PHARMACOTHERAPY FOR NEUROPATHIC PAIN

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OBJECTIVES

- Discuss the use of first line medication treatment used for neuropathic pain
- Outline the most frequently used medications:
 - Elavil, Cymbalta, Neurontin, Lyrica
 - Effectiveness, side effects & safety precautions
- Review recent literature regarding these medications

NEUROPATHIC PAIN

- Description: burning, stinging, shooting, electric-like
- Medications used cause stabilization or "calming" of the over active nerves
 - Tricyclic Antidepressants
 - Amitriptyline (Elavil)
 - Selective Serontonin-Norepinephrine Reuptake Inhibitors
 - Duloxetine (Cymbalta)
 - Anticonvulsants
 - Gabapentin (Neurontin)
 - Pregabalin (Lyrica)

AMITRIPTYLINE (ELAVIL)

Overview

- Tricyclic Antidepressant
 (TCA) Tertiary Amines
- Used off label for pain but well studied
- Works by reducing the nerve cell's ability to reabsorb neural transmitters-results in suppression of pain messages in the spinal cord
- Inhibits serotonin reuptake to a greater degree than norepinephrine

- Dose to treat depression is higher
- Long acting so once daily dosing
- Range: 50-150 mg @ hs
- Start 10-25 mg, titrate
 up 10-25 mg q 3-4 days
- Absorption is rapid
- Not addictive but withdraw over 2-3 weeks

AMITRIPTYLINE (ELAVIL)

Advantages

- Inexpensive-25 mg #30-\$7.30
- Single Daily Dosing
- Beneficial in insomnia
- 1 in 4 people will get significant pain relief
- No dose adjustment for renal or hepatic impairment
- Tolerance can develop to side effects

Common Side Effects

- Dry mouth
- Drowsiness
- Nausea
- Constipation
- Orthostatic hypotension
- Urinary hesitancy
- Fatigue, somnolence
- Confusion, falls

Pain relief in 2 weeks but often need 6-8 weeks for a fair trial

BRIEF LITERATURE REVIEW OF RECENT STUDIES

- A number of placebo-controlled trials examined use of topical amitriptyline for neuropathic pain failed to show significant benefit. However, significant decrease in pain was seen with a combination cream;1% amtrip/0.5% Ketamine (Argoff, 2013).
- Review of anti-depressants use in pain management found amitriptyline had efficacy, high evidence based support but high side effects (Sansone & Sansone, 2008).
- Patient education article: Serpell, M. *Amitriptyline*. Pain Concern. 2013,1-4

DULOXETINE (CYMBALTA)

Overview

- SNRI-inhibits both serotonin & norepinephrine reuptake within CNS synapses (weak inhibitor of dopamine reuptake)
- 2004-Used to treat depression, anxiety, fibromyalgia, diabetic neuropathy
- Approved in 2010 by FDA for chronic musculoskeletal pain caused by osteoarthritis & chronic low back pain
- Minacipran (Savella)-2009
 SNRI used for fibromyalgia

- Delayed release form
- Begin 1st week with 30 mg daily, increase to 60 mg daily, higher doses showed no additional benefits
- Efficacy has not been established beyond 13 weeks, taper dose
- Not recommended in severe renal impairment

DULOXETINE (CYMBALTA)

Advantages

- Established efficacy, evidence based support is moderate and low reported side effects (Sansone & Sansone, 2008)
 - Adverse Effects
- Liver Toxicity <1%
- May impair platelet aggregation (caution with ASA, Nsaids, Warfarin)

Cost

- Cymbalta #30 (30 mg) \$261.72
- Generic #30 (30 mg) \$235.55

Common Side Effects

- Headache 13-14%
- Somnolence 10-12% (dose related)
- Fatigue 10-11%
- Insomnia 10%
- Nausea 23-25%
- Dry mouth 11-15%
- o Dizziness 10%
- Constipation 10%
- Caution when combined with TCA, MOA I, Tramadol, St. John's Wart-Serotonin Syndrome

Brief Literature Review of a Recent Study

- Cochrane Review (2011)-an open comparison study of 29 patients with chronic pain syndrome of the spine
 - 14 patients given Cymbalta
 - Assessed pain intensity on a VAS scale on days 1, 7, 42
 - VAS significantly lower compared to control group on 7 and 43 days
 - Physician reported marked improvement in 58% of main group & 14% in control group
 - Improvements in patients found 36% of main group & 7% in control group
 - Highest s/e nausea 28%

(Odinak, Kashin & Ememlin, 2009)

GABAPENTIN (NEURONTIN)

Overview

- Anticonvulsant used off label for neuropathic pain syndromes
- Blocks voltage dependent Calcium Channels in nerve cells, modulating excitatory neurotransmitter release
- Dose dependent & peak plasma concentrations achieved within 2-3 hours
- o Cost: 100mg (90) \$119.99

- o Start 100 mg tid or 300 mg hs, adjust by 100 mg q 3-4 days, max. range 1800-3600 mg/day
- Must adjust to renal insufficiency
- Taper off, minimum of 1 week
- Adequate trial =1-2 weeks
- Once daily doses available (Gralise, Horizant)

GABAPENTIN (NEURONTIN)

Common Side Effects

- Dizziness-17-28%
- Drowsiness-19-21%
- Ataxia-1-13%
- Fatique-11%
- Peripheral edema-2-8%

Caution Advised

Gabapentin and pregabalin(Lyrica) combination may increase risk of CNS depression, psychomotor impairment (additive effects)

Pregabalin (Lyrica)

Overview

- FDA approved for diabetic peripheral neuropathic pain, postherpetic neuralgia, neuropathic pain 2nd to spinal cord injury, fibromyalgia, partial onset seizures, off label for other neuropathic pain syndromes
- Binds alpha 2 delta subunit of Ca Ch reducing neurotransmitter release

- 75-150 mg bid, start at
 25-50 mg bid adjust 25
 mg q 3-4 days
- Adequate trial=1-4weeks
- Taper off
- Higher bioavailability & is rapidly absorbed after oral dosing
- Schedule V controlled substance due to anxiolytic properties
- Listed on OARRS Report

Pregabalin (Lyrica)

Common Side Effects

- Peripheral edema <16%
- Somnolence 4-36%
- Dizziness 8-45%
- Weight gain <16%
- Tremors <11%
- Headache 5-14%
- Blurred vision 1-12%
 **Some pts. will have effect with pregabalin that did not find benefit with gabapentin, and vice versa

Comparisons

- Pregabalin adverse effects rate higher than gabapentin
- Pregabalin may improve sleep
- Pregabalin has few drugdrug interactions
- Both require renal adjustments
- Both if given with Tramadol may increase risk of CNS depression
- Pregabalin cost=100 mg (#90) \$473.81

Systematic Review & Meta-Analysis

- Clarke, H., Bonin, R., Orser, B., Englesakis, M. ... The Prevention of Chronic Postsurgical Pain Using Gabapentin & Pregabalin: A Combined Systematic Review& Meta-Analysis. Pain Medicine 2012, 115(2) 428-442.
- Examined use of Gabapentin & Pregabalin for the prevention of chronic postsurgical pain (CPSP)
- 11 trials: 8 perioperative Gabapentin, 3 perioperative Pregabalin, approx. 930 patients total in systematic review 2002-2011
 - 4 of the 8 found that perioperative gabapentin decreased the incidence of chronic pain more than 2 months after surgery
 - All 3 perioperative pregabalin studies showed significant preventive analysesic effects in that there was a reduced incidence of pain and/or lower analysesic requirements at long term follow up > 2 months after surgery. 2 also found an improvement in postsurgical pt. function.
- 8 Studies in Meta-Analysis
 - 6 gabapentin trials demonstrated a moderate to large reduction in the development of CPSP (odds ratio 0.52, (95% confidence level)
 - 2 pregabalin trials found very large reduction in the development of CPSP (pooled odds ratio 0.09, 95% CI)

COMPARISON OF MEDICATIONS EFFICACY & SAFETY

Comparison of Drugs by NNT & NNH	NNT	NNH
TCA	2.4	14.7
Gabapentin	3.7	26.1
Pregabalin	4.0	11.7
SNRI	5.0	-

- NNT: Numbers
 needed to treat to
 achieve 50% reduction
 in pain in 1 pt. (low
 number is good)
- NNH: Numbers needed to harm-number needed to treat before there is 1 pt. with intolerable side effects (high number is good)

Grauer, P. Medication Therapy in End of Life Care. Hospice Pharmacotherapy. 2012, 25-26.

ALTERNATIVE THERAPIES

- Non-Pharmacological Pain Management
 - Acknowledging their pain leads to decreased anxiety leading to reduced pain
 - Ice
 - Repositioning
 - Elevation
 - Use of pillows
 - Massage
 - Meditation
 - Yoga

Systematic Review & Meta-Analysis

- Ward, L., Stebbings, S., Cherkin, D., Baxter, G. Yoga for Functional Ability, Pain and Psychosocial Outcomes in Musculoskeletal Conditions (MSCs): A Systematic Review and Meta-Analysis. Musculoskeletal Care, 2013 Dec; 11 (4) 203-17.
- Investigated the effectiveness of yoga on primary outcomes of functional ability, pain and psychosocial outcomes across a range of MSCs
 - 17 Studies, involving 1,626 patients with low back pain, osteoarthritis, rheumatoid arthritis, kyphosis or fibromyalgia
 - 12 Studies rated good quality
 - Showed clinically significant improvement in functional outcomes in mild-moderate low back pain and fibromyalgia
 - Showed significant improvement in pain in OA, RA and mild-severe low back pain
 - Psychosocial outcomes were significantly improved in mild-moderate low back pain and OA
 - Meta-analysis of good quality studies showed a moderate treatment effect for yoga of -0.64 (95% CI-0.89 to -0.39) for functional outcomes and -0.61 (95% CI -0.97 to -.26) for pain outcomes

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NON-STEROIDAL ANTI-INFLAMMATORY DRUGS & MUSCLE RELAXANTS

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TODAY'S OBJECTIVES

- Discuss the use of NSAID's in chronic and acute pain
- Outline the most frequently used NSAID's
 - Effectiveness, side effects & safety precautions
- Review recent literature regarding NSAID's
- Discuss the use of muscle relaxants in chronic and acute pain
- Outline the most frequently used muscle relaxants
 - Effectiveness, side effects & safety precautions
- Review recent literature regarding muscle relaxants

CARDIOVASCULAR RISK

- NSAIDs may increase the risk of serious and potentially fatal cardiovascular thrombotic event, MI, and stroke
- •Risk may increase with duration of use
- •Risk may increase if patient has cardiovascular disease or cardiovascular disease risk factors

(Epocrates, 2014)

GI RISK

- oNSAIDs increase risk of serious GI adverse events including bleeding, ulcer, and stomach or intestine perforation, which can be fatal
- May occur at any time during use and without warning
- Elderly patients at greater risk for serious GI events

(Epocrates, 2014)

NSAIDS

Overview

- Cyclooxygenase inhibitor
- Inhibits Prostaglandins that cause pain, fever and inflammation
- Most effective in mild to moderate pain and inflammatory disorders
- Should be taken with food
- May enhance anticoagulant effects of anticoagulants
- ACE Inhibitors may increase adverse reactions
- Caution patients about OTC use in combination with prescribed NSAIDs

Common Side Effects

- Nausea, abdominal pain, dyspepsia, constipation (1-10%)
- Dizziness, drowsiness (1-3%)
- Headache (1-3%)
- Tinnitus (1-3%)
- Fluid retention (1-3%)
- Allergic reactions (1-3%)
- Photosensitivity (<1%)
- Ecchymosis (<1%)
- Elevated ALT, AST (rarely)
- Renal toxicity (rarely)

COMMONLY USED NSAIDS

- o Ibuprofen: Motrin, Advil
- Naproxen: Naprosyn, Aleve
- Diclofenac: Voltaren, Voltaren XR, Zipsor, Cambia, Cataflam, Voltaren gel, Pennsaid drops, Flector Patch, Solaraze, Arthrotec
- Meloxicam: Mobic
- Celecoxib: Celebrex
- Ketorolac: Toradol, Sprix

IRLIPROFFN (NON-SELECTIVE)

Advantages

- Easily accessible (OTC)
- Inexpensive (\$4)
- Off label use for Ankylosing spondylitis, cystic fibrosis, gout, acute migraine headache, migraine prophylaxis, pericarditis
- Analgesic effect 30-60 minutes
- Anti-Inflammatory effect within 7 days
- Duration 4-6 hrs
- Peak effect 1-2 hours
- Half-life 2-4 hours

- > 200-800mg every 6 hrs prn
- 3200mg maximum daily dose
- Caution advised in renal and hepatic impairment
- Avoid is CrCl<30

NAPROXEN (Non-Selective)

Advantages

- Easily accessible (OTC)
- Inexpensive (\$4)
- Off label use for migraine prophylaxis
- Least CV risk of all NSAIDs
- Analgesic effect 30-60 minutes
- Duration <12 hrs
- Peak effect 2-4 hours
- Half-life 12-17 hours

- 250-500mg every 12 hours
- 1500mg maximum daily dose for acute pain
- 1000mg maximum daily dose for chronic use
- Avoid with CrCl<30
- Caution advised with hepatic impairment

MELOXICAM (PREFERENTIALLY SELECTIVE)

Advantages

- 1-2 times a day dosing
- Inexpensive (\$4)
- Less GI side effects at lower doses
- Analgesic effect 30-60 minutes
- Duration <24 hours
- Peak effect 4-5 hours
- Half-life 15-20 hours

- 7.5-15mg daily
- 7.5mg bid is good option in some patients
- 15mg maximum daily dose
- Avoid with CrCl<20
- No adjustment for hepatic impairment

DICLOFENAC (PREFERENTIALLY

SELECTIVE)

Advantages

- 2-3 times a day dosing
- Inexpensive (\$4 list)
- Less GI side effects at lower doses
- Analgesic effect 15-30 minutes
- Duration <12 hrs
- Peak effect .25-5 hours
- Half-life 2 hours

- Delayed release: 25mg,
 50mg, 75mg bid-tid
- Maximum dose150mg/day
- Extended release: 100mg ER daily
- Avoid with advanced renal disease
- Avoid with hepatic impairment

DICLOFENAC (PREFERENTIALLY SELECTIVE)

Multiple Formulations

- Voltaren 1% gel
- Flector 1.3% patch
- Pennsaid 1.5% & 2% solution
- Diclofenac 1% gel
- Cambia 50mg powder
- Zipsor 25mg liquid capsule
- Zorvolex 18mg & 35mg
- Arthrotec 50/0.2mg,
 75/0.2mg
 (Diclofenac/Misoprostol)

Common Side Effects

- Higher incidence of elevated liver enzymes than other NSAIDs – 15% slight elevation
- 2-4% incidence of significant elevation (3 times normal)

CELECOXIB (SELECTIVE)

Advantages

- 1-2 times a day dosing
- Less GI side effects
- Same CV risk as all NSAIDs
- Analgesic effect 1-2 hours
- Duration <24 hours
- Peak effect 3 hours
- Half-life 11 hours

- 50-200mg daily or bid
- Maximum 400mg daily dose
- Currently being used for familial adenomatous polyposis 400mg bid

KETOROLAC

Advantages

- Oral, Intramuscular, Intravenous routes
- Used in post-op settings
- Short term use

- 10mg po every 6 hrs, not to exceed 5 days
- 15-30mg IM/IV every 6 hrs
- Uses lowest effective dose and shortest effective treatment duration
- Avoid use with advanced renal impairment
- Caution advised with hepatic impairment

LESS COMMONLY USED NSAIDS

- Etodolac: Lodine
- Piroxicam:Feldene
- Nabumetone: Relafen
- Ketoprofen: Orudis, Oruvail
- Oxaprozin: Daypro
- Sulindac: Clinoril
- Tolmetin: Tolectin
- Salicylates -
- Salsalate: Amigesic
- Aspirin: Bayer, Bufferin, Ecotrin
- Diflunisal: Dolobid

Brief Literature Review

 Meta-analysis of 34 studies from 7688 adults found that topical NSAIDs provided adequate pain relief, equivalent to oral NSAIDs for hand and knee osteoarthritis.

(Atchison, 2013)

 Meta-analysis of 639 clinical trials that included more than 350,000 NSAID users revealed Naproxen appears to offer the most favorable cardiovascular safety profile, moderately superior to other traditional NSAIDs and Coxibs.

(Atchison, 2013)

MUSCLE RELAXANTS

- Used since the 16th century by South American Natives
- Helps reduce opiate use
- Improves pain relief and decreases functional impairment when used in conjunction with NSAIDs
- Somatic Pain
- Visceral Pain
- Neuromuscular Blocker Anesthesia, ICU Temporary Paralysis
- Spasmolytic/Antispasmotic Centrally Acting Muscle relaxants, Direct Acting Muscle Relaxants

COMMONLY USED MUSCLE RELAXANTS

- Methocarbamol Robaxin
- Lioresol Baclofen
- Tizanidine Zanaflex
- Metaxalone Skelaxin
- Cyclobenzaprine Flexeril, Fexmid, Amrix
- Carisoprodol Soma
- Benzodiazepines Not shown to have enough benefit to outweigh side effects and abuse potential

MUSCLE RELAXANTS

Overview

- Most are centrally acting
- Dantrolene is direct acting
- For short use in acute pain
- Has helped reduce opiates in chronic pain
- Avoid abrupt withdrawal after long term use
- Start low and titrate slow
- Most are considered inappropriate for elderly

Adverse Side Effects

- Drowsiness > 10%
- \circ Weakness > 10%
- Hypotension 1-10%
- Confusion 1-10%
- Skin rash 1-10%
- Constipation, nausea 1-10%
- Polyuria 1-10%
- Chest pain, dyspnea <1%

METHOCARBAMOL

Advantages

- Least side effects
- Generic available
- Available IM & IV
- TID OR QID dosing
- Onset of action 30 min
- Duration 4-6 hours
- Peak effect 1-2 hours
- Half-life 2 hours
- Metabolized liver
- Excreted Urine primarily

- 500-1000mg TID-QID
 PO
- 1500mg QID for < 3 days acute pain
- Max 4500mg/day chronic use

LIORESOL

Advantages

- Generic available
- Available IT
- TID OR QID dosing
- Onset of action 30 min
- Duration 6-8 hours
- Peak effect 2-3 hours (oral)
- Half-life 3.5 hours
- Metabolized liver
- Excreted Urine primarily

- 10-20mg TID-QID
- Max daily dose 80mg/day
- Caution advised with renal impairment

TIZANIDINE

Advantages

- Generic available
- TID OR QID dosing
- Onset of action 30 min
- Duration 3-6 hours
- Peak effect 1-4 hours
- Half-life 2.5 hours
- Metabolized liver
- Excreted Urine primarily

- 2-8 mg TID-QID
- Max 36mg daily dose
- Decrease dose for CrCl <25
- Caution due to higher incidence of hypotension
- Caution advised in hepatic impairment

METAXALONE

Advantages

- Generic available (still expensive)
- TID OR QID dosing
- Onset of action 1hr
- Duration 4-6 hours
- Peak effect 2-3 hours
- Half-life 4-14 hours
- Metabolized liver
- Excreted Urine primarily

- 800mg TID –QID
- Give on empty stomach
- Caution advised with renal or hepatic impairment
- Contraindicated with significant renal or hepatic impairment
- May cause anemia

CYCLOBENZAPRINE

Disadvantages

- Usually much worse side effects
- Frequently seen on the street
- High risk for diversion

- 5-10mg TID
- 30mg Max daily
- Renal dosing not defined
- Moderate to severe hepatic impairment avoid use

CARISOPRODOL - SOMA

Disadvantages

- Mebprobamate 1st
 metabolite –
 anxiolytic
- High abuse potential
- Frequently seen on the street
- High risk for diversion

- 250-350mg TID & HS
- Renal dosing not defined
- Hepatic dosing not defined

LESS COMMONLY USED MUSCLE RELAXANTS

- Orphenadrine Norflex
- Chlorzoxazone Paraflex, Parafon Forte DSC, Lorzone
- Dantrolene Dantrium

Brief Literature Review

• Study designed to evaluate the analgesic efficacy of placebo and diazepam in patients with temporomandibular disorders found no significant difference between groups.

(Pramod et al, 2011)

• Double blind trial found no significant difference in mean pain scores between diazepam and placebo.

(Richards et al, 2012)

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QUESTIONS??

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