutic agent for several malignancies. The drug is the only agent with multiple credible examples of inordinate toxicity in CMT patients, which can be severe and acute, in some instances after a lone exposure. The oldest report found was from Weiden and Wright (1972) followed by several individual case reports in the mid- to late 1980's [11–16]. However, it was not until Graf et al. reported 3 cases in 1996 that the issue gained widespread attention [17]. The 22 reports reviewed describe 30 affected patients [3,11–30]. One additional report was found of a patient with severe acute demyelinating neuropathy following vincristine but because of no genetic confirmation, a negative family history, and uncharacteristic CMT1A electrophysiologic changes (conduction block), the authors concluded that CMT was less likely than acquired neuropathy [35].

In the general population a minimum total dose of 5–8 mg is the described threshold for inducing sensory neuropathy in most cases; motor involvement usually requires higher doses. In CMT patients, acute worsening or initiation of weakness, sometimes severe quadriparesis including a Guillain–Barré-like pattern, is observed after administration of only 2–4 mg. Eighteen of the 30 patients reviewed developed marked sensory symptoms or new onset weakness after 2 or 4 mg or the equivalent pediatric dose (1.5 mg/m^2/dose). Some developed dysarthria and dysphagia [28]. Nearly all reports describe eventual improvement, but frequently not to baseline levels. Both adult (15) and pediatric (15) examples are reported, most with previously unsuspected and undiagnosed CMT (26 of 30). However 10 cases undiagnosed with CMT prior to vincristine treatment had, in retrospect, overt clinical signs (pes cavus, distal atrophy) or a close relative with known CMT. Some older reports acknowledge a recognized family history of CMT before the phenomenon was sufficiently described. The vast majority, as expected, had clinically compatible or genetically confirmed CMT1A. Genetic testing was performed on 16; 13 demonstrated the characteristic 17p11.2 duplication but several reports were made prior to available genetic testing; 1 test was inconclusive, 1 was negative for 2 common mutations, and 1 positive for the characteristic hereditary neuropathy with liability to pressure palsies (HNPP) PMP-22 deletion.

Six reports were found that discuss either exposures to other agents or vincristine exposure with other CMT subtypes. One patient with a probable axonal form of CMT (type 2) developed moderately severe primarily sensory neuropathy following vincristine treatment but reportedly tolerated extended administration and recovered quickly [27]. Kalfakis et al. reported a 37-year-old man with neuropathy and non-Hodgkin's lymphoma [30]. The patient had earlier developed transient foot drop at age 29 lasting 2 months. Following a treatment regimen including 2 courses of 2 mg of vincristine, new onset numbness and mild weakness developed after course 1; tetraparesis developed after course 2. EMG testing demonstrated diffuse slowing ranging from 23–30 m/s in the arms and 18–27 m/s in the legs; focal sites of conduction velocity slowing in the ulnar and peroneal nerves at typical compression sites were also seen. Following the chemotherapy, the new symptoms eventually improved but recovery was incomplete. Genetic testing for a PMP-22 duplication and a connexin-32 defect was negative. The asymmetric foot drop prompted testing for a PMP-22 deletion (HNPP), which was positive.

Cowie and Barrett reported a 23-year-old man with X-linked CMT and foot drop, areflexia, pes cavus, and a recognized family history; his sister was described as a known carrier of the defect, presumably connexin-32 [31]. He developed an osteosarcoma and underwent 3 rounds of chemotherapy including cisplatin and adriamycin followed by surgery and then 3 additional chemotherapy rounds. He developed subjective paresthesias but his neurologic exam reportedly remained severely affected but unchanged. The author's conclusions were that the patient's CMT-related neuropathy was unaffected despite the sensory symptoms and concluded that the clinical course was not atypical for others without underlying neuropathy. Martino et al. described a 60-year-old woman with longstanding CMT who developed ovarian cancer [32]. Following surgery she underwent 6 cycles of paclitaxel and carboplatin. One week after her first cycle, her neuropathy worsened both subjectively and objectively to the point of severely affecting walking, writing, and temperature sense. She improved slightly over the next 2 weeks and she was rechallenged with two more cycles. Further chemotherapy was discontinued because of increasing neuropathy severity, with less improvement between cycles. The therapy was changed to a combination of docetaxel and carboplatin and she was reportedly able to complete a total of 6 cycles of therapy without additional neuropathy exacerbation. Her peripheral neuropathy was said to return to baseline pretreatment levels within 2–3 months of the initial paclitaxel administration and she regained her ability to walk. However, no objective clinical markers at different time points or description of electrodiagnostic studies are provided.

Fernandez-Torre et al. reported a 40-year-old man with HIV and a syndrome of pes cavus and areflexia, but in retrospect no family history [33]. He was treated with 2 nucleoside analog agents known in some cases to cause predominantly small fiber neuropathy, didanosine (400 mg/d) and stavudine (80 mg/d); he was also given nevirapine. Four months later paresthesias and numbness developed. Electrodiagnostic studies showed uniform conduction velocity slowing suggesting a hereditary neuropathy and prompted the discovery of a 17p11.2 duplication. The

patient was switched to zidovudine (500 mg/d) and lamivudine (300 mg/d) with partial improvement of the sensory symptoms but persistent motor signs. The author's conclusion was that the sensory syndrome was a separate phenomenon and not an exacerbation of CMT manifestations, although neither serial electrodiagnostic studies nor small fiber neuropathy measures were performed. In addition only a minority of HIV patients develop nucleoside analog-induced neuropathy severe enough to prompt a medication change. Miller et al. described 2 HIV infected patients [34]. The first is a 49-year-old man with known HIV infection successfully treated with stavudine, lamivudine and ritonavir (later changed to efavirenz). He reportedly developed mild sensory neuropathy attributed to the stavudine. He then developed acute peroneal neuropathy with motor and sensory signs, which improved over 4 weeks. Eight months later he developed a sural neuropathy and partially recovered followed by a median neuropathy, which persisted. He had no pes cavus and was diagnosed with mononeuritis multiplex; sural nerve biopsy showed perivascular lymphocytic infiltration suggestive of diffuse infiltrative lymphocytic syndrome (DILS). However, teased nerve fiber preparation showed numerous tomaculi, characteristic of HNPP; genetic testing uncovered a PMP-22 deletion. The multiple mononeuropathies were thought to be primary HNPP manifestations. The second is a 29-year-old woman with AIDS successfully treated with lamivudine, stavudine, and nelfinavir. The stavudine was later discontinued because of worsening painful neuropathy and zidovudine, a nucleoside analog not associated with neuropathy, substituted. A later exam revealed distal muscle wasting, reduced proprioception, absent ankle reflexes, pes cavus, and dysesthesias. Mild hyperlactitemia was found (7.4 mmol/l) and electrodiagnostic studies showed evidence of both axonal loss and demyelination, atypical for both primary HIV-neuropathy and nucleoside analog-induced neuropathy. Genetic testing revealed the common PMP-22 duplication, supporting underlying CMT1A. The contribution of nucleoside analogs to the motor syndromes in these 2 cases is not clear. Also unclear is whether the painful sensory neuropathy developed in both cases is more severe than would be expected if no underlying hereditary neuropathy were present.

3.2. CMTNA database

The CMTNA database provided 996 drug entries of 209 persons from 190 families. Nineteen medications were identified by our criteria among the patients indicating clinical worsening associated with a medication (Table 1). Of the 19, 18 are found on the published lists referenced. The majority of reported adverse exposures occurred within one month, increasing the likelihood of a valid association, although details of serial examinations were beyond the available detail preventing the use of the Naranjo probability scale. Medications with multiple reported exposures and more than one claim of symptomatic neuropathy worsening included metronidazole (3 of 13 exposures), nitrous oxide (3 of 6 exposures), statins (2 of 20 exposures), nitrofurantoin (2 of 11 exposures), phenytoin (2 of 11 exposures), and sertraline (5 of 21 exposures). Several others (isoniazid, penicillin — high IV doses) had 1 or 2 adverse reports. Of the patients reporting symptomatic worsening, 1 had underlying diabetes (nitrofurantoin), one had inactive hepatitis-C (metronidazole), but all claimed to drink no more than one drink per day; none had underlying renal failure. Overall, 12 patients had diabetes mellitus and none had excessive alcohol use or renal failure. No pertinent occupational exposure or other medical condition commonly associated with neuropathy was found. Still other agents were notable for exposures without reported neuropathy effect, including adriamycin, chloramphenicol, dapsone, disulfiram, hydralazine, lithium, and pyridoxine. One additional medication not on any of the references lists, gabapentin, was listed to symptomatically worsen neuropathy in one. Entries were also made for 150 exposures to anesthesia; 12 (8%) reported some degree of worsening but without sufficient details to further examine individual associations.

Table 1
Medications listed as exacerbating CMT-related neuropathy in the CMTNA database (percentage of reported exposures)

Multiple examples
•Metronidazole (23%)
•Nitrous oxide (50%)
•Statins (10%)
•Nitrofurantion (20%)
•Phenytoin (11%)
•Sertraline (9.5%)
One or two examples
•Isoniazid
•Penicillin — high IV doses
Listed as used without adverse effect
•Adriamycin
•Chloramphenicol
•Dapsone
•Disulfiram
•Hydralazine
•Lithium
•Pyridoxine (conventional dose)

Genetic information was available for 22 persons in the study group for which the subtype was confirmed by genetic testing. These patients included 28 exposures to medications of interest. Of the 22, 12 had a confirmed CMT1A PMP-22 duplication, 3 had a confirmed HNPP PMP-22 deletion, and 2 had a CMTX Connexin-32 mutation. Each of the following subtypes had one reported individual: CMT1A (nonduplication), CMT1B (myelin protein zero (MPZ)), CMT2E (neurofilament light chain (NFL)), and CMT1D (early growth response-2 (EGR2)); other testing was indeterminate or negative for the subtypes examined. No discernible disparity of one CMT subtype to one agent was noted; however, overall numbers are small.

4. Discussion

Should CMT patients avoid certain medications for concern of neurotoxicity? Vincristine appears to be in a separate high risk category for patients with demyelinating forms of CMT including CMT1A and, in all probability, HNPP; the possibility of acute worsening after a single dose makes cautious administration problematic. No patient in the CMTNA database received vincristine. It is not known whether other patients with demyelinating CMT tolerated vincristine treatment but none are reported. In any event recommendations have been made that CMT patients should not receive vincristine; moreover, genetic testing for minimally symptomatic or asymptomatic patients at risk for the condition or patients with a compatible family history should be strongly considered prior to treatment initiation [17]. The United States Food and Drug Administration has a standing, specific warning that vincristine injection is contraindicated in patients with the demyelinating form of CMT. Vincristine is no longer listed in the physician's desk reference, despite continued production by different manufacturers. Despite these warnings cases of vincristine administration to patients with CMT1A continue to occur; most cases are uncovered by reevaluation after perceived excessive toxicity or a characteristic demyelinating neuropathy pattern uncovered by subsequent electrodiagnostic studies [25,26,29].

The mechanism of this specific effect on demyelinating forms of CMT is unknown, but worthy of further investigation. The association with 2 different defects in the PMP-22 gene is of particular interest and suggests a specific molecular effect and not simply additive effects of two neuropathic processes. This link is especially notable for the absence of reports of neuropathy exacerbation by other medications that inhibit neurotubular aggregation similar to vincristine, such as colchicine, podophyllotoxin, and podophyllin resin. Taxoids promote the assembly of disordered arrays of neurotubules and are discussed later.

Whether vincristine has similar effects on other forms of CMT is less clear. There is insufficient data to comment on vincristine neurotoxicity in less common CMT subtypes affecting other genes. Two cases with probable CMT2 apparently tolerated extended vincristine treatment; induced sensory complaints developed then improved in one [25,27].

There is extremely limited data on other chemotherapeutic drugs including adriamycin, cisplatin, carboplatin, docetaxel, and paclitaxel; however, one patient with a probable connexin-32 defect is reported to have tolerated 6 rounds of cisplatin and adriamycin. However, this single report is not sufficient to deem these medications safe for CMT patients. Martino et al. reported a woman who worsened after paclitaxel and carboplatin but stabilized and improved after challenged with docetaxel and carboplatin [32]. This limited experience also seems inadequate to consider the drugs either safe or inordinately risky for use in appropriate patients with CMT. Of the agents discussed, taxoids are most prone to affect motor function; cisplatin, carboplatin, and oxaliplatin preferentially affect sensory axons or dorsal root ganglia neurons.

Several nucleoside analog agents used to treat HIV infection are well described to induce predominantly small fiber neuropathy, modalities less severely affected in most patients with CMT. Most notable are zalcitabine (ddC), didanosine (ddI) and stavudine (d4T), although others are also associated with the condition. The contribution of the medication to the 3 cases discussed (2 CMT1A, HNPP) is not entirely clear. All 3 were diagnosed with hereditary neuropathy after the fact and only 1 developed a typical small fiber neuropathy pattern that improved with medication change. Use of a nucleoside analog less likely to cause neuropathy is a prudent course, if HIV-infection occurs in a known CMT patient.

Data from the CMTNA database should be interpreted with caution. Although the tool has the advantage of pooled data from a large number of patients, the reporting is dominated by symptomatic reports with limited serial objective data, such as sequential clinical examinations and electrophysiologic studies, a limitation not present in most published case reports. Nevertheless, the data is of interest in identifying which medications are prescribed for CMT patients, which medications are noticeably absent from the exposure list, and which agents not previously recognized as potentially of interest can be found. The vast majority of entries citing neuropathy worsening are associated with drugs of interest. The antibiotics metronidazole and nitrofurantoin are suspected in neuropathy worsening in several cases. Both drugs are well-established causes of toxic neuropathy but in a small minority of patients. Alternative antibiotics are available for most indication for these drugs, but not all. Metronidazole is the agent of choice in some instances and should be used with caution and in limited duration. Nitrofurantion, used in some urinary tract infection cases, is probably best used only if no adequate alternative is available in patients with CMT. Nitrous oxide irreversibly oxidizes the cobalt core of the cobalamin molecule and can precipitate myeloneuropathy in patients with borderline vitamin B_{12} levels or patients who chronically abuse the agent. The unexpectedly high percentage of cases listed in the database suggest that some with CMT experience worsening after nitrous oxide anesthesia. Verification of normal cobalamin levels, or ideally methylmalonate levels, should be considered in CMT patients planning to receive nitrous oxide anesthesia. Phenytoin is long-associated with peripheral neuropathy but more prominently in earlier eras when doses were considerably higher. The listing in this series is of possible interest and suggests that the drug should be used with caution in CMT patients or one of multiple alternative agents employed for seizure control. Patients with CMT who are well controlled on phenytoin should be individually considered. Two patients reported worsening following statin use. This issue is complicated by the more common

Table 2
Proposed list of medications of concern to patients with CMT

Definite high risk (including asymptomatic CMT)
Vinca alkaloids (vincristine)
Moderate to significant risk
Amiodarone
Bortezomib (velcade)
Cisplatin, carboplatin, oxaliplatin
Colchicine (extended use)
Dapsone
Didanosine (ddI)
Dichloroacetate
Disulfiram
Gold salts
Leflunomide
Linezolid (extended use)
Metronidazole/misonidazole (extended use)
Nitrofurantoin
Nitrous oxide (inhalation abuse or vitamin B12 deficiency)
Perhexiline*
Pyridoxine (high dose)
Stavudine (d4T)
Suramin
Tacrolimus (FK506, ProGraf)
Taxoids (paclitaxel, docetaxel)
Thalidomide
Zalcitabine
Uncertain or minor risk
5-Fluoracil
Adriamycin
Almitrine*
Chloroquine
Cytarabine (high dose)
Cyclosporin A
Ethambutol
Etoposide (VP-16)
Gemcitabine
Griseofulvin
Hexamethylmelamine
Hydralazine
Ifosphamide
Infliximab
Isoniazid
Mefloquine
Penicillamine
Penicillin — high IV doses
Phenytoin
Podophyllin resin
Sertraline (Zoloft)
Statins
Tumor necrosis factor-α
Zimeldine*
α-Interferon
Negligible or doubtful risk
Allopurinol
Amitriptyline
Chloramphenicol
Chlorprothixene
Cimetidine
Clioquinil
Clofibrate
Enalapril
Fluoroquinolones
Gabapentin
Gluthethimide
Lithium
Negligible or doubtful risk
Phenelzine
Propafenone
Sulfonamides
Sulphasalzine

*Not available in the United States.

condition of cholesterol lowering agent myopathy, alongside the controversial issue of statin-induced neuropathy. The benefits of these agents are well documented; however, use in CMT patients should be monitored both for onset of induced myopathy, which will cause additional weakness, and the probably less common neuropathy. Historical descriptions, however, involve predominantly sensory function. Anecdotal but unpublished communications have noted an increase in symptoms with certain serotonin reuptake inhibitors (SSRIs), most commonly sertraline. The unexpected number of entries in this series (5) supports this association, although additional detail is needed to establish a stronger association. However, no substantive literature in the general population is known that associates SSRI agents with peripheral neuropathy, but alternative SSRI agents are abundant. This association needs further study to see if it represents symptomatic worsening (pain) or a more objective neuropathy exacerbation.

The other agents listed, associated with peripheral neuropathy is some cases, but with no instance of peripheral neuropathy in this series suggest that either insufficient exposures are documented or the risk is minimally different than with patients with neuropathy from other etiologies. The data on anesthesia in general is problematic to interpret. Whether the effects listed as worsening are because of a true neuropathy exacerbation or non-specific effects of postoperative reduced activity or illness are beyond the detail of this data set.

There is considerable disparity between the perceived risk of potentially neurotoxic medications and the number of reports in the literature, other than for vincristine. There are several possible explanations including: 1) the drugs at high risk are avoided in CMT patients unless the diagnosis is unknown; 2) examples of toxicity occur but are unreported; 3) most drug effects are uncommon and affect only a small percentage of CMT patients or affect nerve modalities minimally affected by CMT; 4) worsening of neuropathy is an inherent process in CMT and drug-induced worsening may be overlooked by both patients and clinicians, or 5) a combination of various possibilities. A number of drugs associated with neuropathy are listed in the database records, but many are not; some were possibly actively avoided. Despite the continued uncertainty for most agents even after this review, drugs strongly associated with toxic peripheral neuropathy should be used with caution in CMT patients. In place of a single list, a collection of agents segregated into probable relative risk to CMT patients should be more clinically useful. Based on the information

gathered in this study combined with consultation of the general toxic neuropathy literature and the sources cited to determine the strength of association of toxic neuropathy in the general population, a revised and updated list is proposed (Table 2). It should be acknowledged that although this list is based on the best available information, determinations remain subjective to some degree; some may disagree with the category placement of some agents. As with any treatment, the risk of neuropathy exacerbation must be weighed against expected treatment benefits and available equivalent, alternative treatments.

Despite the limitations of this review and analysis, this study is likely the first comprehensive look at medication-induced exacerbation of neuropathy in CMT disease. Further research is needed to determine accurate relative risks for specific agents, if possible. A prospective study with direct objective evidence of neuropathy exacerbation is ideal, but problematic to achieve. However, clinicians caring for CMT patients should consider current and potential medications for possible neurotoxicity and probable drug-induced exacerbations of neuropathy documented.

5. Conclusions

Vincristine treatment is clearly an unacceptable risk to patients with known or possible CMT1A and most likely HNPP. Prior to use, a directed family history and screen for overt clinical signs of CMT is prudent; genetic testing may be indicated in suspected cases. Use of other agents in the significant risk category and use of vincristine in other CMT subtypes should be considered with caution, however, this recommendation is based on very limited direct evidence in patients with CMT. Agents most commonly identified in the CMTNA database include nitrous oxide, metronidazole, nitrofurantoin, phenytoin, and surprisingly sertraline. The probable lesser risk of agents in lower categories should also be weighed when prescribing these drugs for patients with CMT. Increased awareness may lead to better reporting of well-documented cases of agent specific worsening for treatments other than vincristine, which may lead to further improved recommendations of risk with other agents.

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