

Iatrogenic Delirium

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Objectives

- ▶ Discuss proposed mechanisms of medication induced delirium
- ▶ Identify potential pharmacokinetic and pharmacodynamic changes which may contribute to development of delirium
- ▶ Recognize limitations of current literature
- ▶ Review most common drug classes associated with delirium
- ▶ Highlight drug induced delirium with case examples

Proposed Mechanisms of Drugs Causing Delirium

- ▶ **Excess of brain dopaminergic activity**
 - ▶ Neuroleptics, ACEis, dihydropyridine CCBs, antiparkinson medications have in vitro dopaminergic activity
- ▶ **Deficit in brain cholinergic activity**
 - ▶ Antihistamine H1 antagonists, H2 antagonists, steroids, digoxin have increased in vitro anticholinergic activity
- ▶ **Rebound decline in GABAergic function**
 - ▶ GABA acting at GABA-A receptors inhibits dopamine release
 - ▶ GABA antagonist or sudden withdrawal from GABA agonist may increase the risk of hyperdopaminergic state → facilitates action glutamate at NMDA receptors

Pharmacokinetic/Pharmacodynamic and Delirium

- ▶ Reduced volume of distribution
 - ▶ Decreased total body water
 - ▶ Lower doses of hydrophilic drugs requires to obtain therapeutic effect
 - ▶ Increased total body fat
 - ▶ Lipophilic drugs may accumulate and result in increased adverse effects
- ▶ Decreased renal clearance
- ▶ Decreased liver function
- ▶ Increased sensitivity to medications
 - ▶ Loss of cholinergic and dopaminergic activity

Limitations of Evidence for Drug Induced Delirium

- ▶ Most evidence from case reports and unsystematic observations
 - ▶ A few RCTs, prospective cohort studies but limited design, sample size
- ▶ Strict criteria for the assessment of adverse drug reactions rarely applied
- ▶ Often studies confounded by multiple medical comorbidities
- ▶ Difficult to demonstrate correlations between drugs and delirium since effects may sometimes be idiosyncratic or subject to pharmacokinetic/pharmacodynamics changes seen in older patients included

Table III. Medications that can precipitate delirium^[3,9,18]

Prescription medications

Antiarrhythmics

Anticholinergics ★

Antihistamines ★

Anti-inflammatory medications

Antiparkinsonian medications

Barbiturates

Benzodiazepines ★

Dihydropyridine calcium channel antagonists

Corticosteroids

Digitalis

Diuretics

Fluoroquinolones

Histamine H₂ receptor antagonists

Lithium

Opioid analgesics: pethidine (meperidine) and dextropropoxyphene ★

Tricyclic antidepressants

Over-the-counter/alternative medications

Medications containing alcohol (ethanol)

Atropa belladonna extract

Henbane

Jimson weed

Mandrake

Anticholinergic agents

▶ Traditional anticholinergic agents

- ▶ Atropine
- ▶ Benztropine
- ▶ Scopolamine
- ▶ Tolterodine

▶ Antihistamines with anticholinergic properties:

- ▶ Chlorpheniramine
- ▶ Diphenhydramine
- ▶ Hydroxyzine

▶ Antidepressants

- ▶ Tricyclic agents (amitriptyline highest anticholinergic burden, nortriptyline least)
- ▶ Paroxetine

▶ Antipsychotics

- ▶ Clozapine
- ▶ Olanzapine

Case 1

- ▶ MJ is a 69 yo F with PMH of HTN, DM, COPD, who was admitted due to recent fall resulting in intertrochanteric fracture of the right hip. She underwent surgical repair and is currently post op day 3. Nursing staff reports that she has been restless and agitated during the night appeared very confused. You are consulted to review her medications and make recommendations.
- ▶ Current medications:
 - ▶ Amlodipine 10 mg daily
 - ▶ Hydrochlorothiazide 25 mg daily
 - ▶ Sliding scale insulin
 - ▶ Lovenox 40 mg daily
 - ▶ Albuterol MDI prn SOB
 - ▶ Oxycodone IR 5 mg q6h prn moderate pain
 - ▶ Oxycodone IR 10 mg q6h prn severe pain
- ▶ You notice that the patient has not received more than 10 mg of oxycodone in the past 12 hours.
- ▶ How would you approach this case?

Analgesics

- ▶ Both undertreated pain and use of analgesics associated with development of delirium (especially in elderly)
- ▶ Morrison et al prospective cohort study 541 hip fracture patients
 - ▶ 16% developed delirium
 - ▶ Patients who received < 10 mg/day parenteral morphine equivalent had 5.4-fold risk of delirium
 - ▶ Patients with severe pain at rest had 9-fold increased risk
- ▶ Studies show mixed results regarding delirium risk with method of administration (oral opioid vs IV, patient controlled device)

Benzodiazepines

- ▶ Numerous studies suggest increased risk of delirium
- ▶ Marcantonio et al prospective case-control study showed delirium was significantly associated with postoperative exposure
- ▶ Longer-acting agents with active metabolites trended toward stronger association
 - ▶ Diazepam, chlordiazepoxide, clorazepate, clonazepam
- ▶ Other studies suggest benzodiazepines may cause increased duration of ICU delirium (Pisani et al)
 - ▶ May be confounded by duration of intubation

Miscellaneous Agents

▶ Digoxin

- ▶ Limited to case reports
- ▶ “digitalis delirium” characterized by heightened agitation, delusional thinking, assaultive behavior
- ▶ Previous reports include neuropsychiatric effects at supratherapeutic and also therapeutic levels!
- ▶ Risk factors include increased age, decreased renal function, reduced muscle mass, DDI (amiodarone, verapamil, quinidine), and electrolyte disturbances

▶ Lithium

- ▶ Several case reports of lithium-induced delirium at therapeutic levels
- ▶ Age, combination with antipsychotics, use during ECT, acute psychosis risk factors
- ▶ Rapid improvement in mental status after d/c lithium often only way to determine if drug induced

Case 2

- ▶ An 80 yo M with PMH hypothyroidism, HTN, GERD was admitted from NH to the community hospital for treatment of suspected pneumonia.
- ▶ Past medications which were continued include levothyroxine 100 mcg daily, omeprazole 40 mg daily, and lisinopril 10 mg daily.
- ▶ Treatment with ciprofloxacin 400 mg IV q12h and cefepime 2 g IV q12h was initiated. After the end of day 2 of treatment, he became extremely restless pulling at IV lines and began c/o a vibration like sensation in his body.
- ▶ What could be contributing to delirious state in this case?

Glucocorticoids

TABLE 1. Risk of Five Severe Neuropsychiatric Outcomes Associated With First Course of Oral Glucocorticoid Prescription, Compared With Unexposed Adult Population Matched for Age, Gender, Practitioner, and Underlying Medical Condition^a

Neuropsychiatric Outcome	Adjusted Hazard Ratio	95% CI
Suicide or suicide attempt	6.89	4.52, 10.50
Delirium, confusion, or disorientation	5.14	4.54, 5.82
Mania (nonpsychotic)	4.35	3.67, 5.16
Depression (nonpsychotic)	1.83	1.72, 1.94
Panic disorder	1.45	1.15, 1.85
>5 neuropsychiatric outcomes	2.26	2.15, 2.37

^a Data From Fardet et al. (6), analysis of records for adult patients in the U.K. Health Improvement Network (THIN) medical database for the period 1989–2008. The overall estimates of incidence rates of five severe neuropsychiatric outcomes of oral glucocorticoid therapy are low because the authors did not analyze psychotic bipolar disorder or depression, generalized anxiety disorder, or other severe neuropsychiatric outcomes.

Glucocorticoid Withdrawal

- ▶ Risk factors for severe psychiatric outcomes during withdrawal:
 - ▶ Older age (particularly > 80 years)
 - ▶ History of delirium
 - ▶ Longer acting glucocorticoids (e.g. dexamethasone, betamethasone, triamcinolone) HR = 4.96; 95% CI = 2.60, 9.49; $p < 0.001$ compared to shorter acting agents (e.g. prednisone, prednisolone, methylprednisolone)

Systematic Review

- ▶ Systematic review including 14 studies
- ▶ Primary outcome: delirium rate (DSM III, IV or ICD criteria)
- ▶ Highly heterogeneous sample:
 - ▶ General medicine, orthopedic hip fracture/surgery, ICU, mixed medical surgical, elective cardiac surgery, long term care
 - ▶ Allowed inclusion of patients with cognitive impairment/dementia in all except 1 study (severe dementia patients excluded in 2 studies)

Table 2. Evidence hierarchy table summarising the risk of delirium with different medication classes and different agents within a class of medications

Medication class	Study	Setting	Agent	Type of analysis	Result OR/RR (95% CI)	Evidence quality
Neuroleptic	Kalisvaart <i>et al.</i> [21]	Orthopaedic (hip surgery)	Haloperidol	RCT	RR 0.9 (0.6–1.3)	High
	Schor <i>et al.</i> [29]	Mixed medicine/surgery	All neuroleptics	Multivariate	OR 4.5 (1.8–10.5)	Moderate
Opioid	Schor <i>et al.</i> [29]	Mixed medicine/surgery	All opioids	Multivariate	OR 2.5 (1.2–5.2)	Moderate
	Marcantonio <i>et al.</i> [24]	Mixed surgical	All opioids	Matched	OR 1.4 (0.5–4.3)	Moderate
	Pandharipande <i>et al.</i> [26]	ICU	Fentanyl	Multivariate	OR 1.2 (1.0–1.5)	Moderate
	Pandharipande <i>et al.</i> [26]	ICU	Morphine	Multivariate	OR 1.1 (0.9–1.2)	Moderate
	Marcantonio <i>et al.</i> [24]	Mixed surgical	Meperidine (pethidine)	Matched	OR 2.7 (1.3–5.5)	Moderate
	Marcantonio <i>et al.</i> [24]	Mixed surgical	Morphine	Matched	OR 1.2 (0.6–2.4)	Moderate
	Marcantonio <i>et al.</i> [24]	Mixed surgical	Fentanyl	Matched	OR 1.5 (0.6–4.2)	Moderate
	Marcantonio <i>et al.</i> [24]	Mixed surgical	Oxycodone	Matched	OR 0.7 (0.3–1.6)	Moderate
	Marcantonio <i>et al.</i> [24]	Mixed surgical	Codeine	Matched	OR 1.1 (0.4–3.6)	Moderate
	Benzodiazepine	Marcantonio <i>et al.</i> [24]	Mixed surgical	All benzodiazepines	Matched	OR 3.0 (1.3–6.8)
Pandharipande <i>et al.</i> [26]		ICU	Lorazepam	Multivariate	OR 1.2 (1.1–1.4)	Moderate
Pandharipande <i>et al.</i> [26]		ICU	Midazolam	Multivariate	OR 1.7 (0.9–3.2)	Moderate
Antihistamine (H ₁)	Marcantonio <i>et al.</i> [24]	Mixed surgical	Diphenhydramine	Matched	OR 1.8 (0.7–4.5)	Moderate
Dihydropyridine	van der Mast <i>et al.</i> [30]	Cardiac surgery	Nifedipine	Multivariate	OR 2.4 (1.0–5.8)	Low
H ₂ Antagonist	Schor <i>et al.</i> [29]	Mixed medicine/surgery	All H ₂ antagonists	Univariate	OR 1.4 (0.8–2.5)	Low
Cardiac glycoside	Schor <i>et al.</i> [29]	Mixed medicine/surgery	Digoxin	Univariate	OR 0.5 (0.3–0.9)	Low
Steroid	Schor <i>et al.</i> [29]	Mixed medicine/surgery	All steroids	Univariate	OR 0.5 (0.2–1.7)	Low
NSAIDs	Schor <i>et al.</i> [29]	Mixed medicine/surgery	All NSAIDs	Univariate	OR 0.4 (0.1–1.5)	Low
Tricyclic antidepressant	Gustafson <i>et al.</i> [20]	Orthopaedic (hip fracture)	All tricyclic antidepressants	Univariate	RR 1.7 (1.4–2.1)	Very low
Antiparkinson	Gustafson <i>et al.</i> [20]	Orthopaedic (hip fracture)	Antiparkinson	Univariate	RR 1.3 (0.9–1.7)	Very low

Strategies For Identifying and Addressing Medication Induced Delirium

- ▶ **Identifying possible medication induced delirium**
 - ▶ Recently added medications
 - ▶ Drug interactions, metabolic pathway
 - ▶ Recently increased doses
 - ▶ Pharmacokinetic/dynamic changes
 - ▶ BEERs list medications
- ▶ **How to address possible medication induced delirium?**
 - ▶ Discontinue suspected offending agent
 - ▶ Decrease the dose
 - ▶ Change to alternative agent
 - ▶ Focus on choosing medications with less anticholinergic activity
 - ▶ Metabolic pathway

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Questions???

