PainWeek

Nonopioid Analgesics:
The Selection and Use of Adjuvant Therapies

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Disclosures

- Nothing to disclose

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Objectives

- Describe where adjuvant analgesics act in the pain pathway and their differences in mechanism of action
- Compare risks and benefits for different adjuvant analgesics
- Choose an adjuvant analgesic based on available evidence-based medicine and individual patient factors

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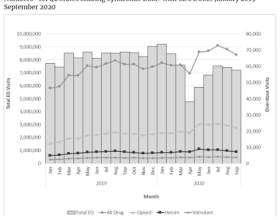
COVID-19 and the impact on opioid overdoses

- Total ED visits began declining after January 2020, reaching the lowest point in April 2020
- Numbers of suspected all drug (including opioid-involved) overdoses were highest in July 2020
- Numbers of suspected heroin and stimulant-involved overdoses were highest in May 2020

Emergency Department (ED) Visit Totals and Suspected Nonfatal Overdose Numbers* for 22 States Sharing Syndromic Data† with CDC DOSE: January 2019–September 2020



https://www.cdc.gov/drugoverdose/data/nonfatal/states/covid-19.html accessed 4.2.2021

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Synthetic opioid versus prescription opioid overdose death maps

2018–2019

CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2020. https://wonder.cdc.gov/ accessed 4.2.2021

2018–2019 Overdose Map

CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2020. https://wonder.cdc.gov/ accessed 4.2.2021

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Risk Factors for Opioid Overdose

- Having an opioid use disorder
- Taking opioids by injection
- Resumption of opioid use after an extended period of abstinence
- Using prescription opioids without medical supervision
- High prescribed dosage of opioids (more than 100 mg MEDD)
- Using opioids in combination with alcohol and/or other substances or medicines that suppress respiratory function such as benzodiazepines, barbiturates, anesthetics or some pain medications
- Having concurrent medical conditions such as HIV, liver or lung disease or mental health conditions.

https://www.who.int/news-room/fact-sheets/detail/opioid-overdose accessed 4.5.2021
MEDD = morphine equivalent daily dose

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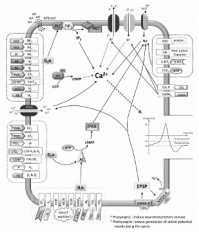
Where Do Adjuvants Work?



IJMS.19; 2164: 2018

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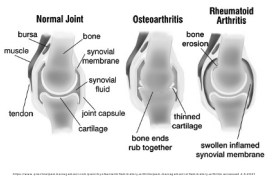
Inflammatory Pain

- Nonsteroidal anti-inflammatory agents
  - –Ibuprofen
  - –Naproxen
  - –Meloxicam
  - –Celecoxib
- Corticosteroids



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Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

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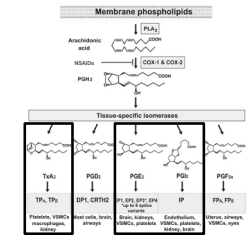
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)



- COX -1
  - PGI_2/PGE_2
    - Immune response
    - GI integrity
  - TXA_2
    - Platelet aggregation and adhesion
- COX -2
  - PGI_2/PGE_2
    - Cardiovascular homeostasis
      - –Vasodilator
      - –Inhibit platelet aggregation
    - Nociceptor sensitization

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Arterio Thromb Vasc Bio 31; 5: 986-1000 2011

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Topical NSAIDs

- Diclofenac sodium 1% gel (over the counter)
  - –Upper extremity (hands, elbows, wrists): 2 g applied three to four times daily up to 8 g on any one joint
  - –Lower extremity (knees, ankles, and feet): 4 g applied three to four times daily up to 16 g on any one joint
- Diclofenac epolamine 1.3% patch
  - –1 patch applied BID to the most painful area
- Both products carry the same boxed warnings but are proposed to have a more favorable safety profile than oral NSAIDs

https://fco.factsandcomparisons.com/fco/action/doc/retrieve/docid/patch_61772965 accessed 4.6.2021

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NSAIDs and overall cardiovascular risks

- Thrombotic events
  - – VIGOR (rofecoxib)
    - Relative risk (RR) of cardiovascular (CV) events 2.37; p =0.0016
  - – APPROVe (rofecoxib)
    - RR of CV events [MI and stroke] 1.92; p = 0.008
- Blood pressure
  - – Meta analysis comparing COX-2 specific with placebo and non-selective agents
    - RR increase in blood pressure 1.49; p = 0.04 (placebo only)
- Heart Failure
  - – Risk of hospitalization with CV history (rofecoxib)
    - RR 1.8 versus not statistically significant for non-selective agents

Cureus 9;4: e144 2017

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NSAIDs and overall cardiovascular risks, cont.

- Meta analysis comparing non-selective NSAIDs and COX-2 inhibitors
  - Primary end point was MI
  - Secondary end points included
    - Stroke
    - CV death (all cause)
  - Highest risk of MI
    - Rofecoxib Relative Risk [RR] = 2.12
  - Highest risk of stroke
    - Ibuprofen (RR = 3.36)
    - Diclofenac (RR = 2.86)

	Myocardial infarction (RR)	Stroke (RR)	Cardiovascular death (RR)	Death (RR)
Naproxen	0.82 (0.37-1.67)	1.76 (0.91-3.33)	0.98 (0.41-2.37)	1.23 (0.71-2.12)
Ibuprofen	1.61 (0.50-5.77)	3.36 (1.00-11.60)	2.39 (0.69-8.64)	1.77 (0.73-4.30)
Diclofenac	0.82 (0.29-2.20)	2.86 (1.09-8.36)	3.98 (1.48-12.70)	2.31 (1.00-4.95)
Celecoxib	1.35 (0.71-2.72)	1.12 (0.60-2.06)	2.07 (0.98-4.55)	1.50 (0.96-2.54)
Etoricoxib	0.75 (0.23-2.29)	2.67 (0.82-8.72)	4.07 (1.23-15.70)	2.29 (0.94-5.71)
Rofecoxib	2.12 (1.26-3.56)	1.07 (0.60-1.82)	1.58 (0.88-2.84)	1.66 (1.04-2.23)
Lumiracoxib	2.00 (0.71-6.21)	2.81 (1.05-7.48)	1.89 (0.64-7.09)	1.75 (0.78-4.17)

Cureus 9;4: e144 2017

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NSAIDs and GI Adverse Effects

- Strategies to prevent gastric mucosal damage in chronic NSAID users
  - Proton pump inhibitor (PPI)
  - Histamine-2 receptor antagonist (H2RA)
  - Use of COX-2 selective agents
- Risk factors for NSAID-related GI toxicity
  - History of peptic ulcer disease or upper GI bleed
    ≥65 years old
  - Presence of comorbidities such as rheumatoid arthritis
  - Concomitant use of anticoagulants, aspirin or corticosteroids

1. Am J Gastroenterol. 2009;104:728-738.
2. JMCP. 2013;19(9):S3-S19.
3. Circulation. 2007;115:1634-1642.

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Post operative bleeding and NSAIDs

- Meta analysis reviewing data related to perioperative NSAID administration and surgery-associated bleeding

Post-operative bleeding complication	Statistical difference	P-value
Hematoma formation	No	0.492
Return to operating room for surgical bleeding	No	0.792
Blood transfusions	No	0.492

- NSAIDs included the following: ketorolac, diclofenac, ibuprofen, celecoxib, ketoprofen, parecoxib and others
- Procedures included: breast, abdominal, ENT, orthopedic, thyroid/parathyroid, plastics procedures, OB/Gyn and others
- These observational data may be useful in engaging in discussions over NSAIDs in the perioperative period

JACS; 1-25: 2021

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Corticosteroids

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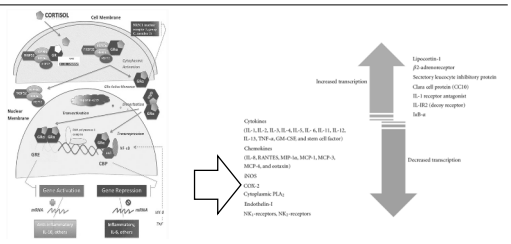
Glucocorticoids



https://jcm-experimentalsciencesopen.com/articles/10.1186/s40635-017-0123-8 accessed 4.5.2021
International Journal of Endocrinology Volume 2012, ID 561018 doi:10.1155/2012/561018

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Glucocorticoids, cont.

- Mechanism of action leads to a increase in anti-inflammatory mediators and a decrease in inflammatory molecules
- Multiple routes of administration
  - –Oral
  - –Parenteral
    - •IV
    - •IM depot
    - •Intra-articular
    - •Peri-neural

Agent	Relative Glucocorticoid Potency	Relative Mineralocorticoid Potency	Duration of Action
Hydrocortisone (Cortisol)	1	1	Short
Prednisolone	4-5	0.25	Short
Methylprednisolone	5-6	0.25	Short
Dexamethasone	18	<0.01	Long

Adapted from http://tmedweb.tulane.edu/pharmwiki/doku.php/glucocorticoid_pharmacology 11.2.2020

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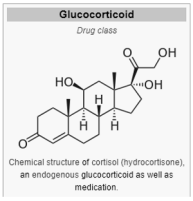
Glucocorticoids, cont.

- Caution should be exercised in patients with the following conditions
  - –Diabetes
  - –Psychiatric history
  - –Heart failure
  - –Adrenal suppression
    - Taper needed when therapy exceeds 10 to 14 days
  - –Immunocompromised



https://en.wikipedia.org/wiki/Glucocorticoid accessed 4.5.2021

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Topical glucocorticoids for pain?

- Skin serves as a physical and a chemical barrier to medication absorption
  - –Stratum corneum contains alternating lipid and hydrophilic regions

Glucocorticoid	Prednisone	Methylprednisolone	Dexamethasone	Hydrocortisone
Molecular weight (Daltons)	360	370	390	362

  - –Keratinocytes possess cytochrome P450 enzymes which metabolize substances that make it into the dermis
- Generally newer delivery techniques (iontophoresis, etc.) for glucocorticoid delivery into the skin are needed to penetrate into deep tissue, joint or bone
- Over the counter creams and ointments will not penetrate sufficiently to reach deep tissue, joint or bone

Blood Purif 38; 154-7: 2014

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Neuropathic Pain

- Anticonvulsants
  - –Gabapentin
  - –Pregabalin
  - –Carbamazepine
  - –Oxcarbazepine
- Antidepressants
  - ❖TCAs
  - –SNRIs
- Local anesthetics

* Off label indication

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Anticonvulsants

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Anticonvulsants Gabapentin & Pregabalin

- Structurally related to GABA but it does not bind to $GABA_A$ or $GABA_B$ receptors or influence the degradation or uptake of GABA
- Binds to the α_2-δ subunit of voltage-gated Ca^{2+} channels in CNS and peripheral nerves
- Reduces the Ca^{2+} -dependent release of pro-nociceptive neurotransmitters, possibly by modulation of Ca^{2+} channel function
- Pregabalin may also interact with descending noradrenergic and serotonergic pathways in the brainstem

J Clin Psychiatry. 2007 Mar;68(3):483-4
GABA = gamma aminobutyric acid
CNS = central nervous system

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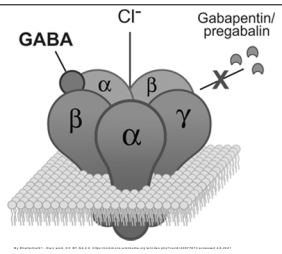
Mechanism of action α_2-δ ligands



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Anticonvulsants

Gabapentin
- ❖Neuropathic pain-100 mg to 300 mg by mouth up to 3 times daily
  - –Increase dose based on response and tolerability to a maximum total daily dose of 3.6 grams
- ▪ Renal dose adjustment required
- ▪ NO hepatic adjustment needed
  - –Gabapentin is not metabolized by hepatic enzymes

Gabapentin Enacarbil
- ▪ Post herpetic neuralgia- 600 mg once daily in the AM for three days then increase to 600 mg in the AM
  - –Doses over 1.2 grams not associated with additional benefit and may lead to increase in side effects
- ▪ Renal dose adjustment required
- ▪ NO hepatic adjustment needed

https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6961 accessed 4.6.2021
*Off label indication for neuropathic pain EXCEPT post herpetic neuralgia

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Anticonvulsants (cont'd)

Pregabalin
- ▪ Initial dose: 25 mg to 150 mg by mouth once or up to three times a day
  - –May increase in increments of 25 mg to 150 mg weekly based on response and tolerability
  - –Usual dose between 300 mg and 600 mg in two to three divided doses
  - –Individual doses up to 600 mg have been evaluated with no significant additional benefit
- ▪ Renal dose adjustment required
- ▪ NO hepatic adjustment needed
  - –Pregabalin is minimally metabolized by hepatic enzymes

https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/152621 accessed 4.6.2021

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Anticonvulsants: Alternative Options

- ▪ Carbamazepine
  - –Indication for trigeminal or glossopharyngeal neuralgia
    - •Initial dosing at 200 mg to 400 mg daily increasing by 200 mg per day as needed
    - •Maintenance dose between 600 mg and 800 mg daily
    - •Maximum of 1200 mg total daily dose
  - –Obtaining baseline CBC and LFTs
    - •Consider periodic monitoring of CBC and LFTs thereafter
    - •Genetic testing for HLA-B*1502 allele

https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/patch_f/6525 accessed 4.6.2021

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Anticonvulsants: Alternative Options

- Oxcarbazepine
  - ❖Trigeminal neuralgia
  - –Initial dose between 300 mg to 600 mg in twice daily divided doses
    - •Maximum dose of 2400 mg total daily dose
  - –Patients allergic to carbamazepine should also avoid oxcarbazepine
    - •25% allergic cross-reactivity
  - –Better tolerability compared to carbamazepine
  - –Caution in severe renal impairment

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https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/patch_f/6525 accessed 4.6.2021
*Off label indication

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Antiepileptic agents and neuropathic pain

- Cochran review for antiepileptic agents in the management of neuropathic pain
  - –Pregabalin/ Gabapentin
  - –Lacosamide
  - –Topiramate
  - –Lamotrigine
  - –Carbamazepine/ oxcarbazepine
  - –Valproic acid
  - –Clonazepam
  - –Phenytoin
  - –Levetiracetam
- Painful diabetic neuropathy
  - –Gabapentin, lacosamide and pregabalin had evidence of efficacy
- Post herpetic neuralgia
  - –Gabapentin and pregabalin had evidence of efficacy
- Central neuropathic pain
  - –Pregabalin had evidence of efficacy
- Trigeminal neuralgia and HIV related neuropathy had not enough data to review

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Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD010567

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Neurocognitive dysfunction

- Many antiepileptic medications have an impact on neurocognitive ability
  1. Attention and concentration
  2. Memory
  3. Motor speed
  4. Visuospatial processing
- Confounders include
  - –Baseline cognition
  - –Formal, objective neuropsychological function testing
  - –Timing and onset of cognitive disturbances
  - –Other substances that may impact cognition
    - •Alcohol use, anticholinergics, etc.
  - –Side effects of the medication
  - –Medication serum concentrations, dosing, side effects or drug interactions

J Clin Psych 62; s14: 27-33 2001

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Antidepressants

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Tricyclic Antidepressants (TCAs)

Secondary amines
- ❖Nortriptyline 10 mg at bedtime
- ❖Desipramine 25 mg at bedtime

Tertiary amines
- ❖Amitriptyline 10-25 mg at bedtime
  - Use with caution in BPH, glaucoma, cardiac disease, and those at risk for suicide

*Off label indication
Lancet Neurol 2015; 162–73
BPH = benign prostatic hyperplasia

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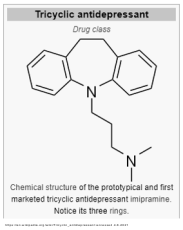
TCAs and neurological side effects

- Muscarinic receptor antagonists
  - –Blurred vision, constipation, dry mouth, urine retention, constipation, tachycardia, confusion, delirium, increased ocular pressure
  - –Secondary amines < tertiary amines
- Antihistaminergic effects
  - –Sedation and delirium
  - –Maprotiline, amitriptyline, doxepin, and trimipramine



Chemical structure of the prototypical and first marketed tricyclic antidepressant imipramine. Notice its three rings.

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TCAs and cardiovascular side effects

- Orthostatic/postural hypotension
  - Alpha adrenergic blockade (even at low doses)
- Slowed cardiac conduction, tachycardia, ventricular fibrillation, heart block, and ventricular premature complexes (similar to Class Ia AA)
- Sudden cardiac death (unclear association with QTc prolongation)
  - Avoid doses > 100 mg per day of amitriptyline equivalents
- Avoid in those with cardiovascular disease or established conduction abnormalities
- Baseline ECG recommended by some in those > 40 years of age
  > 50 years of age based on APA Depression Guidelines
- Routine ECG monitoring not recommended unless CV symptoms arise

https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf accessed 4.6.2021

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TCAs and behavioral health side effects

- Abrupt discontinuation
  - Withdrawal symptoms (GI, malaise, chills, rhinitis, and myalgias)
  - Rebound depression
- **Increased suicidality** vs overdose toxicity
  - Targeting children, adolescents, young adults (18-24 years of age)
  - Cardiac (QTc) and anticholinergic toxicity at doses as little as 10 x prescribed

1. Labbate, LA, Fava, M, Rosenbaum, JF, et al. Drugs for the treatment of depression. In: Handbook of Psychiatric Drug Therapy, 6th ed, Lippincott Williams & Wilkins, Philadelphia 2010.
2. Dallal A, et al. *J Clin Psychopharmacology.* 1998;18:343-344.
3. Frye MA, et al. *Am J Psychiatry.* 2009;166:164-172.
4. Van Schayen JCI, et al. *Arch Gen Psychiatry.* 1979;36:560-565.

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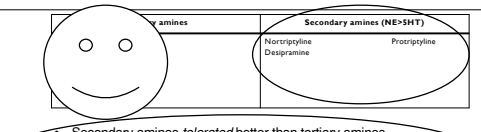
TCA review



- Secondary amines *tolerated* better than tertiary amines
- Secondary amines *equally* effective in pain as tertiary amines
- Therapeutic drug monitoring of questionable utility

Table adapted from Lexi-Drugs Online. www.uptodate.com accessed 4.6.2021

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Serotonin and norepinephrine reuptake inhibitors (SNRI)

Duloxetine

- Chronic musculoskeletal pain with an inadequate response to NSAIDs or non-pharmacological agents
  - Low back and non-radicular: 30 mg daily and may increase to a max dose of 60 mg daily
  - Osteoarthritis: 30 mg daily and may increase to a max dose of 120 mg daily
- Neuropathic pain from diabetes: 30 mg daily and may increase to a max of 120 mg daily
- Avoid use with severe renal or hepatic impairment
- Discontinuing therapy should be done over 2 to 4 weeks
- Serious adverse effects
  - **Suicidal ideations** in patients major depressive disorder or other psychiatric conditions

https://fco.factsandcomparisons.com/fco/action/doc/retrieve/docid/patch_f/6798 accessed 4.9.2021

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SNRI, cont.

Venlafaxine

- Neuropathic pain associated with diabetes: 37.5 mg to 75 mg ER by mouth once a day and increase dose by up to 75 mg ER daily every week to a target dose of 225 mg ER once daily
  - An adequate duration to determine effect is generally between 4 to 6 weeks
- Renal and hepatic dosing adjustments necessary
- Discontinuing therapy should be done over 2 to 4 weeks
- Serious adverse effects
  - **Suicidal ideations** in patients major depressive disorder or other psychiatric conditions

* Off label indication
https://fco.factsandcomparisons.com/fco/action/doc/retrieve/docid/patch_f/7862 accessed 4.9.2021

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SNRI, cont.

- Milnacipran
  - Fibromyalgia
    - 12.5 mg PO once daily on Day 1
    - 12.5 mg PO BID on Days 2-3
    - 25 mg PO BID daily on Days 4-7
    - 50 mg PO BID thereafter
  - Target dose: 50 mg PO BID (100 mg/day)
  - Maximum: 100 mg PO BID (200 mg/day)
  - Dose adjustment required in renal impairment

https://fco.factsandcomparisons.com/fco/action/doc/retrieve/docid/patch_f/518 accessed 4.9.2021

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Serotonin Syndrome

- Mental status changes
  - Anxiety, agitated delirium, restlessness, disorientation
- Autonomic hyperactivity
  - Diaphoresis, tachycardia, hyperthermia, hypertension, vomiting, and diarrhea
- Neuromuscular changes
  - Tremor, muscle rigidity, myoclonus, hyperreflexia, and clonus
- Severity may range from benign to lethal
- Solely a clinical diagnosis
- Patient and caregiver education paramount

N Engl J Med. 2005;352(11):1112-1120
Br J Gen Pract. 1999;49(448):871-874

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Hunter Criteria for serotonin syndrome

- Serotonergic agent PLUS one of the following:
  - Spontaneous clonus
  - Inducible clonus and agitation or diaphoresis
  - Ocular clonus and agitation or diaphoresis
  - Tremor and hyperreflexia
  - Hypertonia
  - Temp above 38°C (100.4°F)
- Although clinical dx, consider CBC, BMP, INR, CPK, LFTs, UA, chest X-ray, head CT, to rule out differentials

QJM. 2003;96(9):635-642

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SNRI Bleeding Risk

- Blocked serotonin uptake into platelet
- De-amplification of platelet aggregation
- Data suggest
  - Minimal risk of upper GI bleed as monotherapy
  - Increased risk of upper GI bleed in combination with NSAIDs
  - Acid suppression therapy decreases risk

Arch Intern Med. 2003;163(1):59-64
Aliment Pharmacol Ther. 2008;27(1):31-40
Transl Res. 2008;151(3):168-172
Arch Gen Psychiatry. 2008;65(7):795-803

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Local Anesthetics

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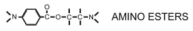
Local anesthetics

- Amino-Amide agents
  - Lidocaine
  - Mepivacaine
  - Bupivacaine/ Levobupivacaine
  - Prilocaine
  - Ropivacaine
- Amino-Ester agents
  - Tetracaine
  - Chloroprocaine
  - Procaine
  - Benzocaine
  - Cocaine

Chemical structure of local anesthetics

Aromatic lipophilic portion - Intermediate chain - Amine hydrophilic portion



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Lidocaine

- May be used topically or by injection
- Topical patch available in 0.5% to 5%
- 5% patch applied directly to area of post-herpetic neuralgia
  - –No more than 3 patches concurrently
  - –12 hours on, 12 hours off
- Trigger point injections
  - –Lidocaine or procaine
  - –Caution in patients on anticoagulants and local anesthetic allergy history

Cochrane Database Syst Rev 2007;18:CD004846
American Family Physician 2002 65 (4): 653-61

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Antispasticity and Antispasmodic Agents

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Muscle Spasms

- Baclofen
- Tizanidine

- Other agents
  - –Cyclobenzaprine, the TCA ?

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Muscle Relaxants

- Antispasticity agents
  - –Spasticity: upper motor neuron disorder characterized by muscle hypertonicity and involuntary jerks
  - –Multiple sclerosis, cerebral palsy and spinal cord injury
    - •Tizanidine
    - •Baclofen
    - •Diazepam

J Pain Symptom Manage. 2004;28:140-75
Cochrane Database Syst Rev. 2003;(2):CD004252

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Muscle Relaxants (cont'd)

Baclofen

- GABA analogue
  - –Selective GABA-B receptor agonist
- Muscle relaxant and analgesic (reduced substance P)
- Spasticity: 5 mg up to three times daily and increase every three days as needed
  - –max dose: 80 mg/day (120 mg has been used in rare cases)
- Adjustment needed for renal impairment

https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/patch_f/6414 accessed 4.9.2021

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Muscle Relaxants (cont'd)

Tizanidine

- Alpha$_2$ agonist
  - –Reduces adrenergic outflow and increase presynaptic inhibition of motor neurons
- Spasticity: 2 mg at bedtime and increase as tolerated to a maximum of 36 mg total daily dose
  - –Discontinuation should be done gradually to reduce rebound symptoms
- Dose reduction for patients with severe renal dysfunction
- No reduction needed for hepatic impairment

https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/patch_f/7778 accessed 4.9.2021

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Muscle Relaxants (cont'd)

- Antispasmodics
  - –Primarily used for treatment of musculoskeletal conditions, such as back pain, sciatica, herniated discs, spinal stenosis, myofascial pain

  - –Cyclobenzaprine
  - –Metaxalone
  - –Methocarbamol
  - –Orphenadrine citrate
  - –Carisoprodol

Indicated for **acute** use in low back pain!

- Less than 4 weeks use to treat an episode
- May be effective for an acute-on-chronic pain episode

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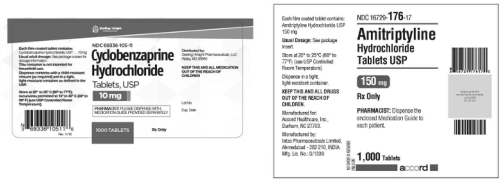
Cyclobenzaprine, or Something Else?



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Conclusions

- Adjuvant and coanalgesics require judicious monitoring for safe use
- Extensive patient education regarding potential adverse effects is paramount
- Comorbid disease processes and concurrent medications may obscure adverse effects

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