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## Neuropathy in the Cancer Patient: Causes and Cures

Identifying the causes of neuropathy in cancer patients can be difficult. This review looks at the common causes of neuropathy in cancer patients, as well as effective therapies—and even preventions.

### Josephine Sasu-Tenkoramaa, PharmD

PGY1 Pharmacy Practice Resident  
Stratton VA Medical Center  
Albany, New York

### Jeffrey Fudin, BS, PharmD, RPh, DAAPM, FCCP

Adjunct Associate Professor of Pharmacy Practice  
Albany College of Pharmacy and Health Services  
Albany, New York

**N**europathic pain is often defined as pain caused by a lesion or disease of the somato-sensory nervous system. Peripheral neuropathies arise from disorders associated specifically outside the central nervous system (CNS) and within the peripheral nervous system.<sup>1</sup> Symptoms of peripheral neuropathy include numbness, tingling, paresthesia (pins and needles sensations), sensitivity to touch, or muscle weakness. In patients with extreme symptoms, they may present with burning pain, muscle wasting, paralysis, or organ dysfunction.<sup>1</sup>

There are multiple causes of peripheral neuropathy, and in the cancer patient, identifying the culprit may be complicated by a plethora of etiologies. This review will focus on potential origins of neuropathic pain in the cancer patient, including both disease- and drug-induced peripheral neuropathy; current treatment modalities of cancer-induced peripheral neuropathy (CIPN); and how to prevent the development of peripheral neuropathy in cancer patients. According to the American Cancer Society, about 11.9 million Americans suffer from cancer pain, but it remains unclear what portion of that pain is specifically neuropathic versus somatic, visceral, or a combination. It

**Table 1. Most Common Cancers Causing Peripheral Neuropathy**

- Breast cancer
- Bone marrow transplantation<sup>a</sup>
- Lung cancer
- Lymphoma (non-Hodgkin's)
- Multiple myeloma
- Waldenström's macroglobulinemia

<sup>a</sup> Bone marrow transplantation is a treatment of certain cancers that may cause neuropathy.

also is equally unclear what percentage of these cases is due to disease, treatments, or both.<sup>2</sup>

### Cancer-induced Peripheral Neuropathy

By virtue of the nature of the disease, cancer alone can cause neuropathy. Certain neuropathies can develop due to remote or paraneoplastic effect; invasion of the cancer or compression of the nerves; or as a side effect secondary to treatment.<sup>3</sup> The cancers commonly associated with neuropathies are listed in Table 1. This section focuses on the role of CIPN in the cancer patient.

#### PEN/SN

Paraneoplastic encephalomyelitis/sensory neuronopathy (PEN/SN) is a type of neuropathy most commonly associated with lung cancer, typically small-cell lung cancer. Unlike other types of pain syndromes, PEN/SN is not due to the effects of the tumor itself, metastasis, treatment, infection, or metabolic abnormalities. Rather, it is thought to be a result of "remote effects" of the cancer that lead to the production of antibodies or inflammatory cells against any neural antigens that the tumor may express.<sup>4</sup> The symptoms can be acute or progressive. Patients typically present with numbness and parasthesias in the distal extremities, usually unilaterally.

Eventually, this type of neuropathy may result in loss of proprioception and sensory ataxia. Oftentimes, these patients develop confusion, memory loss, depression, hallucinations, seizures, and/or cerebellar ataxia. Treating the underlying cancer does not always affect the clinical course of PEN/SN. Some patients may occasionally improve after the tumor has been treated. Other treatments such as plasmapheresis, intravenous immunoglobulin, and immunosuppressive agents have not shown any greater benefit.<sup>3,4</sup>

#### Tumor Infiltration

Peripheral neuropathy may develop secondary to tumor infiltration. Leukemia and lymphoma cells can infiltrate the cranial and peripheral nerves; the result can be mononeuropathy, mononeuropathy multiplex, polyradiculopathy, or plexopathy as a complication. This neuropathy is generally painful and may be an indication of newly diagnosed cancer and/or disease progression. The symptoms can be managed by treating the underlying hematological malignancy or by initiating glucocorticoids if not contraindicated.<sup>3</sup>

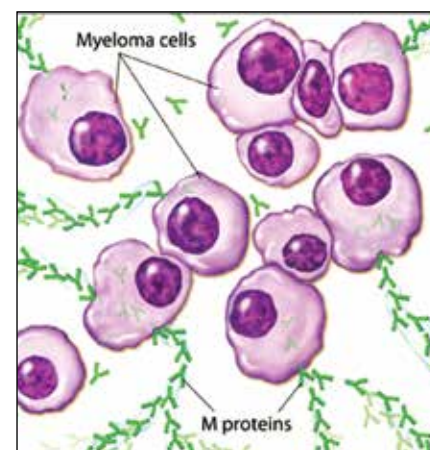
#### Lymphoma

Lymphoma most often causes neuropathy either by infiltration or direct compression of nerves, or by a paraneoplastic process.<sup>3</sup> Most peripheral complications are due to non-Hodgkin's lymphoma (NHL).<sup>5</sup> Hodgkin's lymphoma, on the other hand, rarely causes neuropathy; it generally causes immunological disorders of the peripheral nervous system such as inflammatory plexopathy or Guillain-Barré syndrome.<sup>5</sup> Although the NHL neuropathy may manifest as a sensory or motor symptom, it is commonly seen as a sensorimotor neuropathy. The course of the neuropathy may

be acute, gradually progressive, or relapsing and remitting. The neuropathy may respond to the treatment of the underlying lymphoma.<sup>5</sup>

#### Multiple Myeloma

Multiple myeloma (MM) is a common hematologic malignancy associated with monoclonal gammopathy. About 40% of patients with MM develop some type of peripheral neuropathy. Patients may develop painful paresthesia and loss of differentiating between pinprick and temperature sensations. The mechanism of the neuropathy is primarily due to amyloidosis with infiltration of the nerves. It is also thought to be due to the metabolic or toxic effects of the systemic consequences of renal failure.<sup>3,5</sup>



A myeloma cell (abnormal plasma cell) making M proteins. M proteins are antibodies created by a myeloma cell.

Image courtesy of the National Cancer Institute/Lydia Kibiuk (illustrator)

#### Waldenström's Macroglobulinemia

Waldenström's macroglobulinemia is a cancer of the B lymphocytes. It is caused by a malignant proliferation of lymphoplasmacytoid cells, which produces an overabundance of immunoglobulin M monoclonal proteins with a  $\kappa$  light chain—causing the blood to become hyperviscous. The mechanism of neuropathy

is unknown, but it's thought to be related to myelin-associated glycoprotein antibodies. However, a causal relationship has not been confirmed.<sup>6</sup>

### **Solid Tumors**

The most common solid tumors associated with peripheral neuropathy include breast cancer and lung cancer as reported in case reports and in a prospective, multicenter study in radiotherapy oncology units.<sup>7,8</sup>

### **Bone Marrow Transplantation**

Although not a neoplasm, bone marrow transplantation (BMT) is a treatment for certain malignancies, which may cause neuropathy. Peripheral neuropathy associated with BMT usually occurs concurrently with chronic graft-versus-host disease (GVHD). Chronic GVHD is a clinical syndrome that occurs in approximately 60% to 80% of long-term survivors of allogeneic hematopoietic stem cell transplantation.<sup>3</sup> Chronic GVHD is defined as an autoimmune disorder that occurs 100 days after the allogeneic transplant. Symptoms of chronic GVHD usually include oral ulcerations; keratoconjunctivitis; xerophthalmia; hepatic failure; obstructive lung disease; involvement of the skin and soft tissues; and involvement of the neuromuscular system, CNS, and the gastrointestinal tract.<sup>9</sup> These features are shared with a variety of autoimmune disorders, and it is possible that the etiology of this peripheral neuropathy is an immune-mediated response directed against the peripheral nerves. Patients may develop cranial neuropathies, sensorimotor polyneuropathies, multiple mononeuropathies, and severe generalized neuropathies. Symptoms may improve when the intensity of the immunosuppressive therapy for GVHD is increased.<sup>3</sup>

<b>Category</b>	<b>Drug (Brand)</b>
<b>Antimicrobial Agents</b>	Dapsone (Aczone, generic), Ethambutol (Myambutol) Isoniazid (Nydrizid, generic) Nitrofurantoin (Macrobid, generic) Metronidazole (Flagyl, generic)
<b>Cardiovascular Medications</b>	Amiodarone (Cordarone, generic) Disopyramide (Norpace, generic) Hydralazine (Apresoline, generic) Propranolol (Inderal, generic)
<b>Antirheumatic Medications</b>	Chloroquine (Aralen) Hydroxychloroquine (Plaquenil, generic)
<b>Anticonvulsants</b>	Phenytoin (Dilantin, generic)
<b>Others</b>	Colchicine (Colcrys) Indomethacin (Indocin, generic)

### **Non-cytotoxic-induced Peripheral Neuropathy**

When identifying medication-induced peripheral neuropathy in a cancer patient, it is important to first identify which of the patient's non-cytotoxic medications could cause or contribute to their painful neuropathy. All iatrogenic causes must be considered in order to delineate the various possibilities and capitalize on opportunities for successful prevention and treatment. Table 2 outlines some of the common agents that cause peripheral neuropathy. It excludes the antiretrovirals that are well-known to cause peripheral neuropathy.

#### **Antimicrobial Agents**

Some antimicrobial agents have been shown to induce peripheral neuropathy. Among antituberculosis agents, isoniazid and ethambutol (Myambutol) are well known for inducing peripheral neuropathy.<sup>10</sup> Isoniazid induces a mixed sensorimotor peripheral neuropathy. This neuropathy can be prevented by administering vitamin B<sub>6</sub> or pyridoxine.

Long-term use of isoniazid can cause depletion of pyridoxine by two mechanisms. First, isoniazid metabolites can bind to and inactivate pyridoxine. Second, isoniazid inhibits the enzyme pyridoxine phosphokinase, which is necessary to activate pyridoxine to pyridoxal-5'-phosphate, the active cofactor in many reactions that involve pyridoxine.<sup>11</sup> Ethambutol can also cause peripheral neuropathy of the extremities, which is manifested by numbness and tingling,<sup>12</sup> but it is much less neurotoxic than isoniazid.

Nitrofurantoin, an antibacterial, has also been reported to cause mixed sensorimotor neuropathy. The symptoms may develop during or after treatment with nitrofurantoin.<sup>13</sup> It is more prevalent in patients with renal impairment; however, it has also been reported in patients with normal renal function.<sup>14</sup>

Peripheral neuropathy has also been reported in patients treated with the antibiotic metronidazole (Flagyl) at conventional doses for 6 to 24 weeks.<sup>15</sup> Dapsone, used in the treatment of bacterial skin infections, has

**Table 3. Medications Used to Treat Chemotherapy-induced Peripheral Neuropathy**

Drug (Brand)	Mechanism of Peripheral Neuropathy Toxicity
<b>Bortezomib (Velcade)</b>	Unknown
<b>Cytarabine/Cytosine arabinoside/ Ara-C (Cytosar-U)</b>	Not well understood, potentially due to inhibition of proteins necessary in myelin synthesis or axonal transport
<b>Etoposide (VePesid, generic)</b>	Unknown; potential neurotoxicity effects secondary to inhibiting microtubule function
<b>Ifosfamide (Ifex, generic)</b>	Unknown
<b>Platinum-based agents:</b> • <b>Cisplatin (Platinol, generic)</b> • <b>Oxaliplatin (Eloxatin, generic)</b>	Binding to DNA may inhibit the transcription of important proteins and impair axonal transport
<b>Taxanes:</b> • <b>Paclitaxel (Taxol, generic)</b> • <b>Docetaxel (Taxotere, generic)</b>	Toxic effect to the neuronal cell body, axon, or both
<b>Thalidomide (Thalomid)</b>	Unknown
<b>Vinca alkaloids:</b> • <b>Vincristine (generic)</b> • <b>Vinorelbine (Navelbine, generic)</b> • <b>Vinblastine (Velban, generic)</b>	Inference with axonal microtubule assembly, impairment of axonal transport. Vinblastine is included for completeness but incidence of neuropathy is lower than others listed

been linked to peripheral neuropathy. In a case reported by Koller et al, the patient experienced significant motor deficit and loss of vibration sense shortly after initiation of low-dose dapsone. This reaction was reversible after cessation of the therapy. This patient was a slow metabolizer of isoniazid (slow acetylator), thus also was most likely a slow acetylator of dapsone.<sup>16</sup>

#### **Cardiovascular Agents**

For the cancer patient with cardiovascular comorbidities, it is important to properly evaluate all their medications, as some cardiovascular drugs can cause peripheral neuropathy. Propranolol is a commonly prescribed non-cardioselective  $\beta$  blocker used in the treatment of hypertension, angina, secondary

prevention of myocardial infarction, arrhythmia, migraine headaches, and tremor. It is also used in the management of hyperthyroidism and thyrotoxic crisis. There have been several documented episodes of peripheral neuropathy associated with the use of propranolol—for example, paresthesias of the hands, peripheral neuropathy, and myotonia have been reported with the use of propranolol.<sup>17</sup>

Hydralazine, a vasodilator used in the treatment of hypertension and as an adjunct following heart failure, may cause a subclinical peripheral neuropathy in about 15% of patients.<sup>18</sup> The development of peripheral neuropathy is linked to an antipyridoxine effect, since hydralazine is structurally similar to isoniazid. Peripheral neuropathy has also been linked to the

use of amiodarone and disopyramide (Norpace).<sup>19-21</sup> Studies have shown that long-term use of high-dose amiodarone therapy induces peripheral neuropathy.<sup>22</sup> The agent is thought to cause demyelinating neuropathy.<sup>22</sup>

#### **Other Agents**

Chloroquine (Aralen) is a quinolone derivative with several indications such as malaria, sarcoidosis, systemic lupus erythematosus, scleroderma, and rheumatoid arthritis. Chloroquine is an amphiphilic drug with both hydrophilic and lipophilic properties; thus, it interacts with the anionic phospholipids of cell membranes. The drug-lipid complexes are resistant to lysosomal destructions so the result is formation of vacuoles filled with myeloid debris.<sup>6</sup> Peripheral neuropathy ensues secondary to severe vacuolar myopathy, which has been supported by histological studies showing both axonal degeneration and damage to Schwann cells.

Hydroxychloroquine shares structural similarity with chloroquine and it also causes neuropathy. Patients taking hydroxychloroquine do not have severe abnormalities as they would with chloroquine-induced peripheral neuropathy.<sup>6</sup>

Phenytoin is an anticonvulsant, which, when given long term, could cause predominantly sensory polyneuropathy. This type of neuropathy could be bothersome, but is usually mild and rarely symptomatic.<sup>10</sup>

Colchicine (Colcrys) inhibits the polymerization of tubulin into microtubules. It is used to treat patients with gout. The proposed mechanism of neuropathy lies in the disruption of the microtubules that lead to defective intracellular movement or lysosomes, which accumulate in autophagic vacuoles in muscle and nerve fibers.<sup>6</sup> This mechanism of iatrogenic neuropathy correlates closely with that caused by the vinca alkaloids as outlined below.

Although rare, indomethacin has also been associated with the development of mostly motor peripheral neuropathy.<sup>23</sup>

### Chemotherapy-induced Peripheral Neuropathy (CIPN)

Peripheral neuropathy is a well-documented adverse reaction to several cancer chemotherapeutic agents (Table 3). These agents include the platinum-based salts (eg, cisplatin, carboplatin, oxaliplatin), vinca alkaloids (eg, vinblastine, vincristine), and the taxanes (eg, paclitaxel, docetaxel). The incidence of the neuropathy varies, and the incidence rates can increase to about 38% when agents are combined.<sup>24</sup> However, newer anti-cancer formulations have also proven to cause neuropathies.

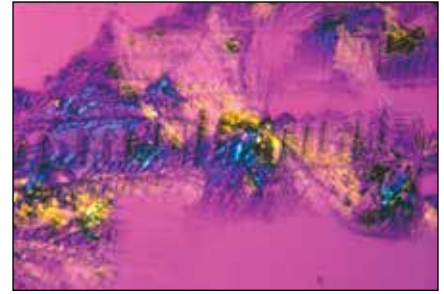
Bortezomib (Velcade), a proteasome inhibitor, is one such agent. It is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells indicated for the treatment of multiple myeloma, and as a second-line therapy in patients with mantle cell lymphoma.<sup>25</sup> It is increasingly being recognized that bortezomib-induced peripheral neuropathy may be a proteasome inhibitor class effect, producing primarily a small fiber and painful, axonal, sensory distal neuropathy.<sup>26</sup>

The mechanism of bortezomib-induced peripheral neuropathy is currently unknown. When bortezomib is administered, metabolic changes are observed secondary to accumulation of the drug in the dorsal root ganglia cells; mitochondrial-mediated dysregulation of calcium ( $\text{Ca}^{2+}$ ) homeostasis and dysregulation of neurotrophins may be responsible for this adverse event.<sup>26</sup> There is no neuroprotective treatment effective to reduce bortezomib-induced peripheral neuropathy; however, a dose modification algorithm is available as a guideline.

Cytosine arabinoside, also known as cytarabine or Ara-C (Cytosar-U), is an antimetabolite used in the management of leukemia and lymphoma. Peripheral neuropathy has been reported in patients at cumulative doses of 36 to 60  $\text{g}/\text{m}^2$ .<sup>27</sup> The mechanism of toxicity is not well understood. It has been hypothesized that the antimetabolite action of cytarabine inhibits proteins that are important in the production of myelin or in axonal transport. These neuropathies may start within hours or weeks after treatment.<sup>28</sup>

### Platinum-based Agents

Platinum-based agents exert their antineoplastic effects by forming covalent bonds and creating a cross-link with DNA, preferentially to guanine. Cisplatin is a platinum agent used widely in the treatment of a variety of malignancies such as ovarian, testicular, and bladder cancer. It produces mainly a sensory neuronopathy at cumulative doses of 225 to 501  $\text{mg}/\text{m}^2$ . The proposed mechanism of this neuropathy is due to potential inhibition of transcription of important proteins and impairment of axonal transport secondary to cisplatin's binding to DNA.<sup>3</sup> Oxaliplatin administration also has been linked to the development of peripheral neuropathy.<sup>29</sup> The neuropathy is mostly sensory and it occurs in two forms—acute and chronic. Acute oxaliplatin-induced neuropathy is the most common form (>90%), develops shortly after infusion, and is transient. Patients will develop dyesthesias that are exacerbated by cold and sometimes muscle contractions and weakness. For chronic oxaliplatin-induced peripheral neuropathy, dose intensity plays a significant role (cumulative doses  $\geq 540 \text{ mg}/\text{m}^2$ ).<sup>29</sup> It is usually observed after a long treatment duration and resembles cisplatin-induced



Cisplatin crystals, a platinum-based salt, is known to cause neuropathy.

Image courtesy of the National Cancer Institute/Larry Osby (Photographer)

neuropathy.<sup>30</sup> This neuropathy can be mitigated by administering intravenous calcium and magnesium prior to and post-oxaliplatin infusions.<sup>31</sup>

### Taxanes

Taxanes are a class of medications that disrupt microtubule function. Paclitaxel is utilized in chemotherapy regimens for the treatment of ovarian cancer, breast cancer, lung cancer, bladder cancer, head and neck cancer, and lymphoma. It has shown to produce dose-dependent neuropathy, predominantly sensory neuropathy.<sup>7</sup> Up to 85% of patients exposed to paclitaxel after 3 to 7 cycles at a dose of 135 to 200  $\text{mg}/\text{m}^2$  develop mild, subclinical peripheral neuropathy.<sup>32</sup> For doses between 250 to 350  $\text{mg}/\text{m}^2$ , neuropathy can develop within the first or second cycle.<sup>33-35</sup> Docetaxel is a semisynthetic analog of paclitaxel that also produces a dose-dependent sensory neuropathy with an incidence rate of 17% to 50%.<sup>36,37</sup> The taxanes induce the peripheral neuropathy secondary to toxic effect to the neuronal cell body, axon, or both.<sup>3</sup>

### Vinca Alkaloids

Vinca alkaloids inhibit microtubule formation by binding to  $\alpha$ - and  $\beta$ -tubulin. Vincristine produces a sensorimotor and autonomic neuropathy. The earliest symptoms presented include paresthesias and numbness that occur in the fingers

prior to the toes. Symptoms can occur within 14 days of a single 2 mg/m<sup>2</sup> dose.<sup>7,38</sup> Vinorelbine, another vinca alkaloid, used in a variety of different cancers, has a much lower incidence of neurotoxicity compared to vincristine.<sup>7,39</sup> In a study of vinorelbine, dose-related peripheral neuropathy has been observed in 20% to 50% of exposed patients, with severe neuropathy reported only in 1% of patients.<sup>40</sup> Impairment of the microtubules interferes with axon transport, which subsequently causes cytoskeletal disarray and degeneration.

#### Other Agents

Etoposide is a semisynthetic derivative of podophyllotoxin used in lymphoma, leukemia, small cell lung cancer, and testicular cancer. Four percent of patients treated with etoposide develop moderate to severe distal, axonal, and mostly sensory polyneuropathy. The potential mechanism for this neurotoxicity is inhibition of microtubule function.<sup>41</sup>

Ifosfamide is an analogue of cyclophosphamide with neuropathy as a side effect at a total dose of at least 14 g/m<sup>2</sup>.<sup>42</sup> Patients often experience numbness and painful paresthesias that begin in both hands and feet within 10 to 14 days after treatment.<sup>42</sup>

Thalidomide (Thalomid) is an antiangiogenic drug used in patients with refractory MM. Greater than two-thirds of patients exposed to thalidomide for at least 6 months experience some form of peripheral neuropathy. Mostly motor, sensory, and autonomic dysfunctions are observed.<sup>43</sup>

### Management of Neuropathic Pain

The World Health Organization's analgesic ladder for cancer pain relief recommends a stepwise approach, starting with non-opioids then moving up the ladder to opioid therapy,

as needed.<sup>44</sup> Several factors have been identified that impede appropriate pain control in cancer patients.<sup>45</sup> Often, when multiple agents are administered at the same time, it is difficult to assess which of the agents are efficacious and which cause adverse events. Proper management of neuropathic cancer pain (NCP) is complex because of the heterogeneity of etiologies, variable symptoms, and the underlying neurogenic pathophysiology. These properties contribute to patients' poor responses to conventional pain management therapy.

An additional consideration is that most of the agents used in the management of neuropathic pain are grouped according to their pharmacological class or original therapeutic category—such as antidepressants and anticonvulsants. Confusion occurs when healthcare professionals unfamiliar with neuropathic pain assume that all anticonvulsants or antidepressants may be efficacious in the management of neuropathic pain. A pain medication that was efficacious for a group of patients with similar mechanisms of neuropathic pain may not translate to equal response in a different patient population or varying neuropathy types.<sup>45</sup>

Lastly, it has been noted that opioid therapy has limited utility in treating neuropathy.<sup>46</sup> However, it is important to note that certain opioids seem to have more usefulness than others for neuropathic pain disorders; these include methadone, levorphanol, tapentadol (Nucynta), and tramadol.<sup>47</sup> Often, higher doses of opioids are required to manage neuropathic pain. However, increased opioid doses usually translate into increased risk of toxicity, which often leads to discontinuation of the therapy. When managing patients with NCP, it is important to initiate pharmacotherapy one medication at a

time, with a slow titration to match the patient's response and tolerability.<sup>48</sup> Thus, the recommendation is to tailor each patient's pain management therapy to suit the individual.

Table 4 highlights treatments for NCP. As noted, addition of adjuvant analgesics to schedule II and III opioids are the mainstay of neuropathy management in a cancer patient; however, non-opioid analgesics that combine multiple mechanisms across two or more agents are often more useful than adding or continuing an opioid. A list of recommended adjuvants include antiepileptic drugs (AEDs), antidepressants (eg, tricyclic antidepressants, duloxetine [Cymbalta], and venlafaxine), corticosteroids, bisphosphonates, -methyl-D-aspartate (NMDA) antagonists, and other substances. Selection of the right agent depends on side-effect profile, and the final choice should be based on identifying the type of painful neuropathy and perhaps comorbid non-neuropathic pain issues. If, for example, the patient does in fact require an opioid other than for neuropathy, it makes sense to select an agent that is particularly useful for both pain types.

### Adjuvant Analgesics

#### Antidepressants

**Tricyclic antidepressants (TCAs)** inhibit norepinephrine and serotonin reuptake by blocking the serotonin and norepinephrine transporters. This action results in an increased synaptic concentration of serotonin and norepinephrine to enhance neurotransmission. TCAs also modulate peripheral sodium channels and antagonize NMDA to a small degree. As a result, they are known to enhance dorsal root inhibition and reduce peripheral sensitization.<sup>49</sup> Since it was first reported by Paoli et al in 1960,<sup>50</sup> TCAs have been shown to exhibit an effect in managing chronic pain. In addition,

**Table 4. Treatments for Neuropathic Cancer Pain<sup>a</sup>**

Drug (Brand)	Mechanism of Action	Common Adverse Reactions	Special Considerations
<b>TCA's</b>			
<b>Amitriptyline (generic)</b>	Inhibits the reuptake of NE. All but desipramine and nortriptyline also block reuptake of 5-HT	Somnolence (drowsiness), confusion, orthostatic hypotension, xerostomia (dry mouth), constipation, urinary retention, weight gain, arrhythmia	Amitriptyline most likely to produce drowsiness
<b>Desipramine (Norpramin, generic)</b>			All TCAs require dose adjustments in cases of hepatic impairment except amitriptyline
<b>Doxepin (Silenor, generic)</b>			
<b>Imipramine (Tofranil, generic)</b>			
<b>Nortriptyline (Pamelor, generic)</b>			
<b>Trimipramine (Surmontil, generic)</b>			
<b>SNRIs</b>			
<b>Duloxetine (Cymbalta)</b>	Inhibits the reuptake of NE and 5-HT	Sedation, nausea, constipation, ataxia, xerostomia	Contraindicated in patients with glaucoma
<b>Milnacipran (Savella)</b>		Nausea, insomnia, hypertension, seizures, dizziness, hot flashes	Contraindicated in closed-angle glaucoma
<b>Venlafaxine (Effexor, generic)</b>		Nausea, dizziness, somnolence, hyperhidrosis, hypertension, constipation	Dosage adjustments required in renal failure
<b>Antiepileptics</b>			
<b>Gabapentin (Neurontin, Gralise, generic)</b>	Binds to $\alpha_2\delta$ subunit on voltage-gated calcium channels to reduce neuronal calcium currents	Lethargy, peripheral edema, back pain, weight gain, somnolence, dyspepsia	Dosage adjustments required if renal impairment (CrCl <60 mL/min)
<b>Pregabalin (Lyrica)</b>		Somnolence, xerostomia	Dose adjustments required if CrCl <60 mL/min; can be removed by hemodialysis
<b>Opioids</b>			
<b>Levorphanol</b>	$\mu$ -opioid receptor agonist, $\kappa_1, \kappa_3 > \kappa_2$ receptor agonist, NMDA-receptor antagonist, inhibits reuptake of NE	Nausea, vomiting, constipation, pruritus, respiratory depression	Phase II glucuronidation to levorphanol-3-glucuronide
<b>Methadone (Dolophine, generic)</b>	$\mu$ -opioid receptor agonist, NMDA-receptor antagonist, inhibits reuptake of NE	Nausea, vomiting, constipation, pruritus, respiratory depression	Metabolized by CYP1A2, CYP2C9, CYP2B6, CYP2D6, CYP2C19, and CYP3A4. P-glycoprotein substrate. Contraindicated in patients with ileus, respiratory depression, status asthmaticus

<sup>a</sup>Only includes selected medications mentioned in text; table not inclusive.

5-HT, serotonin; CrCl, creatinine clearance; CYP, cytochrome; NE, norepinephrine; NMDA, *N*-methyl-D-aspartate; SNRIs, serotonin norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants

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**Table 4. Treatments for Neuropathic Cancer Pain<sup>a</sup> (continued)**

Drug (Brand)	Mechanism of Action	Common Adverse Reactions	Special Considerations
<b>Tapentadol</b>	μ-opioid receptor agonist, inhibits reuptake of NE	Dizziness, vertigo	Phase II glucuronidation to O-glucuronide; CYP2C9/2C19 mediated methylation to N-desmethyl-tapentadol. Listed risk of serotonin syndrome is not supported by mechanism of action
<b>Tramadol (Ryzolt, Ultram, generic)</b>	μ-opioid receptor agonist, inhibits reuptake of NE and 5-HT	Dizziness, vertigo, constipation, vomiting	Substrate of CYP2D6, CYP3A4, and CYP2B6. Increased risk of serotonin syndrome when administered with serotonergics
<b>General Anesthetic</b>			
<b>Ketamine (Ketalar, generic)</b>	NMDA-receptor antagonist	Hypertension, diplopia, nystagmus, hallucinations	Contraindicated in patients with head trauma, hypertension, intracranial bleeding, intracranial mass, myocardial infarction, stroke
<b>Topical Anesthetic</b>			
<b>Lidocaine 5% patch (Lipoderm)</b>	Blocks initiation and conduction of nerve impulses by decreasing nerve membrane permeability to sodium to reduce rate of membrane depolarization	Local rash and erythema	Contraindicated in patients with amide local anesthetic hypersensitivity, sepsis. Used for local neuropathies only and not intended for transdermal absorption

<sup>a</sup>Only includes selected medications mentioned in text; table not inclusive.

5-HT, serotonin; CrCl, creatinine clearance; CYP, cytochrome; NE, norepinephrine; NMDA, *N*-methyl-D-aspartate; SNRIs, serotonin norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants

clinical reports have also demonstrated their effectiveness in treating neuropathic pain and HIV sensory neuropathy. The effectiveness of amitriptyline in relieving neuropathic pain following breast cancer was reported by Kalso et al in a randomized, placebo-controlled study with a 2-week washout period.<sup>51</sup> Fifteen patients participated in the study, and each started at a dose of 25 mg, which was escalated to 100 mg daily over 4 weeks. At the end of the study, 53% of the patients were classified as good responders (50% decrease in pain intensity) with a median dose of 50 mg amitriptyline. The patients who were poor responders reported more adverse effects with amitriptyline and placebo.

Despite efficacy in treating neuropathic pain related to breast cancer,

the adverse effects prevent many patients from regularly using the medication. Tertiary amines such as amitriptyline, imipramine, and doxepin produce a greater anticholinergic activity than the secondary amines: nortriptyline and desipramine. Anticholinergic side effects include dry mouth, impaired diaphoresis, increased thirst, tachycardia and pupillary dilation. Patients may also experience urinary retention, agitation, cognitive impairment, seizures, cardiac arrhythmias, and heart block. The anticholinergic side effects all can add to problematic side effects that are common with opioids.

TCAs should be started at the lowest effective dose possible and should be given at bedtime. The dose can be titrated upward slowly every 3 to 7 days usually until 150 mg or

until adverse events make them intolerable<sup>45</sup>

**Serotonin norepinephrine reuptake inhibitors (SNRIs)** have a different chemical structure compared to TCAs. They exert their antidepressant effects by inhibiting norepinephrine and serotonin reuptake. Venlafaxine is an SNRI with some efficacy for neuropathic pain. Data supporting its use in this patient population reported a number needed to treat (NNT) of 3.6. In a randomized, crossover trial of venlafaxine (220 mg/d) and imipramine (150 mg/d) in patients with polyneuropathy, both antidepressants provided superior relief compared to placebo.<sup>52</sup> However, there were no differences in efficacy between those two groups. Venlafaxine was effective at a dose >150 mg/day in diabetic neuropathy,



whereas 75 mg daily was ineffective. The side effects of venlafaxine include hypertension, which limits its use in patients with pre-existing or uncontrolled hypertension.<sup>53</sup> The efficacy of venlafaxine in cancer patients was demonstrated in a study by Tasmuth et al.<sup>54</sup> In the randomized, double-blind, crossover study, patients given venlafaxine over a 10-week period showed superior pain relief for painful polyneuropathy and neuropathic pain following treatment with venlafaxine compared with placebo.<sup>53</sup>

Duloxetine is an SNRI that is FDA approved for the treatment of diabetic neuropathy. Recently, it was reported in a randomized, placebo-controlled phase III trial to be effective in reducing painful chemotherapy-induced peripheral neuropathy.<sup>55</sup> The study showed that duloxetine 60 mg daily was efficacious and well tolerated for the treatment of either taxane- or platinum-related painful chemotherapy-induced peripheral neuropathy.

Milnacipran (Savella) is also an SNRI, which is FDA approved for the management of fibromyalgia, but not depression.<sup>56</sup> There have been no comprehensive studies involving milnacipran in cancer patients with peripheral neuropathy. However, since it has similar mechanisms as other medications in this class, it is probable that this drug may have utility in some patients.

### **Antiepileptics**

Gabapentin is an analogue of the neurotransmitter  $\gamma$ -aminobutyric acid (GABA). The agent binds to the  $\alpha_2\delta$  subunit of calcium-dependent voltage-gated channels in the nervous system. Gabapentin is an anticonvulsant medication that currently has the broadest evidence for efficacy in the management of neuropathic pain.<sup>57-59</sup> It exerts its action on the brainstem via its glutamate-dependent mechanism.

It has also been shown to have anti-malldynic effects through alteration of the microglial cell function. In one study, 75 patients with CIPN and neuropathic pain were given a fixed low dose of gabapentin (800 mg/d).<sup>60</sup> These patients were compared to 35 patients in the control group (same symptoms and history of similar treatment who refused gabapentin) who were given fixed-dose naproxen (250 mg bid) and codeine/acetaminophen (30/500 mg tid). The authors noted that outcomes were based on four stages of analgesic response: complete, partial, minor, and no response. In the gabapentin arm, the treatment led to 25.3% complete response, 44% partial response, 25.3% minor response, and 5.3% no response. In the control group, none of the patients experienced complete response; percentage for partial, minor, and no response were 5.7%, 45.7%, and 48.6%, respectively.<sup>60</sup>

In another study evaluating gabapentin in cancer patients previously treated with opioids with minimal analgesia response, 121 patients were given gabapentin at a dose of 600 to 1,800 mg daily. The study found a significant difference of average pain intensity between gabapentin (pain score, 4.6) and placebo group (pain score, 5.4;  $=0.0250$ ). Among secondary outcome measures, dysesthesia score showed a statistically significant difference ( $=0.0077$ ) This study demonstrated that patients who were unsuccessfully managed on opioids can transition to gabapentin and obtain pain relief.<sup>61</sup>

In addition, gabapentin has been shown to be helpful in patients with burning pain, shooting pain, and allodynia when pain does not respond to opioids. Results from a study looking at a combination of gabapentin with morphine showed

improvement in sleep, daily activity, mood, and quality of life in cancer-related pain conditions.<sup>61,62</sup> Gabapentin also is a useful medication for patients with malignancies of the upper abdomen such as pancreatic cancer; for reducing pain associated with procedures in cancer; and for decreasing myoclonic movements that are associated with high doses of opioids in cancer pain.<sup>61,62</sup>

Effective doses of gabapentin for neuropathic pain in adults range from 1,800 to 3,600 mg daily, in divided doses, based on a meta-analysis double-blind placebo-controlled, randomized trials in 2003.<sup>63</sup> Effective counseling points for patients include knowing that the drug can induce somnolence, dizziness, and some mild peripheral edema.

Pregabalin's (Lyrica) mechanism of action is similar to gabapentin: both bind to the  $\alpha_2\delta$  subunit of voltage-gated calcium channels of the nervous system. Pregabalin also minimizes the release of the neurotransmitters glutamate, norepinephrine, substance P, and calcitonin gene-related peptide. It does not bind directly to GABA receptors. Pregabalin has been approved for postherpetic neuropathy and peripheral diabetic neuropathy, but not NCP. The efficacy of pregabalin to provide significant pain relief and decrease the need for higher opioid doses in cancer patients battling neuropathic pain was assessed in a prospective, open-label study.<sup>64</sup> In the study, 66 cancer patients with neuropathic pain resistant to a combination of acetaminophen, codeine, non-steroidal anti-inflammatory drugs, and methylprednisolone were randomly divided into two groups. Group one received pregabalin added to their pain regimen. Pregabalin was titrated up to 600 mg

daily until pain relief was observed or patients experienced intolerable side effects. The second group received fentanyl 25 mcg per hour, which was escalated by 25 mcg per hour every 72 hours—up to a maximum of 125 mcg per hour—until the patient experienced adequate pain relief or intolerable toxicities. The authors discovered that pregabalin was effective in providing significant pain relief (69% decrease in a visual analogue scale [VAS] pain score—from 7.8 to 2.4) and both minimized the use of opioids and opioid-induced side effects. Pregabalin was also found to be efficacious in an open-label study of pediatric cancer patients on a daily dose of 150 to 300 mg for 8 weeks.<sup>65</sup> The investigators reported significant and long-lasting pain relief in 86% of the children, and the median VAS score decreased by 59%. Adverse effects were infrequent and transient. According to pharmacokinetic studies, pregabalin is more potent than gabapentin because its binding affinity for the  $\alpha_2\delta$  subunit is six times greater than that of gabapentin, it has faster absorption (does not bind to plasma proteins), and has greater bioavailability (>90%).<sup>66</sup>

Other AEDs have shown efficacy in other types of neuropathic pain but not in neuropathic pain associated with cancer. For instance, lamotrigine is effective in treating HIV sensory neuropathy, painful diabetic neuropathy, central poststroke pain, and pain from spinal cord injury.<sup>67-70</sup> There has been wide application of anticonvulsants in neuropathic pain management; however, only a few trials have shown efficacy in cancer patients. We must be especially cognizant that drugs such as lamotrigine may carry a higher risk of hepatotoxicity in patients receiving hepatotoxic antineoplastics. A huge advantage of

gabapentin is that it's not metabolized in humans, has very limited effect on the liver, and has relatively no drug interactions for this reason.<sup>71</sup> It should be noted, however, that the dose of gabapentin must be adjusted for renal insufficiencies beginning with a creatinine clearance <60 mL per minute. Pregabalin presents less of an issue with reduced renal function.<sup>66</sup>

#### **Other Agents**

Tramadol works by inhibiting norepinephrine and serotonin reuptake, and has indirect monoaminergic action similar to the TCAs.<sup>72</sup> The NNT with tramadol compared to placebo was 3.8, with at least 50% relief of the neuropathic pain alleviated.<sup>72,73</sup> In patients with musculoskeletal pain and NCP, the NNT for tramadol is 3.4. Tramadol has been shown to improve the quality of life in patients with neuropathic pain. There was no change in their level of anxiety, depression, and nervous system function despite obtaining adequate analgesic control. Generally, a common starting dose of immediate-release tramadol is 100 mg daily titrated up to 200 to 400 mg daily (in four divided doses). Efficacy for neuropathic pain can be observed at doses >250 mg daily. Due to its low abuse potential and minimal chance of developing tolerance and dependence during long-term use, tramadol serves as a good alternative for cancer patients with disease-induced neuropathic pain. The most common side effects associated with tramadol include dizziness, nausea, constipation, somnolence, and orthostatic hypotension. It is possible for patients to develop seizures when tramadol is used concomitantly with selective serotonin reuptake inhibitors or monoamine oxidase inhibitors.

Methadone is an opioid that blocks

NMDA receptors and inhibits reuptake of norepinephrine—both activities contributing to its efficacy in the management of neuropathic pain and NCP. Cancer patients who might be ideal candidates for a trial of methadone include patients with poor pain control, those who have received an adequate trial of other schedule II or III opioids, patients with severe or multiple toxicities to other strong opioids, and those receiving opioids who have difficulty swallowing.<sup>74</sup> Methadone is associated with life-threatening adverse effects that are attributable to elevated serum levels from drug interactions. Drugs that inhibit P-glycoprotein and cytochrome P450 isoenzymes CYP2C19, CYP3A4, and CYP2B6 could significantly increase serum levels of methadone and induce methadone toxicity.<sup>75</sup>

Ketamine is a general anesthetic that recently has been studied as a postoperative pain medication. Ketamine is an NMDA-receptor antagonist. The NMDA receptors within the spinal cord have been shown to play a significant role in the pathophysiology of chronic neuropathic pain. At sub-anesthetic doses, ketamine has been shown to reduce hypersensitivity in the dorsal horn.<sup>76</sup> There has been some suggestion that ketamine may reduce opioid-resistant NCP. When combined with morphine, ketamine provided superior pain relief and opioid-sparing ability.<sup>76</sup> There are multiple case reports of ketamine's use, either orally or intravenously, as an adjuvant for cancer-induced neuropathic pain management. What limits the use of ketamine are the potential developments of dissociative reactions and hallucinations after a patient is exposed to it. Ketamine has been used as a recreational drug due to its rapid onset, short duration of action, and psychotropic effects.<sup>77</sup>

### Topical Therapy

The only topical antineuralgic agent shown to have efficacy in NCP is the lidocaine 5% patch (Lidoderm). It is most effective with pain associated with allodynia, a pain due to stimulus that does not normally provoke pain.<sup>78</sup> It has also been used in central neuropathic pain syndrome in patients with metastatic lesions of the spinal cord.<sup>79</sup> Despite some stated efficacy, lidocaine patches did not significantly reduce pain intensity ratings or related secondary endpoints in cancer patients with persistent pain associated with incisions.<sup>80</sup>

Thus far, no single pharmacotherapy has an FDA indication for CIPN. Only pregabalin, tapentadol, and duloxetine are approved for diabetic peripheral neuropathic pain, with pregabalin having an added indication for neuropathic pain associated with spinal cord injury. Carbamazepine has the indication for trigeminal neuralgia.

### Preventing CIPN

infusions have been shown to reduce the incidence of CIPN. Several studies have shown that calcium-magnesium infusions reduce the incidence of neurotoxicity and subsequent peripheral neuropathy in cancer patients undergoing chemotherapy.<sup>81,82</sup> The antitumor efficacy of these chemotherapy agents was not affected; however, patients who received the infusions stayed on therapy longer than the control group.

was studied in an open-label trial in patients receiving oxaliplatin. There was significantly less grade 1-2 and grade 3-4 CIPN after 4 to 6 cycles in patients who were given glutamine compared to the control arm.<sup>83</sup> While there was a lower need for oxaliplatin dose reduction in the glutamine group, a larger randomized placebo-controlled trial

is needed before this can be used in a larger practice.

has been shown to prevent the accumulation of platinum agents in the dorsal root ganglia. Two small trials looked at the effectiveness of glutathione in preventing CIPN in patients receiving either cisplatin or oxaliplatin. There was significantly less peripheral neuropathy of any grade in patients receiving either 4 or 8 cycles of oxaliplatin in the glutathione-treated group, compared with the placebo-controlled group.<sup>84</sup> Moreover, there was no difference in chemotherapy response rates. A similar result was obtained in patients given glutathione while undergoing treatment with cisplatin.<sup>85</sup>

is an antioxidant that increases the body's concentration of glutathione. In a study where 14 patients were receiving oxaliplatin, oral N-acetylcysteine reduced the incidence of CIPN in these colon cancer patients.<sup>86</sup> Additional, larger studies are needed prior to recommendation for widespread use.

There have been some data to suggest that vitamin E has some role to play in decreasing the risk of CIPN. In an open-label study, patients were given vitamin E 300 mg daily during cisplatin therapy and for 3 months after treatment completion. CIPN was observed in 31% of patients who received vitamin E compared to 86% of the control arm ( $<0.01$ ).<sup>87</sup> Subsequent studies have shown that vitamin E reduced CIPN in patients undergoing treatment with cisplatin, paclitaxel, or a combination of cisplatin and paclitaxel.<sup>88,89</sup> The major concern with the use of vitamin E in patients receiving chemotherapy is that as an antioxidant, it might interfere with the oxidative breakdown of cellular DNA and cell membranes necessary for the chemotherapy agents to work.

### Conclusion

Peripheral neuropathy treatment is a challenge in any setting, but requires unique skills and an even more comprehensive evaluation in the presence of cancer, especially with concurrent ongoing or previous antineoplastic therapy. While there has been much progress made in this area, identifying adjuvant analgesics that are safe and effective in the cancer patient requires careful diagnostic delineation, a keen knowledge of rational polypharmacy, and skillful assessment for success. ■

**Authors' Bios:** *Josephine Sasu-Tenkoramaa, PharmD, has accepted a PGY-2 Hematology/Oncology Pharmacy Residency at the VA San Diego Healthcare System.*

*Jeffrey Fudin, BS, PharmD, RPh, DAAPM, FCCP, is Adjunct Associate Professor of Pharmacy Practice at Albany College of Pharmacy and Health Sciences and Clinical Pharmacy Specialist in Pain Management at the Samuel Stratton VA Medical Center in Albany, New York.*

*This commentary is the sole opinion of the authors and does not reflect the opinion of employers, employee affiliates, and/or pharmaceutical companies listed. It was not prepared as part of Dr. Fudin's official government duty as Clinical Pharmacy Specialist.*

*Dr. Fudin is on the speakers' bureau for Janssen Pharmaceuticals, Inc, and Purdue Pharma. He is a consultant to Practical Pain Management in the development of the online Opioid Calculator. Dr. Sasu-Tenkoramaa has no financial information to disclose.*

**Questions/Queries:**  
send to  
[nikki.kean@verticalhealth.com](mailto:nikki.kean@verticalhealth.com)

## Patient With Colorectal Cancer\*



\*Image is of a model, not an actual patient.

Mark is a 55-year-old African American man who presented to his primary care physician (PCP) with complaints of abdominal pain, change in stool color, and pain during defecation for the past week. Upon further workup, the PCP found the patient's stool sample was positive for guaiac and his hemoglobin/hematocrit levels had decreased from 6 months ago. The patient was referred to an oncologist for further evaluation. A colonoscopy was performed and it revealed a narrowing of the transverse colon. The colonoscopy also found significant narrowing at the descending colon with multiple polyps in the sigmoid colon. A biopsy was performed and was shown to be adenocarcinoma of the colon. Staging was performed and computed tomography imaging revealed extensive disease with muscular mucosa invasion and metastases to the liver (Duke's Stage D IV).

### Past Medical History and Medications

Mark is an obese, diabetic patient with hypertension. Diabetes mellitus was diagnosed 25 years ago; current medications include insulin aspart 25 units subcutaneously 5 to 10 minutes before meals and insulin glargine 60 units subcutaneously at bedtime. The patient developed hypertension 12 years ago; current medications include oral lisinopril 10 mg daily and metoprolol tartrate 100 mg twice daily.

Family history: Father died of myocardia infarction at age 45; mother died of breast cancer at age 60; older sister is currently in remission from breast cancer (diagnosed age 40); maternal aunt died of rectal cancer at age 45.

Social history: drinks 3 beers per day; cigarettes, 60-packs-per-year history; he's married and has two daughters ages 25 and 28.

Examination of abdomen, cardiovascular system, pulmonary system, head, ears, eyes, nose, and throat were unremarkable. A neurological exam was normal. He has no known drug allergies. Lab results are highlighted in Table 1.

### Chemotherapy Regimen

Mark was started on a 2-week cycle of chemotherapy that included:

- Leucovorin  $200 \text{ mg/m}^2 \times 2.21 \text{ m}^2 = 442 \text{ mg}$  infused

over 2 hours on days 1 and 2

- Fluorouracil (5-FU)  $400 \text{ mg/m}^2 \times 2.21 \text{ m}^2 = 884 \text{ mg}$  IV bolus days 1 and 2
- Oxaliplatin  $85 \text{ mg/m}^2 \times 2.21 \text{ m}^2 = 188 \text{ mg}$  IV on day 1
- 5-FU  $600 \text{ mg/m}^2 \times 2.21 \text{ m}^2$  IV over 22 hours

After 8 weeks (4 cycles), Mark reported pain in his hands and feet that was sensitive to cold. He reported occasional tingling, but numbness was frequent and was not relieved by movement. He also reported increased back pain (potentially secondary to his weight and potential metastases).

### Risk of Peripheral Neuropathy

Mark has two factors that placed him at high risk for developing peripheral neuropathy. First, he has a history of uncontrolled diabetes, which is no longer sensitive to oral hypoglycemic management. Second, he was given a chemotherapy regimen that included oxaliplatin.

Because Mark's colorectal cancer has metastasized, the peripheral neuropathy needs to be treated so that he can continue with his chemotherapy regimen. To encourage continued treatment and adequate pain management, the patient should expect reasonable pain mitigation to eliminate or minimize discomfort associated with the chemotherapy.

### What Options Are Available to Treat This Patient's Pain?

- Since the patient is actively receiving chemotherapy, non-steroidal anti-inflammatory drugs (NSAIDs) are not recommended; they offer minimal if any efficacy for neuropathic pain and there is an increased risk of thrombocytopenia. Other risks include elevated blood pressure and diabetic nephropathy considering the already elevated serum creatinine. Due to hepatic impairment, his international normalized ratio is also elevated, which presents another risk for NSAIDs.
- Tricyclic antidepressants (TCAs) should be avoided, as they can significantly add to lethargy associated with the disease, anemia, and treatments. Furthermore, titration of TCAs for extended use most likely will eventually become problematic should the need for opioid therapy arise considering the significant constipating effects when combining these therapies.
- Tramadol (25 mg po qid) titrated weekly could be used for management of back pain and neuropathy, but it is not an option in this patient due to uncontrolled hypertension.
- When considering opioids, combination with acetaminophen should be avoided in this patient because of his liver issues. Moreover, most opioids—with the exception of those that block *N*-methyl-D-aspartate receptors (NMDA-R) or inhibit reuptake of norepinephrine—are not as useful for managing neuropathies. Examples of the former are methadone and levorphanol. Examples of the latter are tramadol and tapentadol.<sup>1</sup>
- Pregabalin has to be adjusted for hepatic impairment, but is an option in this case if titrated slowly.<sup>2</sup>
- Gabapentin (100 mg po tid) can be used in this patient even with hepatic injury, as it requires no metabolism in humans and is excreted renally unchanged.<sup>3</sup> Gabapentin can be titrated weekly to a target dose of 3,600 mg daily in divided doses until adequate effect or until unacceptable toxicity.<sup>4</sup>
- Rational polypharmacy is also an option. An example here might be low-dose gabapentin combined with morphine.<sup>5</sup> However, if an opioid is required, it may be more reasonable to try one of the agents emphasized above first.

**Table 1. Physical and Laboratory Results**

Vital Signs:

- Blood pressure: 150/90 mm Hg
- Temperature: 99.1 °F
- Height: 5'9"
- Weight: 100 kg

Significant Lab Results:

- Fasting blood glucose: 200 mg/dL
- Hemoglobin A1C: 9.2%
- Hematocrit: 32.2%
- CEA: 25.6 ng/mL
- Serum creatinine: 1.9 mg/dL
- INR: 1.5
- PTT: 26
- ALT: 837 U/L
- AST: 1,030 U/L
- Alkaline phosphatase: 255 U/L
- Albumin: 2.5 g/dL
- Total bilirubin: 2.4 mg/dL
- WBC: 5.6 x 10<sup>3</sup>/mcg/L

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CEA, carcinoembryonic antigen; INR, international normalized ratio; PTT, partial thromboplastin time; WBC, white blood cells

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