Pharmacological management of substance misuse

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Overview of presentation

• Goals of treatment
• Pharmacotherapies for:
  – opioid dependence
  – alcohol misuse and dependence
  – psychostimulant misuse – cocaine, amphetamine
• Pharmacological approaches to treatment of comorbid substance misuse and mental illness
Goals of treatment

- Management of a withdrawal syndrome
- Short, medium or long-term substitute pharmacotherapy with harm reduction goals
- Maintenance of abstinence
- Prevention of complications
Papaver somniferum
Opioid receptors

mu - for morphine, Greek God of dreams, Morpheus
analgesia
euphoria
respiratory depression
positive reinforcement

kappa - analgesia
dysphoria
depersonalisation

delta - ? analgesia
? addiction
Effects of opiates

• Analgesia
• Drowsiness,
• Euphoria,
• Pupillary constriction
• Respiratory depression,
• Nausea, vomiting, decreased gastric motility, constipation,
• decrease BP & pulse rate
Opioid Withdrawal Syndrome

- craving, anxiety
  - yawning, sweating, runny nose, lacrimation
    - dilated pupils, gooseflesh, hot & cold flushes, abdominal cramps, aches & pains, sleep disturbance, nausea
      - increased BP, pulse & temperature
        - vomiting and diarrhoea

↑ time since last used opioids
Opioid Withdrawal Syndrome 2

From heroin
- onset around 6 hours after last dose
- peak 36 - 72 hours

From methadone
- onset around 24-36 hours after last dose
- peak 4 - 6 days
Neurobiological basis of opiate withdrawal: the locus coeruleus

A. Baseline: Normal production of NA

B. Acute opioid inhibition of converting enzyme: Abnormally low production of NA

C. Chronic opioid inhibition leads to increased converting enzyme activity: Normal NA level

D. Discontinuing opioid leads to increased cyclic AMP due to loss of inhibition: NA excessively high
Pharmacotherapy for opiate dependence

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<th>Use</th>
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<td>full agonist</td>
<td>detox, maintenance</td>
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Pharmacology of methadone

• methadone oral solution 1mg/1ml
• mu receptor agonist
• high oral bioavailability
• half-life with repeated dosing around 24 hours
• peak plasma concentration around 4 hours after oral dose
• hepatic metabolism
Pharmacology of buprenorphine

• partial agonist at μ opioid receptor
  milder effects than full agonist
  less severe withdrawal symptoms

• high affinity for μ opioid receptor
  displaces a full agonist e.g. heroin, methadone
  blocks effect of additional opiates

• peak plasma levels 1.5 - 2.5 hours post dose

• duration of effects
  8-12 hours at low dose (e.g. 2mg)
  24 - 72 hours at high dose (e.g. >16mg)

• sub lingual tablet

• κ antagonist
Full agonist e.g. methadone/heroin

High buprenorphine affinity

Methadone/heroin displaced

→ precipitated withdrawal. Wait 12 hours after last dose of heroin, at least 24 hours after last dose of methadone

Slow dissociation buprenorphine

Full agonist can’t bind
Alpha 2 adrenergic agonists

- lofexidine and clonidine
- act presynaptically on alpha 2 adrenergic autoreceptors
- suppress locus coeruleus hyperactivity
- act on somatic symptoms of opiate withdrawal
- little effect on dysphoria, insomnia, craving
- lofexidine preferable to clonidine for outpatient use - less hypotensive
Opiate antagonists

Naltrexone
- high affinity, no activation
- oral
- licensed for relapse prevention
- 50mg daily (or 100mg every 2 days or 150mg every 3 days)
- hepatotoxicity - LFTs pre and during treatment
- rapid detoxification - not licensed

Naloxone
- parenteral
- short acting
- overdose / rapid detoxification
Pharmacokinetics of Opiates

Time

Effect

“normal”

Heroin

Methadone

Buprenorphine 4mg

Buprenorphine 8mg
Opioids and respiratory depression

**Full Agonists:** Heroin, morphine, methadone, codeine

**Partial Agonists:** Buprenorphine

**Antagonists:** Naltrexone, naloxone

Threshold for respiratory depression

**Drug Dose**

**Size of Opiate Agonist Effect**
Opioid detoxification

- methadone reducing regimes
- buprenorphine
- alpha 2 adrenergic agonists
- antagonist techniques
  - precipitate withdrawal
  - symptomatic treatment
  - varying levels of sedation depending on regime used

See individual Cochrane reviews for methadone, buprenorphine and alpha2agonists
Evidence for methadone maintenance

- increased treatment retention
- reduced illicit heroin use
- reduced crime and imprisonment
- reduced injection related risk behaviour
- reduced HIV infection
- reduced mortality
- improved psycho-social well-being
- increased employment
Methadone maintenance (2)

DOSE
Cochrane review of methadone maintenance at different dosages (*Faggiano et al 2003*)
methadone doses 60 – 100mg more effective than lower doses for:
- retaining patients
- reducing heroin use during treatment

PSYCHOSOCIAL TREATMENTS
Improved outcomes with addition of a range of psychosocial interventions e.g. medical/psychiatric care, social work, family therapy, employment counselling (*McLellan et al, 1993*)
Buprenorphine in maintenance treatment

Mattick et al, 2005

• comparing buprenorphine with methadone in flexible dosing regimes
• methadone 20 -120mg
• buprenorphine 2 - 16mg
• methadone maintenance better retention rates
• no difference in opiate use
• ? Comparison dose of buprenorphine too low?
Relapse prevention: naltrexone

- poor compliance
- highly motivated individuals
- naltrexone and behavioural treatment significantly reduced probability of re-incarceration (Kirchmayer et al. 2002)
- oral naltrexone effective treatment if retention rate adequate (Johansson et al, 2006)
- depot naltrexone
Pharmacological management of alcohol withdrawal

Aims:
• Prevention of complications (seizures, delirium)
• Relief of symptoms

Drugs of choice - benzodiazepines
Medium/long acting - chlordiazepoxide, diazepam
↑ GABA function
↓ seizures, ↓ delirium
issues - side effects, additive with alcohol
caution in hepatic impairment (oxazepam)
Benzodiazepine treatment regimes

Fixed dose schedule
• 20mg - 40mg qds reducing to 0 over 7 - 10 days

Front loading

Symptom triggered therapy
• withdrawal rating scale
• needs careful monitoring
Carbamazepine
• effective in alcohol withdrawal
• no abuse potential
• not better than benzodiazepines
• not contraindicated in liver disease
• increased side effects
• cost

Clomethiazole
• only IV in inpatient severe withdrawal
• fatal respiratory depression with alcohol
• dependence
Acamprosate

- inhibits glutamate NMDA receptor function
- enhances GABA-ergic transmission
- start as soon after detox as possible
- ? neuroprotective therefore start during detox
- ? reduces craving in response to conditioned cues
- possible better outcome in high anxiety individuals, drinking for negative reinforcement
Acamprosate increases continuous abstinence rates (and cumulative abstinence)

Acamprosate 23% : placebo 15% abstinence rate  

Bouza at el, 2004
Naltrexone

- decreases pleasurable effects by blocking endogenous opioid pathways stimulated by drinking alcohol

- therefore may reduce reward from drinking alcohol
Naltrexone reduces relapse to heavy drinking (but may not enhance abstinence)
Disulfiram

Alcohol dehydrogenase

ethanol → acetaldehyde → acetate

Aldehyde dehydrogenase

facial flushing

↑ pulse

↓ BP

↑ temp

nausea & vomiting

headache

palpitations

disulfiram
Disulfiram

• evidence equivocal
• some evidence for supervised treatment in terms of number of drinking days and amount of alcohol consumed
• no support for implants

Hughes and Cook, 1997
Drugs under investigation

- Topiramate – increases GABA function
- Baclofen – GABA B agonist
- Naltrexone depot preparations
Vitamin prophylaxis

i) Suspected or established Wernicke’s Encephalopathy

2 pairs pabrinex ampoules ( =  500 mg Thiamine) tds by IV infusion for 3 days
Followed by 1 pair pabrinex ampoules daily by IM for further 3 - 5 days

ii) At risk group (history/current severe withdrawals, very heavy consumption, malnutrition, peripheral neuropathy)

1 pair pabrinex ampoules (= 250 mg thiamine) daily by IM or IV for 3 - 5 days

iii) Low risk group (well nourished, lower level consumption, no history severe withdrawals)

oral thiamine minimum 300mg per day in divided doses
Vitamin B complex strong 2 tablets tds
Effects of psychostimulants

- Euphoria
- Wakefulness
- Anorexia
- Motor stimulation (locomotion, stereotypies)
- Psychotomimetic effects
- Anxiety
- Hyperthermia
Stimulant withdrawal

Acutely
- ↓ mood
- ↓ energy
- hypersomnia → insomnia
- agitation/anxiety
- craving
- ↑ appetite

first few days ‘the crash’
emergence of suicidal ideas

More protracted
- anhedonia
- dysphoria/depression
- amotivation
- craving
Running through the alphabet…

...trying to find a drug that helps stop cocaine use ….

Amantadine, bromocriptine, cabergoline, carbamazepine, celecoxib, coenzyme Q10/L-carnitine, desipramine, dexamfetamine, disulfiram, donepezil, fluoxetine, gabapentin, gepirona, hydergine, imipramine, levodopa/carbidopa, lamotrigine, lithium, mazindol, modafinil, naltrexone, nefazodone, olanzepine, paroxetine, pergolide, pramipexole, reserpine, riluzole, risperidone, sertraline, tiagabine, topiramate, valproate, venlafaxine….
Please tell me if …

…you know of any RCTs of drugs beginning with e, j, k, q, u, w, x, y or z!
Treatments probably ineffective for stimulant use:

- Dopamine agonists (bromocriptine, amantadine)
- Antidepressants
- Carbamazepine

(see individual Cochrane reviews, Soares et al 2003, Lima et al 2003)
Treatments of potential interest

- **Disulfiram** – inhibits dopamine beta hydroxylase; decreases cocaine use

- **Dexamphetamine** – substitute prescribing: pilot studies only, benefit not established as in opiate dependence

- **Topiramate, gabapentin, baclofen** – increase GABA function

- **Modafinil** – DA partial agonist
Psychostimulants - summary

- At present there remains no established pharmacological treatment for cocaine or amphetamine dependence.
- Psychosocial treatments are the approaches of choice.
- Diagnosis of concurrent psychiatric disorder may guide drug treatment.
Depression and alcohol dependence

If patient still drinking:

- Antidepressant drugs only effective in severe depression
- Tricyclic antidepressants effective in severe depression but not recommended for patients still drinking because of toxicity
- SSRIs: may improve both depression and drinking outcomes in “Type 2” drinkers (older age at onset of alcohol dependence, negative family history, anxious)
- SSRIs: may contribute to poorer drinking outcomes in “Type 1” drinkers (early onset, positive family history, antisocial traits)
Antipsychotic drugs

Are any antipsychotic drugs superior in terms of substance misuse outcomes as well as treatment of psychosis?

Clozapine currently appears superior: consider moving to clozapine earlier in substance-misusing patients with schizophrenia?