Volume 19 Number 11
November 2013

Case Presentation

Treatment of Hidradenitis Supprurativa Associated Pain with Nonsteroidal Anti-Inflammatory Drugs, Acetaminophen, Celecoxib, Gabapentin, Pegabalin, Duloxetine, and Venlafaxine

Noah Scheinfeld MD JD

Dermatology Online Journal 19 (11): 18

Weil Cornell Medical College

Correspondence:

Noah Scheinfeld MD JD
Assistant Clinical Professor of Dermatology Weil Cornell Medical College
150 West 55th Street NYC NY
Scheinfeld@earthlink.net

Abstract

Hidradenitis Supprurativa is a painful dermatological condition. Although the pain of HS has unique aspects, the pain of HS pain shares common elements with essential pain, fibromyalgia, and pure neuropathic pain syndromes. Futhermore, depression plays an important role in the pain of HS. This paper reviews the potential for use of nonsteroidal anti-inflammatory drug (NSAIDS), acetaminophen, celecoxib, gabpentin, pregabalin, and the serotonin and norepinephrine reuptake inhibitors (SNRIs), duloxetine and venlafaxine, for treating HS related pain. No studies exist for pain control in HS. Initially, the pain of HS is treated medically e.g. oral rifampin and clindamycin or adalimumab to decrease inflammation, but an analysis of pain medications to treat the pain of HS merits its own discussion and treatment algorithm. First-line HS pain treatments include: topical analgesics and oral NSAIDs, such as celecoxib (Celebrex®), and acetaminophen. If these are inadequate, which is common, the less expensive gabapentin (Neurontin®) 400-1200 mg TID or the more expensive (Lyrica®) pregabalin 50-100mg BID can be added for synergistic effect. In my experience, HS patients prefer pregabalin, which induces less drowiness than gabapentin. If these combinations are inadequate, an SNRI can be added. Of SNRIs, duloxetine (Cymbalta®) 30-120 mg, given QD or divided BID, is most optimal. I have used gabapetin or pregabalin in combination with duloxtine effectively. Venlafaxine (Effexor®), 75 mg-375mg (divided into BID or TID dosing), or in extended release form Venlafaxine ER (Effexor ER®) (37.5mg-375mg daily) can be combined with pregalin or gabapetin. Venlafaxine's cardiovascular side effects and lesser effectiveness serves HS patients less well then duloxetine, in my experience. An advantage of duloxetine and venlafaxine is that they can be used to treat the depression often associated with HS. If prolonged use of opiates is required, patients should be referred to a pain specialist.

Hidradenitis Supprurativa (HS) is a complex disease with many treatment aspects that require consideration [1]. One treatment area that has received little attention is the treatment of the pain that HS engenders [2]. No studies exist for pain control in HS. This is unfortuate because it has been shown in a variety of studies that HS has more psychosocial impact in terms of pain and psychological distress than almost any other skin disease [3-17]. The pain of HS is both inflammatory and non-inflammatory and HS's associated depression must be treated and its impact on HS's pain taken into account.

In short, HS is a medical problem with both painful sensory and psychological dimensions. This paper is a review of the sources of pain related to HS and the potential for use of NSAIDs, including celecoxib, acetaminophen, the atypical anticonvulsants-gabpentin and pregabalin, and SNRIs, duloxetine and venlafaxine, in the treatment of the pain of HS. Future topics will also deal with other oral and topical pain treatments,the treatment of the acute pain of HS and treatment of the depression that HS engenders.

Anti-inflammatory treatments for HS including rifampin and clindamycin, and or adalimumab can treat the physical findings of HS and thereby mitigate the pain of HS itself [1]. Injections of intralesional kenalog can have anti-inflammatory and anti-pain affects [1]. When considering treatment of the pain of HS, it can be extremely useful to involve a pain specialist, in particular

when opiates are a consideration for pain control. Combination therapy for pain control is often needed and mirrors the need for combination treatment for HS itself.

Types of pain are divided into different categories. I recognize 7 main categories of HS associated pain. These include (1) neuropathic pain (resulting from nerve damage or dysfunction either in the peripheral or in the central nervous system (2) inflammatory/joint-related pain (resulting from peripheral inflammation or peripheral tissue/joint damage (3) non-inflammatory/non-neuropathic pain (also called essential pain or functional pain by some pain researchers), which results from centrally impaired pain processing like in fibromyalgia (FM) [18], (4) ischemic pain, and (5) inflammation-related pain relates to inflammatory mediators such as tumor necrosis factor alpha (TNFa) and IL-1β, which might play an independent role in pain generation in HS [18,19,20]. Neuropeptides, inflammatory cytokines, Calcitonin-Gene–Related-Peptide, free radicals or prostaglandins could play a role in inflammatory pain as well. One may also recognize as (6), the depression and associated anxiety and emotional stress that are common. Pain and depression form a destructive pas-de-deux with insomnia a significant aggravating factor. Finally (7), HS can be associated with arthritis. Table 1 summarizes the types of pain a patient with HS might experience.

Table 1 Types of pain

1. Neuropathic pain
2. Inflammatory/joint-related pain
3. Inflammatory pain due to inflammatory mediators
4. Non-inflammatory/non-neuropathic pain (functional pain)
5. Ischemic pain
6. Pain related to Depression
7. Inflammatory mediator based pain independent of other causes

There are factors that modulate the intensity of pain and temporality. They include (1) menstrual cycle [11], (2) insomnia [21,22], (3) stress [23], (4) focus (itch for example is worse at night when the eyes are closed and other thoughts leave your mind), (5) social isolation [10], (6) ethnic group [24], (7) gender [25], (8) fear [26], (9) ethnic group [27], and (10) random drift. The burden created by pain is substantial in HS or any other disease [28].

In this discussion, I draw on materials that relate to other diseases such as (1) end stage renal disease [29], (2) gout [30,31], including insomnia and disease perception related gout [32,33], (3) pyoderma gangrenosum [34], (4) rheumatic and psoriatic pain [35], (5) cancer related pain, (6) pain of mucositis, (as open wounds of HS resemble oral ulcers) [36], (7) the BLEND AN EGG [blue rubber bleb nevi, leiomyoma, eccrine spiradenoma, neuroma, dermatofibroma, angiolipoma, neurilemmoma, endometrioma, glomus tumor, and granular cell tumor] painful tumors [37], (8) toxic epidermal necrolysis[38], erythromelalgia, and (9) complex regional pain syndrome [39].

HS itself is staged by the Hurley Staging system (Table 4) or by the Sartorius scoring system (Table 5). Understanding the stages of pain can help inform a provider's understanding of of the pain control modalities needed. The higher the HS stage or score, the greater the pain and the greater the need for pain control.

Table 4 Hurley Staging of HS

Hurley stage	Extent of disease in tissue
I	Abscess formation (single or multiple) without sinus tracts and cicatrization

Hurley stage	Extent of disease in tissue
II	One or more widely separated recurrent abscesses with tract formation and scars
III	Multiple interconnected tracts and abscesses throughout an entire area

Table 5 Sartorius scoring system

Lesion Counts (to be assessed at every visit)	Abscess	Non-Draining Fistula	Draining Fistula	Non-Inflammatory Nodule	Inflammatory Nodule	Hypertrophic Scar	Longest distance (mm) between 2 relevant lesions (If only 1 lesion, measure diameter of lesion)	Are all lesions clearly separated by normal-appearing skin? (yes/no)
Left Axilla								
Right Axilla								
Left Sub/Inframammary Area								
Right Sub/Inframammary Area								
Intermammary Area								
Left Buttock								
Right Buttock								
Left Inguino-crural Fold								
Right Inguino-crural Fold								
Perianal								
Perineal								
Other								
Totals								

What skin changes cause pain in HS?

HS flaring can be preceded by mild discomfort and pruritus. The physical manifestations of HS that cause pain are many and overlapping and include: (1) scarring, fibrosis, oval scars (which result in pulling pain), plaque-like induration, rope-like scars, dermal contractures [40], keloids [41]; (2) abscesses, both superficial and deep [42]; (3) open ulcerations that may exhibit rolled, boggy, or ragged edges and clean granulating bases [43]; (4) chronic sinuses and honeycombing [44]; (5) fistulas that can potentially dissect into deep structures including muscle, fascia, lymph nodes, the urethra, and bowels [45]; (6) frictional pain and shearing forces, which originate in skin folds [46]; (7) pain related to the hyperkeratosis and follicular occlusion (giant multiheaded comedones) [47, 48]; (8) pyogenic granulomas [49]; (9) lymphedema and lymphangiectasias causing edema of the vulva or penis and scrotum; (10) anal fissures; and (11) arthritis [50].

Table 6 Sources of Pain in HS

Type of Physical Finding	Comment
Scarring and fibrous and oval scars	A tensile related pain i.e. stretching of skin and possible stricture formation- Best treated topically with lidocain and orally with gabapentin or pregabalin
Keloids	Not inflammatory pain- Best treat with intralesional cortisone injections
Abscesses	Inflammatory pain- best treated with with NSAIDs, acetaminophen, celecoxib gabapentin, pregabalin, duloxetine, and/or venlafaxine. Opitates are sometimes needed
Open ulcerations	Ulcerations should be covered and a

	moisturizer or wound healing gel applied with telfa guaze on top. Topical diclofenac and topical lidocaine can be useful for pain control
Chronic sinuses	As there is usually inflammation sinuses are best treated with NSAIDs, acetaminophen, celecoxib, gabapentin, pregabalin, duloxetine, and/or venlafaxine. Opitates are sometimes needed.
Frictional pain	Use of topical pain medications and telfa gauze is helpful- held in place by fishnet dressing.[1] Weight loss helps
Hyperkeratosis of the infundibulum,	Non-inflammatory pain. Pain comes from tensile stretching best treated by extraction
Pyogenic granulomas	Usually inflammation- Best treated with NSAIDs, acetaminophen celecoxib, gabapentin, pregabalin, duloxetine, and/or venlafaxine. Opiates are sometimes needed. Injections of cortisone helps to bring down lesions.
Lymphedema and lymphangiectasias,	Challenging to deal with-compression and surgery are possible options for treatment
Anal Fissues	Topical 0.2% or 0.4% nitroglycerin ointment is an intra-anal formulation of nitroglycerin (glyceryl trinitrate) or 0.5% nifedipine ointment
Arthritis	Present in a minority of HS patients.Best initially treated with NSAIDs. If NSAIDs do not work a tumor necrosis alpha blocker like adalimumab or infliximab should be considered

Goal Setting in Pain Control

Although many people can function with a background of mild pain, the true effect of the pain on the body and mind is less certain. Chronic pain of HS impairs functions and leads to decreased productivity, unhappiness, and unemployment [51]. As Esman states " Shame and irritation are frequent and relate to smell, scars, itching, and pain [51]". The three most common co-morbidities of HS are pain, depression, and obesity [52]. As pain severity increases, it passes a threshold beyond which it is hard for the patient to ignore. At this point, it becomes disruptive to many aspects of the patient's life. It is not always possible to completely eliminate pain. A more realistic goal of pain management may be to optimize pain relief while focusing on disability issues to make patients more functional in their daily activities.

How to Approach Pain

Pain control strategy requires patients to rate their pain from 0 to 10 (11-point scale) or 0 to 100 (101-point scale). The number that the patient selects represents his or her pain intensity score [29]. Pain management specialists have developed tools for helping patients who are in pain and these can be used in patients with HS. Tables 7, 8, 9, and 10 outline approaches and metrics for pain management. Visual Analogue Scale (VAS) (Table 8), Verbal Rating Scale (VRS)(Table 9), and Visual Analog Scale (VAS) pain scale (table 10) are commonly used scales to rate pain [53].

Table 7 Pain Management [29, 53]

1. Believe the patient's report of pain.
2. Use a simple assessment tool such as a numerical scale of 0–10.
3. Assess pain in its site, character, intensity, extent, relieving and aggravating factors, and temporal relationships.
4. Patients may have more than one kind of pain; each pain syndrome must be indepentent diagnosed and treated.
5. Aim to achieve control at a level acceptable to the patient. It may not be necessary or possible to make the patient completely pain-free.
6. Refer for non-pharmacologic interventions such as physical therapy where appropriate.
7. Educate patients and their caregivers on the goals of therapy, management plan, potential complications, and home pain assessment and charting.

Table 8 Concurrent Psychosocial Issues of Pain [29, 53]

1. Chronic pain is often associated with and aggravated by psychological symptoms. Pain may not be adequately controlled unless these are appropriately treated.
2. Spiritual counseling in pain management may be useful in that spirituality helps the patient understand self better and may help the patient think beyond self and cope with pain better.
3. Psychological factors in response to acute pain are predictive of chronic incapacity. Better management of psychological reactions at early stages of treatment has the potential for preventing unnecessary chronicity.

Table 9 Pain Intensity Verbal Rating Scale (VRS)[29, 53]

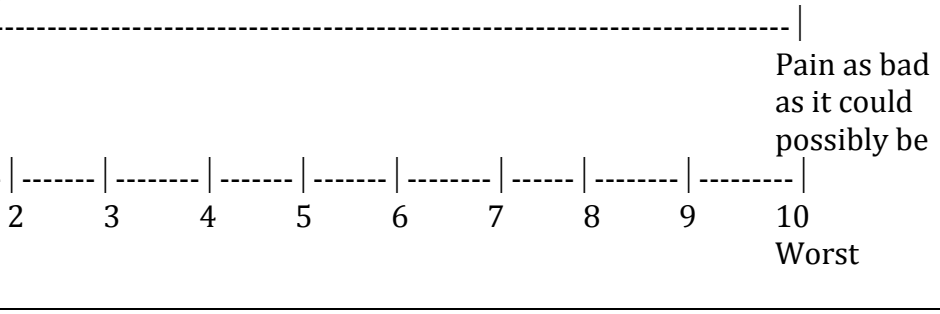
no pain
mild pain
moderate pain
severe pain
very severe pain

Table 10 Visual Analog Scale (VAS) pain scale[29, 53]

Verbal Numerical Scale
If "0" is no pain and "10" is the worst pain that you can imagine
where is your pain now? on average? at its worst? at its best

Word Scale
None Mild Moderate Severe Excruciating

Visual Analogue Scales



Pain agents and HS

A variety of non-opiate based oral medications can be use to treat the pain of HS (Table 11). Table 12 provides an algorithmic approach to HS pain control. Table 13 provides a laddered approach to control the pain of HS involving topical diclofenac 1%, topical lidocaine, topical doxepin, NSAIDS, including celecoxib, acetaminophen, gabapentin or pregabalin, and duloxetine or venlafaxine. Table 14 provides a pharmacokinetic comparison of pregabalin, gabapentin, duloxetine, and venlafaxine obtained from their respective package inserts.

The first place to start with the control of the pain of HS is to (1) decrease the burden of HS with medical or surgical treatments. Initially, pain can be treated with (2) ice packs or (3) topical 5% lidocaine ointment and 1% diclonec gel (4). Over the counter (OTC) pain medication such as naproxen, ibuopren, or celecoxib, and/or acetaminophen are first line oral agents for the treatment of HS pain. There is no clear data that any of these standard OTC NSAIDS are superior to another. Because the pain of HS can be constant and neuropathic in nature, agents that are atypical anticonvulsants or SSRI/SNRIs can change neural thresholds and be useful in the long-term management of HS.

Table 11 Oral pain medication non-opiate treatments of treatment of HS related pain

Oral Pain Medication	Status	Common Side Effects
Nonsteroidal anti-inflammatory drugs (NSAIDS)	OTC	Direct and indirect irritation of the gastrointestinal tract
Nonsteroidal anti-inflammatory drugs (NSAIDS)	Rx	Increased irriation of the gastrointestinal tract relative to OTC NSAIDs
Acetaminophen	OTC	Taken excessively can cause liver damage
COX -2 inhibitors-only celecoxib is available	Rx	Expensive-not clear if more effective than NSAIDs
Typical anticonvulsants	Rx	Complex side effects, weight gain
Atypical anticonvulsants	Rx	Fewer side effects than typical anticonvulsants, less weight gain than typical anticonvulsants
Tricyclic antidepressants	Rx	Complex side effects-best used by those trained in their use
Selective serotonin reuptake inhibitors (SSRIs)	Rx	Weight gain, mood changes
Combination Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Rx	Weight gain, mood changes
Aprepitant	Rx	Asthenia/Fatigue
Opitates including methadone and tramadol	Rx	Addiction, GI upset
Kentamine	Rx	More anesthesia than pain

Cannabinoids	Illegal in most states	Illegal, little data

Rx=prescription OTC=over the counter

Table 12 Pain Control for HS an algorithmic approach

S	Topical Agents	COX 2 blockering drugs	Naproxen	Acetaminophen	Ibuprofen	Gabapentin	Pregabalin	Duloxetine	Venlafaxine	Venlafaxine XR
S1 HS	Topical lidocaine 5% or diclofenic gel 1%	Celecoxib 200-400mg daily-not with NSAID	Start at 250 mg BID increase to 500 bid	1,000 - 4,000 mg TID use with COX2 or NSAID okay	400 mg every 4 to 6 hours.	Start at 400 mg TID than increase to 1200 mg TID as tolerated	Start at 50mg QD increase to 100 mg bid as tolerated	NA	NA	NA
S2 HS	Topical lidocaine5% or diclofenic gel 1% or custom compounds	Celecoxib 200 mg-400mg daily not to be used with NSAID	500 mg BID	1000-4,000 mg TID use with COX2 or NSAID okay	400 mg every 4 to 6 hours.	Start at 400 mg TID then increase to 1200 mg as tolerated	Start at 50mg daily- increase to 100 mg BID as tolerated. Doses as high as 300mg BID can be helpful and tolerated [252253].	Start at 30mg daily- increase to 120 mg daily as tolerated-add on to gabapentin or pregabalin	BID-TID with food. 75 mg/ day-can be increased to 150 mg, 225, to 225 mg/day and up to 375mg .Add on to gabapentin or pregabalin	Start at 37.5 mg QD can increase up to 225mg daily Add on to gabapentin or pregabalin
S3 HS	Custom preparations of topical pain control agents	Celecoxib 200-400mg daily not with NSAIDs	500 mg bid	1000-4,000 mg TID tuse with COX2 or NSAIDs okay	400 mg every 4 to 6 hours.	Start at 400 mg TID than increase to 1200 mg as tolerated	Start at 50mg QD increase to 100 mg BID as tolerated. Doses as high as 300mg BID can be helpful and tolerated.	Add on to gabapentin or pregabalin	Add on to gabapentin or pregabalin	Add on to gabapentin or pregabalin

S=Hurley Stage Do not combine NSAIDS, Can Combine Gabapenin with Pregabalin but usually this is not done; Do not combine Duloxentine with Effexor –QD=once a day, BID=twice a day, TID=three times a day NA=Not applicable

Table 13 Pruritis & Pain ladder for HS: topicals, NSAIDs, celecoxib, acetaminophen gabapentin,pregabalin, duloxetine & venlafaxine

Limited Itch	Topical lidocaine or topical doxepin (compounded 3% doxepin causes less dowsiness than FDA approved 5% doxepin cream)
Limited intermittent pain	Topical diclofenac 1%

Limited intermittent pain not controlled by Topical diclofenac 1%	**Preferred:** Topical diclofenac 1% with liposomal lidocaine 4 or 5% **Alternative:** Topical diclofenac 1% with generic 5% ointment with or without intermittent acetaminophen or intermittent NSAID or Celecoxib 200-400mg
Constant Pain not intense	**Preferred:** Acetaminophen **Alternative:** Naproxen or Ibuprofen (because of GI side effects) or Celecoxib
Constant Pain intense	**Preferred:** Pregabalin start at 50 mg bid titrate up to 100 mg BID can go up to 300mg BID. At 600mg Pregalin causes dowiness and more side effects. Use with NSAID, celecoxib, acetaminophen **Alternative:** Gabapentin, start at 400mg TID titrate up to 1200 my TID with awareness that this dose causes drowsiness- use with NSAID and acetaminophen
Constant Pain accompanied by depression	**Preferred:** Add on duloxetine 60 mg -120mg in divided doses BID, daily with Pregabalin or gabapentin- use with NSAID or celecoxib and/or acetaminophen **Alernative** Venlafaxine BID-TID with food. 75 mg/ day, can be increased to 150 mg, 225, or 375mg. Venlafaxine XR offers once daily dosing-use with NSAID or celecoxib and/or acetaminophen **Alternatives:** SSRI with NSAID or Celecoxib and/or acetaminophen Alternatives: SSRI with gabapentin or pregabalin
Constant Pain uncontrolled by Pregabalin or Gabapentin	**Preferred:** Add on duloxetine 60 mg-120mg daily with pregabalin or gabapentin. Use with NSAID or Celecoxib and/or Acetaminophen. **Alernative:** Venlafaxine BID-TID with food. 75 mg/ day, can be increase to 150 mg, 225or 375mg. Venlafaxine XR offers once daily dosing. Use with NSAID or celecoxib and/or acetaminophen
Constant Pain uncontrolled by NSAIDs, Celecoxib, Acetaminophen, Pregabalin or Gabapentin, duloxetine or Venlafaxine	Consider referral to pain specialist for use of opiate based drugs

Table 14 Pharmacokinetic Comparison of Pregabalin, Gabapentin, Duloxetine & Venlafaxine based on their package inserts

	Pregabalin	Gabapentin	Duloxetine	Venlafaxine
Absorption Tmax	1-1.5 hours	1.5 to 4 hours	6 hours	6 hours
Absorption Tmax with food	2.5 hours.	2.5 hours	10 hours. Food ↓absorption by 10%.	5.5 hours. Food does not affect the bioavailability of venlafaxine or its active metabolite,
Bioavailability	≥90%	Variable based on dose	~ 50% (32% to 80%)	40%-45%
Pharmacokinetic Profile	Linear	Nonlinear	Nonlinear	Linear

Plasma Half Life	6.3 hours	5 to 7 hours	6 hours	6 hours
Steady State	24-48 hours	24-48 hours	72 hours	72 hours
Metabolized	No	No	hepatic metabolism involving CYP1A2 and CYP2D6	hepatic metabolism CYP2D6 and CYP2C19 CYP3A3/4, CYP1A2
Renal Excretion	90% unchanged	Unchanged	~ 70% appears in the urine as metabolites of duloxetine	87% within 48 hours recommend a 50% reduction with creatinine clearance rates of less than 30 mL/min.
Fecal secretion	No	No	20% excreted in the feces	minimal
Protein Binding	No	<3%	Duloxetine >90% to human plasma proteins, mostly albumin and α1-acid glycoprotein.	binding to albumin is ≤30% for both parent and metabolite
Smoking	No clear interaction with smoking	No clear interaction with smoking	bioavailability↓ by ~33% in smokers; no dosage adjustment	No clear interaction with smoking

.

Acetaminophen

Acetaminophen, an analgesic and antipyretic [55], is metabolized by the liver. It is considered the non-narcotic analgesic of choice for mild to moderate pain in patients with who cannot tolerate NSAIDs. NSAIDs can be used in conjunction with acetaminophen. Excessive acetaminophen can lead to liver toxicity. Although the exact site and mechanism of analgesic action is not clearly defined, acetaminophen appears to produce analgesia by elevation of the pain threshold. The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate and substance P and may be related to may be related to an interaction with the central nervous system L-arginine-NO pathway [56,57]. Acetaminophen is not considered an NSAID because it has little anti-inflammatory activity. Oral acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract primarily in the small intestine. This absorption process occurs by passive transport. The relative bioavailability of acetaminophen is ~98% [58].

NSAIDs

NSAIDs are a class of drugs that provide analgesic, antipyretic, and anti-inflammatory effects in higher doses [59]. They only work on inflammatory pain not on non-inflammatory pain (essential pain also known as functional pain). As analgesics, NSAIDs are unusual in that they are non-narcotic and thus are used as a non-addictive alternative to narcotics. The most prominent members of this group of drugs are aspirin, ibuprofen, and naproxen, all of which are available over-the-counter in most countries (Table 15). Some are available by prescription (Table 16). The widespread use of NSAIDs has meant that the adverse effects of these drugs have become increasingly prevalent. The two main adverse drug reactions associated with NSAIDs relate to the gastrointestinal and renal side effects. If gastric upset is an issue with NSAID use, an H2 inhibitor, such as cimetidine, or a proton pump blocker, such as omprezole can be used. Combination preparations of the NSAIDs with anti-acid drugs exist, but are branded, patented, and expensive.

Most NSAIDs act as nonselective inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. This inhibition is competitively reversible (albeit at varying degrees of reversibility) as opposed to the mechanism of aspirin, which is irreversible inhibition. COX catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (itself derived from the cellular phospholipid bilayer by phospholipase A2)

[59]. Prostaglandins act as messenger molecules in the process of inflammation.

Table 15 Types of NSAID that are over the counter and most commonly used [60, 61]

Most Commonly used NSAIDs	Half life	Dosing
Ibuprophen	8 hours	400mg TID
Aspirin	4-6 hours	325mg daily-QID
Naproxen	12 hours	250 mg BID increase to 500 BID

Table 16 Prescription NSAIDs [60, 61]

Prescription NSAIDs	Dose limiting effects	Dosing	Half life	comments
Indomethacin	GI bleeding	50 mg BID-QID, or 75 mg BID	4.5 hours	XR available
Ketorolac	GI bleeding severe if used for more than 5 days	Patients age 17 to 64: 20 mg PO once followed by 10 mg q4-6 hours prn not > 40 mg/day. Patients age ≥ 65, renally impaired, and/or weight < 50 kg (110 lbs): 10 mg PO once than 10 mg q4-6 hours prn not > 40mg/day	2.5-6 hours6	IV or IM PO not first line

Cox 2 Inhibitors

COX-2 selective inhibitors are a form of NSAID that directly targets COX-2, an enzyme responsible for inflammation and pain. Target selectivity for COX-2 theoretically reduces the risk of peptic ulceration. After several COX-2 inhibiting drugs were approved for marketing, data from clinical trials revealed that COX-2 inhibitors caused a significant increase in heart attacks and strokes [60]. However, COX2 drugs can sometimes succeed for pain control when other NSAIDS have failed [58]. However, as a general rule COX2 have similar efficacy as NSAIDs. The mechanism of action of COX2 blockers resembles that of NSAIDs in part. COX2 inhibitors, at least in the short term, have fewer GI problems than other NSAIDs [61]. COX2 inhibitors are expensive and might have negative cardiovascular side effects. Hence, for pharmacoeconomic reasons they should be reserved for situations in which the patient cannot tolerate other NSAIDs. Celecoxib carries a black box warning regarding cardiovascular and gastrointestinal risks.

Combining Acetaminophen and NSAIDS

Superior pain control can be obtained by combining acetaminophen and an NSAID such as ibuprofen [62]. In a randomized, double-blind, controlled study [62], patients undergoing Mohs micrographic surgery and reconstruction for head and neck skin cancers received 1,000 mg of acetaminophen, 1,000 mg acetaminophen plus 400 mg ibuprofen, or 325 mg acetaminophen plus 30 mg codeine immediately after surgery and every 4 hours for up to four doses. Patients rated their pain on a visual analog scale (VAS) 0, 2, 4, 8, and 12 hours after surgery and recorded medication-related side effects. The acetaminophen and ibuprofen group had the lowest pain scores (mean change from baseline/immediately prior to surgery) at each postoperative recorded time interval and a significantly smaller change from baseline pain scores than the acetaminophen and codeine group at 4 hours and acetominophen at 8 hours. The acetaminophen and ibuprofen combination was also superior in pain control for patients with surgical areas smaller than 10 cm^2. Complications in the ibuprofen and acetaminophen group were significantly lower than in the acetaminophen and codeine group, but not than the acetaminophen group. The conclusion was that the combination of acetaminophen and ibuprofen is superior to acetaminophen alone or acetaminophen and codeine in controlling postoperative pain after Mohs micrographic surgery and skin reconstruction.

Gabapentin

Gabapentin (Neurontin®) binds to the α2δ (alpha2delta) subunit of the voltage-dependent calcium channel in the central nervous system and affects γ-aminobutyric acid (GABA). Gabapentin was originally developed to treat epilepsy and currently is also used to relieve neuropathic pain [63]. Gabapentin is in the class of atypical anti-epileptic medications. It changes neural thresholds thereby decreasing pain. Gabapentin is an amino acid derivative of gamma-amino butyric acid (GABA analogue). Gabapentin provides significant pain relief in about a third of people who take it for fibromyalgia or chronic neuropathic pain [64]. It is also effective in reducing narcotic usage post operatively and is helpful in neuropathic pain related to cancer [65]. It has not been

shown useful for HIV associated sensory neuropathy. When used for neuropathic pain it does not appear superior to carbamazepine [66].

Although gabapentin is not a controlled substance, it does produce psychoactive effects that cause it to have potential for recreational use. Even in low doses, gabapentin causes reduced acute pain and anxiety. Larger doses can cause the user to become numb and even fully insensate. Tolerance to gabapentin occurs extremely rapidly with recreational use, with the user often needing to double the dosage within a day or two of misuse. Persons who accidentally or intentionally ingested overdoses have manifested drowsiness, blurred vision, slurred speech, and somnolence or coma. Serum gabapentin concentrations may be measured to confirm diagnosis, although the drug is widely regarded as having little or no potential for misuse. However, gabapentin has been associated with an increased risk of suicidal acts or violent deaths [67]. In 2009, the U.S. Food & Drug Administration issued a warning of an increased risk of depression, suicidal thoughts and behaviors in patients taking gabapentin, along with other anticonvulsant drugs; the package insert now reflects this.

Gabapentin appears as effective as pregabalin and costs less. Evidence shows that anticonvulsant drugs can be used for acute and chronic pain [68]. The combination of pregabalin with a COX2 inhibitor such as parecoxib (not approved in the US) was more effective than the pregabalin alone [69]. This finding can probably be extrapolated to combining gabapentin with an NSAID to increase pain control. Gabapentin does appear to provide some benefit for complex regional pain syndrome and fibromyalgia [70]. Some evidence has suggested that it may be used as a broad-spectrum analgesic [71]. Gabapentin treats idiopathic trigeminal neuralgia with a similar efficacy, safety, and tolerability to duloxetine [72].

Gabapentin has been successfully used in several varieties of pain related to dermatological and non-dermatological conditions [73] including erythromelalgia [74], postherpetic neuralgia [75], notalgia paresthesica [76], continuous pain, acute wound dressing pain, therapy (e.g., radiotherapy), pressure ulceration [77], dysesthetic pain after reconstructive surgery [78], multiple piloleiomyoma-related pain [79], vulvodynia [80], and brachioradial pruritus [81]. Other types of internal pain have been treated with gabapentin. In addition, it has been used to treat interstitial cystitis [82], central post-stroke pain syndrome [83], trigeminal neuralgia in multiple sclerosis patients [84], genitofemoral and ilioinguinal neuralgia [85], neuropathic orbital pain [86], painful neuropathy in diabetics [87], and chronic intractable pain [88].

Dosing of Gabapentin

Based on available data from 5 randomized, placebo-controlled trials [89], it appears that treatment with gabapentin should be started at a dose of 900 mg/d (300 mg/d on day 1, 600 mg/d on day 2, and 900 mg/d on day 3, divided into 3 doses). Additional titration to 1800 mg/d is recommended for greater efficacy. Doses up to 3600 mg/d and can be used and may be needed in some patients in particular if they are obese. The effective dose should be individualized according to patient response and tolerability.

Pregabalin

Pregabalin (Lyrica®) is an anticonvulsant drug used for neuropathic pain, post-herpetic neuralgia, diabetic peripheral neuropathy, and fibromyalgia [90]. Pregabalin is in the class of atypical anti-epileptic medications.

Like gabapentin, pregabalin binds to the α2δ (alpha2delta) subunit of the voltage-dependent calcium channel in the central nervous system and effects GABA levels. Pregabalin decreases the release of neurotransmitters including glutamate, noradrenaline, substance P, and Calcitonin-Gene-Related-Peptide [91]. However, unlike anxiolytic compounds (e.g., benzodiazepines), which exert their therapeutic effects through binding to GABAA, GABAB, and benzodiazepine receptors, pregabalin neither binds directly to these receptors nor augments GABAA currents; it does not affect GABA metabolism [92]. Pregabalin can be started at 50mg once a day and rapidly increased to 100mg twice a day if needed. Pregabalin doses as high as 300mg BID can be helpful and tolerated if needed to control symptoms, in particular, when used to control seizures [93, 94].

The FDA has approved pregabalin for treating epilepsy, as an adjunct therapy for partial seizures with or without secondary generalization in adults, post-herpetic neuralgia, diabetic peripheral neuropathy, and fibromyalgia at a dose of up to 100mg BID. In the EU, pregabalin is approved for generalized anxiety disorder. Pregabalin is also used off-label for the treatment of chronic pain, neuropathic pain, peri-operative pain, and migraines. Doses as high as 300mg twice daily can be helpful and tolerated if lower doses are only partially successful, in particular if seizures are being treated; titation upwards should be as gradual as possible [92, 93].

Pregabalin may also cause withdrawal effects after long-term use if discontinued abruptly. When prescribed for seizures, quitting “cold turkey” can increase the strength of the seizures and possibly cause the seizures to recur. Withdrawal symptoms include

restlessness, insomnia, and anxiety. Pregabalin should be reduced gradually when finishing treatment. Renal failure patients developed myoclonus while receiving pregabalin, apparently as a result of gradual accumulation of the drug [90, 91]. Acute overdosage may be manifested by somnolence, tachycardia, and hypertonicity [90, 91]. Plasma, serum, or blood concentrations of pregabalin are measured to monitor therapy or to confirm a diagnosis of poisoning in hospitalized patients [94].

Pregabalin has been used with duloxetine to give pain relief of cutaneous leiomyomata related to Reed Syndrome [95]. Pregabalin has been used to treat scalp dysesthesia [96]. Successful treatment of adult-onset erythromelalgia with pulse dose corticosteroids and pregabalin has been noted [97]. Treatment of prurigo nodularis with pregabalin has been reported [98]. Pregabalin can help cancer related pain [99], but it is not additive with morphine at low doses [100]. Only the highest dose of pregabalin reduced mechanical allodynia 7 days post-ischemia/reperfusion [101]. Pregabalin may have a role with surgery in treating compression of the superficial branch of the radial nerve by calcinosis cutis that caused neuropathic pain [102]. Pregabalin may have a role in control of pain of chronic pancreatitis [103]. Pregabalin seems helpful in successful reversal of Complex Regional Pain Syndrome (CRPS) of both upper extremities in five patients. In study of patients with CRPS Patients 1–4 were treated with multimodality treatment regimen comprising medication with highest tolerated dose of amitriptyline, pregabalin, and tramadol, along with stellate ganglion block for the less affected extremity, continuous brachial plexus block for 4–5 weeks for the more affected extremity, dry needling, and physical therapy of muscles of both upper extremities with good results [104].

Pregabalin Combined with Other Agents for Pain Control

Pregabalin with lidocaine plaster and other agents appears to work synergistically to control pain. The data in this area is limited [105]. Studies suggest that lidocaine 5% plaster is better overall than pregabalin [106-108]. In patients unresponsive to either mono-therapy, combination therapy provides additional efficacy and is well tolerated [109].

Dosing of Pregabalin

For HS, usually physicians will start the patient on a low dose of pregabalin 50mg daily or twice a day and increase it gradually to the full dose of 100mg twice a day, depending on the patient's tolerance. Pregabalin's therapeutic effect appears after 1 week of use and is similar in effectiveness to lorazepam, alprazolam, and venlafaxine. However, pregabalin has demonstrated superiority by producing more consistent therapeutic effects for psychic and somatic anxiety symptoms [110]. Long-term trials have shown continued effectiveness without the development of tolerance. Additionally, unlike benzodiazepines, pregabalin does not disrupt sleep architecture and produces less severe cognitive and psychomotor impairment. Pregabalin also has a low potential for abuse and dependence and may be preferred over the benzodiazepines for these reasons [110]. Uremic pruritus can be treated by gabapentin and pregabalin, an important fact because patients with HS also experience itch [111].

Gabapentin versus Pregabalin

Because of cost issues, gabapentin is preferred for the chronic control of HS pain over pregabalin, with or without an NSAID or acetaminophen. Several issues should be considered in the choice between gabapentin and pregabalin: (1) A full dose of gabapentin 1200 mg TID can be quite sedating for patients and induce drowiness in many patients. (2) Pregabalin is branded and quite expensive. (3) Pregabalin is a schedule 5 controlled substance. I have found that pregabalin 100 mg BID is usually better tolerated by HS patients than gabapentin 1200 mg TID.

Several additional issues should be considered in the choice between gabapentin and pregabalin. Gabapentin and pregabalin, but not morphine and amitriptyline, block both static and dynamic components of mechanical allodynia induced by streptozocin in the rat [112]. Symptomatic treatment has been attempted with pain blocking medications, such as gabapentin, because of the neuropathic nature of the pain. This approach has met with variable, but always incomplete, pain resolution. Pregabalin and gabapentin reduce the release of substance P and Calcitonin-Gene-Related-Peptide from rat spinal tissues only after inflammation or activation of protein kinase C [91, 113]. A study showed that gabapentin did not abate the pain associated with cutaneous piloleiomyomata [114].

Some studies do suggest that pregabalin might be superior to gabapentin in some situations. In a meta-analysis [115] of the nine studies included, samples sizes were less than 100 patients, except for one pregabalin study (n = 136). Standard errors for the numerical rating scale (NRS) outcome were often not reported, precluding quantitative comparisons across treatments. Estimated 11-point NRS pain reduction relative to placebo was -1.72 for pregabalin, -1.65 for amitriptyline, -1.0 for duloxetine, -1 (median) for levetiracetam, -0.27 for gabapentin, 1 (median) for lamotrigine, and 2 for dronabinol. Risk ratios relative to placebo for 30% improvement were 0.71 for levetiracetam and 2.56 for pregabalin, and 0.94 and 2.91, respectively, for 50% improvement. Meta-

analytic comparisons showed more adverse effects with pregabalin and tramadol compared with placebo and no differences between placebo and any treatment for discontinuations [116].

Another analysis found pregabalin was the most effective drug when compared to other drugs for spinal pain: (-1.72 for pregabalin, -1.65 for amitriptyline, -1.0 for duloxetine, -1 (median) for levetiracetam, -0.27 for gabapentin, 1 (median) for lamotrigine, and 2 for dronabinol). Pregabalin is superior to amitriptyline for post herpetic neuralgia [117]. In sum, pregabalin is an effective treatment for neuropathic pain [118-120]. The choice of whether to use gabapentin versus pregabalin is defined by cost, side effects, tolerance, and patient response. However, both are usually helpful medications in controlling HS pain.

Data on Gabapentin and Pregabalin and Other Agents for Pruritus might be Extrapolated to Pain Control

Both gabapentin and pregabalin have anti-pruritic effects that might allow us to extrapolate data to pain control because similar neural mechanisms control itch and pain. Pregabalin effectively treated chronic pruritus [121]. Gabapentin and pregabalin can be used to treat prurigo nodularis [98, 122]. In addition, pregabalin is useful in treating itch in uremic patients [123]. However, for patients suffering from pruritus associated with HIV infection, indomethacin, an NSAID, was described as the most effective drug as compared to hydroxyzine (with or without doxepin at night), pentoxifylline, indomethacin, and topical moisturization with medium-strength topical steroids [124, 125]. Interestingly, rifampicin may be recommended for patients with cholestatic pruritus and might be part of the treatment and theraputic regimen for HS [126]. Gabapentin treatment for brachioradial pruritus has been found effective [127-129]. A case of post-herpetic itch that resolved with gabapentin has been noted [130]. Burning itch can be treated with both gabapentin [131-135] and pregabalin. This is notable because burn victims can have skin breakdown that mirrors the eroded areas of HS. In a study of 40 patients (50 started the study), there was no difference between gabapentin and pregabalin in terms of efficacy against pain and pruritus. Gabapentin and pregabalin improved both neuropathic pain and uremic pruritus significantly [136]. Gabapentin has been found effective for notalgia paresthetica [137] and itch of unknown origin [138]. Efficacy of pregabalin in the management of cetuximab-related itch has been reported [139]. In chronic kidney disease-associated pruritus gabapentin is effective [140-143]. In sum, if we see itch as a sensory response parallel to pain, additional data underlies the use of gabapentin and pregabalin for HS pain.

Duloxetine (Cymbalta®) a combination SSRI/SNRI for Pain and Depression of HS

Duloxetine is an SSRI/SNRI that is used to treat major depressive disorder, general anxiety disorder, stress urinary incontinence, painful peripheral neuropathy, fibromyalgia, chronic musculoskeletal pain associated with osteoarthritis and chronic lower back pain, and the neuropathic pain of cancer [144-147]. Table 17 presents common conditions treated with duloxetine. A number of other drugs are part of this class of SSRI/SNRIs (Table 18). Duloxetine has a benign side effect profile [148]. This combination of effects in ameliorating depression and pain is of particular interest for patients with HS who are more likely to be depressed than case control patients [149].

Table 17 Entities that have been treated by Duloxetine

Lower Back Pain
Fibromyalgia
Diabetic peripheral neuropathy
Chronic musculoskeletal pain
Stress urinary incontinence (not FDA approved, approved in EU)

Table 18 Combined SSRI/SNRIs

Effexor XR®
generic name: venlafaxine

Pristiq®
generic name: desvenlafaxine (primarily for major depression)

Cymbalta®
generic name: duloxetine

Effexor®
generic name: venlafaxine (generic available)

Savella®
generic name: milnacipran (primarily for fibromyalgia)

Duloxetine is FDA indicated in major depressive disorder [150], general anxiety disorder (GAD), stress urinary incontinence (in EU), painful peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain associated with osteoarthritis and chronic lower back pain. Duloxetine failed to receive US approval for stress urinary incontinence amidst concerns over liver toxicity and suicidal events. Duloxetine can also relieve the symptoms of painful peripheral neuropathy, particularly diabetic neuropathy, and it is used to control the symptoms of fibromyalgia.

Side Effects of Duloxentine

Duloxentine has a different side effect profile than that of pregabalin and gabapentin (Table 19). Duloxentine side effects are generally mild [151-160]. Besides gastric upset, it can cause slight weight gain [151]. In studies greater than3 months, patients with fibromyalgia and chronic lower back pain had overall mean weight increase (up to 1.1 kg), whereas patients in peripheral neuropathic pain studies had overall mean weight loss (-0.33 to -1.7 kg) at end-point. Overall, the percentage of patients with potentially clinically significant weight gain was 0.4-16% and potentially clinically significant weight loss was 2.5-9.9% [152]. During longer-term treatment (34 weeks), duloxetine 40 mg BID did not have weight gain, whereas duloxetine 60 mg BID engendered weight gain. Thus one can conclude that duloxetine-treated patients experienced weight loss after short-term treatment, followed by modest weight gain on longer-term treatment [153].

Although scores differed somewhat from norms for age, substantial cognitive impairment was not evident in patients with fibromyalgia treated with duloxetine as assessed by the Symbol Digit Substitution Test, Trail-Making Test, and Verbal Learning and Recall Test. Overall, duloxetine treatment had neither positive nor negative effects on cognition [154]. Duloxetine treatment is associated with significantly higher rates of nausea, dry mouth, and fatigue versus placebo, regardless of indication or demographic subgroup [151-160]. Differences across indications are likely to be attributable to the underlying condition rather than duloxetine, as suggested by the similar trends observed in placebo- and duloxetine-treated patients [151-160]. In sum, duloxetine has a mild side effect profile regarding weight gain and glycemic control [151-160]. Duloxetine as an antidepressant has a variety of side effects that have been discussed above. Unlike velafaxine, duloxenine does not have cardiovascular effects and does not raise blood pressure. Like other anti-depressants it leads to weight gain and change of glucose control. Duloxetine impairment of cognition remains controversial [159]. Weight gain was reported with duloxetine use in patients with diabetic peripheral neuropathic pain; conflicting results on weight gain were reported with fibromyalgia syndrome [160].

Table 19 Side Effects of Duloxetine

Nausea (23%-34.7%)
Dry mouth, (13%-22.7%)
Constipation (10%)
Sexual dysfunction
Weight gain
Negative effects on glycemic control
Insomnia, 10% to 20%
Dizziness 10% to 20%
Headache

CYMBALTA (Duloxetine Delayed-Release Capsules) for Oral Use. Eli Lily 2012 Package insert

Uses of Duloxetine for depression and pain

Duloxetine amelorates depression and pain. In a study involving of 2496 patients, duloxetine was found effective for major depression [161]. In one study [162], twenty-two patients experiencing unipolar depression were included. During use of duloxetine, heat pain thresholds of patients normalized during treatment, whereas no significant change was observed for ischemic pain thresholds. Improvement in painful physical symptoms was associated with higher remission rates even after accounting for improvement in core emotional symptoms. Duloxetine has a positive effect on depression and anxiety in patients with ankylosing spondylitis [163]. A report has noted the effectiveness of duloxetine in a patient with pain-induced syncope resistant to standard

regimens [164]. The available evidence shows that there does not seem to be any difference in efficacy between duloxetine and other oral pharmacological therapies non-scheduled opioids, cyclooxygenase-2 inhibitors, scheduled opioids, selective serotonin reuptake inhibitors, and 'other' (i.e. glucosamine), providing a valuable alternative for this disabling condition [165]. Duloxetine use in chronic painful conditions exhibited wide variability in individual patient data responder analysis [166]. Comparison of safety outcomes among Caucasian, Hispanic, Black, and Asian patients in duloxetine studies of chronic painful condition detected only minimal differences among safety outcomes assessed in these race/ethnic subgroups in patients treated with duloxetine for chronic painful conditions [167].

A variety of types of pain can be amelorated by duloxeine. Duloxetine controls the pain of knee arthrosis [168]. Treatment of depression and menopause-related symptoms with duloxetine is effective [170]. Duloxetine is effective for chronic nonorganic orofacial pain [171]. As stated above, duloxetine is effective for chronic lower back pain [172]. In sum, duloxetine is efficacious in treating chronic pain (diabetic peripheral neuropathic pain, fibromyalgia, chronic pain due to osteoarthritis, and chronic low back pain) as demonstrated by significant improvement in pain intensity, physical functioning, and patient ratings of overall improvement [173-175]. Some have questioned the utility of duloxetine for pain control [176, 177]. Others have found duloxetine's pain control similar to the SSRI escitalopram [178].

Treatment of Chemotherapy Side Effects with Duloxetine

Duloxetine reduces chemotherapy induced peripheral neuropathy [179]. Duloxetine decreased pain and improved function and quality of life among patients with chemotherapy-induced painful peripheral neuropathy in a randomized clinical trial [180]. Among patients with painful chemotherapy-induced peripheral neuropathy, the use of duloxetine compared with placebo for 5 weeks resulted in a greater reduction in pain [181]. Successful treatment using duloxetine for peripheral neuropathy induced by paclitaxel has been noted [182]. Duloxetine improves oxaliplatin-induced neuropathy in patients with colorectal cancer [183]. A pilot study of duloxetine for treatment of aromatase inhibitor-associated pain improved musculoskeletal symptoms [184].

Other painful conditions treated with duloxetine

Duloxetine has other analgesic affects. A presumed case of phantom limb pain was treated successfully with duloxetine and pregabalin [184]. Burning mouth syndrome responsive to duloxetine has been noted [185]. Duloxetine has positive affects on the primary pain symptoms in Parkinson disease [186]. Duloxetine has treated tinnitus and depression [187]. Duloxetine treatment has effectively treated premenstrual dysphoric disorder [188]. It has been used to treat chronic daily headache [189]. Treatment of depression and menopause-related symptoms with duloxetine has been noted [190]. A review of duloxetine 60 mg once daily added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain related to osteoarthritis found duloxetine effective [191]. Although this association cannot establish causality, these results provide some evidence for the possibility that pain may mediate the sleep problem associated with diabetic peripheral neuropathic pain and perhaps chronic pain in general [192]. In sum, duloxetine has utility to treat pain [193].

Fibromyalgia and duloxetine

Fibromyalgia syndrome is a clinically well-defined chronic condition of unknown etiology characterized by chronic widespread pain that often co-exists with sleep disturbances, cognitive dysfunction, and fatigue. Patients often report high disability levels and poor quality of life. Drug therapy focuses on reducing key symptoms and improving quality of life [194]. In an evaluation of SNRIs for fibromyalgia syndrome in he Cochrane Database, which providess critical review of drugs, few advantages were found for duloxentine over other agents [195]. On the other hand, a number of reports suggest that duloxentine is the preferred agent for fibromyalgia syndrome. Early improvement in pain predicts pain response at endpoint in patients with fibromyalgia in patients using duloxentine [196]. Daily dosing has been useful for the management of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain related to chronic osteoarthritis pain and low back pain [197]. Evaluation of patient-rated stiffness associated with fibromyalgia, a post-hoc analysis of 4 pooled, randomized clinical trials of duloxetine, found decreased stiffness in fibromyalgia patients using duloxetine [198]. Early improvement in pain predicts pain response at endpoint in patients with fibromyalgia [199].

For non-depressed patients with diabetic peripheral neuropathic pain and fibromyalgia syndrome, duloxetine has a statistically significantly greater effect on pain than placebo. Path analysis is used to describe the directed dependencies among a set of variables. These include models equivalent to any form of multiple regression analysis, factor analysis, canonical correlation analysis, discriminant analysis, as well as more general families of models in the multivariate analysis of variance and covariance analyses. Using this set of parameters it is suggested that approximately 50, 90, and 80%, respectively, of the observed effect on pain is a direct analgesic effect rather than an indirect antidepressant effect [200]. Pain is a complex conscious experience,

involving both the physiological responses of the nociceptive system and the processing of that information in brain regions associated with emotion;duloxetine helps both [200].

Combinations of Duloxetine and Pregabalin or Gabapentin or Other Agents to Treat Pain

Duloxetine and prebaglin or gabapentin can work synergistically to decrease pain. In one study [121] a tibial neuroma transposition (TNT) model in which the tibial nervewais transected and the tibial nerve stump was transpositioned to the lateral aspect of the hindlimb was evaluated. After TNT injury, mechanical allodynia and neuroma pain are observed. Morphine, pregabalin, gabapentin, and duloxetine were administered orally and were examined for the antiallodynic and antineuroma pain effects. Morphine, pregabalin, gabapentin, and duloxetine attenuated the level of mechanical allodynia in a dose-dependent manner. Morphine-but not pregabalin, gabapentin, and duloxetine attenuated the neuroma pain. Morphine was less potent in neuroma pain than in mechanical allodynia. In the 2-drug-combination studies (morphine and pregabalin, morphine and duloxetine, and pregabalin and duloxetine), all drug combinations produced a synergistic effect on mechanical allodynia, but not on neuroma pain. Although not significantly superior to high-dose monotherapy, combination therapy was considered to be effective, safe, and well tolerated with a fifty-percent response rate of 52.1% for combination and 39.3% for high-dose monotherapy [121]. In exploratory analyses of the initial 8-week therapy uncorrected for multiple comparisons for diabetic peripheral neuropathic pain 60 mg/day, duloxetine was found superior to 300mg/day pregabalin; combining both medications is superior to increasing each drug to its maximum recommended dose [121]. Utilization of duloxetine and celecoxib in osteoarthritis patients delayed the need to use opiates [201].

Combinations of Duloxetine with NSAIDs or COX2 inhibitors

Some treatment reports of adding duloxetine to an NSAID or COX2 inhibitor suggest additive affect [202]. A recent mouse study found synergy between COX2 drugs and duloxetine [203]. Two randomized studies of duloxetine for chronic low back pain with and without concomitant NSAIDs or acetaminophen were reported. In the following groups: NSAID/acetaminophen user (n = 137), placebo NSAID/acetaminophen user (n = 82), duloxetine NSAID/acetaminophen nonuser (n = 206), and placebo NSAID/acetaminophen nonusers (n = 156) no added benefit with the acetaminophen was found [204].

Duloxetine versus Gabpentin or Pregabalin

The comparison of duloxetine versus gabpentin or pregabalin for neuropathy and related conditions has engendered much controversy. In the Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation the conclusion stated that: Pregabalin is established as effective and should be offered for relief of peripheral diabetic neuropathy (PDN) (Level A evidence). Venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids (morphine sulfate, tramadol, and oxycodone controlled-release), and capsaicin are probably effective and should be considered for treatment of peripheral diabetic neuropathy (PDN) (Level B evidence) [121].

Other treatments, in particular, tricyclic antidepressants, have less robust evidence or their evidence is negative. Effective treatments for painful diabetic neuropathy are available, but many have side effects that limit their usefulness and few studies have sufficient information on treatment effects on function and quality of life [121]. Health outcomes and costs among employees with fibromyalgia treated with pregabalin versus amitriptyline, duloxetine, or venlafaxine showed that despite several comorbidity and drug use differences, most employees benefit outcomes and adherence did not differ among the cohorts [205]. In similar commercially insured patients with fibromyalgia who initiated duloxetine or pregabalin, duloxetine patients had significantly lower health care costs over the 12-month post-index period.

Studies comparing duloxetine, gabapentin and pregablin have been done [206]. A study of emotional and cognitive impairments in mononeuropathic rats has been done. It shows that the use of duloxetine and gabapentin did not reveal any impairment [207]. When FMS complicates a rare disease called Cogan's syndrome, a rare disorder characterized by recurrent inflammation of the cornea and often fever, fatigue, weight loss, episodes of dizziness, and hearing loss, it can lead to deafness or blindness if untreated both duloxetine and pregabalin are effective [208]. In a study of 152 patient with painful diabetic peripheral neuropathy, pregabalin, duloxetine, and gabapentin were effective, but pregabalin had the fastest onset of action [209]. In a study of 828 duloxetine and 1934 pregabalin-treated patients with a mean age of 50 years, the commercially insured patients with diabetic peripheral neuropathic pain who initiated duloxetine or pregabalin therapy had different dosing patterns. The average

daily dose for duloxetine was relatively stable over time, whereas pregabalin-treated patients had significant dose increases over the 12-month post-index period [210].

In cases in which pregabalin cannot be tolerated by patients, then duloxetine can function as an alternative treatment. In one study [211], the subjects of the study were 15 cancer patients with neuropathic pain. Duloxetine was administered to patients in whom pregabalin could not be administered. The influence of duloxetine was investigated retrospectively with the use of a numerical rating scale. Pain was reduced in 7 out of the 15 patients. Sleepiness and a light-headed feeling were improved in four patients, but the pain was not reduced in these. Thus, duloxetine was judged to be effective in 11 patients. The maintenance dose of duloxetine was 20-40 mg/day.

Duloxetine administration may be effective for neuropathic pain in cancer patients who cannot tolerate pregabalin administration. For diabetic peripheral neuropathic pain, a meta-analysis was done [212]. Three studies of duloxetine, six of pregabalin, and two of gabapentin met criteria. In random-effects and fixed-effects analyses of duloxetine, pregabalin, and gabapentin all were superior to placebo for all efficacy parameters with some tolerability trade-offs. Indirect comparison of duloxetine with pregabalin found no differences in 24 hours, but significant differences in Patient Global Impression of Improvement/Change, favoring pregabalin. Regarding dizziness, duloxetine was favored. Duloxetine and gabapentin were statistically similar in efficacy.

From the few available studies suitable for indirect comparison, duloxetine shows comparable efficacy and tolerability to gabapentin and pregabalin in diabetic peripheral neuropathic pain. Other results suggest that the method of action of duloxetine and pregabalin stimulates and augments the bulbospinal-spinal noradrenergic-cholinergic pathway and lowers the dose requirement for each drug to reduce hypersensitivity after nerve injury without sedative effect [213]. Another study showed that patients with a malfunctioning pain modulation pattern, such as less efficient conditioned pain modulation, would benefit more from drugs augmenting descending inhibitory pain control (e.g. gabapentin, duloxetine) than would patients with a normal modulation pattern of efficient conditioned pain modulation [214].

Cost of Duloxetine

Health care costs appear to be higher with duloxetine than with gabapentin or pregabalin. Still, duloxetine seems useful in painful conditions and I have found it useful to treat HS pain even if it is expensive [215]. Furthermore, for cancer patients, duloxetine has benefits for neuropathic pain non-responsive to pregabalin [216]. The effects on pain of duloxetine are independent of the effects on ameliorating depression [217]. The cost of duloxetine should drop in 2014 when duloxetine goes generic.

Venalfaxine (Effexor®)

Venlafaxine appears to have a poorer side effect profile than duloxetine, particularly with regard to cardiovascular side effects, including hypertension (Package insert Effexor® -venlafaxine hydrochloride- tablets Wyeth 2204, 2013). However, as venalfaxine is generic it might find a place in second line therapy for HS pain. However, side effects related to the cardiovacular system may complicate patients who are already complicated; many are already suffering from metabolic syndrome [218]. Venlafazine has more non-cardiac side effects than duloxetine as well. The most important problems include nausea, somnolence, and dry mouth. Its XR form allows for less fequent dosing.

Venlafazine abates pain and depression. In one study, of the 102 outpatients enrolled, 86 (84.3%) completed the study. Venlafaxine extended release treatment (75-225 mg/day) was followed by a significant decrease in the total scores for the 17-item Hamilton Depression Rating Scale from baseline to the second weekend. The remission rate for pain responders (improvement in Visual Analog Scale overall pain from baseline to last observation ≥50%) was significantly greater than that for pain nonresponders (56.1 vs. 20.0%). The most common (≥10%) adverse events were nausea (31.4%), dizziness (26.5%), and somnolence (22.5%). Venlafaxine XR is possibly an effective and safe option in the treatment of depression and associated painful physical symptoms. Efficacy of venlafaxine extended-release monotherapy for first-episode depression with painful physical symptoms has been demonstrated [219].

A number of types of pain are responsive to velafaxine including severe painful peripheral diabetic neuropathy, [220] neuropathic pain, vasomotor symptoms associated with menopause [221], subacute and chronic spondylogenic dorsopathy [222], neuropathic pain following treatment of breast cancer [223], and painful peripheral diabetic neuropathy in a uremic patient undergoing hemodialysis [224]. In young adult patients with functional chest pain based on a randomized, double-blind, placebo-controlled, crossover trial of 43 patients, velafaxine was helpful in controlling pain [225]. A single-blind placebo run-in study of 150-225 mg venlafaxine XR for activity-limiting osteoarthritis pain involving 18 subjects with activity-limiting osteoarthritis pain was

performed. Each subject received 2 weeks of placebo followed by 10 weeks of venlafaxine; most patients had little pain relief although a subset had 30% pain relief [226]. Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity in a randomized, double-blind, placebo-controlled phase III trial has been noted [227].

Velafixine has been used to treat atypical facial pain. Persistent idiopathic facial pain, previously known as atypical facial pain, is described as a persistent facial pain that does not have the classical characteristics of cranial neuralgias and for which there is no obvious cause (International Classification of Headache Disorders in 2004) [228]. According to these criteria, the diagnosis is possible if the facial pain is localized, present daily, and present throughout all or most of the day. By definition, neurological and physical examination findings in persistent idiopathic facial pain should be normal. Forming a diagnosis is not simple and follows a process of elimination of other causes of facial pain. Some have found good effects with velafixine for facial pain [229].

Dosing of Venlafaxine to Control Pain

Higher does of venlafaxine, if tolerated, are more effective than lower doses for the treatment of pain. Researchers [230] studied 505 patients with depressive symptoms suffering from chronic pain in a prospective naturalistic Swiss community based observational trial with venlafaxine in primary care. These patients were treated with venlafaxine by 122 physicians, psychiatrists, general practitioners, and internists. On average, patients were treated with 143+/-75 mg (0-450 mg) venlafaxine daily for a follow-up of three months. Venlafaxine proved to be beneficial in the treatment of both depressive symptoms and chronic pain. These results reflect the complexity in the treatment of chronic pain in patients with depressive symptoms in primary care. Similarly venlafaxine was found effective for symptomatic relief in young adult patients with functional chest pain in a randomized, double-blind, placebo-controlled, crossover trial at a dose of 75mg daily [231].

Physicans prefer Duloxetine over Venlafaxine for the Treatment of Pain with Depression

Twelve randomized placebo-controlled trials with the total number of 4,108 patients suffering from pain associated with major depressive disorder suggested consistent analgesic efficacy of duloxetine, especially in fibromyalgia and peripheral neuropathic pain [232]. Researchers [233] indentified demographic and clinical predictors of treatment initiation with duloxetine and venlafaxine XR using logistic regression. Patients initiating duloxetine (n = 909) were 4 years older than venlafaxine XR recipients (n = 1286). Older age, preexisting unexplained pain, respiratory disease, and pre-period use of anticonvulsants, opioids, and antihyperlipidemics were associated with increased odds of initiating duloxetine compared to venlafaxine XR. Pre-period anxiety disorder was associated with decreased odds of receiving duloxetine. Initial treatment choice with duloxetine versus venlafaxine XR was primarily driven by patient-specific mental and medical health characteristics. General practitioners in the UK favor duloxetine over venlafaxine XR when pain conditions co-exist with depression [233]. Venlafaxine XR remains patented and is expensive.

Wang [234] conducted a retrospective analysis of 15,523 adults with major depressive disorder and chronic pain-related diseases. In the MarketScan Commercial Claims and Encounters Database, Wang noted duloxetine-treated patients had higher adherence and persistence rates than did patients treated with venlafaxine XR or escitalopram during 6 months after medication initiation

Zhao [235] analyzed the electronic medical and pharmacy records from January 2004 to December 2008 from the Veterans Integrated Service Network 16 data warehouse. All select patients received either duloxetine or other treatments [tricyclic antidepressants (TCAs), venlafaxine, gabapentin, and pregabalin] over the study period, with the first dispense date of the index agent as the index date. Patients with self-reported severe pain were 1.66 times more likely to receive duloxetine as those with no pain reported. Diabetic peripheral neuropathic pain patients in the VA healthcare system with prior other treatment use, select co-morbid conditions, prior substance abuse, prior opioid use, and higher pain level were more likely to receive duloxetine.

Some studies compared duloxetine and venlafaxine-XR and suggested that duloxeine is the superior pain medication. Vis [236] studied outcomes from published, randomized, placebo-controlled trials reporting on moderately to severely depressed patients (Hamilton Rating Scale for Depression [HAM-D] > or =15 or Montgomery-Asberg Depression Rating Scale [MADRS] > or =18) using a systematic literature search (1996-January 2005). Differences in remission (8-week HAM-D score < or =7 or MADRS < or =10), response (50% decrease on either scale), dropout rates from lack of efficacy, and adverse events were meta-analyzed using a random effects model. Each rate was contrasted with placebo. Sensitivity analyses were performed to examine the robustness of the results. Data were obtained from 8 trials evaluating 1754 patients for efficacy and 1791 patients for discontinuation/safety. Venlafaxine-XR rates were 17.8% and 24.4% greater than those with placebo for remission and response compared with 14.2% and 18.6% for duloxetine. Although numerically higher for venlafaxine-XR, both demonstrated overall

remission and response rates significantly higher than the rates achieved with placebo. Reported adverse events were comparable between drugs.

In a study from using electronic medical and pharmacy data in the Kaiser Permanente Southern California region, the adherence patterns for patients with a neuropathic pain diagnosis who were prescribed an antidepressant or an anticonvulsant were studied. Compliance and persistence were measured using the medication possession ratio and the refill-sequence model [237]. The study included 1817 patients with a nurse practioner making the diagnosis in patients taking either an antidepressant or an anticonvulsant. Within the antidepressant group, 42.9% were considered compliant, compared with 43.7% in the anticonvulsant group. Subanalysis of the 2 cohorts revealed that patients on venlafaxine were the most compliant (69.4%) compared with patients taking gabapentin (44.4%) and tricyclic antidepressants (41.8%). Only 21.2% of patients in the antidepressant group and 21.4% in the anticonvulsant group were considered persistent with their medication refills. Compliance and persistence rates were similar for patients with nurse practitioner diagnosis taking antidepressants and anticonvulsants. Higher compliance was observed among patients taking venlafaxine. However, this population did have a small sample size. The study did not assess duloxetine.

Venlafaxine versus Imipramine for Control of Pain

Researchers [238] studied venlafaxine for painful polyneuropathy and compared its possible efficacy with that of the tricyclic antidepressant, imipramine. The study design was a randomized, double blind, and placebo controlled, with a three-way crossover. Forty patients were assigned to one of the treatment sequences and 29 completed all three study periods. The daily doses were venlafaxine 225 mg and imipramine 150 mg. During the three treatment periods, each of 4 weeks' duration, patients rated pain paroxysms, constant pain, and touch- and pressure-evoked pain by use of 0- to 10-point numeric rating scales. The sum of the individual pain scores during treatment week 4 was lower on venlafaxine (80% of baseline score) and imipramine (77%) than on placebo (100%) and did not show any statistical difference between venlafaxine and imipramine. The individual pain scores for pain paroxysms, constant pain, and pressure-evoked pain showed a similar pattern, whereas touch-evoked pain was uncommon and was not altered by any of the drugs. Numbers needed to treat to obtain one patient with moderate or better pain relief were 5.2 for venlafaxine and 2.7 for imipramine.

Venlafaxine versus Gabapentin for control of pain

Researchers [239] assessed 150 patients scheduled for either partial or radical mastectomy with axillary dissection. They were randomized in a double-blinded manner to receive extended release venlafaxine 37.5 mg/day, gabapentin 300 mg/day, or placebo for 10 days starting the night before operation. Pain scores were recorded at rest and movement (visual analog scale) at 4, 12, and 24 hours on the first day postoperatively and daily from the second to tenth day postoperatively. The visual analog scale in addition to pain character was also measured 6 months later. Analgesic requirements were compared. Venlafaxine 37.5 mg/d extended release or gabapentin 300 mg/d appeared to have equipotent effects (except on the first day in venlafaxine group) in reducing analgesic requirements, although gabapentin was more effective in reducing pain after movement. Venlafaxine significantly reduced the incidence of post-mastectomy pain syndromes (chronic pain) at 6 months in women having breast cancer surgery. In this study, gabapentin had no effect on chronic pain except decreasing the incidence of burning pain.

Combination Gabapentin and Venlafaxine

Gabapentin and venlafaxine had synergistic analgesic affects for the treatment of painful diabetic neuropathy. One group [240] evaluated the safety and efficacy of gabapentin and venlafaxine in the treatment of painful diabetic neuropathy in patients whose pain did not improve with gabapentin monotherapy. The comparison groups includeda randomized, double-blind, placebo-controlled, 8-week clinical trial comparing gabapentin versus placebo to define a patient population whose pain did not improve with monotherapy a second 8-week trial comparing gabapentin plus venlafaxine with gabapentin plus placebo, and a third uncontrolled 8-week trial of patients who did not improve on gabapentin mono-therapy and then received venlafaxine in addition to gabapentin. The conclusions were: (1) gabapentin is efficacious in the treatment of painful diabetic neuropathy, (2) in patients who do not respond to gabapentin monotherapy, the addition of venlafaxine is also more effective than either agent used alone.

Eardly [241] performed a prospective, non-randomized, unblended, efficacy comparison of venlafaxine, as either monotherapy or as adjuvant therapy with a first-line medication for neuropathic pain, gabapentin, in patients with peripheral neuropathy related peripheral neuropathy. VAS pain scores were assessed after 3 and 6 months in intervention groups and in a cohort of patients receiving no pharmacotherapy. In a total of 223 patients, we analyzed pain quantity and quality (VAS score, Brief Pain Inventory), quality of life and health status measures, Medical Outcomes Sleep Study Scale, Hospital Anxiety and Depression Scale, and Short Form 36 Health Survey) after 6 months of therapy. Significant improvements in VAS pain scores occurred for all treatment groups after 6 months. Improvements in aspects of daily life and anxiety were identified in all treatment groups. Eardly concluded

that monotherapy or adjuvant therapy with venlafaxine is comparable to gabapentin for peripheral neuropathy management.

Administration of Venlafaxine Might Decrease the Activity of Other Pain Treatments

Administration of venlafaxine might decrease the activity of other pain treatments. One study in rats found that venlafaxine counteracted the affects of gabapentin probably as consequence of increased diuresis of gabapentin [242]. Acute co-administration of venlafaxine increased the analgesic activity of morphine, chronic treatment with venlafaxine attenuated opioid efficacy [243].

Issues with using SNRIs: choosing which SNRI to use

Because ≥20% of HS patiens suffer from depression, duloxetine should be considered as a first line agent in treating depression, not because it is the best anti-depressant but because neuropathic pain can be treated without affecting the cardiovascular system [244-255]. Anti-depressants have side effects; SNRIs effect the libio and duloxentine can be rarely hepatotoxic [244]. Venlafaxine in 1-3% of patients has cardiac side effects and obese HS patients are already grappling with cardiac issues due to obestity and metabolic syndrome.

The effects on norepinephrine differ between the class members of SNRIs. Duloxetine has a 10-fold selectivity for 5-HT and venlafaxine a 30-fold selectivity for 5-HT. Yet, clinically it seems that duloxetine is superior to venlafaxine [256]. Venlafaxine also has more potential for addiction than does duloxentine [257, 258].

There is no evidence for major differences between SNRIs and SSRIs in their efficacy in treating anxiety disorders. In contrast to SSRIs, which are generally ineffective in treating chronic pain, all SNRIs seem to be helpful in relieving chronic pain associated with and independent of depression. Tolerability of an SNRI at therapeutic doses varies within the class. Although no direct comparative data are available, venlafaxine seems to be the least well tolerated;serotonergic adverse effects (nausea, sexual dysfunction, withdrawal problems) and a dose-dependent cardiovascular phenomenon, principally hypertension can occur. Duloxetine appears better tolerated and essentially devoid of cardiovascular toxicity [259].

The effects of acute, systemic administration of amitriptyline, duloxetine and mirtazapine, and the selective serotonin reuptake inhibitor citalopram were compared in rat models of experimental pain [260]. None of the drugs (all 3-30 mg/kg, intraperitoneally) affected acute nociceptive responses as measured in the tail flick test. In the hot plate test, duloxetine andmirtazapine significantly increased the nociceptive response latency, whereas amitriptyline and citalopram were ineffective. In the formalin test, duloxetine and citalopram significantly attenuated, whereas amitriptyline and mirtazapine increased, second phase flinching behavior. However, amitriptyline and mirtazapine reduced second phase licking behavior. In the chronic constriction injury model of neuropathic pain, thermal hyperalgesia of the injured hind paw was significantly attenuated by all four drugs. Only amitriptyline and duloxetine fully reversed thermal hypersensitivity. None of the drugs tested attenuated mechanical allodynia. In contrast amitriptyline, duloxetine, and mirtazapine significantly reduced mechanical hyperalgesia; citalopram was ineffective. No drug-related effects on motor performance in the rotarod test were observed. These results (a) highlight the difficulty in correlating antinociceptive effects of drugs from different antidepressant classes across a range of animal pain models and (b) suggest that antidepressants that variously affect both noradrenaline and serotonin levels have more potent and efficacious antinociceptive effects than SSRIs (as exemplified by citalopram) against a range of pain-like behaviors in an animal model of neuropathic pain

To underline the complexity of choosing the right drug for neuropathic pain duloxetine, milnacipran, and pregabalin were compared [250]. The 3 drugs were superior to placebo and similar except that (1) duloxetine caused more fatigue; (2) milcaipran caused more sleep disturbance; (3) pregabalin was not effective for depressed mood. Adjusted indirect comparisons indicated no significant differences for 30% pain relief and dropout rates related to adverse events between the 3 drugs. Significant differences in average symptom reduction were found: duloxetine and pregabalin were superior to milcaipran in reduction of pain and sleep disturbances. Duloxetine was superior to milcaipran and pregabalin in reducing depressed mood. Milcaipran and pregabalin were superior to duloxetine in reducing fatigue. There is evidence for the short-term (up to 6 months) efficacy of duloxetine, milcaipran, and pregabalin. Differences with regard to the occurrence of the key symptoms of FMS and to drug-specific adverse events may be relevant for the choice of medication [250]. The commercially insured patients with diabetic peripheral neuropathic pain who initiated duloxetine or pregabalin therapy had different dosing patterns. Duloxetine showed comparable efficacy and tolerability to gabapentin and pregabalin diabetic peripheral neuropathic pain [252]. Moreover, gabapentin and duloxetine can act synergistically [253].

The Basis of Pain in Painful Conditions

The basis of the pain of HS needs to be defined and it must be understood to be both a disease of acute and chronic pain [254]. The pain of HS is both neuropathic and sometimes ischemic, something anticonvulsants and SSRI/SSNI do not treat. Pain changes the way we experience depression and major depression affects such basic pain responses, such as decreasing cold-pain Studies demonstrate that a) individuals who are more sensitive to one kind of pain are also more sensitive to others and b) factors that increase or decrease one kind of pain alter the other in a similar manner [255]. Finally, what these shared neural responses mean for our understanding of socially painful experience is discussed [256]. Patients have higher heat pain thresholds of patients normalized during treatment for depression, whereas no significant change was observed for ischemic pain thresholds. Thus, these results might change the view on the paradox of pain perception in major depression because decreased heat pain thresholds are associated with augmented pain perception in the disease [257].

Conclusions

It is important to recognize that pain should be treated even when associated with a condition that primarily a skin disease. If we are to treat the pain of HS that is unresponsive to topical anti-pain agents, it seems that gabapentin and pregabalin are the place to start because they have fewer side effects than any SSRI or SSRI/SSNI [259-267]. Gabapentin and pregabalin can be combined with NSAIDs and COX2 drugs. If cost were not an issue pregabalin would trump gabapentin and I have had better compliance and results with pregabalin. Pregabalin is even useful for neuropathic pain associated with spinal cord injury and the pain of HIV [268]. But if cost is an issue gabapentin would be preferred over pregabalin. No medication is side effect free; pregabalin too has side effects and one report associated pregablin withheart failure in a patient [269]. An isolated anecdotal case report, noted that gabapentin caused hearing loss in one patient underlying the fact that rare side effects can occur [270]. Gabapentin or pregabalin can be combined with duloxetine, in particular if the HS is accompanied by depression. In cases of depression the data suggests that duloxetine be tried first and venlafaxine second unless the patient's insurance will not pay for patented duloxetine [271-273]. Because HS can be seen in the spectrum of diseases that are metabolic syndromes [274], venlafaxine, which has cardiovascular side effects, should be used with care in HS patients. To conclude, pain control in HS is complex but it can be achieved. Pain is among the most debilitating aspects of HS and should not be ignored because there are many safe options for its treatment.

HS patients learn to live with pain, but it adversely affects their lives and their functioning. Physicians caring for HS must also be willing to understand useful treatments for pain and use them.

References

1. Scheinfeld S. Hidradenitis suppurativa: A practical review of possible medical treatments based on over 350 hidradenitis patients. Dermatol Online J. 19:4 (2013).
2. Smith HS, Chao JD, Teitelbaum J. Painful hidradenitis suppurativa. Clin J Pain. 2010 Jun;26(5):435-44.
3. Vazquez BG, Alikhan A, Weaver AL, Wetter DA, Davis MD. Incidence of Hidradenitis Suppurativa and Associated Factors: A Population-Based Study of Olmsted County, Minnesota. J Invest Dermatol. 2013 Jan;133(1):97-103.
4. von der Werth JM, Jemec GB. Morbidity in patients with hidradenitis suppurativa. Br J Dermatol. 2001 Apr;144(4):809-13.
5. Canoui-Poitrine F, Revuz JE, Wolkenstein P, Viallette C, Gabison G, Pouget F, Poli F, Faye O, Bastuji-Garin S. Clinical characteristics of a series of 302 French patients with hidradenitis suppurativa, with an analysis of factors associated with disease severity. J Am Acad Dermatol. 2009 Jul;61(1):51-7.
6. Ibler KS, Jemec GB. Cumulative life course impairment in other chronic or recurrent dermatologic diseases. Curr Probl Dermatol. 2013;44:130-6.
7. Matusiak L, Bieniek A, Szepietowski JC. Psychophysical aspects of hidradenitis suppurativa. Acta Derm Venereol. 2010 May;90(3):264-8.
8. Fallon MT. Neuropathic pain in cancer. Br J Anaesth. 2013 Jul;111(1):105-11.
9. Scheninfeld N. Diseases associated with hidranitis suppurativa: part 2 of a series on hidradenitis 19:4 (2013)
10. Onderdijk AJ, van der Zee HH, Esmann S, Lophaven S, Dufour DN, Jemec GB, Boer J. Depression in patients with hidradenitis suppurativa. J Eur Acad Dermatol Venereol. 2013 Apr;27(4):473-8.
11. von der Werth JM, Williams HC. The natural history of hidradenitis suppurativa. J Eur Acad Dermatol Venereol 2000;14:389-392.
12. von der Werth J.M., Jemec G.B.: Morbidity in patients with hidradenitis suppurativa. Br J Dermatol 144;2001:809-813.
13. Alikhan A, Lynch PJ, Eisen DB. Hidradenitis suppurativa: a comprehensive review. J Am Acad Dermatol. 2009 Apr;60(4):539-61; quiz 562-3.
14. Kennedy J. Hidradenitis suppurativa: a diagnostic dilemma for sexual health. N Z Med J. 2008 Aug 22;121(1280):58-62.
15. Wolkenstein P, Loundou A, Barrau K, Auquier P, Revuz J; Quality of Life Group of the French Society of Dermatology. Quality of life impairment in hidradenitis suppurativa: a study of 61 cases. J Am Acad Dermatol. 2007 Apr;56(4):621-3.

16. Solarski ST. Living with hidradenitis suppurativa. Dermatol Nurs. 2004 Oct;16(5):447-9.
17. Jemec GB, Heidenheim M, Nielsen NH. Hidradenitis suppurativa--characteristics and consequences. Clin Exp Dermatol. 1996 Nov;21(6):419-23.
18. van der Zee HH, de Ruiter L, van den Broecke DG, Dik WA, Laman JD, Prens EP. Elevated levels of tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-10 in hidradenitis suppurativa skin: a rationale for targeting TNF-α and IL-1β. Br J Dermatol. 201;164:1292-8.
19. Schlapbach C, Hänni T, Yawalkar N, Hunger RE. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. J Am Acad Dermatol. 2011;65:790-8. [PMID: 21641076]
20. Lapins J, Asman B, Gustafsson A, Bergström K, Emtestam L. Neutrophil-related host response in hidradenitis suppurativa: a pilot study in patients with inactive disease. Acta Derm Venereol. 2001 May;81(2):96-9.
21. Schuh-Hofer S, Wodarski R, Pfau DB, Caspani O, Magerl W, Kennedy JD, Treede RD. One night of total sleep deprivation promotes a state of generalized hyperalgesia: A surrogate pain model to study the relationship of insomnia and pain. Pain. 2013 May 11.
22. Bahouq H, Allali F, Rkain H, Hmamouchi I, Hajjaj-Hassouni N. Prevalence and severity of insomnia in chronic low back pain patients. Rheumatol Int. 2013 May;33(5):1277-81.
23. Matsuzaki K, Upton D. Wound treatment and pain management: a stressful time. Int Wound J. 2012 Aug 21.
24. Campbell CM, Edwards RR. Ethnic differences in pain and pain management. Pain Manag. 2012 May;2(3):219-230.
25. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. Br J Anaesth. 2013 Jul;111(1):52-8.
26. Zale EL, Lange KL, Fields SA, Ditre JW. The Relation Between Pain-Related Fear and Disability: A Meta-Analysis. J Pain. 2013 Jul 11.
27. Raspe H, Matthis C, Croft P, O'Neill T. Variation in back pain between countries: the example of Britain and Germany. European Vertebral Osteoporosis Study Group. Spine (Phila Pa 1976). 2004 May 1;29(9):1017-21; discussion 1021.
28. Doth AH, Hansson PT, Jensen MP, Taylor RS The burden of neuropathic pain: a systematic review and meta-analysis of health utilities. Pain. 2010 May;149(2):338-44.
29. Davison SN. The prevalence and management of chronic pain in end-stage renal disease. J Palliat Med. 2007 Dec;10(6):1277-87.
30. Dalbeth N, Lindsay K. The patient's experience of gout: new insights to optimize management. Curr Rheumatol Rep. 2012 Apr;14(2):173-8.
31. Abeles AM, Park JY, Pillinger MH, Cronstein BN Update on gout: pathophysiology and potential treatments. Curr Pain Headache Rep. 2007 Dec;11(6):440-6.
32. Guevara-López U, Ayala-Guerrero F, Covarrubias-Gómez A, López-Muñoz FJ, Torres-González R. Effect of acute gouty arthritis on sleep patterns: a preclinical study.Eur J Pain. 2009 Feb;13(2):146-53.
33. Dalbeth N, Petrie KJ, House M, Chong J, Leung W, Chegudi R, Horne A, Gamble G, McQueen FM, Taylor WJ. Illness perceptions in patients with gout and the relationship with progression of musculoskeletal disability. Arthritis Care Res (Hoboken). 2011 Nov;63(11):1605-12.
34. Powell FC, O'Kane M. Management of pyoderma gangrenosum. Dermatol Clin. 2002 Apr;20(2):347-55, viii.
35. Thorslund K, Svensson T, Nordlind K, Ekbom A, Fored CM. Use of serotonin reuptake inhibitors in patients with psoriasis is associated with a decreased need for systemic psoriasis treatment: a population-based cohort study. J Intern Med. 2013 May 24.
36. Zur E. Oral mucositis: etiology, and clinical and pharmaceutical management. Int J Pharm Compd. 2012 Jan-Feb;16(1):22-33.
37. Naversen DN, Trask DM, Watson FH, Burket JM. Painful tumors of the skin: "LEND AN EGG". J Am Acad Dermatol. 1993 Feb;28(2 Pt 2):298-300.
38. Valeyrie-Allanore L, Ingen-Housz-Oro S, Colin A, Thuillot D, Sigal ML, Binhas M. Pain management in Stevens-Johnson syndrome, toxic epidermal necrolysis and other blistering diseases. Ann Dermatol Venereol. 2011 Oct;138(10):694-7; quiz 692-3, 698.
39. Moroz A, Lee M-H, Clark J. Reflex sympathetic dystrophy with hidradenitis suppurativa exacerbation: a case report. Arch Phys Med Rehabil. 2001;82:412–414.
40. Poli F, Wolkenstein P, Revuz J. Back and face involvement in hidradenitis suppurativa. Dermatology. 2010;221(2):137-41.
41. Lamfichekh N, Dupond AS, Destrumelle N, Runser C, Humbert P, Mantion G. Surgical treatment of Verneuil's disease (hidradenitis suppurativa): 15 cases Ann Dermatol Venereol. 2001 Feb;128(2):127-9.
42. Haoxiang X, Chengrang L, Baoxi W, Xinfeng W. Modified abscess drainage in treatment of eight cases with hidradenitis suppurativa in China. Dermatol Surg. 2013 May;39(5):779-83.
43. Weiner J, Lewis JE, Samitz MH. Hidradenitis suppurativa occurring on the leg. Cutis. 1976 May;17(5):888-91.
44. Alharbi Z, Kauczok J, Pallua N. A review of wide surgical excision of hidradenitis suppurativa.BMC Dermatol. 2012 Jun 26;12:9.
45. Kołodziejczak M, Sudoł-Szopińska I, Wilczyńska A, Bierca J. Utility of transperineal and anal ultrasonography in the diagnostics of hidradenitis suppurativa and its differentiation from a rectal fistula. Postepy Hig Med Dosw (Online). 2012 Nov 14;66:838-42

46. de Winter K, van der Zee HH, Prens EP. Is mechanical stress an important pathogenic factor in hidradenitis suppurativa? Exp Dermatol. 2012 Mar;21(3):176-7.
47. Pitarch G, Pitarch A, Sánchez-Motilla JM. Flexural comedones. Actas Dermosifiliogr. 2008 Dec;99(10):824.
48. Canoui-Poitrine F, Le Thuaut A, Revuz JE, Viallette C, Gabison G, Poli F, Pouget F, Wolkenstein P, Bastuji-Garin S. Identification of three hidradenitis suppurativa phenotypes: latent class analysis of a cross-sectional study.J Invest Dermatol. 2013 Jun;133(6):1506-11.
49. Jemec GB, Hansen U. Histology of hidradenitis suppurativa. J Am Acad Dermatol. 1996 Jun;34(6):994-9.
50. Moosbrugger EA, Mutasim DF. Hidradenitis suppurativa complicated by severe lymphedema and lymphangiectasias. J Am Acad Dermatol. 2011 Jun;64(6):1223-4.
51. Esmann S, Jemec GB. Psychosocial impact of hidradenitis suppurativa: a qualitative study. Acta Derm Venereol. 2011 May;91(3):328-32. .
52. Vazquez BG, Alikhan A, Weaver AL, Wetter DA, Davis MD. Incidence of hidradenitis suppurativa and associated factors: a population-based study of Olmsted County, Minnesota. J Invest Dermatol. 2013 Jan;133(1):97-103.
53. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005 Aug;14(7):798-804.
54. Björkman R, Hallman KM, Hedner J, Hedner T, Henning M. Acetaminophen blocks spinal hyperalgesia induced by NMDA and substance P. Pain. 1994 Jun;57(3):259-6.
55. Choi SS, Lee JK, Suh HW.Antinociceptive profiles of aspirin and acetaminophen in formalin, substance P and glutamate pain models. Brain Res. 2001 Dec 7;921(1-2):233-9.
56. Hekimoğlu S, Ayanoğlu-Dülger G, Hincal AA. Comparative bioavailability of three commercial acetaminophen tablets. Int J Clin Pharmacol Ther Toxicol. 1987 Feb;25(2):93-6.
57. Weberschock TB, Müller SM, Boehncke S, Boehncke WH. Tolerance to coxibs in patients with intolerance to non-steroidal anti-inflammatory drugs (NSAIDs): a systematic structured review of the literature. Arch Dermatol Res. 2007 Jul;299(4):169-75.
58. Kapoor M, Shaw O, Appleton I. Possible anti-inflammatory role of COX-2-derived prostaglandins: implications for inflammation research. Curr Opin Investig Drugs. 2005 May;6(5):461-6.
59. Kollenberg LO, Hudyma EO, Robbins JM.Nonsteroidal anti-inflammatory agents. A review of the literature. J Am Podiatr Med Assoc. 1985 Oct;75(10):517-22.
60. Vaithianathan R, Hockey PM, Moore TJ, Bates DW.Iatrogenic effects of COX-2 inhibitors in the US population: findings from the Medical Expenditure Panel Survey.Drug Saf. 2009;32(4):335-43.
61. COX2-alternatives and GI protection. Med Lett Drugs Ther. 2004 Nov 8;46(1195):91-2.
62. Sniezek PJ, Brodland DG, Zitelli JA. A randomized controlled trial comparing acetaminophen, acetaminophen and ibuprofen, and acetaminophen and codeine for postoperative pain relief after Mohs surgery and cutaneous reconstruction. Dermatol Surg. 2011 Jul;37(7):1007-13.
63. Hayashida K, Eisenach JC. Multiplicative interactions to enhance gabapentin to treat neuropathic pain. Eur J Pharmacol. 2008 Nov 19;598(1-3):21-6.
64. Moore RA, Wiffen PJ, Derry S, McQuay HJ.Gabapentin for chronic neuropathic pain and fibromyalgia in adults.Cochrane Database Syst Rev. 2011 Mar 16;(3):CD007938.
65. Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain--a systematic review of randomized controlled trials. Pain. 2006 Dec 15;126(1-3):91-101.
66. Phillips TJ, Cherry CL, Cox S, Marshall SJ, Rice AS Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. PLoS One. 2010 Dec 28;5(12):e14433.
67. Patorno E, Bohn RL, Wahl PM, Avorn J, Patrick AR, Liu J, Schneeweiss S. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. JAMA. 2010 Apr 14;303(14):1401-9.
68. Wiffen P, Collins S, McQuay H, Carroll D, Jadad A, Moore A. Anticonvulsant drugs for acute and chronic pain. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD001133.
69. Chizh BA, Göhring M, Tröster A, Quartey GK, Schmelz M, Koppert W. The combination of pregabalin with a COX2 inhibitor such as parecoxib was more effective than the pregabalin alone. Br J Anaesth. 2007 Feb;98(2):246-54.
70. Tran de QH, Duong S, Bertini P, Finlayson RJ. Treatment of complex regional pain syndrome: a review of the evidence.Can J Anaesth. 2010 Feb;57(2):149-66.
71. Gilron I. Is gabapentin a "Broad-spectrum" analgesic? Anesthesiology. 2002 Sep;97(3):537-9.
72. Anand KS, Dhikav V, Prasad A, Shewtengna. Efficacy, safety and tolerability of duloxetine in idiopathic trigeminal neuralgia. J Indian Med Assoc. 2011 Apr;109(4):264-6.
73. Scheinfeld N. The role of gabapentin in treating diseases with cutaneous manifestations and pain. Int J Dermatol. 2003 Jun;42(6):491-5.
74. Ceyhan AM, Gurses I, Yildirim M, Akkaya VB. A case of erythromelalgia: good response to treatment with gabapentin. J Drugs Dermatol. 2010 May;9(5):565-7.
75. Tyring SK. Management of herpes zoster and postherpetic neuralgia. J Am Acad Dermatol. 2007 Dec;57(6 Suppl):S136-42.
76. Loosemore MP, Bordeaux JS, Bernhard JD. Gabapentin treatment for notalgia paresthetica, a common isolated peripheral sensory neuropathy. Can J Anaesth. 2010 Feb;57(2):149-66.

77. Devulder J, Lambert J, Naeyaert JM.Gabapentin for pain control in cancer patients' wound dressing care. J Pain Symptom Manage. 2001 Jul;22(1):622-6.
78. Otley CC. Gabapentin for the treatment of dysesthetic pain after reconstructive surgery. Dermatol Surg. 1999 Jun;25(6):487-8.
79. Alam M, Rabinowitz AD, Engler DE. Gabapentin treatment of multiple piloleiomyoma-related pain. J Am Acad Dermatol. 2002 Feb;46(2 Suppl Case Reports):S27-9.
80. Ben-David B, Friedman M. Gabapentin therapy for vulvodynia. Anesth Analg. 1999 Dec;89(6):1459-60.
81. 81. Bueller HA, Bernhard JD, Dubroff LM. Gabapentin treatment for brachioradial pruritus. J Eur Acad Dermatol Venereol. 1999 Nov;13(3):227-8.
82. Hansen HC. Interstitial cystitis and the potential role of gabapentin. South Med J. 2000 Feb;93(2):238-42.
83. Chen B, Stitik TP, Foye PM, Nadler SF, DeLisa JA. Central post-stroke pain syndrome: yet another use for gabapentin? Am J Phys Med Rehabil. 2002 Sep;81(9):718-20.
84. Khan OA. Gabapentin relieves trigeminal neuralgia in multiple sclerosis patients. Neurology. 1998 Aug;51(2):611-4.
85. Benito-Léon J, Picardo A, Garrido A, Cuberes R. Gabapentin therapy for genitofemoral and ilioinguinal neuralgia. J Neurol. 2001 Oct;248(10):907-8.
86. Sloan PA, Kancharla A. Treatment of neuropathic orbital pain with gabapentin. J Pain Palliat Care Pharmacother. 2003;17(2):89-94.
87. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, Garofalo E Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA. 1998 Dec 2;280(21):1831-6.
88. Gustorff B, Nahlik G, Spacek A, Kress HG. Gabapentin in the treatment of chronic intractable pain. Schmerz. 2002 Feb;16(1):9-14.
89. Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. Clin Ther. 2003 Jan;25(1):81-104.
90. Package Insert Pregabalin (Lyrica) Pfizer 2012
91. Martinotti G, Lupi M, Sarchione F, Santacroce R, Salone A, De Berardis D, Serroni N, Cavuto M, Signorelli M, Aguglia E, Valchera A, Iasevoli F, Di Giannantonio M.The potential of pregabalin in neurology, psychiatry and addiction: a qualitative overview. Curr Pharm Des. 2013;19(35):6367-74.
92. Russell IJ, Crofford LJ, Leon T, Cappelleri JC, Bushmakin AG, Whalen E, Barrett JA, Sadosky A. The effects of pregabalin on sleep disturbance symptoms among individuals with fibromyalgia syndrome. Sleep Med. 2009 Jun;10(6):604-10.
93. Eden B, May TW. Efficacy and safety of pregabalin in refractory focal epilepsy with and without comorbid anxiety disorders - Results of an open-label, parallel group, investigator-initiated, proof-of-concept study.Brandt C, Schoendienst M, Trentowska M, Schrecke M, Fueratsch N, Witte-Boelt K, Pohlmann- Epilepsy Behav. 2013 Nov;29(2):298-304.
94. Johannessen SI, Tomson T.Pharmacokinetic variability of newer antiepileptic drugs: when is monitoring needed? Clin Pharmacokinet. 2006;45(11):1061-75.
95. Kostopanagiotou G, Arvaniti C, Kitsiou MC, Apostolaki S, Chatzimichael K, Matsota P. Successful pain relief of cutaneous leiomyomata due to reed syndrome with the combination treatment of pregabalin and duloxetine. J Pain Symptom Manage. 2009 Sep;38(3):e3-5.
96. Sarifakioglu E, Onur O. Women with scalp dysesthesia treated with pregabalin. Int J Dermatol. 2013 Apr 4.
97. Successful treatment of adult-onset erythromelalgia with steroid pulse and pregabalin. Kakizaki A, Fujimura T, Kambayashi Y, Watabe A, Aiba S. Case Rep Dermatol. 2012 Sep;4(3):242-6.
98. Mazza M, Guerriero G, Marano G, Janiri L, Bria P, Mazza S. Treatment of prurigo nodularis with pregabalin. J Clin Pharm Ther. 2013;38:16–18.
99. Baba M, Gomyo I. Retrospective evaluation of pregabalin for cancer-related neuropathic pain.Masui. 2012 Feb;61(2):147-54.
100. Mercadante S, Porzio G, Aielli F, Ferrera P, Codipietro L, Lo Presti C, Casuccio A. The effects of low doses of pregabalin on morphine analgesia in advanced cancer patients. Clin J Pain. 2013 Jan;29(1):15-19.
101. Millecamps M, Coderre TJ. Rats with chronic post-ischemia pain exhibit an analgesic sensitivity profile similar to human patients with complex regional pain syndrome--type I. Eur J Pharmacol. 2008 Mar 31;583(1):97-102.
102. Wei-Chong C, Yam A.Compression of the superficial branch of the radial nerve by calcinosis cutis causing neuropathic pain. J Hand Surg Eur Vol. 2010 Nov;35(9):766-7.
103. Olesen SS, Graversen C, Bouwense SA, van Goor H, Wilder-Smith OH, Drewes AM. Quantitative sensory testing predicts pregabalin efficacy in painful chronic pancreatitis. PLoS One. 2013;8(3):e57963.
104. Vas L, Pai R. Successful reversal of complex regional pain syndrome type 1 of both upper extremities in five patients. Pain Med. 2012 Sep;13(9):1253-6.
105. Plested M, Budhia S, Gabriel Z.Pregabalin, the lidocaine plaster and duloxetine in patients with refractory neuropathic pain: a systematic review. BMC Neurol. 2010 Nov 19;10:116.
106. Wolff RF, Bala MM, Westwood M, Kessels AG, Kleijnen J. 5% lidocaine-medicated plaster vs other relevant interventions and placebo for post-herpetic neuralgia (PHN): a systematic review. Acta Neurol Scand. 2011 May;123(5):295-309.
107. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. Efficacy and safety of 5% lidocaine (lignocaine)

medicated plaster in comparison with pregabalin in patients with postherpetic neuralgia and diabetic polyneuropathy: interim analysis from an open-label, two-stage adaptive, randomized, controlled trial. Clin Drug Investig. 2009;29(4):231-41.
108. Liedgens H, Hertel N, Gabriel A, Nuijten M, Dakin H, Mitchell S, Nautrup BP Cost-effectiveness analysis of a lidocaine 5% medicated plaster compared with gabapentin and pregabalin for treating postherpetic neuralgia: a german perspective. Clin Drug Investig. 2008;28(9):583-601.
109. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority two-stage RCT study. Curr Med Res Opin. 2009 Jul;25(7):1663-76.
110. Owen RT. Pregabalin: its efficacy, safety and tolerability profile in generalized anxiety. Drugs Today (Barc). 2007 Sep;43(9):601-10.
111. Rayner H, Baharani J, Smith S, Suresh V, Dasgupta I. Uraemic pruritus: relief of itching by gabapentin and pregabalin. Nephron Clin Pract. 2012;122(3-4):75-9.
112. Field MJ, McCleary S, Hughes J, Singh L.Gabapentin and pregabalin, but not morphine and amitriptyline, block both static and dynamic components of mechanical allodynia induced by streptozocin in the rat. Pain. 1999 Mar;80(1-2):391-8.
113. Fehrenbacher JC, Taylor CP, Vasko MR. Pregabalin and gabapentin reduce release of substance P and CGRP from rat spinal tissues only after inflammation or activation of protein kinase C. Pain. 2003 Sep;105(1-2):133-41.
114. Smith G, Heidary N, Patel R, Rosenman K, Meehan SA, Kamino H, Sanchez M. Cutaneous piloleiomyomata. Dermatol Online J. 2009 Aug 15;15(8):10
115. Snedecor SJ, Sudharshan L, Cappelleri JC, Sadosky A, Mehta S, Botteman M. Systematic Review and Meta-Analysis of Pharmacological Therapies for Painful Diabetic Peripheral Neuropathy.Snedecor SJ, Sudharshan L, Cappelleri JC, Sadosky A, Mehta S, Botteman M. Pain Pract. 2013 Mar 28.
116. Snedecor SJ, Sudharshan L, Cappelleri JC, Sadosky A, Desai P, Jalundhwala YJ, Botteman M. Systematic review and comparison of pharmacologic therapies for neuropathic pain associated with spinal cord injury. J Pain Res. 2013 Jul 11;6:539-47.
117. Achar A, Chakraborty PP, Bisai S, Biswas A, Guharay T. Comparative study of clinical efficacy of amitriptyline and pregabalin in postherpetic neuralgia. Acta Dermatovenerol Croat. 2012;20(2):89-94.
118. Frampton JE, Foster RH. Pregabalin: in the treatment of postherpetic neuralgia. Drugs. 2005;65(1):111-8; discussion 119-20.
119. Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology. 2004 Dec 14;63(11):2104-10.
120. Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of fble- and fixed-dose regimens. Pain. 2005 Jun;115(3):254-63.
121. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, Feldman E, Iverson DJ, Perkins B, Russell JW, Zochodne D; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation.Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation.Neurology. 2011 May 17;76(20):1758-65.
122. Fostini AC, Girolomoni G, Tessari G. Prurigo nodularis: an update on etiopathogenesis and therapy. J Dermatolog Treat. 2013 Jun 14
123. Tey HL, Wallengren J, Yosipovitch G. Psychosomatic factors in pruritus. Clin Dermatol. 2013 Jan-Feb;31(1):31-40.
124. Xander C, Meerpohl JJ, Galandi D, Buroh S, Schwarzer G, Antes G, Becker G. Pharmacological interventions for pruritus in adult palliative care patients. Cochrane Database Syst Rev. 2013 Jun 9;6:CD008320.
125. Smith KJ, Skelton HG, Yeager J, Lee RB, Wagner KF.Pruritus in HIV-1 disease: therapy with drugs which may modulate the pattern of immune dysregulation. Dermatology. 1997;195(4):353-8.
126. Xander C, Meerpohl JJ, Galandi D, Buroh S, Schwarzer G, Antes G, Becker G. Pharmacological interventions for pruritus in adult palliative care patients. Cochrane Database Syst Rev. 2013 Jun 9;6:CD008320.
127. Winhoven SM, Coulson IH, Bottomley WW. Brachioradial pruritus: response to treatment with gabapentin. Br J Dermatol. 2004 Apr;150(4):786-7.
128. Bueller HA, Bernhard JD, Dubroff LM. Gabapentin treatment for brachioradial pruritus. J Eur Acad Dermatol Venereol. 1999 Nov;13(3):227-8.
129. Kanitakis J. Brachioradial pruritus: report of a new case responding to gabapentin. J Eur Acad Dermatol Venereol. 2007 Nov;21(10):1440-1.
130. Jagdeo J, Kroshinsky D. A case of post-herpetic itch resolved with gabapentin.J Drugs Dermatol. 2011 Jan;10(1):85-8.
131. Goutos I, Eldardiri M, Khan AA, Dziewulski P, Richardson PM. Comparative evaluation of antipruritic protocols in acute burns. The emerging value of gabapentin in the treatment of burns pruritus. J Burn Care Res. 2010 Jan-Feb;31(1):57-63.
132. Ahuja RB, Gupta GK. A four arm, double blind, randomized and placebo controlled study of pregabalin in the management of post-burn pruritus. Burns. 2013 Feb;39(1):24-9.

133. Ahuja RB, Gupta R, Gupta G, Shrivastava P. A comparative analysis of cetirizine, gabapentin and their combination in the relief of post-burn pruritus. Burns. 2011 Mar;37(2):203-7.
134. Solak Y, Biyik Z, Atalay H, Gaipov A, Guney F, Turk S, Covic A, Goldsmith D, Kanbay M. Pregabalin versus gabapentin in the treatment of neuropathic pruritus in maintenance haemodialysis patients: a prospective, crossover study.Nephrology (Carlton). 2012 Nov;17(8):710-7.
135. Mendham JE. Gabapentin for the treatment of itching produced by burns and wound healing in children: a pilot study. Burns. 2004 Dec;30(8):851-3.
136. Marquez D, Ramonda C, Lauxmann JE, Romero CA, Vukelic VL, Martinatto C, Barrón B, Novoa PA, Peixoto AJ, Orías M. Uremic pruritus in hemodialysis patients: treatment with desloratidine versus gabapentin. J Bras Nefrol. 2012 Jun;34(2):148-52.
137. Loosemore MP, Bordeaux JS, Bernhard JD. Gabapentin treatment for notalgia paresthetica, a common isolated peripheral sensory neuropathy. Eur J Dermatol. 2006 May-Jun;16(3):311-2.
138. Yesudian PD, Wilson NJ. Efficacy of gabapentin in the management of pruritus of unknown origin. Arch Dermatol. 2005 Dec;141(12):1507-9.
139. Porzio G, Aielli F, Verna L, Porto C, Tudini M, Cannita K, Ficorella C. Efficacy of pregabalin in the management of cetuximab-related itch. J Pain Symptom Manage. 2006 Nov;32(5):397-8.
140. Ehrchen J, Ständer S. Pregabalin in the treatment of chronic pruritus. J Am Acad Dermatol. 2008 Feb;58(2 Suppl):S36-7.
141. Shavit L, Grenader T, Lifschitz M, Slotki I. Use of pregabalin in the management of chronic uremic pruritus. J Pain Symptom Manage. 2013 Apr;45(4):776-81.
142. Aperis G, Paliouras C, Zervos A, Arvanitis A, Alivanis P. The use of pregabalin in the treatment of uraemic pruritus in haemodialysis patients. J Ren Care. 2010 Dec;36(4):180-5.
143. Raskin J, Wiltse CG, Siegal A, Sheikh J, Xu J, Dinkel JJ, Rotz BT, Mohs RC.Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial.Am J Psychiatry. 2007 Jun;164(6):900-9.
144. Fava M, Mallinckrodt CH, Detke MJ, Watkin JG, Wohlreich MM. The effect of duloxetine on painful physical symptoms in depressed patients: do improvements in these symptoms result in higher remission rates? J Clin Psychiatry. 2004 Apr;65(4):521-30.
145. Masuda R, Itoh M, Suzuki T. Duloxetine for chronic pain management: pharmacology and clinical use. Masui. 2013 Jul;62(7):814-21.
146. Fallon MT. Neuropathic pain in cancer. Br J Anaesth. 2013 Jul;111(1):105-11.
147. Brunton S, Wang F, Edwards SB, Crucitti AS, Ossanna MJ, Walker DJ, Robinson MJ. Profile of adverse events with duloxetine treatment: a pooled analysis of placebo-controlled studies. Drug Saf. 2010 May 1;33(5):393-407.
148. Bär KJ, Terhaar J, Boettger MK, Boettger S, Berger S, Weiss T. Pseudohypoalgesia on the skin: a novel view on the paradox of pain perception in depression. J Clin Psychopharmacol. 2011 Feb;31(1):103-7.
149. CYMBALTA (Duloxetine Delayed-Release Capsules) for Oral Use. Eli Lily 2012 Package insert
150. Harrison T, Miyahara S, Lee A, Evans S, Bastow B, Simpson D, Gilron I, Dworkin R, Daar ES, Wieclaw L, Clifford DB; ACTG A5252 Team. Experience and Challenges Presented by a Multicenter Crossover Study of Combination Analgesic Therapy for the Treatment of Painful HIV-Associated Polyneuropathies. Pain Med. 2013 Jul;14(7):1039-47.
151. Brunton S, Wang F, Edwards SB, Crucitti AS, Ossanna MJ, Walker DJ, Robinson MJ. Profile of adverse events with duloxetine treatment: a pooled analysis of placebo-controlled studies. Drug Saf. 2010 May 1;33(5):393-407.
152. Gaynor P, McCarberg B, Zheng W, Shoemaker S, Duenas H.Weight change with long-term duloxetine use in chronic painful conditions: an analysis of 16 clinical studies. Int J Clin Pract. 2011 Mar;65(3):341-9.
153. Mohs R, Mease P, Arnold LM, Wang F, Ahl J, Gaynor PJ, Wohlreich MM.The effect of duloxetine treatment on cognition in patients with fibromyalgia. Psychosom Med. 2012 Jul-Aug;74(6):628-34.
154. Brunton S, Wang F, Edwards SB, Crucitti AS, Ossanna MJ, Walker DJ, Robinson MJ. Profile of adverse events with duloxetine treatment: a pooled analysis of placebo-controlled studies. Drug Saf. 2010 May 1;33(5):393-407.
155. Masuda R, Itoh M, Suzuki T. Duloxetine for chronic pain management: pharmacology and clinical use. Masui. 2013 Jul;62(7):814-21.
156. Wise TN, Perahia DG, Pangallo BA, Losin WG, Wiltse CG. Effects of the antidepressant duloxetine on body weight: analyses of 10 clinical studies. Prim Care Companion J Clin Psychiatry. 2006;8(5):269-78.
157. Hardy T, Sachson R, Shen S, Armbruster M, Boulton AJ. Does treatment with duloxetine for neuropathic pain impact glycemic control? Diabetes Care. 2007 Jan;30(1):21-6.
158. Perahia DG, Quail D, Desaiah D, Montejo AL, Schatzberg AF Switching to duloxetine in selective serotonin reuptake inhibitor non- and partial-responders: effects on painful physical symptoms of depression. J Psychiatr Res. 2009 Feb;43(5):512-8.
159. Mohs R, Mease P, Arnold LM, Wang F, Ahl J, Gaynor PJ, Wohlreich MM.The effect of duloxetine treatment on cognition in patients with fibromyalgia. Psychosom Med. 2012 Jul-Aug;74(6):628-34.
160. Mancini M, Sheehan DV, Demyttenaere K, Amore M, Deberdt W, Quail D, Sagman D.Evaluation of the effect of duloxetine treatment on functioning as measured by the Sheehan disability scale: pooled analysis of data from six randomized, double-blind, placebo-controlled clinical studies. Int Clin Psychopharmacol. 2012 Nov;27(6):298-309.

161. Bär KJ, Terhaar J, Boettger MK, Boettger S, Berger S, Weiss T. Pseudohypoalgesia on the skin: a novel view on the paradox of pain perception in depression. J Clin Psychopharmacol. 2011 Feb;31(1):103-7.
162. Fava M, Mallinckrodt CH, Detke MJ, Watkin JG, Wohlreich MM. The effect of duloxetine on painful physical symptoms in depressed patients: do improvements in these symptoms result in higher remission rates? J Clin Psychiatry. 2004 Apr;65(4):521-30.
163. Li Y, Zhang SL, Zhu J, DU XN, Huang ZF, Huang F. Impact of duloxetine on depression and anxiety in patients with ankylosing spondylitis: a case-control study. Zhonghua Yi Xue Za Zhi. 2013 Apr 2;93(13):966-9.
164. Kaplan C, Kocaman SA, Durakoğlugil ME, Kaya E, Senol MG. Cardiac syncope due to pain. Report of a case responsive to duloxetine treatment. Herz. 2013 Apr 17
165. Cawston H, Davie A, Paget MA, Skljarevski V, Happich M. Efficacy of duloxetine versus alternative oral therapies: an indirect comparison of randomised clinical trials in chronic low back pain. Eur Spine J. 2013 May 18.
166. Gaynor PJ, Liu P, Weller MA, Wohlreich MM. Comparison of safety outcomes among Caucasian, Hispanic, Black, and Asian patients in duloxetine studies of chronic painful conditions. Curr Med Res Opin. 2013 May;29(5):549-60.
167. Raskin J, Wiltse CG, Siegal A, Sheikh J, Xu J, Dinkel JJ, Rotz BT, Mohs RC. Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week,double-blind, placebo-controlled trial. Am J Psychiatry. 2007 Jun;164(6):900-9.
168. Moore RA, Cai N, Skljarevski V, Tölle TR. Duloxetine use in chronic painful conditions - individual patient data responder analysis. Eur J Pain. 2013 Jun 3.
169. Sabourin G. Cymbalta. Also controls the pain of knee arthrosis. Perspect Infirm. 2013 Mar-Apr;10(2):62.
170. Joffe H, Soares CN, Petrillo LF, Viguera AC, Somley BL, Koch JK, Cohen LS.
171. Treatment of depression and menopause-related symptoms with the serotonin-norepinephrine reuptake inhibitor duloxetine. J Clin Psychiatry. 2007 Jun;68(6):943-50.
172. Nagashima W, Kimura H, Ito M, Tokura T, Arao M, Aleksic B, Yoshida K, Kurita K, Ozaki N. Effectiveness of duloxetine for the treatment of chronic nonorganic orofacial pain. Clin Neuropharmacol. 2012 Nov-Dec;35(6):273-7.
173. Cawston H, Davie A, Paget MA, Skljarevski V, Happich M.Efficacy of duloxetine versus alternative oral therapies: an indirect comparison of randomised clinical trials in chronic low back pain. Eur Spine J. 2013 Sep;22(9):1996-2009.
174. Skljarevski V, Zhang S, Iyengar S, D'Souza D, Alaka K, Chappell A, Wernicke J. Efficacy of Duloxetine in Patients with Chronic Pain Conditions. Curr Drug ther. 2011 Nov;6(4):296-303.
175. Perahia DG, Pritchett YL, Desaiah D, Raskin J. Efficacy of duloxetine in painful symptoms: an analgesic or antidepressant effect? Int Clin Psychopharmacol. 2006 Nov;21(6):311-7.
176. Spielmans GI. False conclusions regarding duloxetine's purported efficacy in pain among depressed patients. Psychiatr Danub. 2010 Dec;22(4):550; author reply 551.
177. Spielmans GI. Duloxetine does not relieve painful physical symptoms in depression: a meta-analysis. Psychother Psychosom. 2008;77(1):12-6.
178. Mazza M, Mazza O, Pazzaglia C, Padua L, Mazza S. Escitalopram 20 mg versus duloxetine 60 mg for the treatment of chronic low back pain. Expert Opin Pharmacother. 2010 May;11(7):1049-52.
179. Duloxetine reduces chemotherapy induced peripheral neuropathy. BMJ. 2013 Apr 10;346:f2199.
180. Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, Bressler LR, Fadul CE, Knox C, Le-Lindqwister N, Gilman PB, Shapiro CL; Alliance for Clinical Trials in Oncology. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA. 2013 Apr 3;309(13):1359-67.
181. Takenaka M, Iida H, Matsumoto S, Yamaguchi S, Yoshimura N, Miyamoto M. Successful Treatment by Adding Duloxetine to Pregabalin for Peripheral Neuropathy Induced by Paclitaxel. Am J Hosp Palliat Care. 2012 Oct 11.
182. Yang YH, Lin JK, Chen WS, Lin TC, Yang SH, Jiang JK, Chang SC, Lan YT, Lin CC, Yen CC, Tzeng CH, Wang WS, Chiang HL, Teng CJ, Teng HW. Duloxetine improves oxaliplatin-induced neuropathy in patients with colorectal cancer: an open-label pilot study. Support Care Cancer. 2012 Jul;20(7):1491-7
183. Henry NL, Banerjee M, Wicha M, Van Poznak C, Smerage JB, Schott AF, Griggs JJ, Hayes DF. Pilot study of duloxetine for treatment of aromatase inhibitor-associated musculoskeletal symptoms. Cancer. 2011 Dec 15;117(24):5469-75.
184. Spiegel DR, Lappinen E, Gottlieb M. A presumed case of phantom limb pain treated successfully with duloxetine and pregabalin. Gen Hosp Psychiatry. 2010 Mar-Apr;32(2):228.e5-7.
185. Burning mouth syndrome responsive to duloxetine: a case report. Mignogna MD, Adamo D, Schiavone V, Ravel MG, Fortuna G. Pain Med. 2011 Mar;12(3):466-9.
186. Djaldetti R, Yust-Katz S, Kolianov V, Melamed E, Dabby R. The effect of duloxetine on primary pain symptoms in Parkinson disease. Clin Neuropharmacol. 2007 Jul-Aug;30(4):201-5.
187. Chang JP, Wu CC. Serotonin-norepinephrine reuptake inhibitor treatment for tinnitus and depression. J Clin Psychopharmacol. 2012 Oct;32(5):729.
188. Duloxetine treatment of Premenstrual Dysphoric Disorder: case reports. Ramos MG, Hara C, Rocha FL. Prog Neuropsychopharmacol Biol Psychiatry. 2008 Feb 15;32(2):579-80.
189. Artemenko AR, Kurenkov AL, Filatova EG. Efficacy of duloxetine in the treatment of chronic daily headache. Zh Nevrol Psikhiatr Im S S Korsakova. 2007;107(8):24-8.

190. Joffe H, Soares CN, Petrillo LF, Viguera AC, Somley BL, Koch JK, Cohen LS. Treatment of depression and menopause-related symptoms with the serotonin-norepinephrine reuptake inhibitor duloxetine. J Clin Psychiatry. 2007 Jun;68(6):943-50.
191. Frakes EP, Risser RC, Ball TD, Hochberg MC, Wohlreich MM. A review of duloxetine 60 mg once-dailey Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. Curr Med Res Opin. 2011 Dec;27(12):2361-72. Erratum in: Curr Med Res Opin. 2012 May;28(5):822
192. Fishbain DA, Hall J, Meyers AL, Gonzales J, Mallinckrodt C. Does pain mediate the pain interference with sleep problem in chronic pain? Findings from studies for management of diabetic peripheral neuropathic pain with duloxetine. J Pain Symptom Manage. 2008 Dec;36(6):639-47.
193. Marcus DA. Duloxetine use in painful conditions. Expert Opin Pharmacother. 2011 Jun;12(8):1333-1340.
194. Häuser W, Urrútia G, Tort S, Uçeyler N, Walitt B. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. Cochrane Database Syst Rev. 2013 Jan 31;1:CD010292.
195. Wang F, Ruberg SJ, Gaynor PJ, Heinloth AN, Arnold LM. Early improvement in pain predicts pain response at endpoint in patients with fibromyalgia. J Pain. 2011 Oct;12(10):1088-94.
196. Pergolizzi JV Jr, Raffa RB, Taylor R Jr, Rodriguez G, Nalamachu S, Langley Daily dosing for the management of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain due to chronic osteoarthritis pain and low back pain. P. Pain Pract. 2013 Mar;13(3):239-52.
197. Bennett R, Russell IJ, Choy E, Spaeth M, Mease P, Kajdasz D, Walker D, Wang F, Chappell A. Evaluation of patient-rated stiffness associated with fibromyalgia: a post-hoc analysis of 4 pooled, randomized clinical trials of duloxetine. Clin Ther. 2012 Apr;34(4):824-37.
198. Perahia DG, Pritchett YL, Desaiah D, Raskin J.Efficacy of duloxetine in painful symptoms: an analgesic or antidepressant effect? Int Clin Psychopharmacol. 2006 Nov;21(6):311-7.
199. Gore M, Zlateva G, Tai KS, Chandran AB, Leslie D. Retrospective evaluation of clinical characteristics, pharmacotherapy and healthcare resource use among patients prescribed pregabalin or duloxetine for diabetic peripheral neuropathy in usual care. Pain Pract. 2011 Mar-Apr;11(2):167-79.
200. Wang F, Ruberg SJ, Gaynor PJ, Heinloth AN, Arnold LM.Early improvement in pain predicts pain response at endpoint in patients with fibromyalgia. J Pain. 2011 Oct;12(10):1088-94.
201. Peng X, Wu N, Chen SY, Yu X, Andrews JS, Novick D.Utilization of duloxetine and celecoxib in osteoarthritis patients.Curr Med Res Opin. 2013 Sep;29(9):1161-9
202. Frakes EP, Risser RC, Ball TD, Hochberg MC, Wohlreich MM. A review of duloxetine 60 mg once-dailey Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. Curr Med Res Opin. 2011 Dec;27(12):2361-72. Erratum in: Curr Med Res Opin. 2012 May;28(5):822.
203. Sun YH, Dong YL, Wang YT, Zhao GL, Lu GJ, Yang J, Wu SX, Gu ZX, Wang W. Synergistic analgesia of duloxetine and celecoxib in the mouse formalin test: a combination analysis. PLoS One. 2013 Oct 7;8(10):e76603.
204. Skljarevski V, Liu P, Zhang S, Ahl J, Martinez JM. Efficacy and Safety of Duloxetine in Patients with Chronic Low Back Pain Who Used versus Did Not Use Concomitant Nonsteroidal Anti-Inflammatory Drugs or Acetaminophen: A Post Hoc Pooled Analysis of 2 Randomized, Placebo-Controlled Trials. Pain Res Treat. 2012;2012:296710.
205. Kleinman NL, Sanchez RJ, Lynch WD, Cappelleri JC, Beren IA, Joshi AV. Health outcomes and costs among employees with fibromyalgia treated with pregabalin vs. standard of care. Pain Pract. 2011 Nov-Dec;11(6):540-51.
206. Sun P, Zhao Y, Zhao Z, Bernauer M, Watson P. Dosing pattern comparison between duloxetine and pregabalin among patients with diabetic peripheral neuropathic pain. Pain Pract. 2012 Nov;12(8):641-8.
207. Grégoire S, Michaud V, Chapuy E, Eschalier A, Ardid D. Study of emotional and cognitive impairments in mononeuropathic rats: effect of duloxetine and gabapentin. Pain. 2012 Aug;153(8):1657-63.
208. Angeletti C, Guetti C, Piroli A, Angeletti PM, Paladini A, Ciccozzi A, Marinangeli F, Varrassi G. Duloxetine and Pregabalin for Pain Management in Multiple Rheumatic Diseases Associated with Fibromyalgia.Pain Pract. 2012 Nov 5.
209. Devi P, Madhu K, Ganapathy B, Sarma G, John L, Kulkarni C. Evaluation of efficacy and safety of gabapentin, duloxetine, and pregabalin in patients with painful diabetic peripheral neuropathy. Indian J Pharmacol. 2012 Jan;44(1):51-6.
210. Sun P, Zhao Y, Zhao Z, Bernauer M, Watson P. Dosing pattern comparison between duloxetine and pregabalin among patients with diabetic peripheral neuropathic pain. Pain Pract. 2012 Nov;12(8):641-8.
211. Matsuoka H, Makimura C, Koyama A, Otsuka M, Okamoto W, Fujisaka Y, Kaneda H, Tsurutani J, Nakagawa K. Pilot study of duloxetine for cancer patients with neuropathic pain non-responsive to pregabalin. Anticancer Res. 2012 May;32(5):1805-9.
212. Quilici S, Chancellor J, Löthgren M, Simon D, Said G, Le TK, Garcia-Cebrian A, Monz B.Meta-analysis of duloxetine vs. pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. BMC Neurol. 2009 Feb 10;9:6.
213. Hayashida K, Eisenach JC. Multiplicative interactions to enhance gabapentin to treat neuropathic pain. Eur J Pharmacol. 2008 Nov 19;598(1-3):21-6.
214. Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. Pain. 2012 Jun;153(6):1193-8.

215. Skljarevski V, Liu P, Zhang S, Ahl J, Martinez JM. Efficacy and Safety of Duloxetine in Patients with Chronic Low Back Pain Who Used versus Did Not Use Concomitant Nonsteroidal Anti-Inflammatory Drugs or Acetaminophen: A Post Hoc Pooled Analysis of 2 Randomized, Placebo-Controlled Trials. Pain Res Treat. 2012;2012:296710.
216. Matsuoka H, Makimura C, Koyama A, Otsuka M, Okamoto W, Fujisaka Y, Kaneda H, Tsurutani J, Nakagawa K. Pilot study of duloxetine for cancer patients with neuropathic pain non-responsive to pregabalin. Anticancer Res. 2012 May;32(5):1805-9.
217. Briley M, Moret C. Treatment of comorbid pain with serotonin norepinephrine reuptake inhibitors. CNS Spectr. 2008 Jul;13(7 Suppl 11):22-6.
218. Leo RJ. A word of caution about the implied role for duloxetine in pain management. J Clin Psychiatry. 2003 Oct;64(10):1270.
219. Ye W, Zhao Y, Robinson RL, Swindle RW. Treatment patterns associated with Duloxetine and Venlafaxine use for Major Depressive Disorder. BMC Psychiatry. 2011 Jan 31;11:19.J Pain Res. 2010 Apr 1;3:33-49.
220. Simpson DA. Venlafaxine in treatment of severe painful peripheral diabetic neuropathy. J Clin Neuromuscul Dis. 2001 Dec;3(2):53-62.
221. Pae CU, Park MH, Marks DM, Han C, Patkar AA, Masand PS. Desvenlafaxine, a serotonin-norepinephrine uptake inhibitor for major depressive disorder, neuropathic pain and the vasomotor symptoms associated with menopause. Curr Opin Investig Drugs. 2009 Jan;10(1):75-90.
222. Batysheva TT, Kamchatnov PR, Guseva ME, Zaĭtsev KA, Zhuravleva EIu, Kostenko EV, Nesterova OS, Otcheskaia OV, Boĭko AN. Results of a study of velaxin (venlafaxine) efficacy in patients with subacute and chronic spondylogenic dorsalgia. Zh Nevrol Psikhiatr Im S S Korsakova. 2009;109(5):32-5.
223. Tasmuth T, Härtel B, Kalso E. Venlafaxine in neuropathic pain following treatment of breast cancer. Eur J Pain. 2002;6(1):17-24.
224. Yilmaz ME, Kadiroglu AK, Kara IH, Dikici S. Venlafaxine in the treatment of painful peripheral diabetic neuropathy in a uremic patient undergoing hemodialysis.MedGenMed. 2002 Aug 21;4(3):23.
225. Lee H, Kim JH, Min BH, Lee JH, Son HJ, Kim JJ, Rhee JC, Suh YJ, Kim S, Rhee PL. Efficacy of venlafaxine for symptomatic relief in young adult patients with functional chest pain: a randomized, double-blind, placebo-controlled, crossover trial. Am J Gastroenterol. 2010 Jul;105(7):1504-12
226. Sullivan M, Bentley S, Fan MY, Gardner G. A single-blind placebo run-in study of venlafaxine XR for activity-limiting osteoarthritis pain. Pain Med. 2009 Jul Aug;10(5):806-12.
227. Durand JP, Deplanque G, Montheil V, Gornet JM, Scotte F, Mir O, Cessot A, Coriat R, Raymond E, Mitry E, Herait P, Yataghene Y, Goldwasser F. Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity: results of EFFOX, a randomized, double-blind, placebo-controlled phase III trial. Ann Oncol. 2012 Jan;23(1):200-5.
228. Cornelissen P, van Kleef M, Mekhail N, Day M, van Zundert J. Evidence-based interventional pain medicine according to clinical diagnoses. 3. Persistent idiopathic facial pain. Pain Pract. 2009 Nov-Dec;9(6):443-8.
229. Forssell H, Tasmuth T, Tenovuo O, Hampf G, Kalso E. Venlafaxine in the treatment of atypical facial pain: a randomized controlled trial. J Orofac Pain. 2004 Spring;18(2):131-7.
230. Begré S, Traber M, Gerber M, von Känel R.Change in pain severity with open label venlafaxine use in patients with a depressive symptomatology: an observational study in primary care. Eur Psychiatry. 2008 Apr;23(3):178-86.
231. van Kerkhoven LA, Laheij RJ, Aparicio N, De Boer WA, Van den Hazel S, Tan AC, Witteman BJ, Jansen JB. Effect of the antidepressant venlafaxine in functional dyspepsia: a randomized, double-blind, placebo-controlled trial. Clin Gastroenterol Hepatol. 2008 Jul;6(7):746-52; quiz 718.
232. Mohr P, Bitter I, Svestka J, Seifritz E, Karamustafalioglu O, Koponen H, Sartorius N. Psychiatr Danub. 2010 Sep;22(3):476.
233. Shi N, Durden E, Torres A, Cao Z, Happich M. Predictors of Treatment with Duloxetine or Venlafaxine XR among Adult Patients Treated for Depression in Primary Care Practices in the United Kingdom. Depress Res Treat. 2012;2012:815363.
234. Wang J, Liu X, Mullins CD. Treatment adherence and persistence with duloxetine, venlafaxine XR, and escitalopram among patients with major depressive disorder and chronic pain-related diseases. Curr Med Res Opin. 2011 Jul;27(7):1303-13.
235. Zhao Y, Liu J, Zhao Y, Thethi T, Fonseca V, Shi L.Predictors of duloxetine versus other treatments among veterans with diabetic peripheral neuropathic pain: a retrospective study. Pain Pract. 2012 Jun;12(5):366-73.
236. Vis PM, van Baardewijk M, Einarson TR. Duloxetine and venlafaxine-XR in the treatment of major depressive disorder: a meta-analysis of randomized clinical trials. Ann Pharmacother. 2005 Nov;39(11):1798-807.
237. Gharibian D, Polzin JK, Rho JP. Compliance and persistence of antidepressants versus anticonvulsants in patients with neuropathic pain during the first year of therapy. Clin J Pain. 2013 May;29(5):377-81.
238. Sindrup SH, Bach FW, Madsen C, Gram LF, Jensen TS. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. Neurology. 2003 Apr 22;60(8):1284-9.
239. Amr YM, Yousef AA. Evaluation of efficacy of the perioperative administration of Venlafaxine or gabapentin on acute and chronic postmastectomy pain. Clin J Pain. 2010 Jun;26(5):381-5.
240. Simpson DA. Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy. Clin Neuromuscul Dis. 2001 Dec;3(2):53-62.

241. Eardley W, Toth C. An open-label, non-randomized comparison of venlafaxine and gabapentin as monotherapy or adjuvant therapy in the management of neuropathic pain in patients with peripheral neuropathy. J Pain Res. 2010 Apr 1;3:33-49.
242. Rode F, Broløs T, Blackburn-Munro G, Bjerrum OJ. Venlafaxine compromises the antinociceptive actions of gabapentin in rat models of neuropathic and persistent pain. Psychopharmacology (Berl). 2006 Aug;187(3):364-75.
243. Cegielska-Perun K, Bujalska-Zadrożny M, Makulska-Nowak HE. Modification of morphine analgesia by venlafaxine in diabetic neuropathic pain model. Pharmacol Rep. 2012;64(5):1267-75.
244. Feinberg SS. Correction of venlafaxine- and duloxetine-induced transaminase elevations with desvenlafaxine in a patient with Gilbert's syndrome. CNS Spectr. 2010 Jan;15(1):53-5.
245. Park SH, Ishino R. Liver injury associated with antidepressants. Curr Drug Saf. 2013 Jul;8(3):207-23.
246. Ye W, Zhao Y, Robinson RL, Swindle RW. Treatment patterns associated with Duloxetine and Venlafaxine use for Major Depressive Disorder. BMC Psychiatry. 2011 Jan 31;11:19.
247. Perahia DG, Quail D, Desaiah D, Montejo AL, Schatzberg AF. Switching to duloxetine in selective serotonin reuptake inhibitor non- and partial-responders: effects on painful physical symptoms of depression. J Psychiatr Res. 2009 Feb;43(5):512-8.
248. Lieberman DZ, Massey SH. Desvenlafaxine in major depressive disorder: an evidence-based review of its place in therapy. Core Evid. 2010 Jun 15;4:67-82.
249. Griffith JM, Hasley JP, Severn DG. Measurement of pain and medication effect in a study of duloxetine. J Clin Psychiatry. 2008 Jun;69(6):1022.
250. Trivedi MH, Desaiah D, Ossanna MJ, Pritchett YL, Brannan SK, Detke MJ. Clinical evidence for serotonin and norepinephrine reuptake inhibition of duloxetine. Int Clin Psychopharmacol. 2008 May;23(3):161-9.
251. Brecht S, Courtecuisse C, Debieuvre C, Croenlein J, Desaiah D, Raskin J, Petit C, Demyttenaere K. Efficacy and safety of duloxetine 60 mg once daily in the treatment of pain in patients with major depressive disorder and at least moderate pain of unknown etiology: a randomized controlled trial. J Clin Psychiatry. 2007 Nov;68(11):1707-16.
252. Fava M, Mallinckrodt CH, Detke MJ, Watkin JG, Wohlreich MM The effect of duloxetine on painful physical symptoms in depressed patients: do improvements in these symptoms result in higher remission rates? J Clin Psychiatry. 2004 Apr;65(4):521-30.
253. Perahia DG, Quail D, Desaiah D, Montejo AL, Schatzberg AF. Switching to duloxetine in selective serotonin reuptake inhibitor non- and partial-responders: effects on painful physical symptoms of depression. J Psychiatr Res. 2009 Feb;43(5):512-8.
254. McCleane G Antidepressants as analgesics. CNS Drugs. 2008;22(2):139-56.
255. Gore M, Zlateva G, Tai KS, Chandran AB, Leslie D. Retrospective evaluation of clinical characteristics, pharmacotherapy and healthcare resource use among patients prescribed pregabalin or duloxetine for diabetic peripheral neuropathy in usual care. Pain Pract. 2011 Mar-Apr;11(2):167-79.
256. Stahl SM, Grady MM, Moret C, Briley M. SNRIs: their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. CNS Spectr. 2005 Sep;10(9):732-47.
257. Song JH, Yu BH, Lee D, Yoon SC, Jeon HJ. Uncontrolled self-medication with venlafaxine in a patient with major depressive disorder. Psychiatry Investig. 2011 Mar;8(1):74-6.
258. Pinzani V, Giniès E, Robert L, Peyrière H, Abbar M, Blayac JP Physicians must be aware of the frequency, rapidity and potent severity of these withdrawal syndromes. Venlafaxine withdrawal syndrome: report of six cases and review of the literature. Rev Med Interne. 2000 Mar;21(3):282-4.
259. Bomholt SF, Mikkelsen JD, Blackburn-Munro G. Antinociceptive effects of the antidepressants amitriptyline, duloxetine, mirtazapine and citalopram in animal models of acute, persistent and neuropathic pain. Neuropharmacology. 2005 Feb;48(2):252-63
260. Häuser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. J Pain. 2010 Jun;11(6):505-21.
261. 261. Zhao Y, Sun P, Bernauer M. Comparing common reasons for inpatient and outpatient visits between commercially-insured duloxetine or pregabalin initiators with fibromyalgia. J Pain Res. 2012;5:443-51.
262. Quilici S, Chancellor J, Löthgren M, Simon D, Said G, Le TK, Garcia-Cebrian A, Monz B. Neuropathic pain. BMC Neurol. 2009 Feb 10;9:6.
263. Hayashida K, Eisenach JC. Multiplicative interactions to enhance gabapentin to treat neuropathic pain. Eur J Pharmacol. 2008 Nov 19;598(1-3):21-6.
264. Grichnik KP, Ferrante FM. The difference between acute and chronic pain. Mt Sinai J Med. 1991 May;58(3):217-20.
265. Schwier C, Kliem A, Boettger MK, Bär KJ. Increased cold-pain thresholds in major depression. J Pain. 2010 Mar;11(3):287-90.
266. Eisenberger NI. The neural bases of social pain: evidence for shared representations with physical pain. Psychosom Med. 2012 Feb-Mar;74(2):126-35.
267. Nagakura Y, Oe T, Aoki T, Matsuoka N. Biogenic amine depletion causes chronic muscular pain and tactile allodynia accompanied by depression: A putative animal model of fibromyalgia. Pain. 2009 Nov;146(1-2):26-33.

268. Botteman M Snedecor SJ, Sudharshan L, Cappelleri JC, Sadosky A, Desai P, Jalundhwala YJ, Systematic review and comparison of pharmacologic therapies for neuropathic pain associated with spinal cord injury. J Pain Res. 2013 Jul 11;6:539-47.
269. Pierce DA, Holt SR, Reeves-Daniel A. A probable case of gabapentin-related reversible hearing loss in a patient with acute renal failure. Clin Ther. 2008 Sep;30(9):1681-4.
270. Matsuki Y, Morikawa M, Nishimoto T, Yasuda Y, Shigemi K. Heart failure assocated with pregabalin Pain Physician. 2012 Jul-Aug;15(4):E536-7.
271. Wohlreich MM, Watkin JG, Gonzales JS. Duloxetine's role in the treatment of depression and associated painful physical symptoms. J Clin Psychiatry. 2004 Jul;65(7):1018-9.
272. Perahia DG, Quail D, Desaiah D, Montejo AL, Schatzberg AF. Switching to duloxetine in selective serotonin reuptake inhibitor non- and partial-responders: effects on painful physical symptoms of depression. J Psychiatr Res. 2009 Feb;43(5):512-8.
273. Barkin RL, Barkin S. The role of venlafaxine and duloxetine in the treatment of depression with decremental changes in somatic symptoms of pain, chronic pain, and the pharmacokinetics and clinical considerations of duloxetine pharmacotherapy. Am J Ther. 2005 Sep-Oct;12(5):431-8.
274. Sabat R, Chanwangpong A, Schneider-Burrus S, Metternich D, Kokolakis G, Kurek A, Philipp S, Uribe D, Wolk K, Sterry W. Increased prevalence of metabolic syndrome in patients with acne inversa. PLoS One. 2012;7(2):e31810.