I. **General Information**

? Use lower doses  
? “Start low and go slow”  
? Expect prolonged elimination ½ lives  
? Expect sedative-hypnotics to be “dimenting”, 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 $\leftrightarrow$ DOPA (dihydroxyphenylalanine) $\leftrightarrow$ dopamine $\leftrightarrow$ 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 $\leftrightarrow$ lessens body SEs

? “Wearing off” phenomenon: Levodopa becomes less and less effective as time passes (2nd 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 $\leftrightarrow$ increased SEs (e.g. dyskinesias – spasms, restlessness)

? Concern that DOPA may accelerate course of PD…
GERIATRIC PSYCHOPHARMACOLOGY (p.3)

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 sxss 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