Medications: *The Dark Side*

Robert P. Smith, MD
Potential Mechanisms of Drug Effects

- Metabolic effects
- Alterations of Immunologic factors in CNS
- Interference with synaptic transmission
- Excess dopaminergic activity
- Deficit in cholinergic activity
- Withdrawal effects
- Drug-drug interactions (eg, serotonin syndrome)
How Medications Impair Cognition

• Interfere with learning, memory, attention particularly anticholinergic medications

• Alter wakefulness and alertness Benzodiazepines, antiepileptic drugs, low potency antipsychotics

• Impact on orientation and reality awareness narcotics, NSAIDS, steroids, cimetidine, clonidin
Appropriate Medications with Side Effects

• “…most ADEs do not result from improper choices of drugs or drug doses but instead represent known side effects of drugs that have a rightful place in the therapeutic armamentarium.”

• Meds on (drugs to avoid): only 4% ER visits for ADEs

• Warfarin and insulin cause 30% ER visits for ADES

  • Steinman et al; JAGS 59:1513-1520, 2011
Acronym: ACUTE CHANGE IN MS

A  Anti-parkinson medications
C  Corticosteroids
U  Urinary incontinence medications
T  Theophylline
E  Emptying medications
C  Cardiovascular medications
H  H2 blockers
A  Antimicrobials (esp quinolones)
N  NSAIDS
G  Geropsychiatric medications
E  ENT medications
I  Insomnia medications
N  Narcotics
M  Muscle relaxants
S  Seizure drugs
Polypharmacy

- Relative odds of developing drug-induced confusion
  - 1.0 when 0-1 drugs prescribed
  - 9.3 when 4-5 drugs prescribed

PIM’s (Potentially Inappropriate Medications)

- 100 patients at Memory Diagnosis Clinic; 22 had at least one PIM. Barton et al: Am J Geriatr Pharmacother. 2008 Aug;6(3):147-52

- 689 patients with MCI: 143 (20.8%) had at least one PIM (35 had two PIM’s). Weston et al: J Gerontol A Biol Med Sci 2010 Mar;65(3):318-21

- 221 patients at Memory Clinic; 19.9% were taking PIM’s. Weih et al Fortschr Neurol Psychiatr. 2009 Sep;77(9):523-7
### Anticholinergic Drug Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No known anticholinergic properties</td>
</tr>
<tr>
<td>1</td>
<td>Potentially anticholinergic as evidenced by receptor binding studies</td>
</tr>
<tr>
<td>2</td>
<td>Anticholinergic adverse events sometimes noted, often at excessive doses</td>
</tr>
<tr>
<td>3</td>
<td>Markedly anticholinergic</td>
</tr>
</tbody>
</table>

Anticholinergic Drug Scale
Examples of Level 3

- Amitryptiline
- Atropine
- Brompheniramine
- Clemastine
- Chlorpromazine
- Clozapine
- Desipramine
- Dicyclomine
- Diphenhydramine
- Doxepin
- Hydroxyzine
- Hyoscyamine
- Imipramine
- Meclizine
- Nortriptyline
- Oxybutynin
- Promethazine
- Propantheline
- Scopolamine
- Tolterodine
Anticholinergic Drug Scale
Examples of Level 2

- Carbamazapine
- Cimetidine
- Cyclobenzaprine
- Cyproheptadine
- Disopyramide
- Loxapine
- Meperidine
- Methotrimeprazine
- Molindone
- Oxcarbazepine
- Pimozide
- Ranitidine
Anticholinergic Drug Scale
Examples of Level 1

- Amantadine
- Ampicillin
- Benzodiazepines
- Bromocriptine
- Captopril
- Cephalosporins
- Chlorthalidone
- Clindamycin
- Codeine
- Dexamethasone
- Digoxin
- Diltiazem
- Dipyridamole
- Divalproex
- Famotidine
- Fentanyl
- Fluoxetine
- Furosemide
- Gentamicin
- Isosorbide
- Ketotifen ophth
- Morphine
- Nifedipine
- Nizatidine
- Olanzapine
- Oxycodone
- Paroxetine
- Prednisone
- Sertraline
- Theophylline
- Tramadol
- Triamterene
- Volproic acid
- Vancomycin
- Warfarin
Anticholinergic use

- Medical Research Council Cognitive Function and Ageing Study
- 2 yr longitudinal study; community and institutional dwelling patients (13,004 patients over age 65)
- 47% used a medication with possible anticholinergic effect, and 4% used a drug with definite anticholinergic activity

- Fox et al JAGS 59:1477-1483, 2011
Case study LW

- 68 year old man: memory problems; starts sentence and cannot finish; confused; repetitive; couldn’t remember that he had diabetes
- Meds: included
  - Propranolol
  - Pioglitazone
  - Cimetidine 400 mg bid
  - Amitriptyline 200 mg a day
Cognistat Case LW
Case study EB

• Worried about memory
• Initially on amitriptyline 25 mg q hs
• In between RBANS: urologist put on oxybutynin
Case study EB
Longitudinal Study in Elderly: Anticholinergic Medications

- 372 people with no diagnosis of dementia
- 9.2% continuously used anticholinergic medication in the year prior to testing
- 80% of users had cognitive impairment compared to 35% of non-users (poorer reaction time, attention, delayed non-verbal memory, narrative recall, visuospatial construction, and language tasks)

Ancelin et al; BMJ 2006;332:455-459
Drugs Associated with Global Cognitive Impairment

- Patients with cognitive impairment were taken off medications and had improvement when drugs were stopped
- 35 patients
- In general, patients who had minor tranquilizers, major tranquilizers, and antihypertensives had no adverse effects related to stopping the medications

Drugs Related to Cognitive Decline

- Diazepam (7)
- Flurazepam (4)
- Meprobamate (3)
- Oxazepam (1)
- Clorazepate (1)
- Methyldopa (2)
- Propranolol (1)
- Hctz (1)
- Reserpine (1)

- Haloperidol (2)
- Thorazine (1)
- Thioridazine (1)
- Aspirin (2)
- Meperidine (1)
- Cimetidine (3)
- Insulin (2)
- Amoxapine (1)
- Amantadine (1)

Benzodiazepines

• Larson study

• “In our study most patients had used these drugs for years, and the side effect of cognitive impairment developed insidiously as a “late” complication of a drug began at an earlier age”
Case Study

- 86 y/o woman; occasional prn alpazolam use in the past; markedly increased anxiety and started using 0.25 mg bid and then 0.5 mg bid routinely
- Cognitive testing significantly impaired
- Recommendation: decrease alprazolam to 0.25 mg bid and hopefully taper further
WISCONSIN ALZHEIMER’S INSTITUTE

RBANS 8/03/10

![Record Form A](image)

<table>
<thead>
<tr>
<th>Immediate Memory</th>
<th>Unsuppressed Attention</th>
<th>Language</th>
<th>Visuospatial</th>
<th>Delayed Memory</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>89</td>
<td>18</td>
<td>90</td>
<td>68</td>
<td>75</td>
<td>300</td>
</tr>
</tbody>
</table>

**Percentile:**

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>75</td>
<td>30</td>
</tr>
</tbody>
</table>

**Scale Scores:**

<table>
<thead>
<tr>
<th>Scale Name</th>
<th>90</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>100</td>
<td>30</td>
</tr>
</tbody>
</table>

**Inhalation Testing:**

<table>
<thead>
<tr>
<th>Inhalation</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

**Observations:**

- Age: 80 years F
- Education Level: [Blank]
- Examiner: [Name]
- Date of Testing: 8/03/10
- Incontinence: [Blank]

**Pearson**

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Anti-Epileptic Drugs

- Phenobarbital, Primidone and Clonazepam have more cognitive effects than valproic acid, carbamazepine or phenytoin.
- Newer agents may have lower risk, but not well studied in the elderly.
Anti-Epileptic Drugs

- Effect on memory in healthy volunteers:
  - Carbamazepine, phenytoin, valproate, and topiramate lowered memory recall by average of 15%.
  - Gabapentin and lamotrigine did not reduce memory recall on this task.

Meador epilepsyres.2005
Anti-Epileptic Drugs

- 95 patients with seizures and AD; 3 arm parallel-group study of 12 months duration
- Levetiracetam (LEV) had fewer adverse effects and improved attention level and oral fluency items
- Lamotrigine had better effect on mood
- Phenobarbital produced persistent negative cognitive side effects
- Conclusion: LEV side effect profile makes it a safe drug for controlling seizures in patients with AD

- Cumbo E, Ligori L: Epilepsy and Behavior 17 (2010)461-466
Case study MJ

- 80 y/o man
- Lots of trouble with memory, but also tired and fatigued
- On topiramate for headache prophylaxis
- We weaned off topiramate; at follow up visit was on CCB for prophylaxis and headaches essentially resolved
- Family thought he was doing lots better overall, but still with memory issues
Case study MJ
Anti-Parkinson’s Drugs

• Risk factors for adverse effects including aging and higher doses

• Relative excess of dopamine is alleged to be possible cause of delirium and other effects

• Levodopa: 5% delirium; up to 60% have some cognitive symptoms. Pergolide has altered mental function in 11-33%

• Bromocriptine

• Selegiline
Cardiovascular drugs

- Methyldopa
- Clonidine and guanabenz
- Digoxin (can occur at therapeutic levels)
- Beta blockers (including topical)
- Alpha blockers
Clonidine

- Sedation in 20-95% with overall incidence 68%
- Described as drowsiness, lethargy, and fatigue
- Less commonly:
  - Depression
  - Paranoia
Digoxin

- May have cognitive and affective abnormalities
- Agitation, restlessness, insomnia, or euphoria
- Lethargy, fatigue, anorexia
- Confusion, delusions, hallucinations
- Symptoms may occur with therapeutic levels
Beta Blockers: Conflicting Information

• Report of three cases; all had dramatic improvement with stopping beta blocker; 2/3 had underlying dementia and one returned to normal
  – Rogers, Bowman; Postgrad Med J 1990;66:1050-1052

• Two studies reported: no consistent evidence that beta blocker treatment was associated with a deleterious effect on neuropsychiatric functioning.
  – Dimsdale; J Psychosom Res 1992 36(3):229-236
Beta Blockers

• Although beta-blockers do not impair cognition in normal subjects, CNS active beta blockers may affect delayed memory in patients with cognitive impairment. This is hypothesized to occur by interfering with adrenergic signals in the locus ceruleus and hippocampus.

Antihypertensive drugs

- 6 yr follow up study of 318 patients
- Beta blockers increased odds of survival but also increased risk of decline MMSE and memory scores
- ACE-I treatment associated with decrease in memory
- CCB treatment had improved MMSE score and memory scores and performed better on tasks requiring concentration

Antihypertensive therapy

- 378 elderly patients on therapy with at least one drug
- None of the 3 studied areas (memory score, verbal fluency, or visual memory capacity) was associated with blood pressure levels
- CCB use associated with better memory score independent of age, sex, white matter hyperintensities, and carotid wall cross sectional area

Calcium Channel Blockers

• Canadian Study of Health and Aging

• Older people taking CCB’s were significantly more likely than those using other agents to experience cognitive decline (75% vs 59%)

Maxwell et al CMAJ 1999 Sep 7;161(5):501-6
ACE-I

- Centrally acting agents: 65% less decline in 3MSE scores
- Non centrally active agents: increased risk of dementia
- Centrally active: captopril, fosinopril, lisinopril, perindopril, ramipril, trandolapril
- Non centrally active: benazepril, enalapril, moexipril, quinapril
Narcotics

- Unrelieved pain can cause decline in cognition
- Pain medications may cause decline in cognitive function: often occurs at onset of treatment or with dose increase and moderates with chronic use
- Therefore, clinical judgment and close follow up is necessary
Narcotics

• Meperidine: DO NOT USE
  – High risk for delirium; meperidine and normeperidine have anticholinergic effects

• Other agents, including Tramadol may have confusion etc.
NSAIDS

- Indomethacin is medium risk
- Naproxen and ibuprofen low risk
- Salicylates may have confusion even at therapeutic levels
H1 Antagonists

• Diphenhydramine; more commonly used than often appreciated (eg Tylenol PM)
• Anticholinergic effects
• Possible other CNS effects
**H2 Antagonists**

- Delirium has been reported with all agents
- Cimetidine has received the most attention, possibly because it was first one available and initially had more research
- Some patients may be able to use other H2 blockers and some patients have cross reactivity
- Some studies indicate full or partial reversal of symptoms with physostigmine so anticholinergic effects may be related
H2 Antagonists-2

- CNS toxicity reported in 1-2% hospitalized patients and 15-80% in ICU patients; mainly in elderly patients
- One study: CNS toxicity in 6/20 patients with creatinine clearance <50 and 0/20 with patients >50

Slugg et al; Arch Int Med 1992; 152: 2325-9
Corticosteroids

- Cognitive effects typically at higher doses (such as 40 mg prednisone or equivalent) but may occur at lower levels in elderly
Antibiotics

- Difficult to ascertain whether cognitive changes related to the antibiotics or underlying infection
- Cephalosporins, penicillins and quinolones in particular
Serotonin Syndrome Symptoms

- CNS: confusion, delirium, agitation, euphoria, anxiety hallucinations, seizures, coma
- Neuromuscular: hyperreflexia, tremor, myoclonus, ataxia, incoordination, muscle rigidity, nystagmus, Babinski’s sign
Serotonin Syndrome Symptoms-2

- Autonomic instability: fever, hypertension, tachycardia, shivering, diaphoresis, tachypnea, dilated or poorly reactive pupil, skin flushing, hypotension
- GI: nausea, vomiting diarrhea, abdominal pain, excess salivation
Drugs with Serotonin Activity

- SSRI’s: trazodone, mirtazapine
  - buspirone, clomipramine, venlafaxine
- MAOI’s: meperidine, fentanyl
  - tramadol, pentazocine, ondansetron
- triptans: sibutramine, lithium
  - ginseng, tryptophan, linezolid
- metoclopramide, dextromethorphan
Serotonin Syndrome

- Consider the additive effect of all the possible medications with serotonergic activity
- One report found 4 nursing home patients with serotonin syndrome related to SSRI and opioid therapy
- Treatment is discontinuing medications and supportive

- Gnanadesigan; JAMDA 2005:265-269
Summary

• Use medications that may affect cognition judiciously and avoid polypharmacy; remember the wide number of medications that have anticholinergic effects

• Consider adverse drug effects when a patient has cognitive decline

• Many patients improve cognitively with medication withdrawal and often have no adverse effect for the prescribed conditions