# Venlafaxine for prevention of oxaliplatin-induced peripheral neuropathy - A randomised clinical trial

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Given the significant number of patients with OIPN and the possible prophylactic properties of venlafaxine, this study is designed. This study will consist of a randomised placebo-controlled clinical trial to study the prophylactic effect of...

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| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Miscellaneous and site unspecified neoplasms benign |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON42624

**Source**
ToetsingOnline

**Brief title**
VENLOX

### Condition

- Miscellaneous and site unspecified neoplasms benign
- Peripheral neuropathies

**Synonym**
nerve damage, neuropathy

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Maasstad Ziekenhuis
**Source(s) of monetary or material Support:** uit ziekenhuisbudget

## Intervention

**Keyword:** oxaliplatin, peripheral neuropathy, venlafaxine

## Outcome measures

### Primary outcome

The primary endpoint is the incidence of oxaliplatin-induced peripheral neuropathy grade >=1 during treatment, measured by the NCI-CTCAE scale. It will be measured after 3 cycles of 3-weekly (130mg/m2) treatments. At this point in treatment total dose is 390 mg/m2. Retrospective research showed that at this time point the chronic neuropathy usually manifests.

### Secondary outcome

1. To study the effect of venlafaxine on the incidence of acute OIPN (NCI-CTCAE scoring) in patients treated with oxaliplatin containing chemotherapy

2. To study the effect of venlafaxine on the maximal severity of OIPN (NCI-CTCAE scoring) in patients treated with oxaliplatin containing chemotherapy

3. To study the effect of venlafaxine on the onset of chronic OIPN as defined by cumulative dose of oxaliplatin when first symptoms occur

4. To study the effect of venlafaxine on the Quality of Life (QOL) during chemotherapy and after 3, 6 and 12 months of oxaliplatin use as scored by the EORTC QLQ-CIPN20 questionnaire.

5. To determine safety of venlafaxine in patients treated with oxaliplatin containing chemotherapy.

# Study description

**Background summary**

Oxaliplatin is a third generation platinum based cytotoxic agent that is widely used for the treatment of colorectal cancer, in adjuvant and metastatic setting. In addition, oxaliplatin is also used in the treatment of other forms of digestive cancer. The mechanism of action of oxaliplatin is not entirely clear but it is hypothesized that oxaliplatin causes DNA damage which leads to apoptosis of cancer cells.
When compared to its platinum-analogue cisplatin, oxaliplatin causes little or no nephrotoxicity, less haematological toxicity and less gastrointestinal side effects. Peripheral neuropathy is a side effect very commonly observed with all platina-analogues, but the oxaliplatin-induced peripheral neuropathy (OIPN) has its unique spectrum and is associated with dose-limiting toxicity. Peripheral neuropathy is a painful disorder characterised by pain due to dysfunction or disease of the nervous system at a peripheral level, a complex entity with many symptoms and signs that fluctuate in number and intensity over time. Important components of neuropathy are steady and neuralgic pain and hypersensitivity. Neuropathic pain can be very disabling, severe and intractable, causing distress and suffering for individuals, including dysesthesia and paresthesia. Sensory deficits, such as partial or complex loss of sensation, are also commonly seen. In addition, there are significant psychological and social consequences linked to chronic neuropathic pain, which contribute to a reduction in quality of life.
In OIPN, two different types of neuropathy are commonly observed: the acute and more chronic form. Acute neuropathy occurs in approximately 60% of patients and manifest itself particularly as intolerance to cold, paresthesia and dysesthesia in the extremities and the perioral region, and an uncomfortable feeling in the throat. These side effects occur mostly within hours after infusion up till 1-2 days after first treatment. Acute neuropathy is generally reversible and disappears within 7-14 days. The mechanism behind acute neuropathy is unclear but experimental data suggest it is caused by oxaliplatin affecting the axonal sodium channel function through damaging of microtubules. The chronic form of neuropathy lasts longer and is associated with cumulative doses and a significant reduction in quality of life. It is characterized by distal dysesthesia and paresthesia that increase in intensity and duration with the cumulative dose. Many patients experience effects still after 12 months after cessation of chemotherapy. The mechanism that is most accepted to be the cause of chronic neuropathy is accumulation of oxaliplatin in the dorsal root ganglia and subsequent progressive loss of function. OIPN symptoms can be so severe, that chemotherapy regimens have to be adjusted by treatment delays, dose reductions or early discontinuations, which may affect cancer treatment outcomes.
Treatment of neuropathy is not easy. Patients with neuropathic pain do not always respond to standard analgesics such as non-steroidal anti-inflammatory

drugs (NSAIDs) and to some extent neuropathic pain is resistant to opiates. The pharmacologic agents best studied and longest used for the treatment of neuropathic pain are antidepressants and anticonvulsants. Several agents have been examined and tested for the prevention and treatment of neuropathy resulting from chemotherapy, with varying success. Intravenous calcium and magnesium infusions have been extensively used for prevention of OIPN, after earlier suggested beneficial effects, but the latest studies showed that the effect of the electrolyte combination can not be proven and may even have negative effects on cancer therapy outcome.
The mechanisms of action of antidepressant drugs in the treatment of neuropathic pain remain uncertain. Analgesia is often achieved at lower dosage and faster (usually within a few days) than the onset of any antidepressant effect which can take up to six weeks. In addition, there is no correlation between the effect of antidepressants on mood and pain. Furthermore, antidepressants produce analgesia in patients with and without depression. Two main groups of antidepressants are in common use. The older tricyclic antidepressants (TCAs) such as amitriptyline and imipramine, and a newer group of selective serotonin reuptake inhibitors (SSRIs). The clinical impression was that TCAs are more effective in treating neuropathic pain. There is no evidence that antidepressants have a pre-emptive effect in preventing the development of neuropathic pain. ASCO guidelines describe a literature search to identify possible preventive and therapeutic measures for chemotherapy induced peripheral neuropathy. Two agents are proposed to have possible beneficial effect: duloxetine and venlafaxine. The use of duloxetine, a selective serotonin- and norepinephrine reuptake inhibitor, is based on a prospective randomized clinical trial by Smith et al. In this study, duloxetine decreased neuropathy pain score by 1,06 on a 11-point scale.
Venlafaxine is an antidepressant, a serotonin and, in higher dosages, a norepinephrine reuptake inhibitor (SNRI); it has shown therapeutic effects for the management of chronic and neuropathic pain, particularly in patients with diabetes mellitus. It is suggested that venlafaxine blocks neuronal sodium channels and thereby can prevent detrimental effect of neurotoxic agents such as oxaliplatin. The rapid onset of the action of the SNRI is an advantage, regarding the consideration that dose reduction of oxaliplatin can be prevented by immediate control of neuropathic symptoms.
Two case reports describe the successful treatment of patients with severe disabling oxaliplatin-induces neuropathy who greatly benefited from venlafaxine. A prospective study from this group with venlafaxine showed promising results for the treatment of acute neuropathy. It gave full relief of neuropathy in 31,3 % of patients (n=54) versus 5,3% in the placebo group (P = 0.03). Venlafaxine was generally well tolerated as evidenced by the relatively low incidence of adverse effects. Nausea, dizziness, fatigue, somnolence and insomnia were the most frequently reported adverse effects, and they were primarily of grade 1 and 2. These results are promising but due to the small sample size of the study and the methodological limitations, the use of venlafaxine is not recommended for routine use in the clinic, and the authors suggest that additional research is necessary to provide supporting data.

Retrospective research in the Maasstad Hospital showed that in 92% of the patients, treated with at least three cycles of oxaliplatin, any form of OIPN occurred. This percentage is comparable to the findings in literature. Dose reduction is currently the strategy to alleviate symptoms. In patients with grade 3 or higher, stopping oxaliplatin is mandated, thereby hampering the success rate of chemotherapy. Some patients are seen by a neurologist. Electromyograms (EMG) are sometimes performed in these patients to examine the extent of peripheral nerve damage. For patients with persisting complaints, either antiepileptic agents (e.g. carbamazepine, pregabalin, gabapentin) or antidepressants (TCA, venlafaxine) are prescribed. The choice for a specific drug is made on the basis of the physician*s preference.

## Study objective

Given the significant number of patients with OIPN and the possible prophylactic properties of venlafaxine, this study is designed. This study will consist of a randomised placebo-controlled clinical trial to study the prophylactic effect of venlafaxine on the incidence and severity of OIPN in patients treated with oxaliplatin.

To determine the effect of venlafaxine versus placebo on the incidence of patients with chronic OIPN (%) after 3 cycles of oxaliplatin containing chemotherapy (130 mg/m2 every three weeks regimen). Incidence is defined as the occurrence of patients with any grade neuropathy symptoms as defined by adverse event criteria of the US National Cancer Institute (Common Terminology Criteria for Adverse Events 2010).

## Study design

Double blind, placebo-controlled phase III clinical trial to evaluate the efficacy of venlafaxine for prevention of OIPN during treatment with oxaliplatin. The study will take place in the Maasstad Hospital Rotterdam, Ikazia Hospital Rotterdam, Spijkenisse Medical Center and Van Weel Bethesda Hospital in Dirksland. Patients who receive oxaliplatin as part of their adjuvant or palliative XELOX regimen (iv oxaliplatin 130 mg/m2 every 3 weeks combined with po capecitabine 1000 mg/m2 bid for 2 weeks, with or without bevacizumab) for colorectal, oesophageal, pancreatic or stomach cancer will be asked to participate. A total of 150 patients will be recruited and randomised to the intervention arm or placebo arm in a 1:1 ratio. Inclusion will take place over a period of about 2 years.

## Intervention

Patients will be randomly assigned to receive one of the following double-blind treatments during the course of chemotherapy:

Venlafaxine hydrochloride extended release capsules (XR) or matching placebo 37,5 mg once daily (OD) in week 1 of cycle 1 and twice daily (BID) in week 2 and further. Increase to 75 mg BID is possible (to doctors insight) after cycle 2 if OIPN Grade >=2 occurs. This dose escalation option is based on the data in neuropathic pain.

**Study burden and risks**

Retrospective research in the Maasstad Hospital showed that in 92% of the patients, treated with oxaliplatin, OIPN occurred. This percentage is comparable to the findings in literature. Given the significant number of patients with OIPN and the possible prophylactic properties of venlafaxine this study is designed. The use of venlafaxine for neuropathy is based on several preliminary small scale clinical studies. This study attributes additional data on the use of venlafaxine, and can thereby lead to a recommendation for venlafaxine in the prevention of OIPN.

# Contacts

**Public**
Maasstad Ziekenhuis

Maasstadweg 21
Rotterdam 3079 DZ
NL
**Scientific**
Maasstad Ziekenhuis

Maasstadweg 21
Rotterdam 3079 DZ
NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

### Inclusion criteria

• 24 years or older
• Oxaliplatin based chemotherapy, XELOX regimen (with or without bevacizumab)
• Performance state of at least 2 (ECOG) or 60 (Karnofsky)
• Written informed consent

### Exclusion criteria

• Participating in other clinical trial (eg CAIRO 4 or Orchestra studies in colorectal carcinoma patients)
• Brain or leptomeningeal metastasis
• Previous treatment with platinum based chemotherapy
• Alcohol addiction
• (Pre)existing neuropathy
• Use of anti-epileptics, anti-depressants, anti-retroviral drugs, MAO-inhibitors or lithium.
• Use of strong enzyme modulating drugs (CYP2D6): fluoxetine, bupropion, kinidine, paroxetine or ritonavir
• Psychologically instable, psychiatric disorder
• Known allergy for venlafaxine
• Pregnancy or breast feeding

## Study design

### Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

### Recruitment

NL

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|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-02-2016 |
| Enrollment: | 150 |
| Type: | Anticipated |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Generic name: | Venlafaxine |
| Registration: | Yes - NL outside intended use |

## Ethics review

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|---|---|
| Approved WMO Date: | 01-02-2017 |
| Application type: | First submission |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2015-005060-42-NL |

| Register | ID |
| --- | --- |
| CCMO | NL55698.101.15 |