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## Case report

# Dramatic recovery of paclitaxel-disabling neurosensory toxicity following treatment with venlafaxine

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**Venlafaxine is an antidepressant which acts through the inhibition of the reuptake of norepinephrine and serotonin. Venlafaxine is active against neuropathic and chronic pain. We report the case of a 69-year-old woman who presented a paclitaxel-induced neuropathy. She presented paresthesias, pin pricks in both hands with functional impairment. Venlafaxine hydrochloride was introduced at 37.5 mg twice daily. The patient noticed a dramatic recovery of her symptoms within 2 days, with both reduction of the paresthesias and functional improvement. This is the first report of efficacious use of venlafaxine for the treatment of paclitaxel cumulative neurosensory toxicity. [© 2002 Lippincott Williams & Wilkins.]**

*Key words:* Antidepressant agent, neuropathy, paclitaxel, pain, venlafaxine.

## Introduction

The taxanes are an important recent class of anticancer agents that exert their cytotoxic effects through a unique mechanism.[1] The prototypical taxane, paclitaxel, was identified in 1971 as the active constituent of an extract from the bark of the Pacific yew (*Taxus brevifolia*)[2] and was the first taxane in clinical trials. The unique structure of paclitaxel is characterized by the unusual taxane ring system. Its binding site on microtubules is distinct from that of vincristine and other vinca alkaloids.[3] Paclitaxel has demonstrated clinical activity against a variety of solid tumors. This has led to the regulatory approval of paclitaxel in many countries for the treatment of metastatic breast, ovarian and lung cancers.[1,4,5] Neutropenia was the principal dose-limiting side effect in phase I clinical trials. Although neutropenia has been the acute limiting toxicity, it remains an easily manageable toxicity.[6]

Given the neurotoxicity of other agents which affect microtubules, such as vinca alkaloids, it is not surprising that paclitaxel has been associated with similar neurotoxic symptoms. Peripheral neuropathy has become the principal dose- and duration-limiting toxicity of paclitaxel.[7,8] Paclitaxel induces a peripheral neuropathy that is characterized by sensory manifestations. The most common symptoms have been numbness and paresthesias in a glove-and-stocking distribution.[7] Severity is associated with increased cumulative dose. As with other polyneuropathies, patients with pre-existing peripheral neuropathies, such as those caused by diabetes mellitus or ethanol, appear to be particularly predisposed to develop neurological toxicity.

No treatment has demonstrated activity for the treatment of severe paclitaxel-induced neuropathies. Venlafaxine is an antidepressant that inhibits reuptake of both serotonin and norepinephrine.[9,10] Venlafaxine has previously shown therapeutic effects for the management of chronic and neuropathic pains, particularly in patients with diabetes mellitus.[11,12]

We report here the case of a remarkable recovery of major functional impairments secondary to paclitaxel neurosensory toxicity following treatment with venlafaxine hydrochloride. This is the first publication of the potential efficacy of venlafaxine for the treatment of chemotherapy-induced neurotoxicity.

## Case report

A 69-year-old woman was treated for a stage III ovarian adenocarcinoma with a post-surgical

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chemotherapy combining paclitaxel at 175 mg/m$^2$ as a 3-h infusion and carboplatin AUC 5, repeated every 4 weeks.

In her medical history, we noticed a Parkinson's disease which begun 5 years ago, well stabilized, hypothyroidism and hypertension. She did not have diabetes or alcoholic intoxication, or any underlying neuropathy.

After the third cycle, she developed a neurosensory toxicity with paresthesias of the fingers of both hands. She described feelings like pin pricks and swarmings in the whole hands up to the wrist. She also described minor functional impairments: she could not easily hold thin objects. We started treatment with clonazepam, 0.5 mg at night. She did not notice any benefit even with up to 1.5 mg of clonazepam per day, given for 2 months.

After the fifth cycle of chemotherapy, the symptoms progressed. She presented severe functional impairments; she could not use her fingers to grasp any object and could no longer knit.

Venlafaxine hydrochloride (Effexor XR; Wyeth, Collegeville, PA) at 1 pill of 37.5 mg/day was introduced. She reported a very quick recovery of the use of her fingers, her ability to knit again and a reduction of the paresthesias to the last phalanx of the fingers. We increased the chlorhydrate of venlafaxine to 1 pill of 37.5 mg twice daily and reduced the posology of clonazepam. As the patient completely recovered, she did not find it necessary to continue venlafaxine. Two days after the interruption of venlafaxine, she complained because of the re-emergence of functional impairments, as previously described. The reintroduction of venlafaxine led to the same dramatic recovery of the neurosensory symptoms.

## Discussion

The neurotoxicity of paclitaxel is cumulative and progressively worsens after multiple cycles at higher doses. Initially, most patients complain of burning pain, particularly in the feet.[1,7,13–15] The pain is often associated with hyperesthesias. Neurological examination usually reveals distal sensory loss to large (proprioception, vibrations) and small (pin prick, temperature) fiber modalities. Lost of decreased distal deep tendon reflexes are also common in patients with neuropathic complaints. Paclitaxel also induces myalgias in the peri-treatment period. Only a few studies describing the clinical and electrophysical features of paclitaxel-induced neurotoxicity are available in the literature. The neurotoxicity was reported to predominantly consist in sensory-motor, axonal, length-dependent and symmetrical neuropathy.[7] However, paclitaxel sensory neuropathy may be due to an axonopathy, a dorsal root ganglionopathy, a Schwann cell abnormality or more likely a combination of these mechanisms.[7,14–18] The deficit appears to resolve slowly.

Pain and functional impairments secondary to paclitaxel toxicity are commonly resistant to pharmacologic interventions.

Tricyclic antidepressants are used for the first-line treatment for most neuropathic pains.[19–22] They block the central neuronal reuptake of both serotonin and norepinephrine. They decrease pain transmission through the afferent nerves. Unfortunately, the use of these agents is limited by numerous side effects[19–22] even if the doses used for analgesic effects are often one-third to one-half of the antidepressant doses. Amitryptiline has also been proposed to improve the management of residual neuropathic symptoms.[23] Narcotic analgesics appear more reliable for relieving drug-induced dysesthesias.[24–26]

Anticonvulsant agents, such as clonazepam, are also useful in the management of neuropathic pain and provide approximately the same benefit. Selective serotonin reuptake inhibitor antidepressants have been found less effective for neuropathic pain.[24–26]

Venlafaxine is an antidepressant which is also a serotonin and norepinephrine reuptake inhibitor (SNRI), but causes fewer adverse effects than tricyclic antidepressants. In particular, venlafaxine does not bind to muscarinic–cholinergic, histaminic or $\alpha_1$-adrenergic receptors.[9,10] The most common adverse effect is nausea.[11,12]

Reproducible evidence of the efficacy of venlafaxine for the treatment of neuropathic pain has been recently reported.[27–29] The first reported case was a patient with a radicular back pain, which markedly decreased under treatment with venlafaxine.[30] An initial open-label experience of venlafaxine has been described for the treatment of 12 patients with chronic pain, primarily headache (four patients) or neuropathic pain (seven patients).[11] Most of the patients experienced a mild (20–49% pain reduction in three patients) to moderate (50–79% pain reduction in seven patients) pain relief. One patient experienced a complete relief. In the painful peripheral diabetic neuropathy, venlafaxine has shown interesting effects. A 75–100% pain reduction within 3–14 days in 11 type 2 diabetic patients has been first reported.[12] A clinical benefit of venlafaxine, in

association with gabapentin, was also reported in a 26-year-old type 1 diabetic woman who developed burning pains.[31] A randomized trial included 244 patients with painful diabetic neuropathy.[32] Venlafaxine was significantly ($p < 0.05$) more active than placebo on pain relief. Since depression was an exclusion criterion, symptom improvement could be attributed to an analgesic rather than antidepressant effect.

The mechanism of pain relief of venlafaxine seems to be complex. Some similarities between venlafaxine and tramadol, a non-opiate analgesic, have been pointed out.[33] These agents share certain molecular and pharmacological features. The antinociceptive effect was studied in mice.[34] Venlafaxine-induced nociception involved $\kappa_1$ and $\delta$ opioid mechanisms as $\alpha_2$-adrenergic mechanisms.[34] Venlafaxine appeared also effective in thermal hyperalgesia relief in rats.[35] More recently, venlafaxine was shown to increase, in humans, the pain tolerance threshold in response to a single electrical stimulation via monoaminergic mechanisms, especially through serotonin reuptake inhibition.[36] Nevertheless, the mechanism of action of the pain relief obtained with venlafaxine in paclitaxel-induced neuropathy remains poorly understood. Based on the mechanism of action of venlafaxine and on the pathophysiology of oxaliplatin-induced neurosensory toxicity, we may expect venlafaxine to be also active in the symptoms observed in the neuropathy due to oxaliplatin cumulative toxicity. The neurosensory symptoms induced by oxaliplatin are exacerbated by exposure to cold.[37] Hence, the thermal hyperalgesia relief induced by venlafaxine might be beneficial for oxaliplatin-induced neuropathy. The typical neurotoxicity of oxaliplatin has been linked to the accumulation of di-chloro-DACH platinum, a biotransformation product of DACH platinums in axonal and dorsal root ganglia neurons.[38] Recently, we have shown that intra-erythrocytic oxaliplatin may be liberated in the plasma during surgery and this may account for the frequent exacerbation of oxaliplatin neurosensory toxicity immediately following surgery.[39] We consider that the results observed in our patient treated with paclitaxel are encouraging, and invite us to prospectively evaluate the efficacy of venlafaxine in taxane-induced neuropathies and in other chemotherapy-induced neurosensory toxicities such as those observed with platinum compounds.

## Conclusion

This case report is the first evidence of the potential interest of venlafaxine in the treatment of taxane-induced cumulative neurosensory toxicity. This treatment might improve the quality of life of advanced cancer patients who experience severe chronic toxic neuropathies. A prospective clinical trial to study its potential activity seems worthwhile.

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