Pain Management for Primary Care

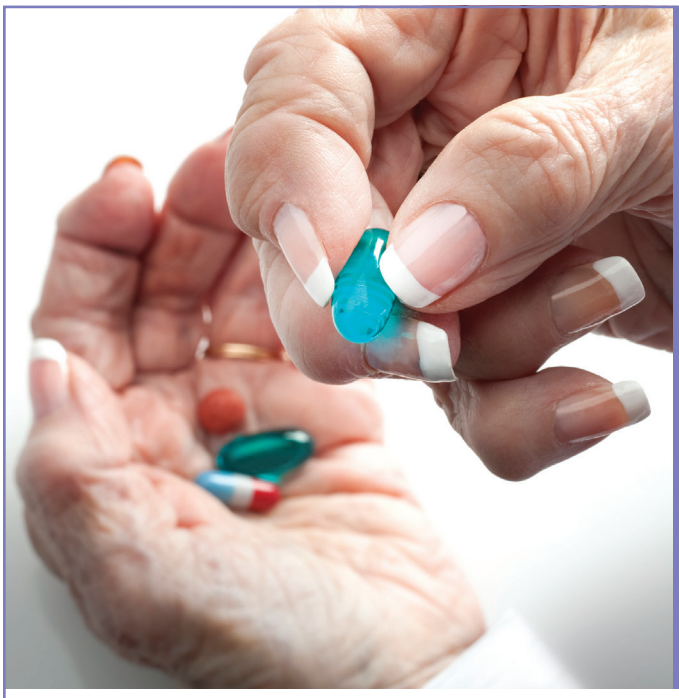
DoD/VHA
JOINT INCENTIVE FUND (JIF)
PROJECT

Series: Four

Pharmacologic Approach to Pain Management

Module 4-2

Analgesic Adjuvant Medications, Anti-depressant and Antiepileptic Agents Other Oral and Topical Medications



Module 4-2

Analgesic Adjuvant Medications Anti-depressant and Antiepileptic Agents Other Oral and Topical Medications

By the end of the module, you will be able to:

- Identify classes of drugs commonly used as analgesic adjuvants.
- State the purported mechanism of action for each agent.
- State which type(s) of pain each drug may typically be used to treat.
- Identify key safety concerns for select drugs/classes.
- Identify typical dose ranges for the various drugs.

We will review:

Topic One: Diagnosis-Based Drug Selection

Topic Two: Antidepressants

Topic Three: Antiepileptics Drugs (AEDs)

Topic Four: Other Adjuvants – Oral and Topical Agents

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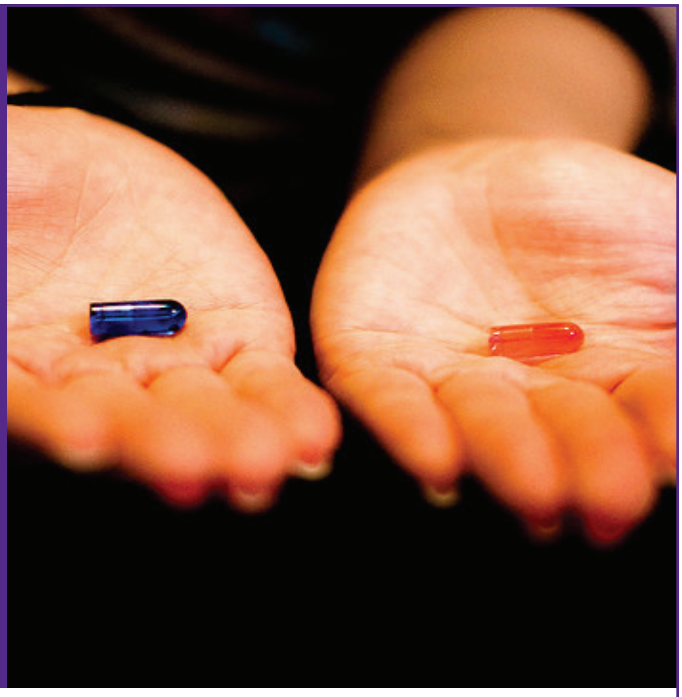
Topic One

Diagnosis-Based Drug Selection



Why use analgesic adjuvants?

- Best evidence currently supports multimodal analgesia, i.e. the use of combinations of analgesic medications with different mechanisms of action.
- Understanding the basic pharmacologic principles and comparative effectiveness of adjuvant drugs in the management of chronic pain should:
    - increase the success of pharmacologically based pain treatments
    - reduce over-reliance on opioids
    - reduce the associated challenges of opioid-related
    - side effects such as accidental overdoses, dependency and addiction
    - reduce poor pain care outcomes

An appropriate therapeutic choice is dependent upon accurate identification of the cause of the pain and type of chronic pain syndrome.

- Nociceptive pain
  - Somatic and visceral subtypes
  - Caused by stimuli that threaten or provoke actual tissue damage
  - Often due to musculoskeletal conditions, inflammation or mechanical/ compressive problems

Treatment: NSAIDs, Acetaminophen, Opioids (acute pain) Antidepressants (chronic pain)

- Neuropathic pain
  - Peripheral and central subtypes
  - Result from damage to or pathology within the nervous system

Treatment: Antidepressants, antiepileptic drugs (AEDs)

- Migraine, some other headache syndromes, and trigeminal neuralgia
  - Thought to represent an overlap of nociceptive and/or neuropathic mechanisms

Treatment: Antidepressants, AEDs

Notes

The more common somatic nociceptive pain comes from muscles or joints, is typically well localized and often results from degenerative processes such as arthritis. Visceral pain originates in an internal organ, usually due to ischemia, distension, perforation, or inflammation and may be diffuse, difficult to localize.

Neuropathic pain is caused by injury or malfunction either in the peripheral nervous system or the central nervous system.

Central neuropathic pain is found in spinal cord injury, multiple sclerosis, and some strokes.

The more common causes of peripheral neuropathic pain are related to herpes zoster infection (ex, postherpetic neuralgia), diabetes (painful diabetic neuropathy), trauma, surgery, amputation, HIV disease, nutrition (vitamin deficiency), or toxins (alcohol, chemotherapy)

Analgesic adjuvant choice should also be guided by individual patient factors.

Comorbidities and perceived risks

- Insomnia
- Depression
- Bipolar disease
- Suicidality
- Cardiovascular disease
- BPH
- Obesity
- Fall risk

Renal/hepatic function

Other medications

Notes

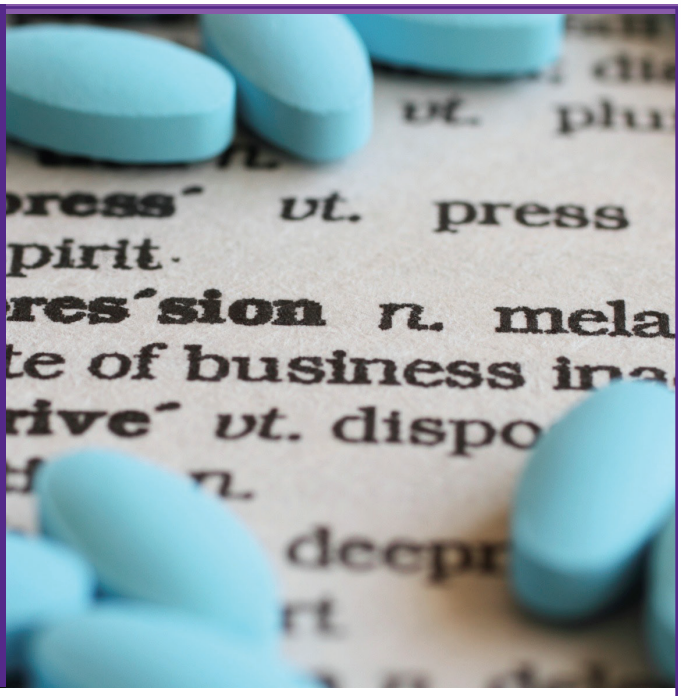
Consideration of other comorbidities and ability to clear drugs will not only increase the opportunity for drug benefit but also reduce the likelihood of adverse effects.

Hepatic function will determine ability to metabolize most drugs; some drugs may require dose reduction when renal function is impaired.

Other medications must be considered because of the potential for significant drug interactions between some adjuvant agents and medications commonly used in patients with chronic non-malignant pain.

Topic Two

Antidepressants



Antidepressants in pain management

Antidepressants are effective analgesic adjuvants; the two classes that are most useful are:

- Tricyclic antidepressants (TCAs)
    - Tertiary amines (amitriptyline and imipramine) are relatively selective norepinephrine reuptake inhibitors
    - Secondary amines (nortriptyline and desipramine) inhibit the reuptake of both serotonin and norepinephrine; they have less anticholinergic side effects including less sedation
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
    - Duloxetine and venlafaxine

The increased serotonergic and/or noradrenergic activity resulting from the administration of antidepressants is thought to promote normalization of descending pain inhibitory activity from the brainstem to the spinal cord.

Notes

There are also tetracyclic antidepressants like maprotiline…..

Pure selective serotonin reuptake inhibitors (SSRIs), like fluoxetine, citalopram, sertraline and others, have very limited usefulness in the treatment of pain

Serotonin and norepinephrine normally mediate endogenous pain inhibitory mechanisms via descending pain inhibitory pathways in the brain and spinal cord. In chronic pain states, this activity is believed to be reduced or lost; this change results in a shift in the descending pain modulatory system from a state of inhibition to one of pain facilitation.

Tricyclic antidepressants (TCAs) are very effective but have side effects which must be taken into consideration.

- TCAs are first line agents for treatment of peripheral and central neuropathic pain, and may benefit patients with musculoskeletal pain. Due to side effects, use with caution. They are usually not recommended for older adults.
- Headache:
  - Amitriptyline has Level A evidence for tension headache prophylaxis; Level B evidence for migraine prophylaxis
  - Nortriptyline has Level C evidence for migraine prophylaxis
- Use well suited in patients with comorbid depression or anxiety, or in people with sleep difficulty
- Adverse effects include:
  - drowsiness (can be exploited as an aid for sleep)
  - orthostatic hypotension (increased fall risk)
  - anticholinergic side effects (dry mouth, urinary
  - retention, constipation, increased intraocular pressure in glaucoma, confusion)

QTc prolongation – avoid in patients with clinically significant cardiac arrhythmia or those taking other

QTc prolonging agents (like some opioids)

Notes

Moderate to high dose TCAs may cause orthostatic hypotension through alpha1 blockade – mention Beers list here

TCAs are contraindicated in patients with glaucoma, symptomatic prostatic hypertrophy, and significant cardiovascular disease

Many individuals are aware that methadone prolongs QTc interval – so do fentanyl, buprenorphine, oxycodone, and hydrocodone (dose-related)

Reduced seizure threshold is described with TCAs and some other antidepressants – use should probably be avoided in patients with a history of epilepsy.

Proper drug and patient selection, dosing and titration of TCAs is necessary for best response and avoidance of side effects.

- Anticholinergic side effect greater with tertiary amines (ex: amitriptyline) than with secondary amines (ex: nortriptyline)
- Doses of TCAs for analgesic benefits are typically less than those utilized in depression
- Starting dose should be 10-20 mg at bedtime; increase weekly by 10mg/day; usual maintenance dose is 10-100 mg/day
- Analgesic onset may not be apparent for 2-4 weeks
- Older patients are at increased risk of side effects; alcohol increases sedation
- TCAs are Pregnancy Category C
- Withdrawal of therapy/need for taper not a concern due to prolonged half-life of TCAs
- All antidepressant medications have potential to increase risk of suicidal ideation and precipitate mania in patients with bipolar mood disorder

Notes

Doses of TCAs for pain management are usually less than those used in depressive illness; this may help to avoid some of the higher-dose concerns, such as intolerable anticholinergic or sedative side effects, or QTc prolongation.

No need to dose adjust in patients with renal or hepatic impairment

Pregnancy Category C = Risk in pregnancy cannot be ruled out; drug should be given only if the potential benefits justify the potential risk to the fetus. The risk of teratogenicity with TCAs is generally regarded as low.

Serotonin –Norepinephrine Reuptake inhibitors (SNRIs) are also effective but have a side effect profile significantly different from that of tricyclic agents.

- Both duloxetine and venlafaxine are first line agents for treatment of neuropathic pain
- Duloxetine has FDA-indication for diabetic peripheral neuropathy, fibromyalgia and chronic musculoskeletal pain; venlafaxine has Level B evidence for prophylaxis of both migraine and tension-type headache
- Use of either SNRI is well-suited for use in patients with comorbid depression and anxiety
- Adverse effects:
  - Nausea (duloxetine >> venlafaxine)
  - Somnolence (duloxetine > venlafaxine)
  - Insomnia (duloxetine ≈ venlafaxine)
  - Dry mouth (duloxetine > venlafaxine)
  - Hyperhidrosis (duloxetine >>> venlafaxine)
  - Increased risk of hypertension (venlafaxine >>> duloxetine)
  - Sexual dysfunction (venlafaxine > duloxetine)
  - Mydriasis

  Hepatotoxicity (rare; duloxetine only)

Notes

Generally speaking, venlafaxine is better tolerated than duloxetine.

The up to 30% incidence of nausea due to SNRIs often leads to drug discontinuation; nausea less frequent with venlafaxine (especially the extended-release formulation)

Potential for insomnia is similar for the two SNRIs.

Duloxetine has a somewhat higher incidence of dry mouth and other anticholinergic side effects (constipation, urinary retention) compared to venlafaxine; both have less than that seen with TCAs

Venlafaxine can cause both transient and sustained elevations of diastolic blood pressure; regular monitoring of blood pressure is recommended. The effect is dose-related – clinically significant hypertension usually does not occur at doses < 300mg daily. Duloxetine would be the preferred SNRI in patients with pre-existing hypertension.

Both drugs have the potential to increase heart rate.

Sexual side effects include decreased libido and erectile dysfunction; this is less likely with duloxetine vs. venlafaxine

Both drugs can cause mydriasis (excessive dilation of the pupil) and should be avoided in patients with increased intraocular pressure. Duloxetine is contraindicated in patients with uncontrolled narrow-angle glaucoma.

Hepatotoxicity is rare with duloxetine; when it occurs it is usually in patients with current or past risk factors. Duloxetine should not be used in patients with hepatic function impairment or in heavy drinkers. Venlafaxine is not expected to exert hepatotoxic effects.

As previously mentioned, all antidepressant medications have potential to increase risk of suicidal ideation and precipitate mania in patients with bipolar mood disorder – this applies to SNRIs

Consideration of comorbid conditions and concomitant medications is necessary before initiation and titration of SNRIs.

Patients should practice good compliance to avoid Discontinuation Syndrome.

- Duloxetine is contraindicated in patients with uncontrolled narrow-angle glaucoma and should not be prescribed in patients with hepatic dysfunction. Avoid use in patients with severe renal impairment or end-stage renal disease (ESRD).
- SNRI is contraindicated in patients on a MAOI.
- Serotonin syndrome may occur in patients on a selective serotonin reuptake inhibitor (SSRI), MAOI, tramadol, or triptan drug
- Duloxetine may be initiated at 30 mg/day; increase weekly by 30mg/day to usual maintenance dose of 60 mg/day (for pain, up 120 mg/day for depression). In elderly patients begin with 20 mg/day.
- A venlafaxine initial dose of 37.5mg/day is recommended; increase weekly by 37.5mg/day to usual maintenance dose of 150-225mg/day. Dose-adjusted venlafaxine may be used in mild to moderate renal impairment and ESRD.
- Abrupt discontinuation of a SNRI can lead to Discontinuation Syndrome
- Duloxetine and venlafaxine are Pregnancy category C

Notes

As in hepatic dysfunction, use of duloxetine should generally be avoided in patients who abuse alcohol.

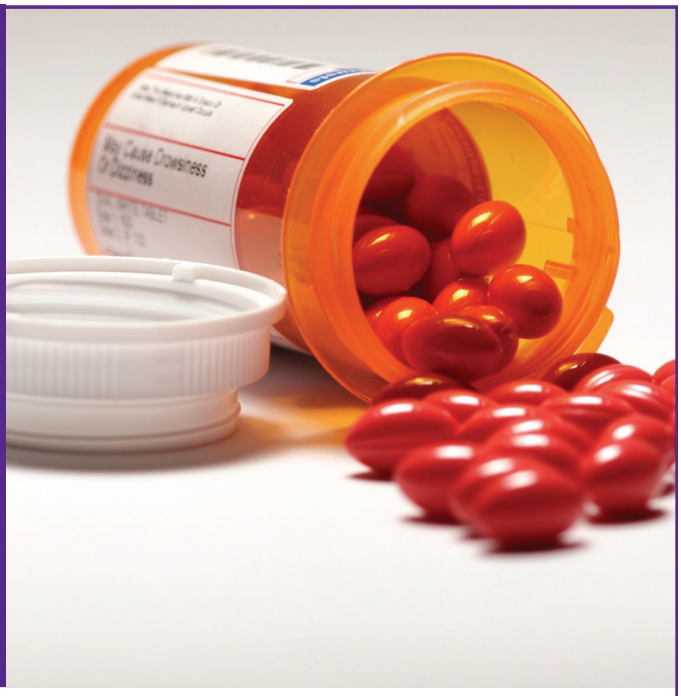
Combination of SNRI with SSRI, monoamine oxidase inhibitors (MAOIs), tramadol or triptan drug can cause SEROTONIN SYNDROME: Mental status changes (agitation, hallucinations), autonomic instability (tachycardia, hypertension, hyperthermia), hyperreflexia, and gastrointestinal symptoms (N, V, D)

Severe renal impairment = creatinine clearance < 30ml/min

Symptoms of Discontinuation Syndrome: headache, nausea, fatigue, dizziness, irritability, insomnia, dysphoria. May occur on stopping, missing doses, or dose reduction. Venlafaxine is much more likely to cause this likely due to its relatively short half-life.

Topic Three

Antiepileptic Drugs (AEDs)



Gabapentinoid antiepileptic drugs (AEDs) play an important role in management of various neuropathic pain syndromes.

- Gabapentin and pregabalin (known collectively as gabapentinoids) are calcium channel blockers. Calcium blockade decreases excitability in injured nerves which can reduce hyperalgesia and spontaneous pain.
- Gabapentinoids are first line therapy for treatment of neuropathic pain. Gabapentin is FDA-approved for post-herpetic neuralgia (PHN), while pregabalin is labeled for use in diabetic peripheral neuropathy, PHN, neuropathic pain due to SCI, and fibromyalgia.
- The gabapentinoids have a good safety profile; common adverse effects: cognitive slowing, drowsiness, dizziness, peripheral edema, visual blurring.
- Weight gain can occur with higher dosages; more likely with pregabalin.
- Suicidal ideation and behavior, worsening of depression, and unusual changes in mood or behavior can occur with AEDs

Notes

Hyperalgesia = exaggerated pain perception as a result of damaged peripheral pain fibers

Spontaneous pain results from ectopic nerve discharges from an injured nerve

Allodynia = painful response to a normally innocuous stimulus.

Gabapentin can also be used in neuropathic pain associated with SCI

continued on next page

Notes - ***Continued***

Only gabapentin and pregabalin are highlighted, the others just acknowledged.

carbamazepine indicated in trigeminal neuralgia

lamotrigine useful in post stroke pain and HIV/AIDS-related neuropathy

tegretol indicated in --any antiepileptic may be worth a try in neuropathic pain syndromes if standard treatments have failed, proven inadequate. Typically use the others at their usual antiepileptic doses.

Both VHA and DOD require a trial of gabapentin, in most situations, before trial of pregabalin.

Based on a small amount of direct comparison and more indirect evidence, efficacy for Cymbalta (duloxetine) and Lyrica (pregabalin) are expected to be the same.

The last bullet addresses some common misconceptions about pregabalin versus gabapentin. Ease of use/tolerability with respect to Titration, Taper, Somnolence and Weight Gain were the "selling" points of pregabalin early in the drug's life cycle, but have largely not borne-out in long-term study.

The usual effective dose of gabapentin, in particular, is important to highlight because many patients are appropriately started low (to promote toleration of the side effects), but declared treatment failures before they are even close to an effective dose.

The details on this slide highlight that one class is not really safer than another with respect to suicidality. Should probably not be a driver in the decision of which agent to choose. In the typical chronic pain patient, who is above 25 years of age, antidepressants are protective while antiepileptics are not.

The data are from the FDA-approved Package labeling for duloxetine and pregabalin, but are common to the entire classes.

Gabapentinoid dosing and monitoring.

- There are no significant drug interactions; no blood tests or drug levels to monitor with either drug
- Gabapentin should be initiated at a dose of 100-300mg/day; increase weekly by 100-300mg/day to usual maintenance dose of 300-1200mg three times daily
- A faster titration is possible with pregabalin. Initiate at 25-150mg/day; increase weekly by 25-150mg/day to usual maintenance dose of 150 mg twice daily.
- Low range dosing should be targeted in the elderly
- Single bedtime dosing regimen may be considered to improve sleep and reduce daytime sedation
- Both drugs require dosing adjustments in renal impairment
- Pregabalin is a schedule V controlled substance; gabapentin also has potential for abuse

Notes

Gabapentin CrCl 30-59 ml/min – reduce to 400 to 1400mg/day in 2 divided doses; CrCl 15-29 ml/min – reduce to 200-700mg given once daily.

Pregabalin CrCl 30-60 ml/min – reduce to 75 to 300mg/day in 2 or 3 divided doses; CrCl 15-30 ml/min – reduce to 25 to 150mg given once daily or in 2 divided doses.

Dosing guidance exists (for both agents) for patients with CrCl < 15 ml/min and for those on hemodialysis.

AEDs that work through sodium blockade are effective in trigeminal neuralgia and for migraine prophylaxis.

- Carbamazepine, oxcarbazepine, topiramate, lamotrigine and valproic acid are sodium channel blockers. The increased expression of sodium channels in injured nerve fibers can lower the stimulation threshold and provoke spontaneous pain. The spread of sodium channels may also trigger central sensitization, leading to allodynia.
- Both carbamazepine and oxcarbazepine are first line treatments for trigeminal neuralgia (carbamazepine has FDA-approval for this use). Weak evidence exists for use of lamotrigine for this indication.
- Topiramate and valproic acid are FDA-labeled for migraine prophylaxis (both drugs Level A evidence for efficacy).
- Drug levels can be drawn for some of the sodium blockade ADEs to monitor for treatment and compliance; other blood testing may be necessary to monitor for adverse effects.
- Many of the sodium blockade AEDs have mood stabilizing properties and can be beneficial in patients with co-morbid bipolar disease.

Notes

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Only gabapentin and pregabalin are highlighted, the others just acknowledged.

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- lamotrigine useful in post stroke pain and HIV/AIDS-related neuropathy
- tegretol indicated in --any antiepileptic may be worth a try in neuropathic pain syndromes if standard treatments have failed, proven inadequate. Typically use the others at their usual antiepilectic doses.

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There are marked differences in the side effect profiles and other characteristics of carbamazepine and oxcarbazepine.

- Carbamazepine
  - Most common side effects: diplopia, headache, dizziness, nausea and vomiting, drowsiness and diarrhea
  - Leukopenia and thrombocytopenia are common (up to 10% incidence)
  - Aplastic anemia, agranulocytosis & hepatic failure rarely occur
  - Hyponatremia, liver function test abnormalities
  - Drug rash (occurs 2nd week, or later)
  - Carbamazepine is Pregnancy category D.
- Tolerance of oxcarbazepine is similar to that of carbamazepine.
  - Most common side effects: sedation, headache, dizziness, ataxia, blurred or double vision
  - Leukopenia, skin rash, and liver function abnormalities less common than with carbamazepine
  - Hyponatremia more common than with carbamazepine
- Oxcarbazepine is Pregnancy category C.

Both agents: Check CBC, LFTs, creatinine, and electrolytes at baseline, after 2 weeks, then quarterly for a year.

Treatment considerations and dosing of carbamazepine and oxcarbazepine.

- Carbamazepine and oxcarbazepine are both potent cytochrome P-450 enzyme inducers and can reduce the effectiveness of dozens of medications including warfarin, oral contraceptives, antipsychotics, cyclosporine, chemotherapeutic agents and cardiovascular drugs.
- Initiate carbamazepine at 100 mg BID to TID, increase at weekly intervals to usual maintenance dose of 200 to 300 mg TID. No renal adjustment required.
- Initiate oxcarbazepine at 300 mg daily; increase after 3 days to 300 mg BID, then adjust in increments of 300 mg every 5 days to maximum of 900 mg BID. Renal dosing required in severe impairment.
- Suicidal ideation and behavior, worsening of depression, and unusual changes in mood or behavior can occur with AEDs.

Notes

Severe renal impairment = CrCl < 30 ml/min

Topiramate side effects and dosing.

- Side effects of topiramate include: CNS depression, cognitive impairment, paresthesias in hands, kidney stones.
- Weight loss and reduced craving behaviors can occur with topiramate (may be beneficial).
- Topiramate inhibits carbonic anhydrase (black box warning with acetazolamide) and reduces effectiveness of oral contraceptives.
- Initiate at 25 mg/day (bedtime); titrate slowly. Maximum is 200mg BID, such high doses usually result in significant side effects, in particular cognitive dysfunction. Consider single bedtime dosing to minimize side effects.
- Suicidal ideation and behavior, worsening of depression, and unusual changes in mood or behavior can occur with AEDs.

Divalproex sodium side effects and dosing.

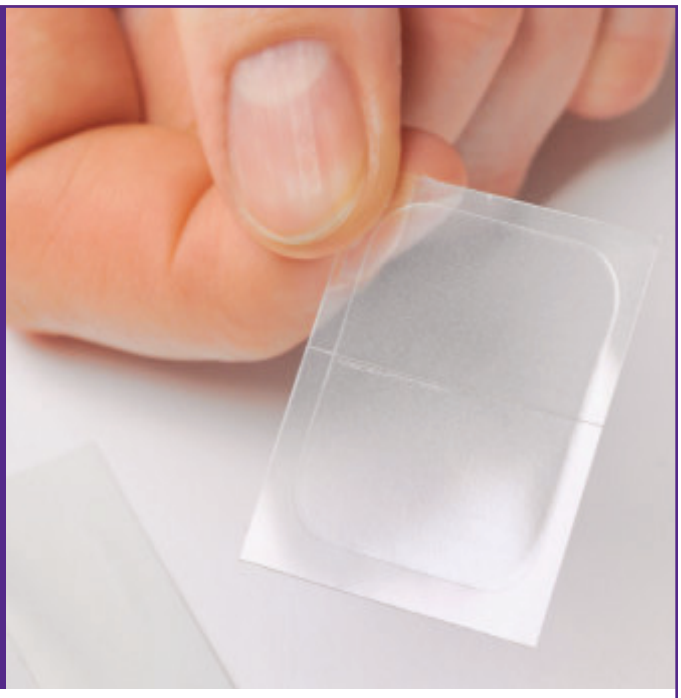
- Common side effects of divalproex sodium: headache, dizziness, insomnia, alopecia, abdominal pain, nausea, vomiting, diarrhea, tremor, weakness, blurred vision
  - Dose-related thrombocytopenia
  - Hepatic failure is rare but can be fatal, usually occur early in therapy
  - Life threatening pancreatitis (also rare)
- Initiate divalproex sodium at 500mg/day for one week, then increase to 1000mg daily. Frequency of dosing is dependent upon formulation. If single daily dosing is best tolerated when given at bedtime.
- Divalproex sodium is Pregnancy category X (migraine prophylaxis); category D for other indications
- Suicidal ideation and behavior, worsening of depression, and unusual changes in mood or behavior can occur with AEDs

Lamotrigine side effects and dosing.

- Common side effects of lamotrigine: rash (5-10%), blurred vision, abdominal pain, diarrhea, nausea and vomiting, dizziness, ataxia, headache, insomnia, somnolence.
- Lamotrigine may cause serious, life threatening skin rashes; risk is increased when drug titrated too quickly, when dose exceeds the recommended limit, or when given in combination with divalproex sodium (black box warning).
- Dosage and titration schedule depends upon concurrent medications. In absence of these concerns, begin with 25mg daily or every other day, slowly titrate to maximum dose of 200mg daily.
- Lamotrigine is Pregnancy category C.

Topic Four

Other Adjuvants Oral and Topical Agents



Most muscle relaxant drugs have limited or no analgesic efficacy and are best avoided

- Muscle relaxant drugs are widely used in chronic musculoskeletal pain but have limited or no analgesic efficacy.
- Most muscle relaxants are centrally acting and function primarily as sedatives, i.e. have CNS depressant action.
- They may be appropriate for short term use in selected patients with significant muscle spasms during flare up of neck or back pain.
- Regular use for more than a few days or chronic use is generally not recommended. In some patients, low dose limited to bedtime may help with muscle spasms and sleep.
- If an anti-spasticity agent is required because true spasticity is present, then either baclofen or tizanidine may be trialed.
- Cyclobenzaprine is a tricyclic drug, chemically nearly identical to amitriptyline. It shares the same side effect profile as other TCAs and should not be prescribed for patients on these drugs because of the risk for combined adverse effects.
- Carisoprodol (C-IV) is not recommended due to the significant potential for misuse, abuse and addiction, and even diversion.

Notes

- Muscle relaxant drugs are widely used in chronic musculoskeletal pain but have limited or no analgesic efficacy.
  - Orphenadrine has been shown to have some NMDA antagonist effects (NMDA lowers activation thresholds and increases neuronal excitability and neurotoxicity) which, to some extent, sets it apart from methocarbamol and metoxazole.

The intent here is certainly not to highlight benzodiazepines. Most emphasis should be placed on taking pause in the decision of whether or not to prescribe these to folks with psychiatric comorbidities, especially PTSD or addictive personalities.

Generally, the shortest-half-life agents—xanax and halcion—should not be used, and the long-half-life agents are probably not very effective as muscle relaxants. Valium (diazepam 5mg or 10mg) would be the go-to drug for this indication.

Flexeril (cyclobenzaprine 5-10 mg TID-QID) may also be appropriate. It is functionally a TCA, so serotonin syndrome is possible in the presence of several other serotonergic agents.

Zanaflex (tizanidine 2-4 mg, max 32mg/day) is particularly not favored by the DVA (limited to certain prescribers) and may not be carried in all DOD MTFs. There is perhaps more potential for abuse/misuse than with some other agents.

SOMA compound has probably the worst reputation for misuse. Generally avoid.

Again, pretty limited role for these.

DM has historically been a hallucinogen of abuse at very high doses. Of course at appropriate doses it suppresses cough.

Ketamine used in some patients with chronic pain, but that would not be appropriately initiated by the typical primary care provider.

I only include alcohol as a reminder that people self-treating pain with alcohol have some pharmacologic rationale for why it actually works …

Capsaicin is classified as a counterirritant. 8% cream. There is a higher concentration for office-based testing.

Topical NSAIDS include diclofenac in gel, drops (liquid), and patch preparations. Others may be compounded if desired.

There are a couple of issues with compounds:

- Some bulk powders are not FDA-approved. It is against the law for Tricare to pay for non-FDA-approved drugs;
- Many high-volume compounding pharmacies are making standardized products but using a loophole of “individualized” to avoid FDA inspection and scrutiny. They send out standard prescription pads with their compounds, so clearly not much individualization is going on. The lack of oversight/inspection has led to some high profile safety issues (not for topicals, per se, but the analogy is valid).
- Also true is that there is a lot of fraud or near-fraud in billing for these compounds, with some pharmacies charging $5k/month that a more reputable pharmacy might only charge $100/month for essentially the same thing.

For these reasons and more Medicare (CMS) stopped reimbursement for compounds several years ago.

Baclofen

- Baclofen is FDA-approved for muscle spasticity; it is a gaba-aminobutyric acid (GABA) B agonist that inhibits electrical transmission at the spinal cord level.
  - Initial dosing is 5 mg BID to TID, first dose at bedtime. Increase by 5 mg per dose every 3 days until optimal response is reached. Usual dosage range is lower for muscle spasms (5 to 20 mg TID) than may be used for spasticity (maximum total daily dosage of 80 mg)
  - Go slowly; it can be very sedating
  - May also be administered intrathecally via implanted pump
  - Abrupt discontinuation of high-dose baclofen may cause seizures and be life-threatening; a hypercontractile state causing hyperpyrexia and rhabdomyolysis can occur - taper the drug over 1-2 weeks, with dosage reduction not faster than every 3 days.

Tizanidine

- Tizanidine is also FDA-approved for spasticity; it acts as an alpha 2-adrenergic agonist that decreases spasticity by reduction of facilitation of spinal motor neurons.
  - Side effects include dose-related orthostatic hypotension, dry mouth and sedation. Monitor for LFT elevation. Subject to interactions (contraindicated with ciprofloxacin)
  - Initiate with 2 mg at bedtime (1/2 tab of 4 mg), or lower depending on size and age of patient and presence of anti-hypertensive drugs. Increase gradually to optimal effect in
  - 2-4 mg increments, with minimum of 1-4 days between dosage increases. Bedtime dosing may help with sleep. For spasticity, TID dosing is usually required;
  - For muscle spasms, use lower doses than may be required for spasticity, with maximum of 12 mg TID.
  - Abrupt withdrawal of tizanidine can result in rebound hypertension – taper drug if it is to be discontinued.

Benzodiazepines

- Benzodiazepines have limited clinical value as skeletal muscle relaxants. They may be useful short-term only as a sedative, when required for short-term antianxiety effects, and as sleep aids before transitioning to more effective drugs.
- There are numerous risks associated with the use of benzodiazepines in chronic pain management:
  - rapid development of tolerance
  - rebound insomnia
  - respiratory suppression, including overdose death, in particular when combined with opioids and other sedating drugs or alcohol).
- Benzodiazepines pose significant risks of misuse/abuse, and addiction. Physical dependence may be expected after only a few weeks of use.
- Abrupt discontinuation of benzodiazepines results in an abstinence syndrome/ withdrawal symptoms
- Current evidence-based pain treatment guidelines strongly recommend against co-prescribing benzodiazepines with opioids in chronic non-malignant pain due to high risk of overdose due to respiratory depression.

Notes

The abstinence syndrome resulting from abrupt discontinuation of benzodiaepines is similar to delirium tremens and can be life-threatening – benzodiazepines must be tapered slowly (after prolonged use).

Topical analgesic adjuvants

- Lidocaine 5% patch is FDA-approved for treatment of postherpetic neuropathy (PHN). There is less evidence for efficacy for other peripheral neuropathies but is considered 2nd line (after TCAs, SNRIs, and gabapentinoids) for that indication.
  - Skin penetration is only 4-5mm, so the therapeutic target is skin nociceptors
  - Lidocaine 5% patch has virtually no side effects
  - Lidocaine is also available as 5% cream and ointment
- Capsaicin is available for topical use in different formulations including cream/lotion and as patch. The 8% patch is FDA-approved for treatment of PHN. It has the advantage of every 3 months use but requires application by a healthcare provider and pretreatment with local anesthetic.
  - Application of capsaicin inhibits pain transmission initiation in cutaneous nociceptors via desensitization of sensory neurons (through depletion of substance P)
  - A sensation of warmth or mild burning at application site is common and usually lessens over time. Discontinue with any significant redness or rash
  - Capsaicin is available in different strengths. Begin at lower strength and increase as tolerated.
  - When applying capsaicin cream topically, it is important to avoid contact with mouth, eyes and nose. Immediately wash hands with soap after application. Use of disposable gloves is recommended.
- Methyl salicylate and menthol (analgesic balm) is an OTC product with limited usefulness for the temporary relief of minor aches and pains of muscles and joints.
  - The mechanism of action of action of this product is not fully established
- Diclofenac gel 1% and Diclofenac epolamine 1.3% patch are available for topical use in patients that cannot tolerate or should not be treated with oral NSAIDs due to side effects or risks, including impaired renal function, liver disease, cardiovascular risk or GI side effects.

Summary

The use of combinations of analgesic medications with different mechanisms of action can reduce reliance on opioids and improve pain outcomes.

Antidepressants and antiepileptic drugs are most likely to be effective in the setting of peripheral neuropathic pain or pain from central sensitization.

Counsel patients and family about the risks of suicidality when any antidepressant or AED is prescribed.

TCAs are effective agents but have side effects that limit usefulness, especially in the elderly who may have comorbid BPH, cardiovascular disease, or other risk for falls.

SNRIs are especially useful as adjunctive pain medications in patients with comorbid depression. Patients should be counseled regarding risk of discontinuation syndrome.

Gabapentinoids are generally well tolerated with side effects that are usually clinically evident: cognitive slowing, weight gain, and edema.

Sodium channel blocking AEDs have a wide range of potential adverse effects and drug interactions; side effects are not always evident and laboratory monitoring is recommended.

Muscle relaxant agents have limited evidence for effectiveness, are predominately sedative, and add little benefit. When true spasticity is present – baclofen and tizanidine may be useful.

Benzodiazepines add limited or no benefit in the management of chronic pain and should not be used in conjunction with opioids.

Resources

Bril V, England J, Granklin GM, et al. 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; 76: 1758-65.

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Finnerup NB, Attal N, Haroutounian S et al. Pharmacotherapy for Neuropathic Pain in Adults: A Systematic Review and Meta-Analysis. Lancet Neurol 2015; 162-73, published online, January 7, 2015 at http://dx.doi.org/10.1016/S1474-4422(14)70251-0

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