

GERIATRIC PSYCHOPHARMACOLOGY

SENIORS' MENTAL HEALTH TELE-
EDUCATION SESSION

OCTOBER 1ST, 2008



Special Thanks

- Thanks to:
 - Dr. Terry Chisholm
 - Dr. Margaret Hahn
 - Slides taken from their prior presentations were used in preparing the majority of this presentation

Objectives

- ❑ Review changes in drug metabolism with aging
- ❑ Review changes in drug effects with aging
- ❑ Review adverse drug effects in the elderly
- ❑ Review inappropriate prescribing practices in the elderly
- ❑ Review a responsible general approach to prescribing in the elderly
- ❑ Be aware of drug interactions in the elderly
- ❑ Review side effect profiles of psychotropic medications including:
 - Antipsychotics
 - Antidepressants
 - Lithium
 - Benzodiazepines

Pharmacokinetics

DEFINITION – *“Factors determining availability of a drug to its bioactive sites”*

Pharmacokinetics

“All stages of the journey of a drug through the human body may be affected by aging”

- Processes that are affected by aging include:
 - Absorption
 - Distribution (body composition, protein binding)
 - Metabolism (hepatic)
 - Elimination (renal)

Pharmacokinetics: Absorption

- Age related changes affecting absorption:
 - Decreased gastric acid secretion
 - Decreased surface of intestinal epithelium
 - Decreased absorptive surface area
 - Decreased carrier-mediated transport mechanisms
 - Decreased intestinal motility
 - Increased transit time
 - Decreased mesenteric blood flow
 - Reduced tissue blood perfusion
 - Dermal, subcutaneous, and muscular tissue

Pharmacokinetics: Absorption

□ Effects:

- In spite of the changes, intestinal absorption of most drugs is NOT significantly affected
- Decreased rate of absorption of carrier-mediated drugs
 - Calcium, iron, vitamins
- Decreased transdermal, subcutaneous, and intramuscular absorption

□ Clinical implications:

- Onset of action delayed with certain drugs
- Clinical effect reduced

Pharmacokinetics: Distribution

- Age related changes affecting distribution:
 - Decreased muscle mass
 - Increased total body fat
 - 18 to 36% in men
 - 33 to 45% in women
 - Decreased total body water
 - Falls by 10-15% until age 80
 - Blood-brain barrier (BBB)
 - Decreased integrity with age
 - Decreased albumin, increased α_1 acid glycoprotein

Pharmacokinetics: Distribution

□ Effects:

- Increased volume of distribution of lipophilic drugs
 - Greater half-life
 - Longer interval to reach steady-state levels
 - Longer to evaluate drug effect
 - E.g. diazepam, verapamil
- Decreased volume of distribution of hydrophilic meds
 - Shorter half-life
 - Higher plasma concentrations with “normal” doses
 - E.g. lithium, aspirin

Pharmacokinetics: Distribution

□ Effects (cont):

■ Blood-brain barrier

- Protein bound, charged, hydrophilic drugs or active metabolites cross easier
- Increased sensitivity to psychotropic meds

■ Decreased albumin levels

- Unbound drug fraction is pharmacologically active
- Decreased binding could increase plasma concentrations of free drugs → TOXICITY
- Competition for protein binding by co-administered drugs → INCREASE IN PLASMA CONCENTRATION

Pharmacokinetics: Distribution

- Clinical implications:
 - Greatest effects in malnourished pts or those with comorbid medical conditions
 - Need to watch for adverse effects when new medications are added

Pharmacokinetics: Metabolism

□ Hepatic biotransformation:

- Intestinal absorption → portal vein → systemic circulation
- **Phase I, or oxidative reactions**
 - Catalyzed by CYP450 enzyme system
 - Subfamilies CYP1A2, 2D6, 3A3/4 account for metabolism of most psychotropic medications, **often to active metabolites through demethylation**
 - Yields progressively more water soluble compounds for excretion via the gut and kidneys
 - **Metabolic activity can decrease up to 20-40% with age**
- **Phase II, or conjugation reactions**
 - Produces polar, hydrophilic compounds devoid of pharmacologic activity
 - **Usually unchanged with age**

Pharmacokinetics: Metabolism

- Age related changes in hepatic clearance:
 - Decreased liver volume
 - 25-35% decrease
 - Decreased hepatic blood flow
 - Up to 40% decrease
 - Decreased oxidative metabolism
 - Decreased N-demethylation
 - Little effect on conjugation

Pharmacokinetics: Metabolism

- Effects:
 - Increased plasma levels
 - Variable ratios of parent drug to demethylated drug (active)
- Clinical implications:
 - Reduce dosages
 - Especially upon initiation to avoid excessive plasma levels
 - Caution when adding new medications
 - Drug interactions may occur if a new medication inhibits the CYP450 enzymes
 - CHF may further decrease hepatic metabolism by compromising blood flow to liver

Pharmacokinetics: Elimination

- Age related changes:
 - Decreased renal blood flow
 - 1% decrease/year after age 40
 - Decreased GFR (glomerular filtration rate)
 - Declines by 25-50% between ages 20 and 90
- Pharmacokinetic effects:
 - Longer half-life
 - Greater steady-state plasma concentration

Pharmacokinetics: Elimination

- Clinical implications:
 - Renal function should be evaluated prior to initiation of treatment
 - Plasma creatinine overestimates GFR due to reduction in muscle mass
 - Can use Cockcroft-Gault formula to estimate creatinine clearance (CrCl)
 - CrCl is a good estimate of renal function
 - Elevated/potentially toxic steady-state levels of lithium and other drugs excreted by the kidneys may occur
 - Often need to adjust doses as compared to younger counterparts

Pharmacodynamics

DEFINITION – *“Factors influencing sensitivity to the drug at its receptor”*

- Factors include:
 - Number of receptors in target organ
 - Ability of cells to respond to receptor occupation
 - Preservation of **homeostatic mechanisms**
 - Preserve the original functional equilibrium

Pharmacodynamics: Sensitivity

- Age dependant change in tissue sensitivity to drug action:
 - E.g. Increased sensitivity to muscarinic antagonism
 - Results from decreased number of cholinergic neurons
 - Peripheral effects: Constipation, glaucoma, urinary retention, blurred vision, tachycardia
 - Central effects: Mild depression, mild impairment of recent memory, confusion, delirium

Pharmacodynamics: Sensitivity

- E.g. Increased sensitivity to dopaminergic blockade
 - Results from decreased number of dopaminergic neurons
 - Results in increased incidence of motor effects
 - Antipsychotic-induced extra-pyramidal side effects (EPSE)
 - SSRI-induced EPSE

Pharmacodynamics: Sensitivity

- E.g. Increased susceptibility to syndrome of inappropriate anti-diuretic hormone (SIADH)
 - 12% will experience some degree of hyponatremia (low sodium) with SSRI or SNRI use
 - Median time to onset is 13 days
 - Lethargy, weakness, muscle cramps, disorientation, delirium

Pharmacodynamics: Sensitivity


- E.g. Increased risk of GI bleeding
 - Direct effect of SSRI on platelets
 - Recent comprehensive literature review (*Yuan et al. 2006*):
 - Supports the link between SSRIs and upper GI bleeds (UGIB) at a population level
 - The risk of UGIB increases with concomitant use of SSRIs and NSAIDs and/or aspirin, and advanced age
 - Preventive measures
 - Monitor bleeding parameters in high risk individuals (especially if on anticoagulants)
 - Switch from NSAID to selective COX-2 inhibitor
 - Addition of PPI may be helpful
 - Consider using non-SSRI in pts with bleeding risk

Pharmacodynamics: Sensitivity

- E.g. Increased sensitivity to α_1 - adrenergic blockade
 - Results from:
 - Reduced central noradrenergic (NA) tone
 - Decreased response to inotropic effects of adrenergic stimulation
 - Results in orthostatic hypotension
 - 5-33% have drug-induced orthostatic reactions
 - Increase in falls and hip fractures
 - 20% one year mortality post-hip fracture

Homeostatic Mechanisms

- With increased age:
 - Impaired orthostatic circulatory responses
 - Impaired thermoregulation
 - Impaired thirst response
 - Impaired glucose tolerance
 - Impaired vascular stability
 - Impaired cognitive reserve



**AS DRUG SENSITIVITY INCREASES AND
HOMEOSTATIC MECHANISMS
DECLINE, WE CAN CONCLUDE THE
ELDERLY ARE MORE SUSCEPTIBLE TO
SIDE EFFECTS!**

Delicate Balance of Prescribing

BENEFITS	MORBIDITY & MORTALITY
Elderly patients benefit from drugs	Risk of adverse reaction rises exponentially with # meds
Puts focus on "appropriate" drugs	Many inappropriate drugs are use

Compliance

# MEDS	COMPLIANCE
1-2	73%
>5	37%

*most common reason: fear of side effects

Adverse Drug Reactions

- 8-21% of elderly in the community
- 56-74% nursing home residents
- Often missed:
 - Falls - benzodiazepines, psychotropics
 - Constipation - anticholinergics
 - Dementia - benzodiazepines

Adverse Drug Reactions

- Morbidity and mortality:
 - Hospitalization - 8% of admissions
 - 16% of admissions from nursing homes
 - Leads to increased length of stay
 - Between 4th - 6th leading cause of death in the US
 - Cost to society is more than for diabetes

Prescribing Cascade

- *A prescribing cascade occurs when a 2nd medication is used to treat side effects of the 1st medication*
 - E.g. Metoclopramide (Reglan) → EPSE
 - Levodopa (Sinemet) then used to treat EPSE

- E.g. NSAID → HTN
- HTN then treated with antihypertensive

Inappropriate Medication Use

- Examples of inappropriate med use:
 - Polypharmacy
 - Correlates with adverse drug reactions, noncompliance
 - Use of contraindicated meds
 - Beers Criteria
 - Excessive dosing
 - High risk of interactions
 - Safer choice available

Common Clinical Scenarios

- Inappropriate med use is common in the following situations:
 - Anxiety (often presenting symptom of depression)
 - 78% get anxiolytic
 - 32% get antidepressant
 - Drug side effects misdiagnosed as new disease
 - Multiple specialists
 - May be prescribing similar drugs
 - GP's reluctant to discontinue meds started by specialist

General Approach to Pharmacotherapy

- Identify target symptoms
- Initiate appropriate treatment
- Try non-pharmacologic methods first
- Consider patient: medical conditions, diet, environment, drug interactions
- Start low, go slow
- Initiate at half the normal adult dose

General Approach to Pharmacotherapy

- ❑ Simplify the regimen
- ❑ Evaluate for response frequently
- ❑ Make dose changes only after steady-state achieved
- ❑ Increase dose until benefit or toxicity
- ❑ Reevaluate and taper as necessary
- ❑ Avoid undertreatment

Avoid Certain Medications

Benzodiazepines

- Cognitive impairment, falls, hip fractures, MVAs, addiction
- short-acting benzodiazepines safer (controversial)
- Used by 30% of elderly Nova Scotia women

NSAIDS

- GI bleeds, HTN, CHF, renal failure
- Acetaminophen should be first line for osteoarthritis (OA)

Avoid Certain Medications

Meperidine (Demerol)

- Higher incidence of central nervous system (CNS) effects than other opioids
- Interaction with monoamine oxidase inhibitors (MAOIs)

Amitriptyline (Elavil)

- Strongly anticholinergic
- Postural hypotension and falls
- Other tricyclic antidepressants (TCAs) can be used to treat neuropathic pain

Avoid Certain Medications

- Fluoxetine (Prozac)
 - long half-life
- Benztropine (Cogentin)
 - anticholinergic
- Metoclopramide (Maxeran)
 - EPSE
- Dimenhydrinate (Gravol),
diphenhydramine (Benadryl),
hydroxyzine (Atarax)
 - anticholinergic

Use Appropriate Doses

Medication	Too high	Why
HCTZ	> 25 mg	↓Na, ↓K, ↑glucose
Iron	> 325 mg	Abdominal pain, constipation
Digoxin	>0.125 mg	Delirium, nausea, arrhythmia
Haldol	>2 mg	EPSE
Lithium	Level >0.4-0.8	Toxicity

Antipsychotics: EPSE

Parkinsonism: shuffling gait (sticky feet), rigidity, tremor, drool, *common in seniors*

Dystonia: abnormal postures produced by sustained, contorting, twisting muscle spasms most often involving the head and neck, *uncommon in seniors*

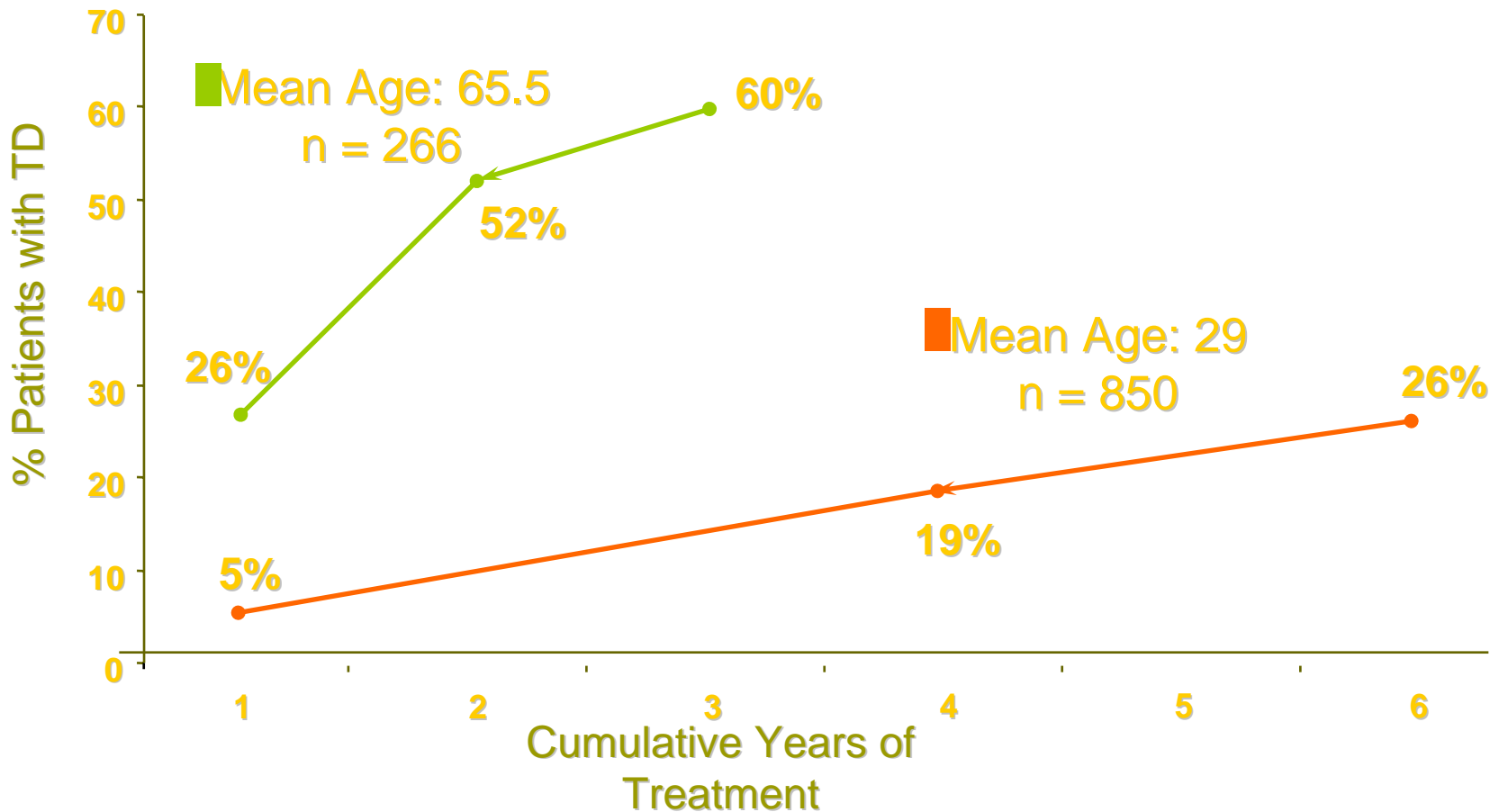
Akathisia: subjective sense of restlessness, e.g., shifting from foot to foot, inability to sit still (often misinterpreted as agitation)

From Jibson and Tandon. J Psychiatr Res 1998;32:215-228; and Bilder. Can J Psychiatry 1997;42:255-264

Tardive Dyskinesia

- ❑ Abnormal writhing involuntary movements
- ❑ Orofacial: tongue, mouth, face
 - Most common site
 - Impaired eating and swallowing, dental problems, speech problems
- ❑ Limbtruncal:
 - Gait disturbances may lead to falls, injuries
- ❑ Stigma
- ❑ May last years after stopping medication
- ❑ 5.6X more prevalent in elderly

Incidence of Tardive Dyskinesia in Older and Younger Patients



■ Jeste et al. Arch Gen Psychiatry 1995;52:756-765

■ Kane JM. Psychopharmacology: The Fourth Generation of Progress. Raven Press Ltd. 1995;1485-1495.

TD – Atypical Antipsychotics

- Lower incidence of TD than with typical antipsychotics
 - Best established with clozapine
 - Risperidone - compared to haldol after 9 months of treatment
 - Risperidone - 5% TD
 - Haldol - 30% TD
- ? Due to serotonin antagonism

TD – Risk Factors

- Length of drug exposure
 - > 90 days
 - Cumulative amount of antipsychotic (especially high-potency typicals)
- * Increased age
- EtOH abuse/dependence
- Subtle movement disorder at baseline, early EPSE
- Dementia

Jeste, 2001

TD – Prevention

- ❑ Avoid typicals, especially in high risk patients
- ❑ Use lowest effective doses
- ❑ Examine patients at baseline and at regular intervals thereafter
- ❑ Reduce and discontinue ASAP after TD detection
 - TD will likely worsen after discontinue of an antipsychotic
- ❑ Switch to an atypical (cross over)

Antipsychotic Side Effects

□ Conventional

- *EPSE (falls) / TD*
- sedation*
- postural hypotension*
- anticholinergic*
- ↓ cognition
- ↑Prl, osteoporosis
- cardiac (QTc)

*low potency

□ Novel

- minimal EPSE
- minimal or no TD
- ? improve cognition
- *weight gain*
- sedation

Elderly are more vulnerable to SEs

Anticholinergic Side Effects

- ❑ Confusion
 - Incontinence meds or increased anticholinergic load associated with worse cognition
- ❑ Tachycardia
- ❑ Dry mouth
- ❑ Constipation
- ❑ Urinary hesitancy / retention
- ❑ Blurred vision
- ❑ Exacerbation of narrow-angle glaucoma

Common Medical Drugs with Anticholinergic Effects

- ❑ Furosemide
- ❑ Digoxin
- ❑ Theophylline
- ❑ Warfarin
- ❑ Prednisone
- ❑ Triamterene and hydrochlorothiazide
- ❑ Nifedipine
- ❑ Isosorbide
- ❑ Codeine
- ❑ Cimetidine
- ❑ Captopril
- ❑ Ranitidine
- ❑ Ditropan

Psychotropic Medications With Anticholinergic Properties

- Thioridazine
- Mesoridazine
- Chlorpromazine
- Perphenazine
- Loxapine
- Cogentin
- Trifluoperazine
- Thiothixene
- Clozapine
- Olanzapine
- Tricyclic antidepressants

SSRIs – Selected Effects

- Hyponatremia
- CP450 interactions
 - Fluoxetine inhibits 3A3/4 (alprazolam), 2D6
 - Fluvoxamine inhibits 3A3/4, 1A2 (warfarin)
 - Citalopram has no reported interactions
- Bleeding (GI, bruising, epistaxis)
 - Low absolute risk but be cautious if there are other risk factors (eg warfarin use)
 - Consider stopping if bleeding occurs

TCA's - Selected Effects

- Sedation
- Orthostatic hypotension
 - Drop of systolic pressure greater than 10mm associated with dizziness
 - Risk of falls/fractures
- Anticholinergic
 - Amitriptyline and imipramine are the worst
 - Desipramine has the least effect

Lithium – Drug Interactions

DRUG	[Li]	COMMENT
Diuretic: Thiazide (HCT) * Loop (lasix)	↑ ↑	-thiazides act in distal tubule -loop - may not be significant
ACE-inhibitors	↑	-unknown mechanism -1-2 months after started
NSAIDs	↑	-especially indomethacin -unpredictable effect

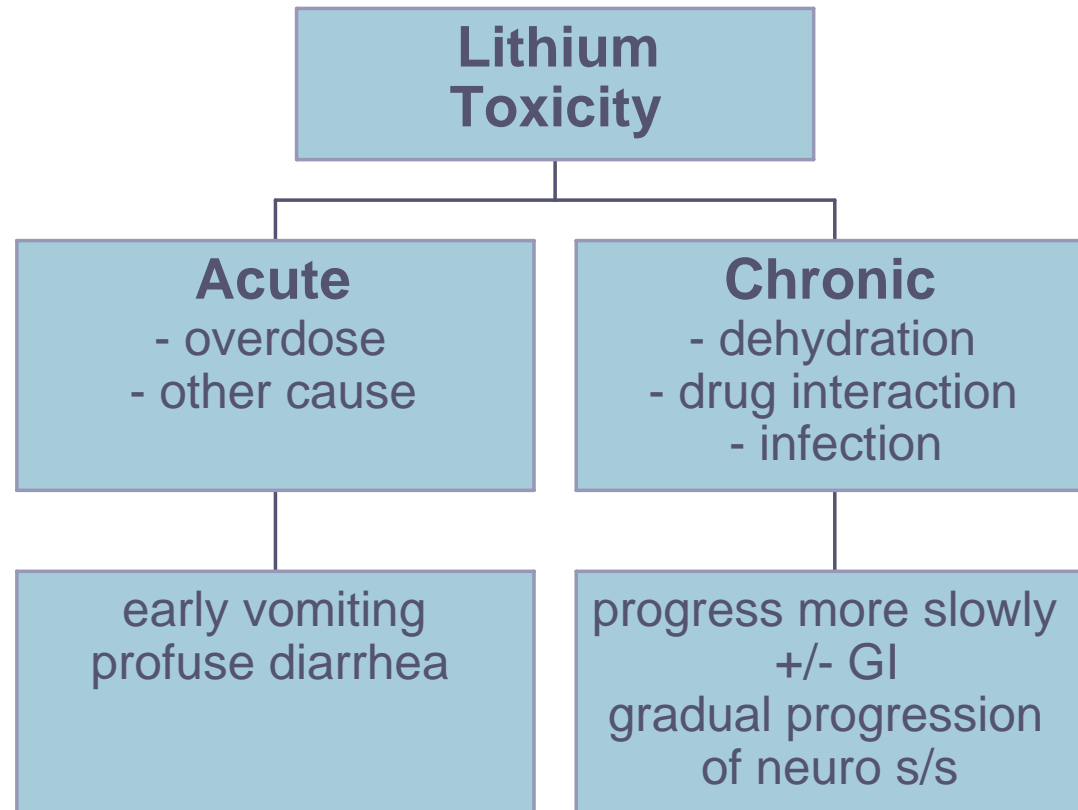
*Pharmacokinetic interaction - interferes with clearance

Lithium – SEs and Toxicity

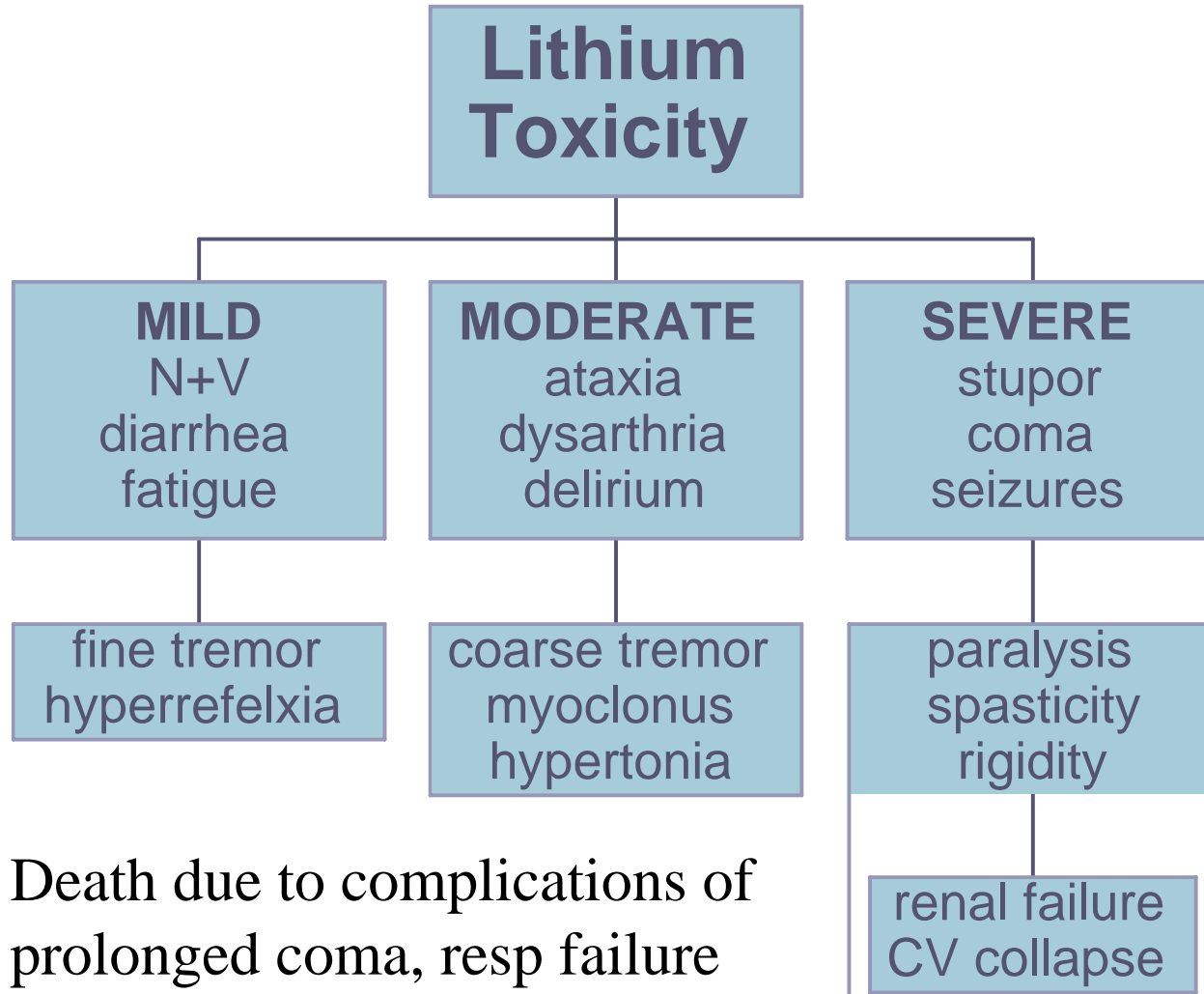
System	Side effects	Toxicity
GI	+	+
Neuro	+	+
Renal	+	*
CV	+	*
Endocrine	+	-
Other	+	-

* Only if severe toxicity

Lithium Toxicity



Lithium Toxicity



Lithium Levels

<u>Group</u>	<u>Level</u>
QEII Lab	0.6-1.2
Adult	
□ Mania	0.8-1.1
□ Maintenance	0.8-1.1
Elderly	0.5-0.8

*Level depends on side effects

Lithium Toxicity

- Lithium toxicity can lead to irreversible effects
 - Most patients completely resolve
 - Effects can last for months
 - Permanent if > 6 months
 - Cerebellar most common
 - Cognition
 - ↓STM, ↓comprehension, dementia
 - Choreoathetosis
 - EPSE
 - History of antipsychotic use

Lithium Toxicity – Irreversible Cerebellar Effects

COMMON

- ❑ Dysarthria (common, most likely to improve)
- ❑ Truncal ataxia
- ❑ Gait ataxia
- ❑ Incoordination of limb movements

UNCOMMON

- ❑ Tremor in head, hands (intention tremor)
- ❑ Nystagmus

Benzodiazepines – Risks of Use

- BMJ Nov 05 (Glass et al)
 - They help with sleep, but compared to placebo:
 - 4.8X more adverse cognitive effects
 - 2.6X adverse psychomotor events (falls, dizziness, loss of balance)
 - 3.8X daytime fatigue
- Arch Int Med 2004; 164: 1567
 - Risk of hip # highest in first two weeks of use
 - 54% increase risk
 - Short half-life probably not safer

Benzodiazepines

- ❑ Do not use long-term (> 6 months)
- ❑ Recommended in seniors:
 - lorazepam, oxazepam, temazepam, ?clonazepam
 - ❑ Do not rely on liver metabolism
- ❑ Taper slowly
 - Over weeks to months
- ❑ If abrupt discontinuation:
 - Withdrawal
 - ❑ Tremor, tachycardia, delirium, seizures
 - Rebound anxiety

Stopping Benzodiazepines

- ❑ Consolidate to one benzodiazepine
 - Consider equivalent dose of clonazepam
- ❑ Can take months/years (outpatient)
- ❑ Patient involvement in drafting schedule
- ❑ Maintain same number of doses for as long as possible
- ❑ Can cut by larger amounts in the beginning
 - Up to one half of the dose depending on duration of benzo use
- ❑ Cut by smaller amounts later in taper
- ❑ Be prepared to hold taper during stress

References

- ❑ Bilder. Can J Psychiatry. 1997;42:255-264.
- ❑ Glass et al. BMJ. Nov 2005.
- ❑ Gordon, J. Drugs and Ther. Jan-Feb 2000.
- ❑ Hermann, N. "Principles of Geriatric Psychopharmacology", *In Practical Psychiatr in the Long-term Care Facility*. 2001.
- ❑ Jeste et al. Arch Gen Psychiatry. 1995;52:756-765.
- ❑ Jeste, D. J Clin Psych. 2000.
- ❑ Jibson and Tandon. J Psychiatr Res. 1998;32:215-228.
- ❑ Maletta et al. Geriatrics. 2000;55(3):65.
- ❑ Tune et al. Am J Psychiatry. 1992;149(10):1383-1394.
- ❑ Wagner et al. Arch Intern Med. 2004;164:1567-1572.
- ❑ Yuan et al. Am J Med. 2006;119(9):719-727.