Pharmacological Treatment of Substance Use and Addiction Disorders

Introduction to the topic from a clinical perspective

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General Outlines

Target Election and Specific Strategy

- Detoxification without maintenance
- Detoxification with maintenance
- Craving
- Co-occurring mental disorder
- Rehabilitation
General Outlines

Substances

- Narcotics (natural-occurring – opiates and synthetics opioids)
- Stimulants (natural-occurring and synthetics)
- Hallucinogens (natural-occurring and synthetics)
- Depressants (natural-occurring and synthetics)

*Substances are classified according to their maximal effects.*
Clinical aspects of adjunctive medications

Strategies

- Mono or multiple targets?
  For example: treating craving from the beginning

- Co-occurring (*psychiatric*) and co-morbid (*physical*) disorders?
  For example: treating diagnosed concomitant disorders from the beginning

- Sequential treatment?
  For example: treating primarily narcotic withdrawal and secondarily psychiatric disorder

- Simultaneous treatment?
  For example: treating primarily narcotic withdrawal and secondarily cocaine use disorder

- Abrupt or gradual tapering?
  Depending on setting, available medications and clinical approach
Clinical aspects of adjunctive medications

Cocaine

- Salt: alkaline substance that could combine with acids and transform in a salt
  - Like cocaine hydrochloride.
- Free base: smoking base frees Methylecgonidinewhich is a pyrolysis product formed when crack cocaine is smoked, making this substance a useful biomarker to specifically test for use of crack, as opposed to powder cocaine which does not form methylecgonidine as a metabolite.
- Crack: it is a lower purity form of free-base made with a solution of baking soda or ammonia. Smoking or vaporizing crack leads to the crack-like sound due to popping up impurities.

Medications

- Acetylcysteine: management of paracetamol (acetaminophen) overdose (food supplement)
- Baclofen
- Bupropion
- Vanoxerine: is a piperazinederivative which is a potent and selective DRI that binds to the target site on the DAT ~ 500 times more strongly than cocaine, but concomitantly inhibits the release of dopamine. This combined effect only slightly elevates dopamine levels, giving vanoxerine only mild stimulant effects.
- Vigabatrin
- Vaccination that would cure cocaine addiction: Molecules like cocaine are small so the immune system tends to ignore them. It should be attached a hapten that is either a bit of the drug itself or a synthetic version of it — to a larger protein that acts as a platform. The last part of the vaccine is an adjuvant, a chemical cocktail that attracts the immune system’s notice, effectively tricking it into making antibodies against a substance it usually wouldn’t see.
- SSRIs, anti-epileptics, Dopamine agonists.....

Clinical aspects of adjunctive medications

Clinical approaches

Medications may treat more than one target

- α2A receptors agonists
- Benzodiazepines
- Antidepressants
- Anti-seizures
- Non opioid analgesics
- Opioid antagonists
- First and second generation antipsychotics
Clinical aspects of adjunctive medications

**α2a receptor agonists**

- Clonidine: Normopressan (0.15 mg) and Clonnirit (25 mcg)

- Clonidine has specificity towards the presynaptic α2A receptors in the vasomotor centre in the brainstem. This binding decreases presynaptic calcium levels, and inhibits the release of norepinephrine (NE).

- Clonidine treats high blood pressure by stimulating α2A receptors in the brain, which decreases cardiac output and peripheral vascular resistance, lowering blood pressure. The net effect is a decrease in sympathetic tone.

- The antihypertensive effect of clonidine is due to agonist effect on the I1-receptor (imidazoline receptor), which mediates the sympatho-inhibitory actions of imidazolines to lower blood pressure.

**Mark S. Gold, D. Eugene Redmond JR, Herbert D. Kleber (1978):** CLONIDINE BLOCKS ACUTE OPIATE-WITHDRAWAL SYMPTOMS. The Lancet: 8090 (2) 599-602
Clinical aspects of adjunctive medications

**α2 receptor agonists**

- Lofexidine: BritLofex (0.2 mg)

- Lofexidine is an alpha 2A adrenergic receptor agonist, historically used as a short-acting anti-hypertensive, but more commonly used to alleviate physical symptoms of narcotic withdrawal. These receptors close a negative feedback loop that begins with descending sympathetic nerves from the brain that control the production of norepinephrine in the adrenal medulla. By fooling the brain into believing that catecholamine levels are higher than they really are, lofexidine causes the brain to reduce its signals to the adrenal medulla, which in turn lowers catecholamine production and blood levels. The result is a lowered heart rate and blood pressure. This central action is responsible for the suppression of opiate withdrawal symptoms.

Clinical aspects of adjunctive medications

Benzodiazepines receptors agonists

- BZs bind to GABA A complex enhancing the effect of the neurotransmitter GABA which results in sedative, hypnotic, anticonvulsant, muscle relaxant and amnesic action.
- After stabilization is achieved BZ should be gradually and wisely reduced.
- Every BZs appear to be effective in controlling in-progress narcotic withdrawal syndrome.
- Diazepam (available and easy to manage), lorazepam, oxazepam, clorazepate and alprazolam.
### Clinical aspects of adjunctive medications

**Approximate Therapeutic Equivalent Doses of Benzodiazepines**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>1</td>
</tr>
<tr>
<td>Alprazolam XR</td>
<td>1</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>25</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>15</td>
</tr>
<tr>
<td>Diazepam</td>
<td>10</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>30</td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.25</td>
</tr>
<tr>
<td>Estazolam</td>
<td>1</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>30</td>
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<tr>
<td>Prazepam</td>
<td>80</td>
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<tr>
<td>Temazepam</td>
<td>20</td>
</tr>
<tr>
<td>Quazepam</td>
<td>15</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>10</td>
</tr>
</tbody>
</table>
Clinical aspects of adjunctive medications
Benzodiazepines

Generic name
- Alprazolam
- Alprazolam XR
- Chlordiazepoxide (Nirvaxal)
- Clonazepam
- Clorazepate (Tranxal)
- Diazepam
- Lorazepam
- Oxazepam
- Flunitrazepam
- Nitrazepam
- Clobazam (Frisium 10 mg)
- Bromazepam (Lenitin 3 mg)
- Brotizolam
## Clinical aspects of adjunctive medications Insomnia

### Mechanism of action of sleeping pills

<table>
<thead>
<tr>
<th>Drug</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem (Stilnox and Zodorm 10 mg)</td>
<td>They work on the benzodiazepine site on the GABA(_A) receptor complex similarly to BZ.</td>
</tr>
<tr>
<td>Zopiclone (Nocturno and Imovane 7.5 mg)</td>
<td>Some but not all of the non-BZ are selective for the (\alpha_1) subunit on GABA(_A) receptors, which is responsible for inducing sleep and may therefore have a cleaner side-effect profile than the older benzodiazepines.</td>
</tr>
<tr>
<td></td>
<td>Zopiclone like benzodiazepine drugs bind unselectively to (\alpha_1), (\alpha_2), (\alpha_3) and (\alpha_5) GABA(_A) complex.</td>
</tr>
<tr>
<td></td>
<td>Zolpidem is more selective and is highly selective for the (\alpha_1) subunit, thus giving them an advantage over benzodiazepines in terms of sleep architecture and a reduction in side-effects.</td>
</tr>
<tr>
<td></td>
<td>The non-BZ drugs have milder activity at the (\alpha_1) subunit on GABA(_A) receptors compared to most benzodiazepines, rendering them ineffective for moderately severe to severe insomnia.</td>
</tr>
<tr>
<td></td>
<td>Z-drugs and BZ decrease time to fall asleep, increase total sleep time (depending on half-life) and enhance GABA function through allosteric modulation (regulation of an enzyme or other protein by binding an effector molecule at the protein's allosteric site that is, a site other than the protein's active site).</td>
</tr>
<tr>
<td></td>
<td>These drugs appear to cause both psychological dependence and physical dependence, though less than traditional benzodiazepines and can also cause the same memory and cognitive disturbances along with morning sedation.</td>
</tr>
</tbody>
</table>

- Trazodone and mirtazapine increase total sleep time and blocks 5HT receptors.
- Olanzapine and quetiapine decrease awakening.
- Ramelteon decreases time to fall asleep. Is a melatonin agonist.
- Promethazine increases total sleep time and decreases awakening. Blocks H1 receptors.
Melatonin and melatonin agonists

- The hormone melatonin is effective in several types of insomnia. Melatonin has demonstrated effectiveness in inducing sleep and regulating the sleep/waking cycle. One particular benefit of melatonin is that it can treat insomnia without altering the sleep pattern, which is altered by many prescription sleeping tablets. Another benefit is it does not impair performance related skills.
- Melatonin OTC: 2 and 4 mg.

- Melatonin (Circadin prolonged-release 2 mg)
  - Circadin is indicated as monotherapy for the short-term treatment of primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over.
  - The recommended dose is 2 mg once daily, 1-2 hours before bedtime and after food. This dosage may be continued for up to thirteen weeks.
  - Caution should be exercised in patients on fluvoxamine, which increases melatonin levels (by 17-fold higher AUC and a 12-fold higher serum $C_{max}$) by inhibiting its metabolism by hepatic cytochrome P450 (CYP) isozymes CYP1A2 and CYP2C19.
  - Caution should be exercised in patients on contraceptive or hormone replacement therapy and cimetidine a CYP2D inhibitor, which increases plasma melatonin levels, by inhibiting its metabolism
  - CYP1A2 inducers such as carbamazepine and rifampicin may give rise to reduced plasma concentrations of melatonin.
  - Alcohol should not be taken with Circadin, because it reduces the effectiveness of Circadin on sleep.
  - Circadin may enhance the sedative properties of benzodiazepines and nonbenzodiazepine hypnotics, such as zolpidem and zopiclone.
Clinical aspects of adjunctive medications insomnia

- **Antihistamines**
  - Promethazine (Phenergan 25 mg).
  - Diphenhydramine (Nytol 25 mg).
  - Doxylamine (Sleep Aid, Unisom 25 mg).
  - Doxepin (Gillex 25 mg) is the most antihistaminic antidepressant.
Some antidepressants such as amitriptyline, doxepin, mirtazapine, and trazodone can often have a very strong sedative effect and are prescribed off label to treat insomnia.

The major drawback of these drugs is that they have properties that can lead to many side-effects:

- Amitriptyline and doxepin both have antihistaminergic, anticholinergic, and antiadrenergic properties, which contribute to their side-effect profile.
- Mirtazapines side-effects are primarily antihistaminergic. It is known to decrease sleep latency, promoting sleep efficiency and increasing the total amount of sleeping time in patients suffering from both depression and insomnia.
- Trazadone is a potent $\alpha_1$-adrenergic blockade (~3-fold lower relative to 5-HT$_{2A}$). It may cause some side effects like orthostatic hypotension and sedation.

Some also alter sleep architecture. As with benzodiazepines, the use of antidepressants in the treatment of insomnia can lead to discontinuation & withdrawal syndrome which may induce rebound insomnia.

Mianserin is an antagonist at the H$_1$, 5-HT$_{1D}$, 5-HT$_{2M}$, 5-HT$_{2C}$, 5-HT$_{3}$, 5-HT$_{6}$, $\alpha_1$-adrenergic, and $\alpha_2$-adrenergic receptors, and also acts as a norepinephrine reuptake inhibitor (NRI) via blockade of the norepinephrine transporter (NET). As a high affinity H$_1$ receptor antagonist, mianserin has strong antihistamine effects; however, it has negligible affinity for the muscarinic acetylcholine receptors, and therefore lacks any anticholinergic properties.
Clinical aspects of adjunctive medications

Mechanism of action of antidepressant medications
(Representative non exhaustive list)

- Antidepressants, in addition to their anxiety/depression beneficial profile, are thought to affect pain transmission in the spinal cord by inhibiting the reuptake of NE and SE, both of which influence descending pain pathways.
- H1 – receptor affinity associated with sedation may be correlated with the analgesic affect.

- TCAs
  - Secondary amines
    - Nortriptyline
    - Desipramine
  - Tertiary amines
    - Amitriptyline (also has an analgesic affect in patients with acute pain)
    - Doxepin (strong anti-histaminic effect)
    - Imipramine
    - Quaternary amines
    - Maprotiline (strongly non recommended)
- Mianserin
- Trazodone
- Mirtazapine
- Milnacepran
- Venlafaxine
- Duloxetine
- SSRIs
Antiepileptic medications which may have mood stabilizing and anti-craving properties, act at several sites that may be relevant to pain, but the precise mechanism of their effect remains unclear.

These agents are thought to limit neuronal excitation and enhance inhibition.

Relevant sites of action include voltage-gated ion channels (sodium and calcium channels), ligand-gated ion channels, excitatory receptors for glutamate and NMDA (N-methyl-D-aspartate) and the inhibitory receptor for GABA and glycine.
Clinical aspects of adjunctive medications
Management of craving and substance seeking behavior

Antiepileptic medications

- The main rationales for using anticonvulsants in substance-abuse patients are their lack of addiction potential, evidence support a role of kindling mechanisms in withdrawal syndromes and their efficacy in co-occurring psychiatric disorders.

- Carbamazepine (Tegretol, Teril 200 – 400 mg)
- Valproate (Depalept 200 – 500 mg) and valproic acid (Valporal 200 mg)
- Gabapentine (Gabapentin, Neurontin 300-400 mg)
- Vigabatrine (Sabrilan 500 mg)
- Topiramate (Topamax 25-50 mg)
- Lamotrigine (Lamictal and generics)
- Oxcarbazepine (Trileptin 300 – 600 mg)
- Pregabalin (Lyrica 25, 50, 75, 100, 150, 200 and 300 mg)
- Tiagabine: tiagabine acts as a GABA-uptake inhibitor from synaptic cleft into neurons and glia
Pregabalin

- Like gabapentin, pregabalin binds to the α2δ (alpha2delta) subunit of the voltage-dependent calcium channel in the central nervous system.
- Pregabalin decreases the release of neurotransmitters such as glutamate, noradrenaline, and substance P.
- Pregabalin increases neuronal GABA levels by producing a dose-dependent increase in glutamic acid decarboxylase activity.
- Glutamic acid decarboxylase (GAD) is the enzyme that converts the excitatory neurotransmitter glutamate into the inhibitory GABA in a single step.
- For this reason, pregabalin greatly potentiates benzodiazepines, barbiturates & other depressants.
# Clinical aspects of adjunctive medications

## Non opioid analgesics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Aspirin 500 Bayer, Abitren, Dicoplast, Voltaren</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Optalgin, Etopan, Artofen, Advil, Nurofen</td>
</tr>
<tr>
<td>Dipyron</td>
<td>Ketonal, Oruvail, Profenid</td>
</tr>
<tr>
<td>Etodolac</td>
<td>Topadol</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Naproxi, Naxyn, Narocin</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Tramadex, Trabar, Tramal</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Lyrica</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Tramadol</td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td></td>
</tr>
</tbody>
</table>
Clinical aspects of adjunctive medications
Management of craving and substance seeking behaviour

Opioid antagonists

- Naltrexone is a full opioid competitive receptor antagonist used primarily in the management of alcohol dependence and opioid dependence.
- It is marketed in generic form as its hydrochloride salt, naltrexone hydrochloride, and marketed under the trade name Revia.
- In some countries including the United States, an extended-release formulation is marketed under the trade name Vivitrol. Also in the US, Methylnatrexone Bromide, a closely related drug, is marketed as Relistor, for the treatment of opioid-medications related constipation.
- Naltrexone, and its active metabolite 6-β-naltrexol, are competitive antagonists at μ- and κ-opioid receptors, and to a lesser extent at δ-opioid receptors.
- Mechanism of action:
  - Primarily, naltrexone blocks opioid receptors, impeding narcotic access to these receptors thus producing extinction response.
  - Secondarily, naltrexone modulates dopaminergic mesolimbic pathway which may reduce craving.

Clinical aspects of adjunctive medications
Management of craving and substance seeking behaviour

**Opioid antagonists**

- Naltrexone may be particularly efficacious in individuals with genetic susceptibility.
- Preliminary evidence suggests that individuals with the Asp variant of the OPRM1 gene are less likely to experience relapse when receiving naltrexone, but further study is needed to confirm the finding.
- Patients who were heterozygous for the Asp-40 allele were almost six times more likely to have a favorable outcome with naltrexone treatment than those who did not carry this allele.

- **Anton RF, O’Malley SS, Ciraulo DA, et al.**


- **Oslin DW, Berrettini W, Kranzler HR, et al.**
Clinical aspects of adjunctive medications
Management of craving and substance seeking behaviour

**Opioid antagonists**

- Nalmefene is a full opioid competitive receptor antagonist used primarily in the management of alcohol and opioid dependence. It has been also used in Gambling and Shopping Disorder.
- It is marketed under the trade name Selincro 18 mg.
- **Mechanism of action:**
  - Primarily, Nalmefene blocks opioid receptors, impeding narcotic access to these receptors thus producing extinction response.
  - Secondarily, Nalmefene modulates dopaminergic mesolimbic pathway which may reduce craving.

- Alcohol stimulates release of Dopamine in Ventral Tegmental Area projecting to Nucleus Accumbens. Dopamine release produces inhibition of GABA interneurons which releases B-endorphins acting on Mu receptors. Naltrexone & Nalmefene block opioid receptors.

- Advantages of Nalmefene over naltrexone may include:
  - Longer half-life: 11 + - 5 Hours
  - Greater oral bioavailability
  - No observed dose-dependent liver toxicity
Acamprosate

GABA agonist and glutamate inhibitor
Suppresses delayed sub-acute cravings by suppressing glutamatergic excitation associated with alcohol withdrawal
Most research trial evidence is for maintaining abstinence (cumulative abstinence duration)
Use soon after detoxification to encourage abstinence
Few contraindications, not metabolized in liver
Dose - 333 mg tablets, 2 tablets three times a day (weight > 60kg)
Clinical aspects of adjunctive medications

Disulfiram (Antabuse)

Used for over 50 years, but not as much recently
Difficult to conduct blinded clinical trials – variable results in published studies, but many positive
Blocks oxidation of alcohol – acetaldehyde accumulates – flushing reaction ensues
An abstinence model medication
Does not diminish cravings
Requires close supervision and patient compliance over one year or more
Avoid in heart disease, pregnancy, psychosis, liver disease
Dose - 250 mg daily maintenance dose (125-500mg range)
Should not be used for aversive conditioning – time lag and intensity of reaction is unpredictable
**Baclofen**

Anti-spasticity agent GABA(b) receptor agonist blocks dopamine release in central reward areas (ventral striatum and prefrontal cortex)

Preliminary controlled trials and open-label studies showed improvements in cumulative abstinence duration and reduced alcohol cravings

A recent controlled trial was not supportive

Can be used in patients with liver disease

Dose – 10mg three times daily

Dose response effect observed – may need 20mg three times daily
Clinical aspects of adjunctive medications

**Atypical antipsychotics**
- Quetiapine
- Olanzapine
- Amylsulpiride.

Side effects should be taken into account. They do not lead to significant tolerance.

**Typical antipsychotics**
- Chlorpromazine
- Levomepromazine
- Thiorizadine

Side effects should be taken into account. They may lead to significant tolerance.
Clinical aspects of adjunctive medications
Management of craving and substance seeking behaviour

- Simultaneous or sequential treatment
- Dual (multiple) disorder treatment
- Co-occurring psychiatric disorder
- Co-morbid physical disease

- Craving and SSB have been interpreted as an acquired ruminative or obsessive compulsive – like behavior
- Treatment should take into account mechanism of action or/and other clinical features of prescribed medications
Clinical aspects of adjunctive medications
Management of craving and substance seeking behaviour

Treatment target: dopamine reward system

- Directly affect dopamine reward system
  - Block reuptake
  - Inhibit metabolism
  - Increase synthesis

- Indirectly modulate dopamine reward system
  - Serotonin
  - Glutamate
  - GABA
  - Endocannabinoids (CB1 receptor)
  - Endogenous opioids (μ-opioid receptor)
Clinical aspects of adjunctive medications
Management of craving and substance seeking behaviour

**Medications to Increase Dopamine Activity**

- Anti-depressants (block reuptake)
  - Bupropion, venlafaxine, mirtazapine
- Inhibitors of dopamine metabolism
  - Monoamine oxidase B inhibitors: selegiline (Jumex)
- Precursors of synthesis: tyrosine, L-DOPA
Clinical aspects of adjunctive medications
Management of craving and substance seeking behaviour

**Serotonin (5-HT) Modulation of Dopamine Reward System**

- Reuptake (transporter) blockers (SSRI’s)
  - Fluoxetine, sertraline, paroxetine
- Receptor agonists
  - Buspirone (5-HT\textsubscript{1A})
- Precursors of synthesis (amino acids)
  - L-tryptophan
- Receptor antagonist
  - Ondansetron (5-HT\textsubscript{3}) (Zofran)
Clinical aspects of adjunctive medications
Management of craving and substance seeking behaviour

Glutamate Modulation of Dopamine Reward System

✓ Block glutamate receptor
  – Memantine-NMDA type (*Ebixa-* Alzheimer treatment)
  – Topiramate-AMPA/kainate type (*Topamax*)

✓ ↓ Presynaptic reuptake
  – Lamotrigine (*Lamictal*)

✓ ↑ Synthesis
  – *N*-acetylcysteine (*Mucolysin*- mucolitic agent)
Clinical aspects of adjunctive medications
Management of craving and substance seeking behaviour

### GABA Modulation of Dopamine Reward System

- **↑ GABA receptor activity** (mechanism ?)
  - Levetiracetam (Keppra)
  - Topiramate

- **GABA<sub>B</sub> receptor agonist**
  - Baclofen (Baclosal 10, 25 mg)

- **Block GABA reuptake**
  - Tiagabine

- **↓ GABA metabolism** (inhibit GABA transaminase)
  - Vigabatrin (γ-vinyl-GABA)

- **↑ GABA action** (mechanism ?)
  - Gabapentin
  - Valproate
Clinical aspects of adjunctive medications
Management of craving and substance seeking behaviour

**Other Modulation of Dopamine Reward System**

- **Endocannabinoids**
  - Block CB1 receptor
  - Rimonabant – Acomplia (Sanofi-Aventis)
  - Taranabant (Merck)
  - SLV319 (Solvay)
  - CP-945598 (Pfizer)

- **Endogenous opioids**
  - Block \( \mu \)-opioid receptor
  - Naltrexone
  - Partial \( \mu \) agonist & \( \kappa \) antagonist
  - Buprenorphine
Basic topics in Pain Disorders

- **Acute pain** is a protective response to injury or inflammation of somatic or visceral tissue.
- Acute pain most often is nociceptive.
- Nociceptive pain usually is treated with anti-inflammatory or analgesic medications.

- **Chronic pain** may be a maladaptive response.
- Chronic pain may be nociceptive or neuropathic (resulting from neuronal maintenance of pain either peripherally or in the CNS).
- Chronic neuropathic pain typically is treated with medications that influence neurotransmitters (antidepressants and antiepileptics agents) or with opioids in refractory pain.
Basic topics s in Pain disorders

Classification of Pain

- **Nociceptive**: represents the normal response to noxious insult or injury of tissues such as skin, muscles, visceral organs, joints, tendons, or bones.
  - Examples include:
    - Somatic: musculoskeletal (joint pain, myofascial pain), cutaneous; often well localized
    - Visceral: hollow organs and smooth muscle; usually referred
- **Neuropathic**: pain initiated or caused by a primary lesion or disease in the somatosensory nervous system.
  - Sensory abnormalities range from deficits perceived as numbness to hypersensitivity (hyperalgesia or allodynia), and to paresthesias such as tingling.
  - Examples include, but are not limited to, diabetic neuropathy, postherpetic neuralgia, spinal cord injury pain, phantom limb (post-amputation) pain, and post-stroke central pain.
- **Inflammatory**: a result of activation and sensitization of the nociceptive pain pathway by a variety of mediators released at a site of tissue inflammation.
  - The mediators that have been implicated as key players are proinflammatory cytokines such IL-1-alpha, IL-1-beta, IL-6 and TNF-alpha, chemokines, reactive oxygen species, vasoactive amines, lipids, ATP, acid, and other factors released by infiltrating leukocytes, vascular endothelial cells, or tissue resident mast cells
  - Examples include appendicitis, rheumatoid arthritis, inflammatory bowel disease, and herpes zoster.
- **Clinical Implications of classification**: Pathological processes never occur in isolation and consequently more than one mechanism may be present and more than one type of pain may be detected in a single patient; for example, it is known that inflammatory mechanisms are involved in neuropathic pain.
- There are well-recognized pain disorders that are not easily classifiable. Our understanding of their underlying mechanisms is still rudimentary though specific therapies for those disorders are well known; they include cancer pain, migraine and other primary headaches and wide-spread pain of the fibromyalgia type.
- **Pain Intensity**: Can be broadly categorized as: mild, moderate and severe. It is common to use a numeric scale to rate pain intensity where 0 = no pain and 10 is the worst pain imaginable:
  - Mild: <4/10
  - Moderate: 5/10 to 6/10
  - Severe: >7/10
- **Time course**: Pain duration
  - Acute pain: pain of less than 3 to 6 months duration
  - Chronic pain: pain lasting for more than 3-6 months, or persisting beyond the course of an acute disease, or after tissue healing is complete.
  - Acute-on-chronic pain: acute pain flare superimposed on underlying chronic pain.
Basic topics in Pain disorders

MECHANISM OF PAIN PERCEPTION

- Microscopic structures called pain receptors are present throughout our body.
- When a painful event happens, the damaged area releases chemicals, which excite the C-type nerve fiber nociceptors.
- They transmit the pain signal to the spinal cord area called the dorsal horn.
- There, the pain signal intensity is filtered, modified and sent to the brain through a bundle of nerve fibers called the spinothalamic tract.
- The brain area called the somatosensory cortex controls the sensory aspect of the pain and certain areas of hippocampus and amygdala control the emotional component of pain.
- In addition, the brain also releases the body’s own painkillers called endorphins and enkephalins which act in the injured area to decrease the intensity of the pain.
Basic topics in Pain disorders

Mechanism of chronic pain

- In chronic pain, pain signals continue to be generated in the injured area long after it has healed.
- It results in permanent pain processing changes in the brain and spinal cord giving rise to chronic pain.
- The peripheral nerve fibers convey pain signal to spinal cord using a glutamate. It binds to AMPA receptors present in the dorsal horn of spinal cord thereby transmitting the pain signal to spinal cord and brain.
- In chronic pain, repetitive signals from the periphery produces excess glutamate at NMDA receptors.
- NMDA receptor activation results in hyper sensitization of brain and release of a pain-amplifying chemical called Substance P.
- At this stage, the acute pain changes into chronic pain.
Tobacco use disorders

Smoking cessation
Pharmacological treatment

First line pharmacological treatments:
- Nicotine replacement therapy (NRT): patch, gum, inhaler, lozenge, spray and sublingual tablet
- NDRIs: bupropion (Zyban)
- Nicotine receptor agonist: varenicline (Champix)

Second line pharmacological treatments:
- Clonidine (Normopressan 0.25 mg, Clonnirit 75 mcg)
  (Normopressan = 6 Clonnirit)
- Nortriptyline (Nortylin 10 and 25 mg)

Third line pharmacological treatment - augmentation strategies:
- NRT + bupropion
- NRT + nortryptilin
- NRT + antidepressants

Nicotine replacement therapy (NRT) is the use of various forms of nicotine delivery methods intended to replace nicotine obtained from smoking or other tobacco usage.

Types
- Nicotine patch – Nicotinell TTS, Niquitin CQ (nicotine 7, 14 and 21 mg)
- Nicotine gum – Nicorette - Nicotinell (nicotine 2 and 4 mg)
- Nicotine inhaler – Nicorette inhaler (nicotine 10 mg)
- Nicotine lozenge – Nicotinell (nicotine 1 mg)
- Nicotine spray
- Nicotine sublingual tablet

Transdermal nicotine patches deliver doses of the addictive chemical nicotine, thus reducing the unpleasant effects of nicotine withdrawal. These patches can give smaller and smaller doses of nicotine, slowly reducing dependence upon nicotine and thus tobacco. This method becomes most effective when combined with other medication and psychological support.
Tobacco use disorders

Bupropion

- Bupropion – Wellbutrin (PPC 2 hours), Wellbutrin<sub>SR</sub> (PPC 3 hours), Wellbutrin<sub>XR</sub> (PPC 5 hours), Zyban), previously known as amfebutamone, is an atypical antidepressant (NDRI) and smoking cessation aid. It acts as a NE and DA reuptake inhibitor, as well as α3β4-nicotinic non competitive receptor antagonist. Bupropion belongs to the chemical class of aminoketones and is similar in structure to stimulants cathinone and diethylpropion, and to phenethylamines in general.
- Bupropion lowers seizure threshold and its potential to cause seizures was widely publicized. However, at the recommended dose the risk of seizures is comparable to that observed for other antidepressants.
- Bupropion is an effective antidepressant on its own but it is particularly popular as an add-on medication in the cases of incomplete response to the first-line selective serotonin reuptake inhibitor (SSRI) antidepressant.
- Bupropion does not cause weight gain or sexual dysfunction.


PPC: peak plasma concentration
Tobacco use disorders

Bupropion
Smoking cessation

- Bupropion reduces the severity of nicotine cravings and withdrawal symptoms.
- Bupropion treatment course lasts for seven to twelve weeks, with the patient halting tobacco use about ten days into the course.
- The efficacy of bupropion is similar to that of nicotine replacement therapy.
- The combination of bupropion and nicotine appears not to further increase the cessation rate.
- Bupropion slows weight gain that often occurs in the first weeks after smoke quitting.

Tobacco use disorders

Bupropion
Method of administration

- Zyban should be used in accordance with smoking cessation guidelines.
- Prescribers should assess the patient's motivation to quit.
- Smoking cessation therapies are more likely to succeed in those patients whom are motivated to quit and have motivational support.
- Zyban tablets should be swallowed whole. The tablets should not be crushed or chewed as this may lead to an increased risk of adverse effects including seizures.
- Zyban can be taken with or without food.
- Patients should be treated for 7-9 weeks.
- Although discontinuation reactions are not expected with Zyban, a tapering-off period may be considered.
- If at seven weeks no effect is seen, treatment should be discontinued.
Tobacco use disorders

Bupropion
Common side effects

- Headache
- Insomnia
- Dry mouth
- Weight loss
- Tremor
- Nausea
- Constipation
- Hypertension
- Seizures – incidence of 0.05 percent at 300 mg SR
Tobacco use disorders

**Varenicline**

- **Varenicline** *(Champix 0.5 and 1 mg)* is a nicotinic receptor partial agonist. In this respect, it is different from the nicotinic antagonist (bupropion), and nicotine replacement therapies (NRTs) like nicotine patches and gum.

- As a partial agonist, it both reduces cravings for and decreases the pleasurable effects of cigarettes and other tobacco products, and through these mechanisms it can assist some patients to quit smoking.

- Varenicline is an alternative to NRTs and agonist medication.

- The FDA has approved its use for twelve weeks. If smoking cessation has been achieved it may be continued for another twelve weeks.

Tobacco use disorders

Varenicline
Mechanism of action

- Varenicline is a partial agonist of the α4β2 subtype of the nicotinic acetylcholine receptor.
- It also acts on α3β4 and weakly on α3β2 and α6-containing receptors.
- A full agonism was displayed on α7-receptors.
- Acting as an agonist varenicline binds to, and partially stimulates, the receptor without creating a full nicotine effect on the release of dopamine.

Tobacco use disorders

Varenicline
Method of administration

- The patient should set a date to stop smoking. CHAMPIX dosing should start 1-2 weeks before this date.
- Patients who cannot tolerate adverse effects of CHAMPIX may have the dose lowered temporarily or permanently to 0.5 mg twice daily.
- CHAMPIX tablets should be swallowed whole with water. CHAMPIX can be taken with or without food.
- Patients should be treated with CHAMPIX for 12 weeks.
- For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHAMPIX at 1 mg twice daily may be considered.
- No data are available on the efficacy of an additional 12 weeks course of treatment for patients who do not succeed in stopping smoking during initial therapy or who relapse after treatment.
- In smoking cessation therapy, risk for relapse to smoking is elevated in the period immediately following the end of treatment. In patients with a high risk of relapse, dose tapering may be considered.
Tobacco use disorders

Varenicline

Side effects

- Nausea
- Headache, difficulty sleeping, and abnormal dreams
- Change in taste, vomiting, abdominal pain, flatulence and constipation
- Suicidal ideation and occasional suicidal behavior
- Erratic behavior and mood swings

Muchas gracias!

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