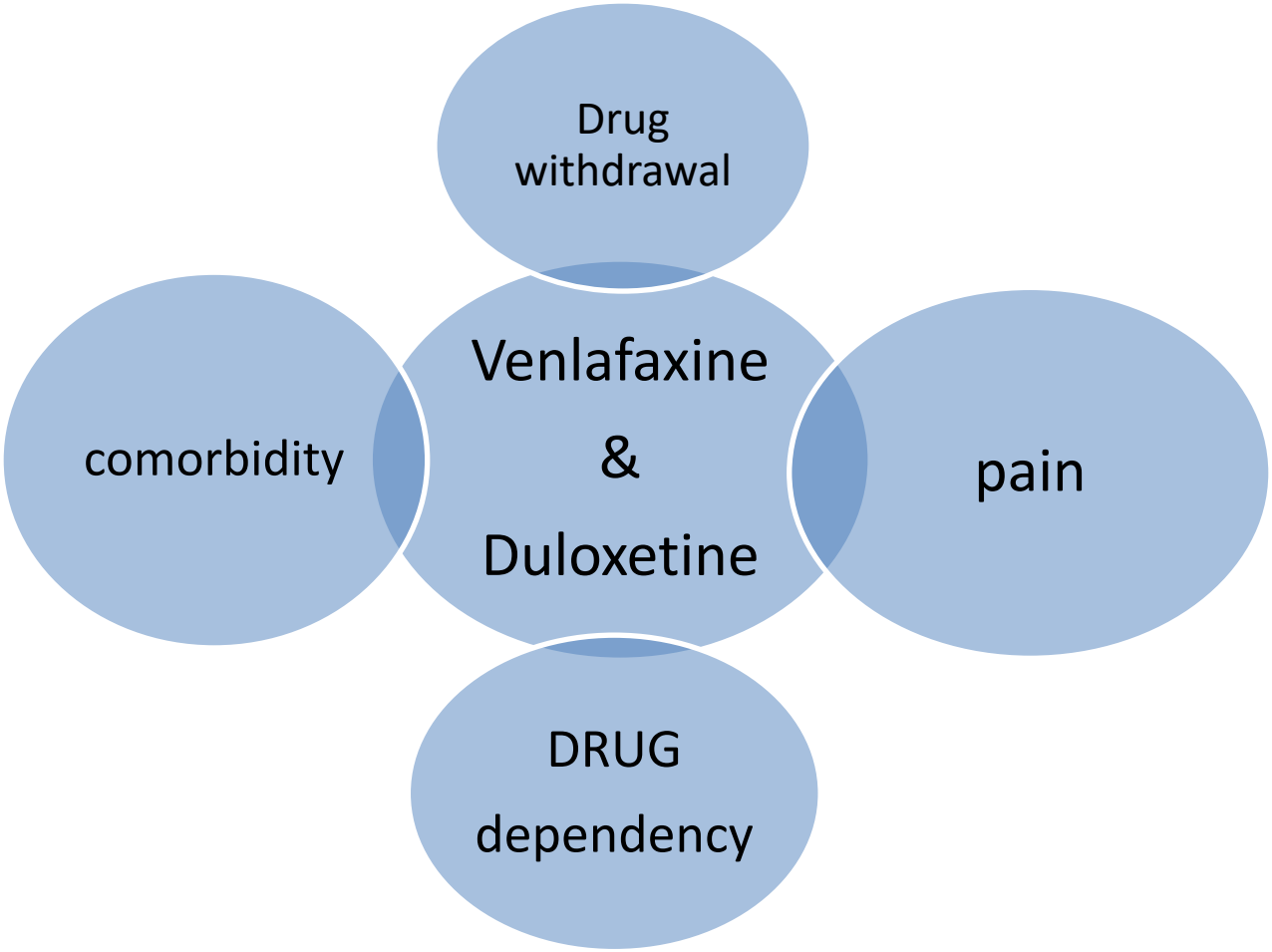
SNRIها در درمان سوءمصرف مواد

دکتر کمال الدین علاالدینی شورمستی
دکتری تخصصی مطالعات اعتیاد
عضو هیئت علمی دانشگاه علوم پزشکی مازندران


Drug withdrawal
comorbidity
Venlafaxine & Duloxetine
pain
DRUG dependency

Venlafaxine

- **Venlafaxine is indicated (HSCIC, 2016) for the treatment of**:

- major depressive episodes,
- generalized anxiety disorder
- and social phobia,

- **with off-label uses including:**

obsessive-compulsive disorder,
and chronic pain syndromes (EMA, 2007).

The reuptake effects of venlafaxine are dose-dependent:

- with action on 5-HT transmission at low doses (150 mg/day);
- on both 5-HT and NE systems at moderate doses (>150 mg/day);
- and on DA at high doses (>300 mg/day)

morphine withdrawal

- **Opioid-induced neuroinflammation** plays a role in the development of opioid physical dependence. Moreover, nitric oxide (NO) has been implicated in several oxidative and inflammatory pathologies

- Co-administration of venlafaxine (40 mg/kg) with morphine not only inhibited the naloxone-precipitated withdrawal signs including jumping and weight loss, but also reduced the up-regulation of TNF-α, IL-1β, IL-6, NO and MDA contents in mice brain tissue.

Venlafaxine inhibits naloxone-precipitated morphine withdrawal symptoms: Role of inflammatory cytokines and nitric oxide Mohammad
Taghi Mansour

morphine withdrawal

- However, repeated administration of venlafaxine inhibited the decrease in the brain levels of BDNF, GPx..

- These results provide evidences that venlafaxine could be used as a candidate drug to inhibit morphine withdrawal through the involvement of inflammatory cytokines and l-arginine-NO in mice.

Venlafaxine inhibits naloxone-precipitated morphine withdrawal symptoms: Role of inflammatory cytokines and nitric oxide Mohammad
Taghi Mansour

morphine withdrawal

In another study, taking venlafaxine at a dose of 10 to 20 mg / kg further reduced the symptoms of morphine withdrawal as well as CPP (reinstatement) in mice.

- Attenuation of morphine dependence and withdrawal in rats by venlafaxine : a serotonin and noradrenaline reuptake inhibitor

METH-induced reinstatement

- In another study, VEN treatment has been shown, to inhibit METH-induced reinstatement of CPP (in a rat model of relapse to drug use).

- Role of venlafaxine in relapse to methamphetamine seeking

alcohol consumption

A study in mice found that venlafaxine (in alcohol-dependent mice who had been deprived of alcohol for some time) not only did not reduce alcohol consumption, but also increased it.

Increased alcohol consumption in rats after subchronic antidepressant treatment

heroin withdrawal(RCT)

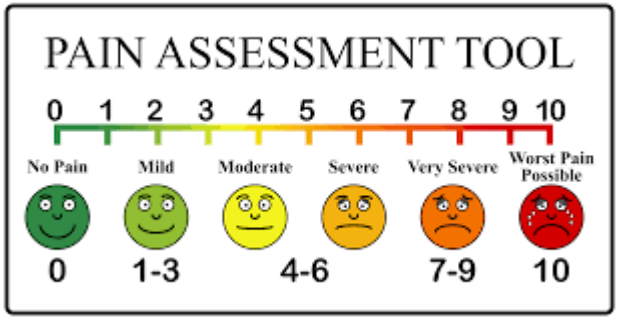
In a double-blind clinical trial study, it was found that daily intake of 300 mg of venlafaxine compared to placebo was significantly effective in reducing the symptoms of heroin withdrawal with good safety and tolerance:

Objective Opioid Withdrawal Scale,

visual analog scale,

and total sleeping time

- Shih-Ku Lin -2008



Methadone withdrawal

- A randomized evaluation reported significantly lower withdrawal symptoms among participants who received venlafaxine versus placebo

- Non-Opioid Neurotransmitter Systems that Contribute to the Opioid Withdrawal Syndrome: A Review of Preclinical and Human Evidence
- (Lin et al., 2008).

cocaine craving

- Because many human cocaine abusers report depressive symptoms after a cocaine binge or during abstinence (antidepressant) medications have received extensive attention in both clinical and laboratory studies

- Cocaine inhibits reuptake of DA, 5-HT, and NE, all of which likely contribute to its effects

cocaine craving

Venlafaxine(225mg) decreased cocaine craving in the absence of cocaine and decreased the subjective(10-20%), but not reinforcing, effects of cocaine in opioid-and non-opioid-dependent cocaine abusers

- The Effects of Venlafaxine on the Subjective, Reinforcing, and Cardiovascular Effects of Cocaine in Opioid-Dependent and Non-Opioid-Dependent Humans
- Richard W. Foltin,2003

cocaine-dependent patients with depression

- Venlafaxine was not superior to placebo on either mood or cocaine use outcomes.

- This suggests that the subgroup of cocaine-dependent patients with depressive disorders is relatively treatment resistant.

- A randomized, double-blind, placebo-controlled trial of venlafaxine for the treatment of depressed cocaine-dependent patient

cannabis abstinence

- Venlafaxine extended-release was associated with worse cannabis abstinence and caused more adverse events

- Pharmacotherapies for cannabis use disorder: A systematic review and network meta-analysis
- Anees Bahji- 2021

Cannabis severe withdrawal

- Cannabis-dependent participants with depressive disorder are less likely to achieve abstinence with venlafaxine-XR (VEN-XR) treatment.
- Individuals on VEN-XR reported more severe withdrawal, despite not reducing their smoking behavior.
- We hypothesized that withdrawal-like symptoms, likely medication side effects, led to continued marijuana smoking in this group.

- Do withdrawal-like symptoms mediate increased marijuana smoking in individuals treated with venlafaxine-XR?

depressed, cannabis-dependent

- For depressed, cannabis-dependent patients, venlafaxine-extended release does not appear to be effective at reducing depression and may lead to an increase in cannabis use.

- A Randomized Double-blind, Placebo Controlled Trial of Venlafaxine-Extended Release for Co-occurring Cannabis Dependence and Depressive Disorders
- Frances R. Levin -2013

Treatment of depressive alcoholic patients

- Venlafaxine demonstrated to be effective in the treatment of depressive alcoholic patients. Furthermore, it seems to be useful to decrease the severity of problems related with the alcohol use.

Significant decreases from baseline to week 24 were obtained in four areas of Europ ASI:

- medical status
- alcohol use
- family/ social relationships
- and psychiatric status .

Tolerance was excellent or good in 76.7% of the patients.

- [Effectiveness of venlafaxine in the treatment of alcohol dependence with comorbid depression]

ADHD & alcohol use

- Results from two case reports and one case series suggest successful outcomes in the treatment of alcohol use disorders when comorbid ADHD is treated by venlafaxine

- **There have been several reports of successful open clinical trials with venlafaxine in the treatment of adult ADHD.**

- The results of this preliminary study suggest that venlafaxine may be effective treatment for ADHD in adults with comorbid alcohol use disorders and may decrease alcohol craving,frequency and intensity.

Pharmacotherapy (OCD) and SUD:

- Among the newer generation of antidepressants, SSRIs are beneficial but two SNRI antidepressants, venlafaxine and duloxetine, have recently been found to be among the best antidepressants for treatment of OCD.

Treatment of Substance Abusing Patients with Comorbid Psychiatric Disorders

Pharmacotherapy of anxiety disorders and SUD:

The SSRIs or SNRIs (e.g., venlafaxine) are generally considered first-line treatments with tricyclics and, due to the high risk for addiction, the use of benzodiazepines is not recommended for use in substance-abusing populations.

Overall, venlafaxine appears to be effective in reducing withdrawal symptoms of opioids, cocaine and possibly alcohol.

It helps …alcohol use disorders when comorbid ADHD or depression

It helps …substance use disorders when OCD or anxiety disorders…

It does not help to improve the symptoms of the disorder and reduce the withdrawal symptoms in people with **cannabis** and **cocaine** use disorder who are also suffering from depressive disorder.

Venlafaxine withdrawal syndrome

- Venlafaxine is structurally similar to phencyclidine and thus should not be discontinued abruptly.

- If the drug has been administered for longer than 1 week, the dose should be tapered over 7 to 10 days to prevent a withdrawal syndrome

Venlafaxine withdrawal syndrome :

nausea,
depression,
suicidal thoughts,
disorientation,
stomach cramps,
panic attacks,
sexual dysfunction,
headache,
and occasional psychotic symptoms

Is there a potential of misuse for venlafaxine and bupropion?

Venlafaxine withdrawal syndrome :

in some cases, the clinical picture may resemble a stroke

Although how the withdrawal syndrome develops is unknown, it may well be associated with electrophysiological changes in 5-HT receptors.

This is similar to what can be observed with the SSRIs, although the severity of withdrawal may be higher with venlafaxine

Is there a potential of misuse for venlafaxine and bupropion?

Venlafaxine dependency?!

- There was no indication of problems of abuse/dependence during the clinical trials.

- A 53-year-old client with a history of alcohol misuse and a history of recurrent depression, for which he was prescribed venlafaxine tablets.

- Over time, he increased the dosage to 50 tablets daily (3750 mg). Large venlafaxine dosages produced amphetamine-like effects, due possibly to the related increase in dopamine turnover.

❑ Conclusions: Physicians should be aware that patients with a history of drug and alcohol abuse might develop venlafaxine dependence.

Venlafaxine dependence in a patient with a history of alcohol and amineptine misuse

duloxetine

methamphetamine-induced neurodegeneration

- The Akt/GSK3 signaling pathways might have a critical role in the protective effects of duloxetine against methamphetamine-induced neurodegeneration and cognition impairment.

Duloxetine by Modulating the Akt/GSK3 Signaling Pathways Has Neuroprotective Effects against Methamphetamine-Induced Neurodegeneration and Cognition Impairment in Rats
Mehrasa Rahimi Borumand

- Duloxetine, via modulation of production of P-CREB, BDNF, can inhibit methamphetamine induced neurodegenerative effects in adult rats.

- Niloofar Mohammad 2019

- **Duloxetine** has potential to attenuate opioid-induced withdrawal syndrome in opioid dependence status

E¨cacy of Duloxetine Compared with Opioid for Postoperative Pain Control Following Total Knee Arthroplasty Man Soo Kim

pain

Duloxetine

- Research indicates that selective serotonin re-uptake inhibitors (SSRIs) are fairly ineffective in analgesia treatment.

- These SSRIs were studied because tricyclic antidepressants **(TCAs**), which inhibit both serotonin and norepinephrine, have proven to be very effective in pain relief.

- Since SSRIs are not effective and TCAs are, it is now widely thought that it is specifically the inhibition in reuptake of norepinephrine and not serotonin that plays a crucial role in analgesia.

Perioperative Duloxetine

- Researches suggest that adding perioperative administration duloxetine 60 mg to a multimodal analgesia regimen within the orthopedic surgery setting signifcantly lowers total postoperative opioid consumption and reduces pain without signifcant adverse efects.

after knee arthroplasty

- Duloxetine can be used to reduce opioid usage after knee arthroplasty in selected patients that can be appropriately monitored for potential side effects of the medication.

Jacques T. YaDeau, MD, PhD 2022

after total hip arthroplasty

- 96 patients in this randomized controlled trial. were randomized (1,1) to either the duloxetine group or the placebo group and received daily doses of 60 mg duloxetine or placebo, respectively, from 2 d pre-operation to 14 d after surgery.

- Perioperative administration of 60 mg of duloxetine daily significantly:

- alleviated pain in the postoperative 3 weeks
- and morphine requirements during the postoperative 48 h

studies have demonstrated the efficacy of duloxetine in reducing postoperative pain and opioid consumption.

Hao Li 2021

Combination therapy

- These results suggest the combination of duloxetine and methadone reduces cancer-related pain and emotional symptom burden compared to either medication as a single agent.

- Combination therapy with methadone and duloxetine for cancerrelated pain: a retrospective study
  Zachary A. Curry

Duloxetine Compared with Opioid

- Opioid is known to be effective in pain control after total knee arthroplasty (TKA). However, recently it has become a major concern due to addiction.
- **Duloxetine** (30 mg /day for 6 weeks) has a similar effect to opioid on postoperative pain control.
- Thus, duloxetine can be considered as an alternative to opioid for postoperative pain control following TKA.

E¨cacy of Duloxetine Compared with Opioid for Postoperative Pain Control Following Total Knee Arthroplasty Man Soo Kim

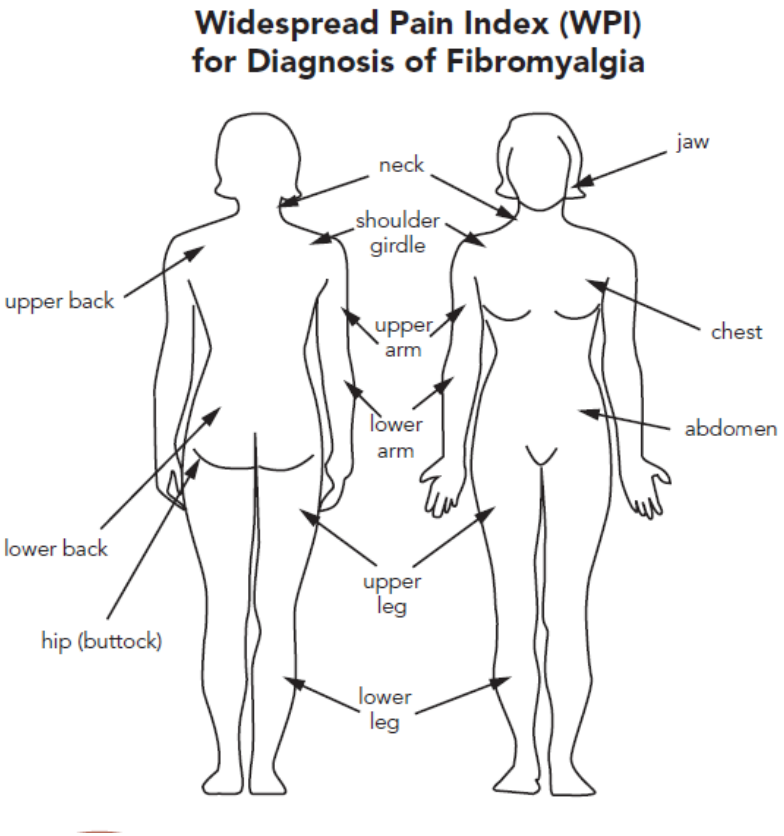
Duloxetine Compared with Opioid

- **Duloxetine**, a potent SNRI, can inhibit the reuptake of serotonin and norepinephrine that could modulate descending inhibitory pain pathway in the central nervous system (CNS) [10].

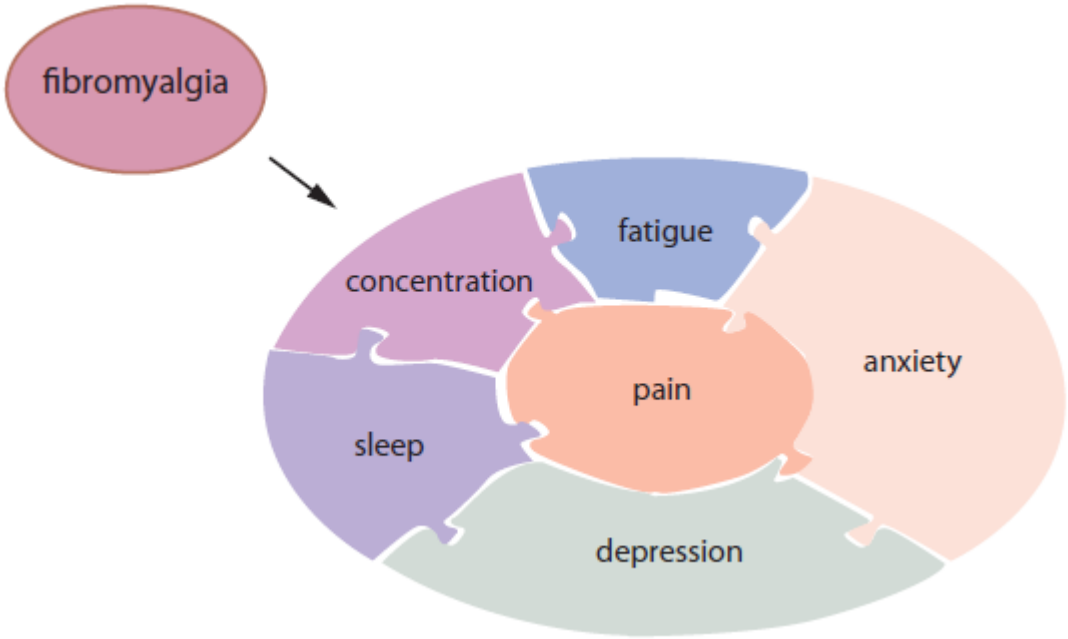
- Therefore, theoretically duloxetine can reduce postoperative pain after TKA

E¨cacy of Duloxetine Compared with Opioid for Postoperative Pain Control Following Total Knee Arthroplasty Man Soo Kim

Fibromyalgia



It has been well defined that FM is a chronic condition of unknown etiology, characterized by widespread pain and often associated with other symptoms such as poor sleep, fatigue, depression and cognitive dysfunction.

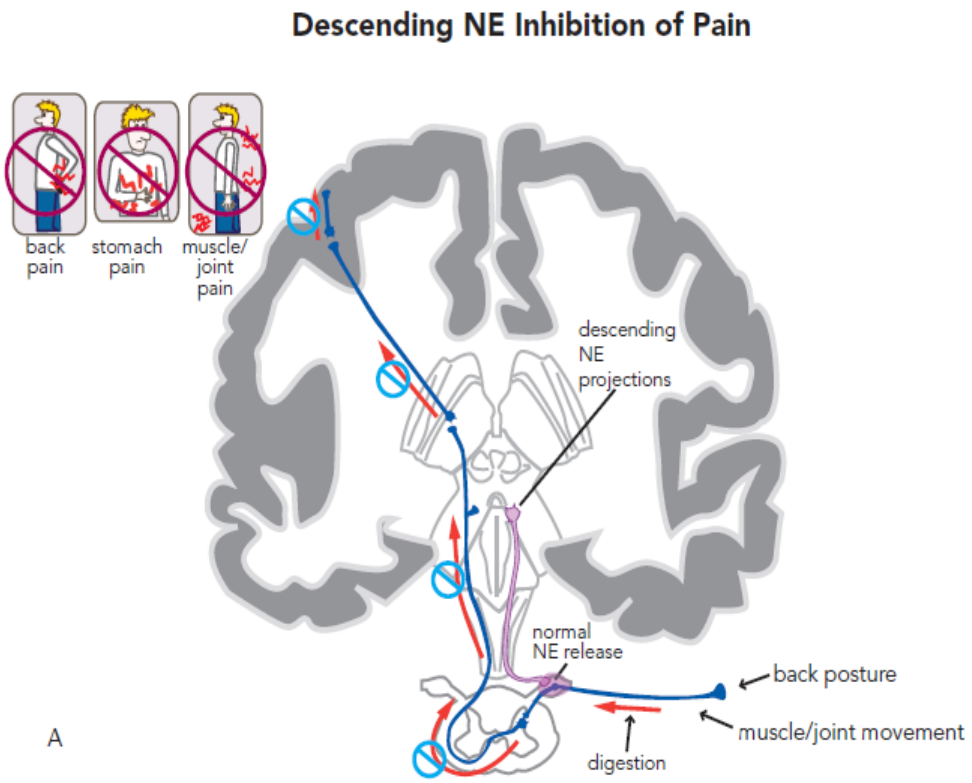

fibromyalgia
fatigue
concentration
anxiety
pain
sleep
depression

PAIN IN FMS

- There is evidence for modified serotonergic and noradrenergic neurotransmission in FMS.
- **Reduced levels of the 5-HT metabolite**, 5-hydroxyindole acetic acid, have been reported in the cerebrospinal fluid (CSF) of FMS patients compared with controls
- **Evidence for a noradrenergic disturbance** in FMS includes decreased levels of the NE metabolite, 3-methoxy, 4-hydroxy phenylglycol (MHPG), in FMS patients

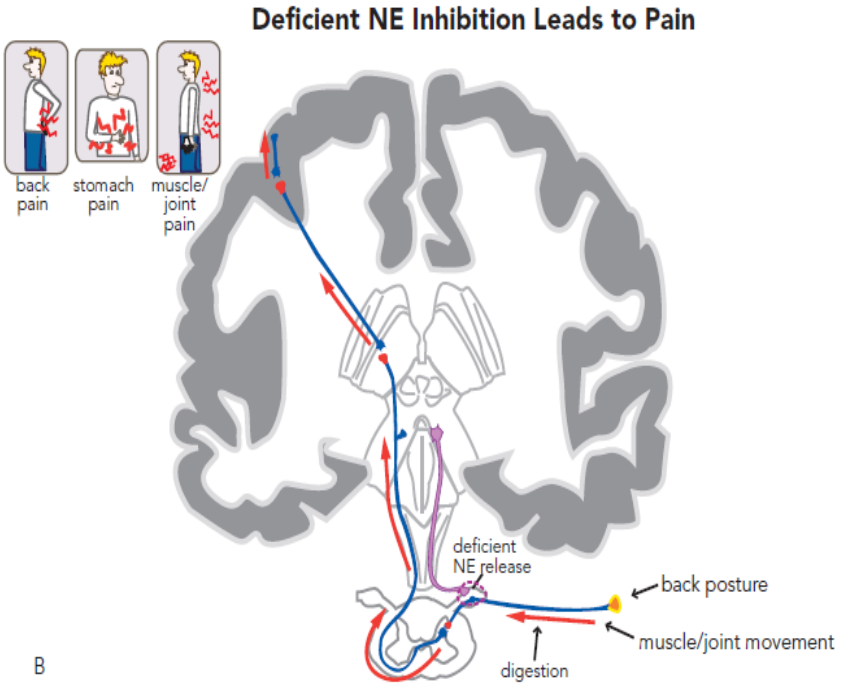
- DLX is a serotonin norepinephrine reuptake inhibitor (SNRI) licensed by the US Food and Drug Administration (FDA) in 2008 and used to treat:

  - major depression,
  - generalized anxiety disorder,
  - FM,
  - diabetic peripheral neuropathy,
  - chronic pain due to chronic low back pain and osteoarthritis

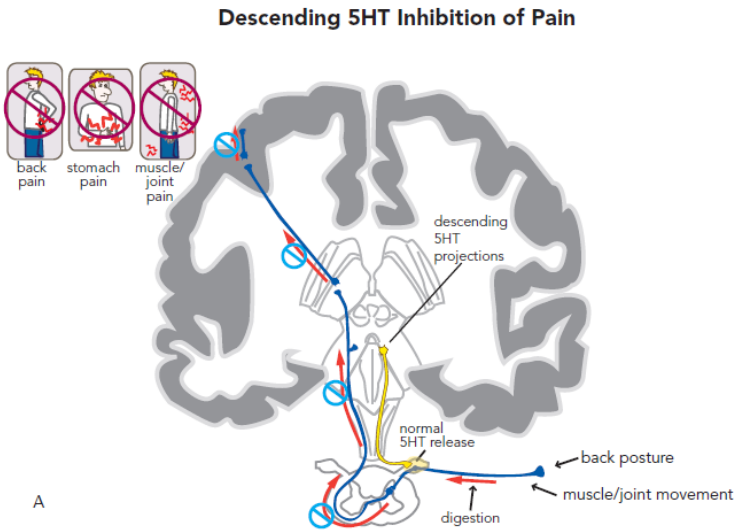


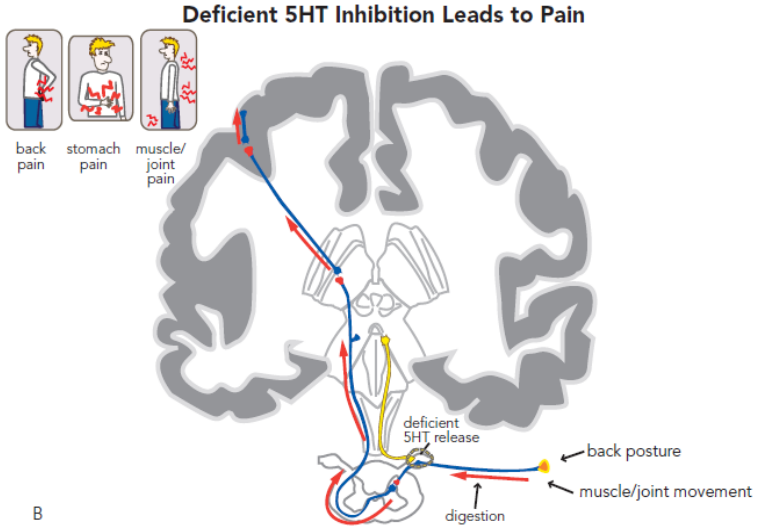
- In addition to these ascending serotonergic and noradrenergic pathways, neurons in the raphe nucleus and the locus coeruleus also project to the spinal cord where they serve to inhibit input from the periphery.

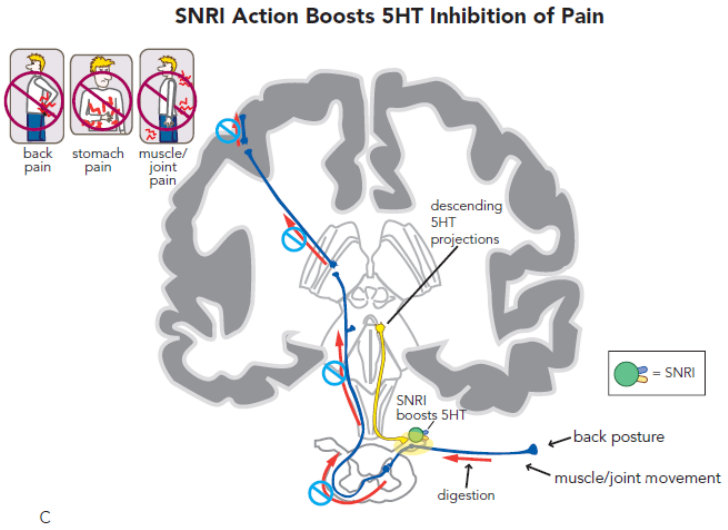
There is thus an involvement of both 5-HT and NE in the mediation of endogenous analgesic mechanisms via the descending inhibitory pain pathways in the brain and spinal cord



- A dysfunction of these 5-HT- and NE-mediated descending pain-inhibitory pathways can therefore result in heightened sensitivity to pain (hyperalgesia) and even in the induction of pain (allodynia), and is a potential mechanism for the pain experienced by patients with FMS.


Descending 5HT Inhibition of Pain
back pain
stomach pain
muscle/ joint pain
descending 5HT projections
normal 5HT release
back posture
muscle/joint movement
digestion
A


Deficient 5HT Inhibition Leads to Pain
back pain
stomach pain
muscle/ joint pain
deficient 5HT release
back posture
muscle/joint movement
digestion
B



- It could be argued that the FMS patients treated with antidepressants feel relief from pain and other symptoms as a result of the effect of these drugs on their depression

دولوکستین فیبرومیالژیا

In general, DLX was a great choice for pain relief in FM. Moreover, 60mg/d DLX produced less withdrawal effects than 120mg/d DLX.

- Duloxetine for pain in fibromyalgia in adults: a systematic review and a meta – analysis
- Yan-Na Lian

Venla FMS

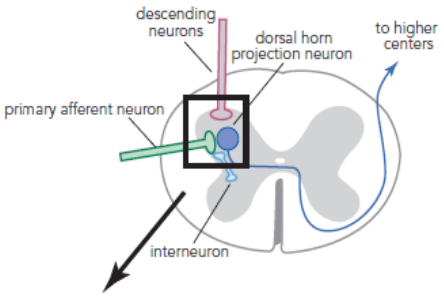
- .
- Although robust evidence supporting the use of venlafaxine for fibromyalgia is lacking…
- there are several factors that may make venlafaxine a preferred option compared to the other SNRIs:
- Despite the lack of robust evidence supporting its use, venlafaxine may be effective for the treatment of fibromyalgia:
- Most trials of venlafaxine demonstrate positive or neutral benefits for fibromyalgia.
- Venlafaxine is generally well tolerated, and given its lower cost.
- L. A. VanderWeide 2014

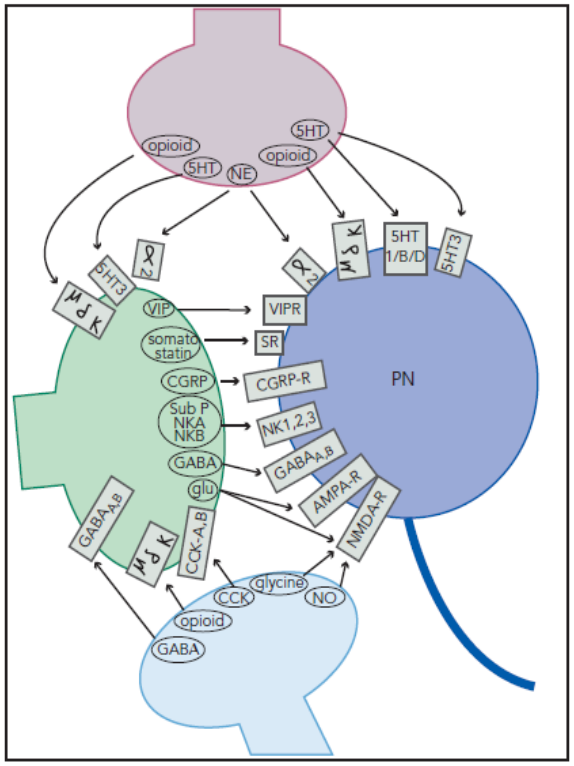
Diabetic neuropathic pain

Neuropathic pain is the result of injury or dysfunction of the somatosensory system.

This pain is characterized by the activation of abnormal pathways of pain at the peripheral nerves and posterior roots [3].

The pain manifestation can be focal, multi- focal, or generalized.





- **Figure 9-2** Multiple neurotransmitters modulate pain processing in the spinal cord. There are many neurotransmitters and their corresponding receptors in the dorsal horn. Neurotransmitters in the dorsal horn may be released by primary afferent neurons, by descending regulatory neurons, by dorsal horn projection neurons (PN), and by interneurons. Neurotransmitters present in the dorsal horn that have been best studied in terms of pain transmission include substance P (NK1, 2, and 3 receptors), endorphins (μ-opioid receptors), norepinephrine (α2 adrenoceptors), and serotonin (5HT1B/D and 5HT3 receptors).

- **Do withdrawal-like symptoms mediate increased marijuana smoking in individuals treated with venlafaxine-XR?**

• Neuropathic pain

- These SSRIs were studied because
  tricyclic antidepressants (TCAs), which inhibit both serotonin and norepinephrine, have proven to be very effective in pain relief. Since SSRIs are not effective and TCAs are, it is now widely thought that it is specifically the inhibition in reuptake of norepin- ephrine and not serotonin that plays a crucial role in an- algesia.
  -N
  europathic pain can be divided into four broad catego- ries: complex neuropathic disorders (such as complex regional pain syndrome), peripheral focal and multifocal nerve lesions (inflammatory, traumatic, or ischemic), per- ipheral generalized polyneuropathies (metabolic, heredi- tary, inflammatory, or toxic), and CNS lesions (e.g., spinal cord injury, stroke, multiple sclerosis) [14]. Clinical presentation of neuropathy involves at least one of the following three elements.

Diabetic neuropathy

- Neuropathy is a common and costly complication of both type 1 and type 2 diabetes. The prevalence of neuropathy is estimated to be about 8% in newly diagnosed patients and greater than 50% in patients with longstanding disease

- Sensorimotor neuropathy is marked by pain, paraesthesia and sensory loss (table 1). The different mechanisms involved in different pain sensations are still poorly understood, but there is ample evidence that abnormal discharges from diseased somatosensory neurons are responsible [4, 5].

- Spontaneous activity in the peripheral nociceptor system may also trigger central nervous system changes responsible for hyperalgesia and allodynia

Diabetic neuropathy

- Sensing ongoing spontaneous pain and paroxysmal shooting pain in the absence of any external stimulus is caused by ectopic impulse generation within the nociceptive pathways [13].

Venlafaxine & Neuropathic pain

- Research indicates that venlafaxine inhibits serotonin re-uptake at lower doses (less than 100 mg/day), whereas norepinephrine re-uptake increases over the dose range of 100 to 375 mg/day [20].

- Additionally, venlafaxine has a 30-fold higher affinity for the re-uptake inhibition of serotonin compared with norepinephrine

- Based on the literature, it is suggestive that venlafaxine is effective for the management of neuropathic pain at doses of 150 mg per day or higher [22].

- In conclusion, venlafaxine is a safe and well-tolerated analgesic drug for the symptomatic treatment of neuropathic pain

ونلا فكسين تداخلات

- In addition to adverse effects, there are drug interactions that need to be considered. Venlafaxine is primarily metabolized through the liver (2D6, 3A3/4 isoenzymes) and is therefore at risk to cause drug interactions

- Treatment of Neuropathic Pain with Venlafaxine: A Systematic Review

Drug interaction

- Venlafaxine & duloxetine in interaction with methadone Increase risk for serotonin syndrome; increased risk for QTc prolongation and (arrhythmia)

- many antidepressants are CYP2D6 inhibitors (fluoxetine, paroxetine, and to a lesser extent duloxetine).
- This means combinations of codeine or tramadol with these antidepressants may lead to reduced analgesia.

- Opioids and antidepressants

Interactions

- Duloxetine is both a substrate and an inhibitor of CYP2D6 [94]. Therefore, **duloxetine** and **methadone** may inhibit each other's metabolism, increasing serum levels of both drugs and potentially resulting in adverse effects and/or toxicity.

- This combination should be avoided, if possible. Similarly, the combination of methadone and venlafaxine has not been studied thus far.

- **Venlafaxine** mildly inhibits CYP2D6 in vivo, and therefore may inhibit methadone's metabolism [95]. Because venlafaxine is also a substrate of CYP2D6, levels of venlafaxine may be increased when co-administered with methadone [96].

Actual and Potential Drug Interactions Associated with Methadone

Duloxetine- cannabis interaction

- Elimination of duloxetine is mainly through hepatic metabolism involving CYP1A2 and to a lesser extent CYP2D6.

- There is evidence that co-administration of duloxetine with CYP1A2 and CYP2D6 inhibitors increased duloxetine levels [69].

- As stated before, CBD is an inhibitor of CYP1A2 and **THC, CBD**, and CBN inhibit CYP2D6, so if cannabinoids are used as a concomitant medication, an increase in duloxetine plasma levels may be seen.

- Duloxetine is known to have a discontinuation syndrome, not an addiction

E¨cacy of Duloxetine Compared with Opioid for Postoperative Pain Control Following Total Knee Arthroplasty Man Soo Kim

Duloxetine discontinuation

- In a analysis of 6 short-term treatment trials, in which treatment was stopped abruptly, discontinuation-emergent adverse events (DEAEs) were reported by 44.3% and 22.9% of duloxetine- and placebo-treated patients, respectively.

Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder
David G Perahia

Duloxetine discontinuation

- The mean number of symptoms was 2.4.

- DEAEs reported significantly more frequently on abrupt discontinuation of duloxetine compared with placebo were:
- dizziness (12.4%),
- nausea (5.9%),
- headache (5.3%),
- paresthesia (2.9%),
- vomiting (2.4%),
- irritability (2.4%),
- and nightmares (2.0%).
- .

- **Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder**
- David G Perahia