Adjunctive pharmacological treatment in the management of narcotic withdrawal syndrome and related pain

Introduction

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Issues to be presented

- Short review of opioid receptors and their ligands
- Full and partial opioid agonists
- Opioid antagonists
- Clinical aspects of narcotic withdrawal syndrome
- Clinical aspects of adjunctive medications
- Management of craving and substance seeking behaviour

Clinical aspects of adjunctive medications

Clinical approaches

- Adjunctive mono treatment
- Adjunctive add-on treatment

Medications may treat more than one target

- α2A receptors agonists
- Benzodiazepines
- Antidepressants
- Antiepileptics
- Non opioid analgesics
- Opioid antagonists
- First and second generation antipsychotics

Clonidine

α2A receptor agonists

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

- Clonidine has specificity towards the presynaptic α2A receptors in the vasomotor center 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 agonism on the I1-receptor (imidazoline receptor), which mediates the sympa-tho-inhibitory actions of imidazolines to lower blood pressure.

Clonidine

Clonidine has been firstly investigated and prescribed as an antihypertensive drug in the 1950s. Later was used for the treatment of neuropathic pain, narcotic and alcohol detoxification, sleep hyperhidrosis. Clonidine was used in pet veterinary anesthesia. Clonidine is off-label used to treat GAD, panic disorder, manic episodes and other conditions. It is becoming a more accepted treatment for insomnia, migraine and menopausal hot flushes-related symptoms. Clonidine can be used in the treatment of Tourette syndrome and disorder. This medication may also be used to ease withdrawal symptoms associated with the long-term use of narcotics, alcohol and nicotine.

Clonidine is regularly prescribed off-label to help alleviate narcotic and alcohol withdrawal symptoms. It is mainly used to combat the sympathetic nervous system response to narcotic (opiate and opiate) withdrawal, namely tachycardia and hypertension. In the initial days of withdrawals, it helps take away the sweating, hot/cold flushes, and general restlessness. The sedation effect is also useful although its side effects can include insomnia, thus exacerbating an already common feature of opiate withdrawal. Clonidine is also a mild sedative and can be used as pre-medication before surgery or procedures. Its epidural use for pain during heart attack, postoperative and intractable pain has also been studied extensively.

Clonidine has also been found to prolong the effects of analgesia when used together with a local anesthetic such as ropivacaine or levobupivacaine.

Side effects

- Clonidine may cause lightheadedness, dry mouth, dizziness and constipation. Clonidine may also cause hypotension.
- Clonidine also has peripheral alpha agonist activity which can lead to hypertension especially when it is injected intravenously.
- This blood pressure increase is sometimes witnessed in cases of overdose in children.
- As the clonidine is eliminated by the body, the peripheral effects wear off and its basic hypotensive effect becomes evident.
- Both the hypertensive and hypotensive effects can be harmful.

Extended-release clonidine

Kapvay (clonidine hydrochloride) extended-release tablets are indicated for the treatment of attention deficit/hyperactivity disorder (ADHD).

When combined with a stimulant medication Kapvay may help ADHD patients as part of a comprehensive ADHD treatment plan.

Clonidine extended-release: 0.1mg and 0.2mg

Children's dosing for KAPVAY

<6yrs: not recommended. Swallow whole. Titrate by response. Initially 0.1mg at bedtime for 1 week, then 0.1mg in the morning and 0.2mg at bedtime for 1 week, then 0.2mg twice daily. Withdraw gradually; reduce by 0.1mg/day at 3–7 day intervals. Renal dysfunction: may need reduced dose.

Warnings/Precautions for KAPVAY


Interactions for KAPVAY

- Potentiates alcohol, other CNS depressants, antihypertensives. Hypotensive effect may be antagonized by tricyclic antidepressants. Additive AV block, bradycardia with drugs that affect cardiac conduction (eg, digitals, calcium channel blockers, β-blockers). Avoid other forms of clonidine. May need to adjust dose of concurrent stimulant medication.

Adverse Reactions for KAPVAY

- Somnolence, fatigue, upper respiratory tract infection, irritability, sore throat, insomnia, nightmares, emotional disorder, constipation, nasal congestion, fever, dry mouth, ear pain.
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 antihypertensive, 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.


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Short review of opioid receptors and their ligands

Four main types of opioid receptors

- There are four principal classes of opioid receptors, \( \mu \) - *morphine* (mu), \( \kappa \) - *ketocyclazocine* (kappa), \( \delta \) - *vas deference* (delta) and NOP1.

- There have been reported up to seventeen opioid receptors including the \( \epsilon \), \( \iota \), \( \lambda \), and \( \zeta \) (Epsilon, Iota, Lambda and Zeta) receptors.

- The pharmacodynamic response to an opioid depends on the receptor to which it binds, its affinity for that receptor, and whether the opioid is an agonist or an antagonist.


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Short review of opioid receptors and their ligands

**Pharmacodynamic response**

- **Receptor affinity**
  - How tightly the drug binds to the receptor (docking)

- **Drug dissociation**
  - How fast the drug leaves the receptor (undocking)

- **Intrinsic activity**
  - How much the drug stimulates the receptor

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Short review of opioid receptors and their ligands

**Bentley compounds**

- Bentley compounds are a class of semi-synthetic opioids that were first synthesized from thebaine (minor constituent of opium that is chemically similar to both morphine and codeine, but has stimulatory rather than depressant effects) by K. W. Bentley.

- The compounds include: oxycodone, oxymorphone, nalbuphine (is a semi-synthetic opioid agonist-antagonist analgesic- Nubain), naloxone, naltrexone, buprenorphine and etorphine.

- They represent the first series of more potent \( \mu \)-opioid agonists, with some compounds (etorphine) in the series being over 1000 times the potency of morphine as an analgesic.

- The latter was then used in veterinarian medicine as a narcotic for elephants and other large animals.

- Etorphine - *Immobilon* is often used to immobilize elephants and other large mammals.

- Etorphine is available legally only for veterinary use and is strictly governed by law.

- Diprenorphine – *Reviron* is an opioid receptor antagonist that can be administered in proportion to the amount of etorphine used (1.3 times) to reverse its effects.

- Veterinary-strength etorphine is fatal to humans. For this reason the package as supplied to vets always includes the human antidote as well as Etorphine.

Fentanyl

- Fentanyl (TP Durogesic, Fenta) was first synthesized by Dr. Paul Janssen in 1960.
- Fentanyl is a potent synthetic narcotic analgesic with a rapid onset and short duration of action. It is a strong agonist at the μ-opioid receptors. Historically it has been used to treat pain and is commonly used in pre-procedures as a pain reliever as well as an anesthetic in combination with a benzodiazepine.
- Fentanyl is approximately 100 times more potent than morphine, with 100 micrograms of fentanyl approximately equivalent to 10 mg of morphine and 75 mg of pethidine (meperidine) in analgesic activity.
- Following this, many other fentanyl analogues were developed and introduced into the medical practice, including sufentanil, alfentanil, remifentanil (Ultiva Inj.), and lofentanil.


Short review of opioid receptors and their ligands

Opioid Receptors

Subtypes with known clinical significance

- μ (mu)
- δ (delta)
- κ (kappa)
- NOP1 (ORL-1)

They are involved in the functioning of distinct physiological processes


μ (mu)-opioid receptor

β-endorphins are endogenous ligands which exert their effects primarily through the μ-opioid receptor.

μ1: analgesia and physical dependence
μ2: respiratory depression, euphoria, miosis, reduced GI motility and physical dependence
μ3: unknown

δ (delta)-opioid receptor

Leu-enkephalins, Met-enkephalins and deltorphins are endogenous ligands which exert their effects primarily through the delta-opioid receptor

δ (δ 1 and δ 2) receptor mediates:

Analgesia
Antidepressant effects
Physical dependence
Many delta agonists may also cause seizures at high doses, although not all delta agonists produce this effect

Endorphins are two novel endogenous opioid peptides. Endomorphin-1 and endomorphin-2 are tetrapeptides with the highest known affinity and specificity for the μ opioid receptor.

**Short review of opioid receptors and their ligands**

**K (kappa)-opioid receptor**

Dynorphins are endogenous ligands which exert their effects primarily through the κ-opioid receptor.

Kappa receptor (K1, K2 and K3) mediates:
- Analgesia
- Sedation
- Miosis
- Inhibition of ADH (anti-diuretic hormone) release
- Dysphoria

Salvinorin A12 is a potent and selective κ-opioid receptor agonist.

The κ-opioid receptor also mediates the action of the hallucinogenic side effects of opioids such as pentazocine (Talwin NX).

**Short review of opioid receptors and their ligands**

**Nociceptin opioid receptor (NOP1- O like-R-1)**

- Nociceptin is the endogenous ligand for the nociceptin receptor (NOP1).
- Nociceptin is an opioid-related peptide, but it does not act at the classic opioid receptors and its actions are not antagonized by the opioid antagonist naloxone.
- Nociceptin is a potent anti-analgesic.
- There is some evidence that nociceptin may be involved in the phenomenon of opioid-induced hyperalgesia. Individuals taking opioids might develop an increasing sensitivity to noxious stimuli (hyperalgesia) even evolving a painful response to previously non-noxious stimuli (allodynia).

NOP1 receptor mediates:
- Anxiety
- Depression
- Development of tolerance to mu agonists
- Nociception
- Food intake
- Memory processes
- Cardiovascular and renal functions
- Spontaneous locomotor activity
- Gastrointestinal motility

**Epsilon – opioid receptor**

Epsilon receptor is stimulated by the endogenous opioid peptide beta-endorphin, which induces the release of Met-enkephalin, which, in turn, acts on spinal delta 2-opioid receptors to produce antinociception.

Role of protein kinase C (PKC) in agonist-induced mu-opioid receptor down-regulation: II. Activation and involvement of the alpha, epsilon, and zeta isoforms of PKC: Kramer HK and Simon EJ


**Full and partial opioid agonists**

Full agonists – bind to the µ receptor producing an almost linear increase in physiological effect:
- Opium, morphine, codeine, heroin, methadone

Partial agonists – bind to the µ receptor but have a ‘ceiling’ effect on receptor activation:
- Buprenorphine: The agonist effects of buprenorphine (32 mg) increase linearly with increasing doses until it reaches a plateau and no longer continue to develop respiratory depression with further doses, meaning “ceiling effect”.
- A compound that has an affinity for & stimulates physiological activity at the same cell receptors as opioid agonists but that produces only a partial (i.e., submaximal) bodily response.

Mu partial opioid agonist
NOP-1 agonist
Kappa antagonist
Delta antagonists

The antinociceptive effect of buprenorphine mediated primarily by the mu opioid receptor is attenuated by the ability of the drug to activate the NOP-1 receptor.

Partial agonism at the mu opioid receptor and antagonism at the kappa or delta opioid receptor (“anti-physical dependence”) have been considered as possible underlying mechanisms for the ceiling effect.
Full and partial opioid agonists
(Representative not exhaustive list)

- Oxycodone: Percocet (5 and 10 mg), Oxycodin 10, 20, 40, 80 mg, Oxycod Syrup
- Oxicodone/Nx: Targin 10mg/5mg 20mg/10mg
- Propoxyphene: Proxol, Rogaan, Algolysin
- Morphine: MCR, MIR, Morphex
- Hydromorphone: Palladone Inject and SR: 4, 8 and 24 mg, Jurnista: 4, 8, 16 and 32 mg
- Fentanyl: Duragesic 25, 50, 75, 100 mcg/Hs
- Codeine: Cod-Acamol, Codical, Rekod
- Buphrenorphine: Nopan (0.2 mg), BuTrans (5, 20, 20 mg), Subutex (2 and 8 mg)
- Buphrenorphine/Nx: Suboxone: 2mg/0.5 mg, 8mg/2mg
- Methadone: Adolan
- Tramadol: Tramadex: 100mg, 200mg, 300mg
- Opium: Opium pelvis 10%

Tramadol hydrochloride is a centrally acting synthetic opioid analgesic used in treating severe pain. The drug has a wide range of applications, including treatment for restless legs syndrome and fibromyalgia. Tramadol possesses weak agonist actions at the μ-opioid receptor, releases serotonin, and inhibits the reuptake of norepinephrine. While its action is not like that of other opioids, Tramadol is a synthetic analogue of the phanethrene alkaloid codeine. It is converted to O-desmethyltramadol, a significantly more potent μ-opioid agonist. The euphoria and respiratory depression of opioids are mainly caused by the μ1 and μ2 receptors. The addictive nature of tramadol, as well as other opioids, is due to these effects, but tramadol’s serotonergic and noradrenergic effects may contribute to possible dependence as well. The opioid agonistic effect of tramadol and its major metabolite(s) are almost exclusively mediated by the substance’s action at the μ-opioid receptor. This characteristic distinguishes tramadol from many other substances (including morphine) of the opioid drug class, which generally do not possess tramadol’s degree of subtype selectivity.

Opioids antagonists

Antagonists – bind to the μ receptor but do not produce a biological response and are able to block agonist effects: naloxone, naltrexone, nalmefene

Nalmefene (Revex) is an opioid receptor antagonist and used primarily in the management of alcohol dependence, and also has been investigated for the treatment of other addictions such as pathological gambling and shopping. All of the opioid antagonists used in medicine are non-selective, either blocking all three opioid receptors, or blocking the mu-opioid receptor but activating the kappa receptor.

Highly selective antagonists:
- Cyprodime is a selective mu opioid receptor antagonist
- Naltrindole is a selective delta opioid receptor antagonist
- Norbinaltorphimine is a selective kappa opioid receptor antagonist

In the absence of any ligand, a neutral antagonist has no activity in the presence of an agonist or inverse agonist but can block the activity of either.

Opioids antagonists

Naloxone

Inverse agonist is an agent that binds to the same receptor as an agonist but induces a pharmacological response opposite to that agonist. A prerequisite for an inverse agonist response is that the receptor must have a constitutive also known as intrinsic or basal level activity in the absence of any ligand. An agonist increases the activity of a receptor above its basal level while an inverse agonist decreases the activity below the basal level. A neutral antagonist has no activity in the absence of an agonist or inverse agonist but can block the activity of either.
Understanding Opioid Effects

Positive effect = addictive potential

Agonist + partial agonist = additive potential

Full agonist - morphine/heroin hydromorphone

Super agonist - fentanyl

Partial agonist - buprenorphine

Antagonist + agonist/partial agonist

Antagonist - naltrexone

Clinical aspects of narcotic withdrawal syndrome

Dependence diagnosis is strictly defined by DSM-IV-TR (2000) and ICD 10 (1992) criteria.

Continuous unsupervised (legal and illegal) use might lead to tolerance. Tolerance elevates plateau.

Doses beyond plateau lead to overdose.

Reduction or cessation of used narcotic substances might lead to withdrawal syndrome:

- Yawning
- Mydriasis
- Sweating, lacrimation, rhinorrhea and sialorrhea
- Tachycardia, tachypnea and hypertension
- Pilo-erection
- Diarrhea
- Nausea and vomiting
- Muscle, bones and articulation aches
- Cramps
- Insomnia
- Cold and hot flashes
- Fever

Only narcotics can almost instantaneously stop the progress of withdrawal syndrome

DSM V (2013)

The work group has proposed to tentatively re-title the category Addiction and Related Disorders. This change is meant to help differentiate between the compulsive drug-seeking behaviour that defines addiction and the tolerance and withdrawal that can be seen even with appropriate use of prescribed drugs. It has been confusing to physicians and has resulted in patients with normal tolerance and withdrawal being labeled as “addicts.” This has also resulted in patients suffering from severe pain having adequate doses of opioids withheld because of fear of producing “addiction.”

The diagnostic category will include both substance use disorders and non-substance addictions. Gambling disorder has been moved into this category and there are other addiction-like behavioural disorders such as “Internet addiction” that will be considered as potential additions to this category as research data accumulate.

Alcohol use disorder is proposed to be diagnosed as an independent category.

There will not be two different categories of substance abuse and dependence.

Accordingly, the word “dependence” is now limited to physiological dependence, which is a normal response to repeated doses of many medications including beta-blockers, antidepressants, opioids, anti-anxiety agents and other drugs.

The presence of tolerance and withdrawal symptoms are not counted as symptoms to be counted for the diagnosis of substance use disorder when occurring in the context of appropriate medical treatment with prescribed medications.

Discontinuation vs withdrawal
Clinical aspects of narcotic withdrawal syndrome

The euphoric effect

- Primary
- Short term exposure
- Dopamine related
- May lead to sensitization
- Reverse tolerance
- Absence of use is associated to desire
- Chronic course
- Desire to use after withdrawal
- Craving related
- Slowly reversible or irreversible

The analgesic effect

- Secondary
- Long term exposure
- Endogenous opioids related
- May lead to dependence
- Physical tolerance
- More use produces less effect
- Acute course
- Desire to use during withdrawal
- Non craving related
- Reversible syndrome

Clinical aspects of narcotic withdrawal syndrome

1. Short (acute) withdrawal: short acting substances (opiates and opioids)
   Heroin (diacetylmorphine or diamorphine or morphine diacetate) is an opioid analgesic synthesized from morphine, a derivative of the opium poppy.

2. Prolonged (sub-acute) withdrawal: long acting substances (opioids)

3. Protracted withdrawal (residual or post-withdrawal syndrome - PWS):
   - Fatigue, irritability, anxiety and depressive features
   - Sleep disturbances (insomnia)
   - Dysphoria (feeling down or emotionally blunted)
   - Hyperalgesia
   - Craving
   - Impairment in executive functions: is an umbrella term for cognitive processes such as planning, working memory, attention, problem solving, verbal reasoning, inhibition, mental flexibility, multi-tasking, initiation and monitoring of actions

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

- Abrupt or gradual tapering?
  - Depending on setting, available medications and clinical approach

Clinical approaches

- Adjunctive mono treatment
- Adjunctive add-on treatment

Medications may treat more than one target

- α2A receptors agonists
- Benzodiazepines
- Antidepressants
- Antiepileptics
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The result is a lowered heart rate and blood pressure.

This central action is responsible for the suppression of opiate withdrawal symptoms.


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.


A nonopioid procedure for outpatient opioid detoxification.

Ockert DM, Volpicelli JR, Baier AR Jr, Coons EE, Fingesten A. Parallax Center, Inc., New York, NY, USA. ockert@parallaxcenter.com

OBJECTIVES:

To describe a new protocol using nonopioid medications (clonidine, lorazepam, trazodone, and a stimulant) to successfully complete outpatient opioid detoxification, (2) to determine clinical and demographic characteristics of patients who successfully complete an outpatient opioid detoxification, and (3) to determine the safety and clinical utility of the use of this combination of medications in the treatment of opioid withdrawal.

METHODS:

In a posthoc evaluation study in a New York State-licensed outpatient detoxification unit of a substance abuse treatment facility, 223 heroin-dependent adults presenting for treatment were provided outpatient opioid detoxification. In the course of the opioid detoxification protocol of the facility, patients received clonidine, lorazepam, trazodone, and either a stimulant (methylphenidate or modafinil) or no stimulant, in combination on a daily basis. At each daily visit, signs and symptoms were assessed, and medications and dosing instructions were given for the following 24 hours. On completion of the detoxification protocol, patients were induced with oral naltrexone.

RESULTS:

Overall, 61.0% (136) of the patients in this study successfully completed outpatient detoxification protocol and were induced with naltrexone. Pretreatment demographic variables that predicted successful treatment included full-time employment, family support, private medical insurance, and referral by an employee assistance program. About 77% of patients with good prognosis successfully completed outpatient detoxification treatment. The addition of a stimulant improved patient retention and reduced the incidence of hypotension.

CONCLUSIONS:

The outpatient detoxification of opioid-dependent patients without the use of opioids has traditionally led to such high drop out rates that most clinical programs do not even consider the option. This makes it difficult to induce patients with opioid antagonists such as oral naltrexone or sustained release naltrexone. We describe a protocol here that leads to excellent rates of successful detoxification. This non-opioid detoxification methodology permits induction of naltrexone without the delay experienced in opioid-based titrations, and it thus facilitates the use of opioid antagonists for sustained abstinence, enhanced aftercare treatment outcomes, and opioid-free recovery.
Clinical aspects of adjunctive medications

### Benzodiazepines

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<td>Zolpidem</td>
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### Clinical aspects of adjunctive medications

#### Insomnia

**Mechanism of action of sleeping pills**

- **Zolpidem** (Stilnox and Zodorm 10 mg)
- **Zopiclone** (Nocturno and Imovane 7.5 mg)

They work on the benzodiazepine site on the GABA<sub>A</sub> receptor complex similarly to BZ. Some but not all of the non-BZ are selective for the α<sub>1</sub> subunit on GABA<sub>A</sub> receptors, which is responsible for inducing sleep and may therefore have a cleaner side-effect profile than the older benzodiazepines.

- Zopiclone: like benzodiazepine drugs bind unselectively to α<sub>1</sub>, α<sub>2</sub>, α<sub>3</sub>, and α<sub>5</sub> GABA<sub>A</sub> complex.
- Zolpidem: is more selective and is highly selective for the α<sub>1</sub> subunit, thus giving them an advantage over benzodiazepines in terms of sleep architecture and a reduction in side-effects.

The non-BZ drugs have milder activity at the α<sub>1</sub> subunit on GABA<sub>A</sub> receptors compared to most benzodiazepines, rendering them ineffective for moderately severe to severe insomnia.

2-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).

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.

- 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.
- Alcohol should not be taken with Zopiclone, because it reduces the effectiveness of Zopiclone on sleep.
- Zolpidem (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<sub>max</sub>) 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 CYP2D6 inhibitor, which increases plasma melatonin levels, by inhibiting its metabolism CYP1A2 inducers such as carbamazepine and rifampin 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.

Baclofen

Baclofen is a derivative of gamma-aminobutyric acid (GABA).
It is primarily used to treat spasticity and is under investigation for the treatment of alcoholism (withdrawal and craving) and opioid dependence.
It is an agonist for the GABA-B receptors.
Its beneficial effects in spasticity result from actions at spinal and supraspinal sites.
Baclofen can also be used to treat hiccups, and has been shown to prevent rises in body temperature induced by the drug MDMA in rats.

**Antidepressants**

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.
- 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 α1-adrenergic blockade (~3-fold lower relative to 5-HT2A). 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 H1, 5-HT2A, 5-HT2C, 5-HT3, 5-HT4, α1, α2-adrenergic, and 5-HT7 receptors, and also acts as a norepinephrine reuptake inhibitor (NRI) via blockade of the norepinephrine transporter (NET). As a high affinity H1 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 effect.
- 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)
- Secondary amines
  - Mianserin
  - Trazodone
  - Mirtazapine
- Tertiary amines
  - Milnacipran
  - Venlafaxine
  - Duloxetine
- SSRIs

Drugs Aging (1996) 8:459-76
Bryson HM, Wilde MI.

Abstract
Amitriptyline is a tricyclic antidepressant agent which also has analgesic properties. Whether its analgesic effects are linked to its mood-altering activity or attributable to a discrete pharmacological action (or a combination of both) is unknown. Clinical trials demonstrate that oral amitriptyline achieves at least a good or moderate response in up to two-thirds of patients with post-herpetic neuralgia and three-quarters of patients with painful diabetic neuropathy, neurogenic pain syndromes that are often unresponsive to narcotic analgesics. Amitriptyline has also demonstrated efficacy in heterogeneous groups of patients with chronic non-malignant pain. Other possible areas of use for amitriptyline are in patients with fibromyalgia or as an adjuvant for uncontrolled cancer pain, although evidence for the latter application is limited. Adverse events resulting from the antimuscarinic activity of amitriptyline (primarily dry mouth and sedation) are commonly reported, even at the low dosages used for the control of pain. Low starting doses and careful dosage titration may help to minimise these effects. Orthostatic hypotension and tachycardia, sometimes associated with tricyclic antidepressant agents, may also pose a problem in the elderly. In summary, amitriptyline has a valuable place in the treatment of chronic pain conditions that affect the elderly provided that the drug is used judiciously to minimise adverse effects. Importantly, amitriptyline remains the best studied of the antidepressant agents in post-herpetic neuralgia and diabetic neuropathy and is an important and effective treatment option in these syndromes.

Clinical aspects of adjunctive medications

Mechanism of action of antiepileptic medications

- 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 behaviour

**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 (Depakote 200 – 100 mg) and valproic acid (Valporal 200 mg)
- Gabapentin (Neurontin 300-400 mg)
- Vagabatrine (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 (alpha 2 delta) subunit of the voltage-dependent calcium channel in the central nervous system.
- It 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.

**Some references of antiepileptic treatment**

Clinical aspects of adjunctive medications

Non opioid analgesics

- Aspirin
- Aspirin 500 Bayer
- Diclofenac
- Diclofenac Dicotan, Dicoplast, Voltaren
- Dipyron
- Optalgin
- Etodolac
- Etopan
- Ibuprofen
- Artopen, Advil, Nurofen
- Ketoprofen
- Ketonal, Oruvail, Profenid
- Ketorolac
- Topadol
- Naproxen
- Naproxin, Naxyn, Narocin
- Tramadol
- Tramadex, Trabar, Tramal
- Lyrica
- Gabapentin
- Pregabalin
- Gabapentin

Opioid antagonists

- Naltrexone is a full opioid competitive receptor antagonist used primarily in the management of alcohol dependence. It is marketed in generic form as its hydrochloride salt, naltrexone hydrochloride, and marketed under the trade name Vivitrol. Also in the US, Methylnaltrexone 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.
  - Secondly, naltrexone modulates dopaminergic mesolimbic pathway which may reduce craving.

Clinical aspects of adjunctive medications

Typical and Atypical antipsychotics

Typical antipsychotics:
- Chlorpromazine
- Levomepromazine
- Thioridazine

Atypical antipsychotics:
- Quetiapine
- Olanzapine
- Amisulpiride

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

Reduction of opioid-withdrawal symptoms with quetiapine.
Pinkofsky HB, Hahn AM, Campbell FA, Rueda J, Dyley D, Douaihy A.
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Abstract
OBJECTIVE: To determine the utility of quetiapine in a population undergoing ambulatory detoxification from opioids.
METHOD: Mediations utilized in our outpatient clinic for opioid withdrawal were evaluated for quality-assurance purposes. The treatment regimen generally included clonidine, hydroxyzine (Vistaril), trazodone, diphenoxylate/atropine (an opioid agonist/atropine combination used for the treatment of diarrhea), and sometimes chlordiazepoxide. Patients were also initially given eight 25-mg tablets of quetiapine and instructed to take 1 or 2 tablets every 4 hours as needed for symptoms of withdrawal or craving (with a maximum daily dose of 200 mg). Data were based on patient evaluations from June 2003 to June 2004.
RESULTS: 41% of all patients (N = 213) successfully completed the detoxification phase of the program (i.e., completed at least 5 days of abstinence). A medication questionnaire was instituted for quality-assurance purposes after some apparent initial success with quetiapine. A retrospective analysis of these data revealed that, of the 107 patients evaluated for medication response, 79 reported that quetiapine helped reduce craving for opioids, 52 reported that quetiapine helped reduce their anxiety, 24 reported a reduction in somatic pain, 22 reported that quetiapine helped alleviate insomnia, and 14 reported an improved appetite. Four individuals did not feel quetiapine had any benefit, and another 7 were unable to tolerate quetiapine because of side effects. The quetiapine dose used ranged from 25 to 600 mg/day (mean +/- SD dose = 206 +/- 122 mg/day).
CONCLUSIONS: Quetiapine use during opioid cessation was found to help abate symptoms of opioid withdrawal in our patient population and was generally well tolerated.
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

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)

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

Serotonin (5-HT) Modulation of Dopamine Reward System
- Reuptake (transporter) blockers (SSRI’s)
  - Fluoxetine, sertraline, paroxetine
- Receptor agonists
  - Buspirone (5-HT$_{1A}$)
- Precursors of synthesis (amino acids)
  - L-tryptophan
- Receptor antagonist
  - Ondansetron (5-HT$_{3}$) (Zofran)
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 (Mucolyxin- mucolitic agent)

GABA Modulation of Dopamine Reward System

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

Other Modulation of Dopamine Reward System

- Endocannabinoids
  - Block CB1 receptor
    - Rimonabant – Acomplia (Sanofi-Aventis)
    - Taranabant (Merck)
    - SLV319 (Solvay)
    - CP-945598 (Pfizer)
- Endogenous opioids
  - Block µ-opioid receptor
    - Naltrexone
  - Partial µ agonist & κ 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 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: muscularkeletal (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 parasthesias 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 as IL-1-alpha, IL-1-beta, IL-6 and TNF-alpha, chemokines, reactive oxygen species, vasodynamic amines, nitric oxide, 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: Painful processes never occur in isolation and consequently more than one mechanism may be present and more than one type of pain may be identified in a single patient; for example, it is known that inflammatory mechanisms are involved in neuropathic pain.

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 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.

Muchas gracias!