Duloxetine for chronic osteoarthritis pain; an important alternative?

Published: 26-02-2015
Last updated: 14-04-2024

The objective of this proposal is to investigate if duloxetine is effective as a third choice pain medication for treating chronic pain in OA compared to usual care. Furthermore, we will assess the cost-effectiveness of duloxetine treatment and if...

Ethical review	Not approved
Status	Will not start
Health condition type	Joint disorders
Study type	Interventional

Summary

ID

NL-OMON42274

Source
ToetsingOnline

Brief title
Duloxetine for chronic osteoarthritis pain

Condition

- Joint disorders

Synonym
osteoarthritis

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: Chronic pain, Duloxetine, General practice, Osteoarthritis

Outcome measures

Primary outcome

The primary outcome of this study will be pain at 3 months measured with the WOMAC pain subscale.

Secondary outcome

Secondary outcomes will be pain at one year (WOMAC pain subscale), disability (WOMAC function subscale), adverse reactions, quality of life, compliance to treatment, patients*satisfaction, OARSI-OMERACT, co-interventions, costs (iMCQ, iPCQ).

Study description

Background summary

Osteoarthritis (OA) is a highly prevalent chronic condition of the musculoskeletal system. In the Dutch population it is the single largest contributing factor to decreased physical wellbeing. The vast majority of patients suffering from OA are treated in a primary care setting. The general practitioner (GP) plays a key role in the treatment of pain, the most debilitating symptom of this condition. Currently, usual care by GPs consists of education, exercise training and pain medication in the form of paracetamol, NSAIDs or opioids. Thus far, however, the effectiveness of symptomatic treatment has proven to be limited. Improved analgesic treatment is therefore needed, especially since there are no treatment options available aimed at delaying or halting progression of the disease, with the exception of surgical joint-replacement, an intervention which is not only costly but also of limited durability.
Until now, the effectiveness of analgesia in OA has only been studied for the total population of OA patients. However, there are strong indications of specific subgroups, especially with regard to pain symptomatology. Pain in OA consists of nociceptive pain in the joint itself, peripheral sensitized pain from locally generated inflammatory factors, and centrally sensitized pain.

Central sensitization, sometimes called neuropathic pain, leads to hypersensitivity to pain. Inhibition of descending input from the brain stem operates through norepinephrine and serotonin. Disinhibition of this descending input contributes to central sensitization. This type of pain, or sensitized pain mechanism, is present in a large percentage of OA patients with chronic pain (37%) and is probably responding particularly poorly to currently available analgesia, as it requires medication with a centrally acting effect.
A common given analgesic for non-OA neuropathic pain is amitriptyline in the Netherlands. However, there are no randomized placebo controlled trials about the efficacy of amitriptyline for chronic pain in knee or hip OA. Moreover, in the most recent guidelines of the Osteoarthritis Research Society International (OARSI) for non-surgical management of knee OA, duloxetine is recommended for individuals. Duloxetine is traditionally an antidepressant, which in the Netherlands is also indicated for the treatment of diabetic peripheral neuropathy. Duloxetine and amitriptyline belong to a different medication group. Duloxetine is a serotonin norepinephrine reuptake inhibitor (SNRI) and the mechanism is that it strengthens the inhibition of the descending input, while amitriptyline is a tricyclic antidepressant (TCA) of which the actual mechanism is not completely clear; hypothesized is that it inhibits the reuptake of serotonin and norepinephrine, but less selectively than a SNRI.
Several randomized placebo-controlled trials have now demonstrated the efficacy of low dose duloxetine versus placebo in the treatment of pain in OA (clinically relevant effect sizes of 0.5 for pain of OA9, 0.6 for disability of OA9, and 0.4 for average pain of OA). These trials are short-term (10-16 weeks) randomized placebo-controlled trials in a highly controlled and secondary care settings. Not known is the effectiveness of duloxetine as third choice analgesia in a pragmatic and primary care setting. Neither is clear whether the efficacy of duloxetine is predominantly found in those patients suffering from neuropathic pain, or whether duloxetine as third choice analgesia in primary care is cost-effective. Measurement of neuropathic pain traditionally required sophisticated quantitative measurements not suited for use in clinical practice. However, a simple questionnaire modified for OA (modified painDETECT) which can be applied in a GP setting, has recently been demonstrated to correspond well with such traditional, more extensive measurements. Knees with higher modified painDETECT scores (>12.0) had higher odds of having signs of central sensitization.5
Currently, besides education, lifestyle advice, physiotherapy and dietary therapy, the usual care of the GP follows a stepped approach when prescribing analgesics in patients chronic OA pain. Paracetamol is the first treatment option, as it is relatively safe and has few contraindications. If the analgesic effect of paracetamol proves to be insufficient, GPs have the option of prescribing non-steroidal anti-inflammatory drugs (NSAIDs), and subsequently tramadol or other opioids. However, these medications are often contraindicated, particularly in elderly patients, and they are associated with the occurrence of serious adverse reactions. The availability of a well indicated, effective and relatively safe medicine, to be used when current analgesic options fail, would help improve the quality of life in these chronic

pain patients and would allow GPs to deliver better and more targeted care. In the long term, this could potentially help postpone the need for a joint-replacement and revision surgery, whilst retaining quality of life.

Study objective

The objective of this proposal is to investigate if duloxetine is effective as a third choice pain medication for treating chronic pain in OA compared to usual care. Furthermore, we will assess the cost-effectiveness of duloxetine treatment and if the presence of neuropathic pain component favorably modifies the response to treatment and if the presence of neuropathic pain will be necessary for (cost-)effectiveness.

Study design

Open-labeled cluster randomized controlled trial with a follow up period of one year, in which general practices are randomized to either prescribing duloxetine and providing usual care versus providing usual care only.

Intervention

Patients in the intervention group will be treated with duloxetine 1dd60mg and usual care during one year. The patients in the control group will be treated with usual care which consists of analgesics, education, lifestyle advice, physiotherapy and dietary therapy.

Study burden and risks

Patients receiving duloxetine may benefit from the analgesic effect of duloxetine. Patients in the intervention arm may experience side-effects. Duloxetine is a registered drug in the Netherlands. Side-effects are well known. In addition, in studies with duloxetine in OA patients no unexpected side-effects occurred.
The control group receives usual care according to the guidelines; there is no additional burden associated with this.
In addition, patients in both groups have to answer questionnaires at baseline, 3, 6, 9 and 12 months.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Wytemaweg 80

Rotterdam 3015 CN
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Wytemaweg 80
Rotterdam 3015 CN
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) having hip or knee OA based on the clinical ACR criteria, and 2) having chronic pain (most days of the last three months) in hip or knee, and 3) either: (i) a contra-indication for NSAIDs; (ii) adverse reactions of NSAIDs; or (iii) insufficient benefit of NSAIDs.

Exclusion criteria

1) on waiting list for hip/knee replacement, and 2) use of antidepressants, 3) contra-indication of duloxetine (use of Monoamine Oxidase Inhibitors, having uncontrolled narrow-angle glaucoma, in combination with (other) central nervous system acting drugs, in combination with thioridazine, hypersensitivity to duloxetine, disturbed liverfunction, renal insufficiency (creatinine clearance <30)).

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	362
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Cymbalta
Generic name:	Duloxetine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	26-02-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Not approved

Date:	17-03-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
Other	19506
EudraCT	EUCTR2014-003919-11-NL
CCMO	NL50590.078.15