Duloxetine for chronic osteoarthritis pain; an important alternative?

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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	Approved WMO
Status	Recruitment stopped
Health condition type	Joint disorders
Study type	Interventional

Summary

ID

NL-OMON47264

Source
ToetsingOnline

Brief title
DUO-trial

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

Pain at three months measured with the WOMAC pain subscale.

Secondary outcome

Pain at one year (WOMAC), disability (WOMAC), adverse reactions, quality of

life, compliance to treatment, patients* satisfaction, OARSI-OMERACT,

co-interventions and costs (iMCQ and 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 a 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 GP*s consists of education, exercise training and pain medication in the form of paracetamol, NSAID*s 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 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 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 an 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 OA, 0.6 for disability of OA and 0.4 of average pain of OA). These trials are short-term (10-16 weeks) randomized placebo-controlled trials in a highly controlled secondary care setting. 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 a third choice analgesia in primary care is cost-effective. Measurements 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.
Currently, besides education, lifestyle advice, physiotherapy and dietary therapy, the usual care of the GP follows a stepped approach when prescribing analgesics in patients with 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, GP*s have the option of prescribing non-steroidal anti-inflammatory drugs (NSAID*s), 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 well indicated, effective and relatively safe medicine, to be used when current analgesic options fail, would help to improve the quality of life in these chronic pain patients and would allow GP*s 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 will be necessary for (cost)-effectiveness.

Study design

Open-labeled cluster randomized controlled trial with a follow-up period of one year.

Intervention

Patients in the intervention group will be treated with duloxetine 60mg once a day during one year in addition to usual care. Patients in the control group will receive care as usual.
Usual care consists of analgesics (according to the NHG farmacotherapeutische richlijn pijnbestrijding), 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 of duloxetine. Duloxetine is a registered drug in the Netherlands and side-effects are well known. In addition, is 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 expected in this group.
In both groups patients have to answer questionnaires during six moments in the study; patients may experience this as a burden.

Contacts

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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 or neuropathic pain medication 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 < 30ml/min), usage of strong CYP1A2-inhibitors and CYP2D6-inhibitors and substrates).

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:	Recruitment stopped
Start date (anticipated):	15-06-2016
Enrollment:	224
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	06-05-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	21-12-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	29-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	24-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-06-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-09-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-10-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-01-2017
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-12-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	07-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	09-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	16-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	26-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	17-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	19-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	20-12-2018
Application type:	Amendment
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	EUCTR2015-001669-16-NL
CCMO	NL53130.078.15