475 GERIATRIC PSYCHOPHARMACOLOGY (p.1)

I. General Information

- Use lower doses
- "Start low and go slow"
- Expect prolonged elimination ½ lives
- Expect sedative-hypnotics to be "dementing", to impair cognitive functions
- Expect sedative-hypnotics to impair psychomotor coordination, to increase risk of falls & driving problems
- Expect problems with depression and with mixed depression/anxiety and treat same
- Use psychological (cognitive/behavioral) therapies when possible to treat anxiety, sleep and other disorders
- Keep medication use to a minimum whenever possible (in general, psychoactive meds tend to be overused in elderly)

II. Parkinson's Disease

A. Description

- Results from loss (death) of dopaminergic neurons in basal ganglia (caudate & putamen), whose somas are in substantia nigra in midbrain
- Can be caused by genetic factors, exposure to neurotoxic agents (e.g. pesticides), secondary to use of dopamine blocking drugs (e.g. neuroleptics)
- Behavioral Sxs: Extrapyramidal motor losses – *bradykinesia* (slowness & poverty of movement), *muscle rigidity* (esp. "cogwheel" rigidity), *resting tremor* (abates during voluntary movements),and *impairment of postural balance* ✍ gait disturbances, falling
- Other Sxs: difficulties swallowing, mask-like facies, lowered sex drive, dementia, ANS sxs (see Table 13.1, p.424, 10th Ed.)
- Above sxs are seen when > 80% of dopaminergic neurons are lost (perhaps after years of gradual neural losses w/o sxs)

2nd most common neurodegenerative disease (after Alzheimers)

II. **Parkinson's Disease** (cont.)

A. **Description of Disease**

- PD occurs in 0.5 – 1% of persons 65-69 yrs., 1 – 3% of persons = or > 80 yrs. old
- Pharmacological treatments involve: DA replacement or agonists, and DA breakdown antagonists/inhibitors
- Non-pharmacological treatments involve: stem cell transplants, neural lesions (e.g. of globus pallidus), physical therapy, occupational therapy, family therapy, etc.

B. **Pharmacological Treatments**

1. **Levodopa (l-DOPA) (dopamine replacement)**

- Tyramine ✍ DOPA (dihydroxyphenylalanine) ✍ dopamine ✍ norepinephrine (each step using its own enzyme)
- Dopamine does not cross the BBB, DOPA does
- DOPA is converted into dopamine in CNS
- L-DOPA is more active than D-DOPA (isomers)
- 95% of initial PO dose of l-DOPA is converted into dopamine in plasma, where is causes unwanted SEs in body (e.g. nausea)
- 1 – 5% of initial PO dose crosses BBB and is converted into dopamine in presynaptic terminals of basal ganglia
- The enzyme dopa decarboxylase converts DOPA into dopamine, both in body and in CNS
- carbidopa (is an enzyme that blocks dopa decarboxylase in body, but cannot pass BBB)
- **Sinemet** = carbidopa + levodopa, effectively blocks 75% of conversion into dopamine in body ✍ lessens body SEs
- "*Wearing off" phenomenon*: Levodopa becomes less and less effective as time passes (2^{nd} to short ½ life + other factors), develops over 1-5 years of use, limits this treatment
- Can increase dose levels and/or reduce time intervals between doses, but both ✍ increased SEs (e.g. dyskinesias – spasms, restlessness)
- Concern that DOPA may accelerate course of PD…

II. **Parkinson's Disease**

C. **Pharmacological Treatments** (cont.)

2. **COMT Inhibitors**

- COMT = catechol-o-methyltransferase (enzyme found in synaptic cleft, some in presynaptic membrane), degrades catecholamines, incl. DA
- Found also in GI tract and liver (converts levodopa into inactive metabolite)
- **Comtan (entacapone)** inhibits COMT peripherally (not in CNS), thus more levodopa remains in body to pass into CNS to be converted into dopamine; not yet associated with liver toxicity
- **Stalevo** = **levodopa + carbidopa + entacapone** (available '04), this new drug has become the starting point for pharmacotherapy for PD: provides more dopamine to the CNS (vs. giving just levodopa), and lessens the "wearing off" effects, and reduced the dose of levodopa needed (which reduces SEs)

3. **Dopamine Receptor Agonists**

- "Wearing off" phenomenon may also be due to gradual loss of the ability to synthesize and/or store DA by presynaptic neurons; may also be due to continued death of DA neurons
- If this is the case, then using drugs that were DA RS agonists would bypass the above problems and would directly stimulate the basal ganglia structures
- Might then use such drugs in the later stages of PD, even after all DA neurons were lost
- DA RS agonists: **selegiline (Eldepryl), pergolide (Permax), bromocriptine (Parlodel)** all primarily affect the **DA2** RS; **pramipexole (Mirapex)** and **ropinirole (Requip)** both primarily affect the **DA3** RS
- SEs: somnolence, dizziness, nausea, hallucinations, & insomnia
- **modafinil (Provigil)** is used to tx EDS
- Mirapex & Requip are both used for early-onset PD, are efficacious, have fewer SEs, & long ½ lives (✍ less "wearing off" effects)

II. **Parkinson's Disease**

B. **Treatment**

3. **Dopamine Receptor Agonists** (cont.)

- **selegiline (Eldepryl)** acts via a unique mechanism: is a selective and irreversible inhibitor of MAO-B enzyme (which has a preferential affinity for DA) in CNS
- if taken in doses > 10 mg/day will inhibit MAO-A enzyme ✍ would act as a norepinephrine and serotonin agonist
- selegiline (Eldepryl) has no effect on peripheral levels of MAO-B ✍ no "cheese reaction" with tyramine-containing foods
- selegiline appears to slow down the progression of PD, may delay necessity of starting levodopa therapy
- selegiline is metabolized into several active metabolites, including *amphetamine* and *methamphetamine* (✍ usual SEs)
- attempts are being made to give selegiline in a non-PO route, in order to avoid 1st pass metabolism (transdermal patch?)
- after using selegiline > 5 yrs. morbidity (unknown causes) may increase…

4. **Acetylcholine Muscarinic Receptor Antagonists**

- used prior to development of levodopa therapy
- based on assumption (probably valid) that some of the PD sxs were due to too little DA vs. "too much" ACh
- antiACh drugs can help reduce tremor in about 50% of PD pts., although they do not reduce rigidity or bradykinesia
- SEs include reduced cognitive function & memory (which limits the use of these drugs)
- **trihexyphenidyl (Artane), procyclidine (Kemadrin), biperiden (Akineton), ethopropazine (Parsidol),** & **benztropine (Cogentin)**
- **diphenhydramine (Benadryl)** (anti-H) is sometimes used due to is significant antiACh properties

5. **CEP-1347**

- drug in development that may help DA neurons survive whatever is killing them ("neuroprotective" effects)

III. **Alzheimer's Disease**

A. **Description of Disease**

- the most common neurodegenerative disease
- comprises 2/3rds of all cases of dementia
- remaining 1/3rd of dementias caused by vascular (e.g. multi-infarct dementia) or other causes (e.g. Pick's Disease)
- irreversible loss of neurons (esp. ACh neurons), esp. in cerebral cortex, hippocampus
- onset usually > 60 yrs.
- 1 – 5% in 65-69 yrs., 40 – 50% in 95+ yrs. in USA
- Prevalence doubles every 5 years after age of 65 yrs.
- Time between sx onset and death = about 8 – 10 years (shorter interval the younger AD is diagnosed, more aggressive form)
- Sxs: cognitive deterioration (memory, judgment, decision making impairment), loss of orientation to place and time, loss of language, dementia (anterograde amnesia),
- Pharmacological treatment: *AChE inhibitors* (for mild to moderate cases)
- specific drug therapy for other sxs as they develop in more severe cases: antidepressants for *depression* (drugs that lack antiACh effects – e.g. SSRIs); "energizing" drugs for *apathy* (CNS psychostimulants, bupropion/Wellbutrin, DA RS agonists - bromocriptine/Parlodel, and antiPD drugs – memantine/Namenda; atypical antipsychotics for *psychosis*, agitation, etc.; possible use of mood stabilizers, trazadone/Desyrel, or SSRIs also for *behavioral problems*

B. **AChE Inhibitors**

- 4 drugs approved for AD so far, all are AChEIs: **tacrine (Cognex), donepezil (Aricept), rivastigmine (Excelon),** & **galantamine (Reminyl)**
- All produce modest improvements in cognition, but all have SEs 2nd to peripheral effects (nausea, diarrhea, abdominal cramping, anorexia, and rarely increased aggression)
- tacrine (Cognex) now rarely used: liver enzyme inducer in 50% pts.

III. **Alzheimer's Disease**

B. **AChE Inhibitors** (cont.)

- donepezil (Aricept) appears to be more selective for AChEI in CNS vs. periphery…why is this a good thing?; has a long half-life; not helpful with vascular dementias
- both rivastigmine (Excelon) and galantamine (Reminyl) produce modest improvements in cognition, with former drug having a very long-lasting effect

C. memantine (Namenda)

- is a new "moderate affinity" noncompetitive NMDA RS antagonist that has neuroprotective properties in AD pts.,(perhaps for same reasons that blocking "glutamate cascade" helps after a CVA), may block "excitotoxicity"
- does not seem to have adverse SEs (different from ketamine with its high affinity for NMDA RS); at high doses can have some amnestic effects (= ketamine)
- may be modestly helpful in improving cognitive abilities in vascular dementias as well
- may be safely combined with AChEIs

D. New Drugs Under Investigation

- alzhemed ( ) prevents formation/depositing of beta amyloid fibrils, prevents inflammatory process that follows
- ampalex (CX516) is a modulator of glutamate AMPA RS
- NS-2330 increases activity in DA, NE, & ACh neurons