

Interactions between drugs of abuse and psychotropic medications: focus on the elderly

Dr Enrico Cementon

SUMITT & DAS West

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Special challenges in treatment of dual diagnosis

- ↑ clinical severity
 - Comorbid disorders ↑ chronicity
 - 1° disorder more severe *or* adverse life situations?
- ↑ exposure to environmental risks
- ↓ set of pharmacoRx options
 - Abuse potential
 - **Risk of interactions**
 - Rx less effective



Kessler (2004)



Comorbid Depression & Substance dependence

- Meta-analysis of 14 RCT's of antidepressant Rx in depression & substance dependence
 - 5 TCA, 7 SSRI, 2 other
 - Pooled effect size 0.38 (antidepressant response 52.1% vs. 38.1% placebo)
 - Dx depression >1/52 abstinence predicted stronger AD response
 - Pooled effect size on substance use 0.25

Why is this now an issue for our aged patients?

- Aged population forms large part of consumers of prescription & OTC drugs
- ‘Baby-boomers’ & former ‘Flower children’ continuing illicit substance use
- Likely under-recognition of substance misuse & consequences by clinicians
 - Frequently considered problem of young people
 - Consequences ‘masquerading’ as disease & other problems of ageing

Gossop & Moos (2008)

Schlaerth (2007)

Which psychoactive drugs used in this age group?

- Alcohol
- Benzodiazepines
 - Sedatives
 - Hypnotics
- Analgesics esp. opioids
- Over-the-counter preparations
- Polypharmacy common
- Illicits: context of family as ‘facilitator’

Adverse drug reactions in the elderly

- Pattern of prescribing
 - alter prescribing habits
- Vulnerability of the aged to react adversely to individual drugs
 - informed use of drugs

Ramsay & Tucker (1981)

Pharmacology of Drug interactions

Pharmacokinetic

Effect of one drug on another drug's

- 1. Absorption**
- 2. Distribution**
- 3. Metabolism**
- 4. Excretion**

Pharmacodynamic

Effect of one drug on another's activity at site of biological action

- 1. Additive**
- 2. Synergistic**
- 3. Antagonistic effects**

★ *Even at standard blood concentrations*

★ *Advancing age will affect all the above*

1. Drug absorption & aging

- Process of drug movement external world → bloodstream
- 6 routes
 - Oral, parenteral, transdermal, rectal, inhaled, across mucous membranes
- Gastrointestinal disease, ↓ gastric acid secretion,
↓ gastric emptying
 - Delayed absorption
 - Slower onset
 - Delayed peak action

2. Drug distribution & aging

- ↓ lean-to-fat body mass ratio :
 - ↓ lean body mass & ↑ fat body mass
- Lipid-soluble psychotropic drugs
 - fat tissue including CNS
 - prolonged drug action



3. Drug metabolism & aging

- Or drug detoxification or breakdown
- **Liver** cells *enzymatically biotransform* drug into less fat-soluble metabolites
- Liver disease →
↓ ability to metabolise drugs

Metabolites less fat-soluble



Bloodstream



Kidneys



Urine

Drug metabolism systems

- *Cytochrome P450 enzyme family*
 - >12 different types: CYP-1,2,3,etc
 - CYP-3A4 ~50% biotransformations
 - 2D6 ~25%
 - 2C ~20%
 - 2E1 for alcohol and paracetamol
- *Alcohol dehydrogenase (ADH)*
- *Acetaldehyde dehydrogenase (ALDH)*

Julien (2001)

Alcohol's effects on liver drug metabolism

1. Acute dose

- May compete for drug's metabolism →
↓ metabolism of eg. Narcotics, benzo's, barb's, warfarin

2. Long-term ingestion

- ↑ CYP2E1 →
 - ↑ drug metabolism when sober
 - ↓ drug metabolism when intoxicated
- Other CYP enzymes not so affected



Other drugs' effects on liver drug metabolism

- **CYP1A2**
 - Metabolises TCA, clozapine, HPD, methadone
 - Inhibited by fluvoxamine, grapefruit juice
 - Induced by smoking (nicotine, polycyclic hydrocarbons, CO)
- **CYP2D6**
 - Metabolises TCA, SSRI, HPD, TDZ, risperidone
 - Inhibited by SSRI, venlafax, nefaz, HPD
- **CYP3A4**
 - Metabolises benzos, some TCA, CBZ, opioids, protease inhibitors
 - Inhibited by nefaz, fluvox, SSRI, venlafax, protease inhibitors, grapefruit juice
 - Induced by CBZ

Tanaka (1998)

Examples of *Metabolic pharmacokinetic* drug interactions

- Fluvoxamine → Methadone levels ↑

Alderman & Frith (1999)

- Nefazodone → Heroin metabolism ↓

- SSRI's, protease inhibitors → Ecstasy (MDMA) metabolism ↓



Oesterheld, Armstrong & Cozza (2004)

4. Drug excretion or elimination & aging

- Mainly via kidneys
- Alcohol a diuretic → effects on drugs reliant on urinary excretion eg. Lithium
- Alcohol also may cause direct dilution from large water quantities
- THC ↓ renal lithium clearance reported
- Kidney disease → ↓ drug clearance
- Heart disease & ↓ cardiac output → affect *both* renal & hepatic drug clearance

Pharmacodynamic drug interactions

Effect of one drug on another's activity at site of biological action

1. Additive
2. Synergistic
3. Antagonistic

★ Changes in receptor sensitivity

TOXICITY MORE COMMON IN ELDERLY

Pharmacodynamic drug interactions

1. Additive effects

- When drugs affect different parts of CNS e.g. different neurotransmitters systems
 - Sedation
 - Slowed reflexes, motor coordination, falls
 - Slowed cognition, impaired memory
 - ↓ respiratory drive



Examples of Additive pharmacodynamic interactions

- Alcohol & antidepressants (esp. TCA)
 - Sedation, impaired driving skills
- Deaths associated with heroin
 - Alcohol 30-40%
 - Benzos 40-60%
 - Antidepressants 5-20%



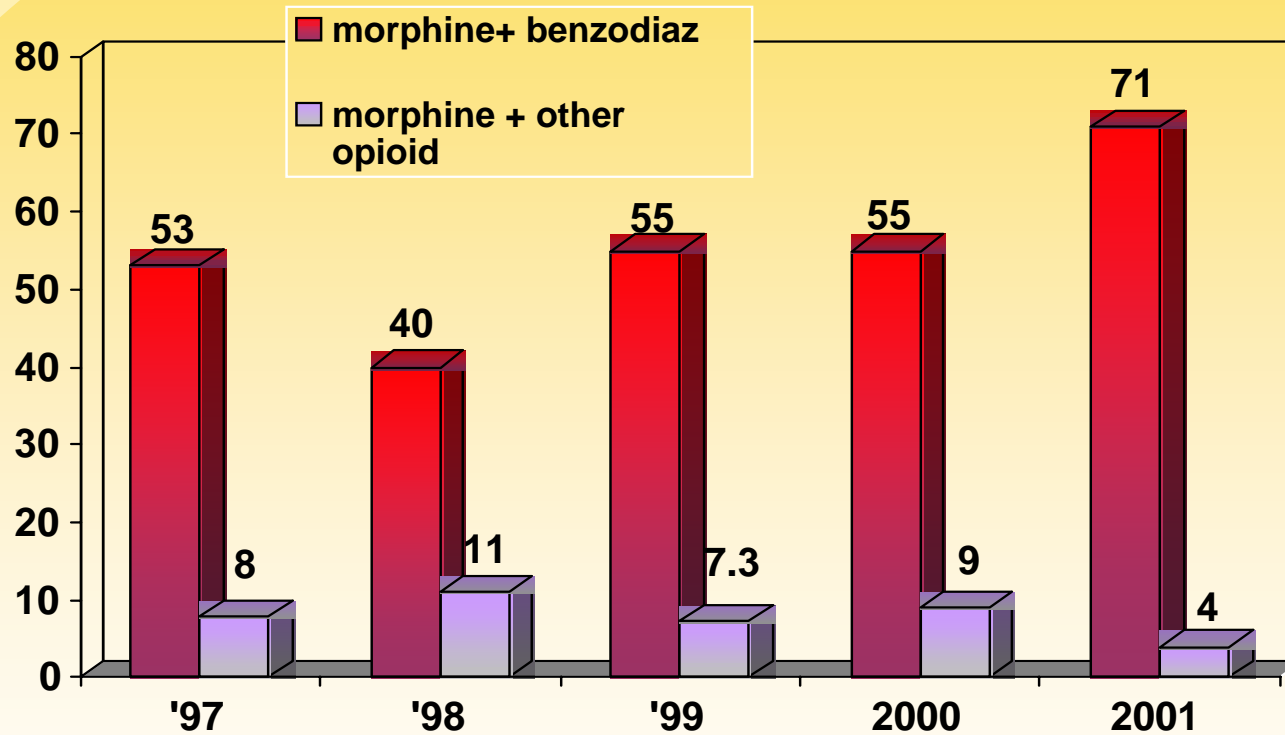
Drummer & Odell (2001)

- “Polydrug toxicity” with heroin, cocaine
- Heroin OD with TCA

Darke (2003)

Darke & Ross (2000)

Prescription drugs in heroin-related deaths, Victoria



Courtesy of Dr Malcolm Dobbin 2004

Pharmacodynamic drug interactions

2. Synergistic

- Effects multiplied as effects on same receptors in CNS
 - Sedation
 - ↓ respiratory drive
 - Impaired motor coordination, reflexes (eg. gag or cough), falls
 - Impaired cognition

Examples of Synergistic drug interactions

- Alcohol + benzodiazepines + barbiturates
 - sedation, drowsiness, coma, falls
- Drugs with anticholinergic effects
 - delirium, hallucinations
 - e.g. TCA, phenothiazines, THC, antihistamines, etc.
- Ecstasy (or PMA) + other pro-serotonergic drugs
 - Serotonin syndrome
 - E.g. SSRI's, Tramadol, Lithium, Moclobemide, St John's Wart, Amphetamine
 - Fatalities reported



Oesterheld *et al* (2004)
Vuori *et al* (2003)
Freezer *et al* (2005)

Pharmacodynamic drug interactions

3. Antagonistic

- When drugs oppose in action
 - Very common, but clinical relevance unclear
 - E.g. antipsychotic Rx - stimulants - dopamine
 - E.g. numerous serotonin receptor subtypes
 - Effects unpredictable

Special clinical situations

- Medical consequences of drug use interferes with psychotropic Rx and their side effects
 - Acute **intoxication** → susceptible to additive effects of psychotropic Rx eg. Sedation, confusion, lethargy
 - Acute **withdrawal** → sensitive to ↓ BP, cardiac SE's, seizures, delirium
 - Chronic **liver impairment** (alcoholic, Hep C) → ↓ Rx metabolism, sedation, respiratory depression, confusion
 - **Cognitive impairment** → vulnerable to delirium
 - ↑ movement disorders eg. Stimulants & tics

Decker & Ries (1993)

Medication adherence

- Often poor in dual diagnosis situations
- Impaired impulse control
- Disorganised behaviour
- General confusion
- Rx diversion

Decker & Ries (1993)



Minkoff's Clinical practice guidelines in treatment of co-occurring disorders

- 1. Welcoming approach & engagement**
- 2. Access to treatment**
 - No arbitrary sobriety period
 - Maintain existing psychotropic Rx during detox
- 3. Safety**
 - Patient
 - Staff



Minkoff's Clinical practice guidelines in treatment of co-occurring disorders

4. Longitudinal, integrated assessment

- Chronological relationships
- Dx can be difficult
- Nevertheless: immediate initiation/continuation of psychotropic Rx for severe psychopathology or unstable SUD

5. Continuity

- Review over time: Dx, indication for Rx, Rx effectiveness

6. Peer consultation:

- Continuation of benzo's
- Discontinuation of Rx because of substance use
- Unilateral termination of clinical care for any DD patient

Minkoff (2005)

General treatment principles

- Treatment for psychosis generally urgent
- Non-psychotic patients: may use longitudinal assessment, stabilise drug use first
- If reasonable probability of treatable disorder → treat e.g. depression, anxiety
- Medication in SUD treatment is only ever an adjunct → own work in recovery important
- Avoid prn's esp. benzo's due to difficulties regulating Rx



Conclusions

- Interactions unpredictable, but *more likely* in aged people
 - Wide individual variations
 - Multiple potential reactions
- Paucity of evidence & literature
- Apply basic *pharmacokinetic & dynamic* principles
 - ➔ informed decisions re Rx doses & choices
 - ➔ *start low, go slow* in elderly
- Balance of risks :
 - Continued substance use during psychiatric Rx Vs
 - Poor outcome of not treating known mental illness
 - ➔ Closer monitoring & frequent review, not Rx discontinuation