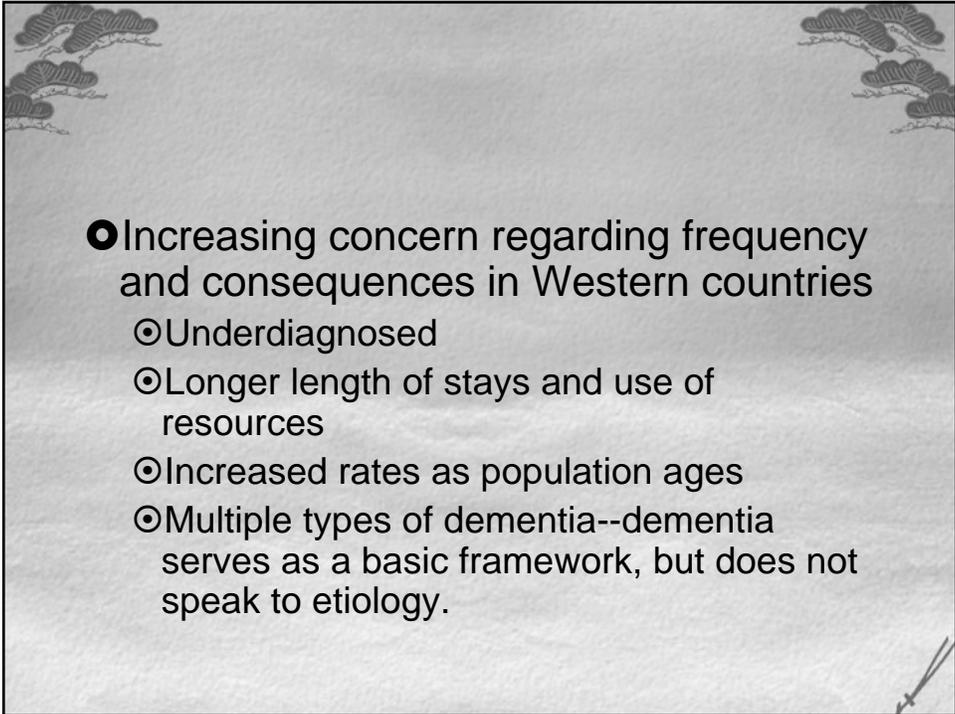


Vascular Dementia: An update for primary care practitioners

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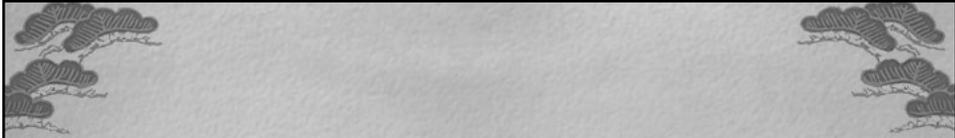
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- Increasing concern regarding frequency and consequences in Western countries
 - ⊙ Underdiagnosed
 - ⊙ Longer length of stays and use of resources
 - ⊙ Increased rates as population ages
 - ⊙ Multiple types of dementia--dementia serves as a basic framework, but does not speak to etiology.

Dementia Criteria

- Impairment of memory
 - ⊙ Also requires deterioration in at least 2 other cognitive domains;
 - ⊙ Aphasia, apraxia, agnosia, executive function
 - ⊙ Clear consciousness
 - ⊙ Impairment in ADL's/social/occupational activities are impaired due to the decline in cognition;
 - ⊙ Duration of 6 months.

Etiologies

- Associated with multiple conditions
 - ⊙ Prevalence 9.6% for all types after age 65
 - ⊙ Incident may double every 5 years after 65
 - ⊙ DAT 6.5% prevalence (65% of dementia)
 - ⊙ Remainder of cases secondary to vascular, HIV, mixed, frontotemporal, and others.
 - ⊙ Mixed vascular/DAT or VaD comprises the second largest group (20-25%).



● Vascular and Mixed Dementias

- ⊙ Often conceived of as a subcortical dementia...except when it's not.
- ⊙ Better conceptualized as a disseminated brain disease--systematic workup and treatment required.
- ⊙ Major differences with DAT, so diagnosis and treatment differ significantly.



● Vascular dementia (VaD)

- ⊙ Dementia resulting from ischemic, ischemic-hypoxic, or hemorrhagic brain lesions due to cerebrovascular or cardiovascular pathology (Roman 2002).
- ⊙ Heterogeneous concept/presentation;
 - ⊙ Later in life...or not;
 - ⊙ Cumulative effects of cerebrovascular disease in all forms--diagnostic criteria acknowledge these differences.



● NINDS-AIREN 1993 Specific Types

- ◎ 1. Multi-infarct dementia (large-vessel infarcts)
- ◎ 2. Strategic single-infarct dementia (PCA, ACA, B thalamic, BF)
- ◎ 3. Small-vessel disease with dementia-multiple lacunes (basal ganglia, frontal WM, PVWM = Binswanger's)
- ◎ 4. Hypoperfusion (global due to arrest or hypotension; watershed)
- ◎ 5. Hemorrhagic dementia (chronic SDH, SAH, ICH, CAA)
- ◎ 6. Other mechanisms (combinations of above, or unknown)



● Total volume of infarcted brain and total number of infarcts correlate well with VaD severity;

● Locations of infarcts also common;

- ◎ 2/3--pathological correlate is a lacunar state with multiple lacunar infarcts in subcortical structures (BG & thalamus)

● Vascular cognitive impairment proposed to broaden definition of VaD...why?



VaD vs. Mixed vs. DAT

- Data show emerging role of vascular disease in DAT & other dementias;
- Pure VaD now considered quite unusual;
- Most DAT have a cerebrovascular comorbid overlay;
- Mixed previously underestimated--now considered quite common;
- VaD & DAT may share pathogenetic mechanisms.

- Thus, a heterogeneous presentation of cerebrovascular disease leads to heterogeneous clinical presentations:

- ⊙ Cortical

- ⊙ Infarcts affecting primarily the cortex;
- ⊙ Focal neurological signs more common;

- ⊙ Subcortical

- ⊙ History of hypertension
- ⊙ Deep lacunae infarcts in white matter;
- ⊙ Accumulative white matter destruction.

⊙ Subcortical (continued)

⊙ Important variant: subcortical arteriosclerotic encephalopathy (Binswanger's disease)

- Pseudobulbar palsy
- Spasticity
- Weakness
- Profound apathy/avolition/amotivation;
- Extensive diffuse demyelination of white matter in periventricular regions;
- More frequent than previously estimated.

● Vascular dementia

- ⊙ Commonly understood as a stepwise progression...except when it doesn't.
- ⊙ VaD may progress as smoothly as patients with DAT--supported by recent neuroimaging techniques;
- ⊙ Affective changes common;
- ⊙ Personality changes uncommon...except when they occur, in which case prominent;



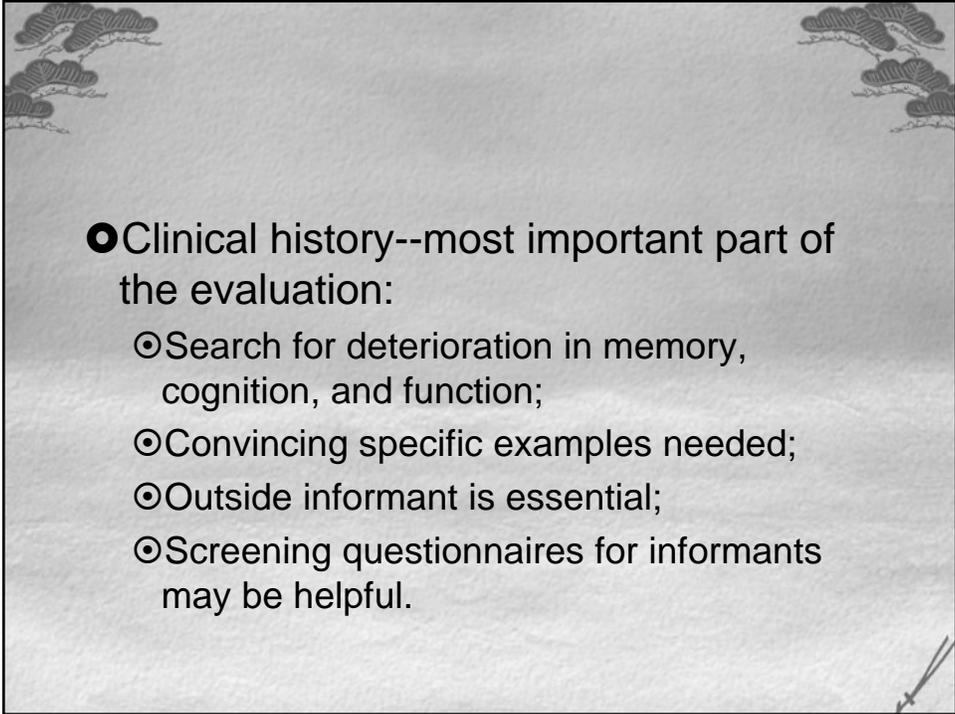
- Post-stroke depression

- ⊙ Stroke is 3rd leading cause of mortality;
- ⊙ Most common serious neurological disorder--50% of all acute neuro hospitalizations.
- ⊙ Mean prevalence rates 23% for all ambulatory samples of stroke patients.
- ⊙ Affects functional rehabilitation & cognitive functioning in post-stroke period.
- ⊙ Little association b/w location--more likely associated with lesions in subcortical white matter, thalamus, BG, and brain stem (Bogouslavsky 2003).



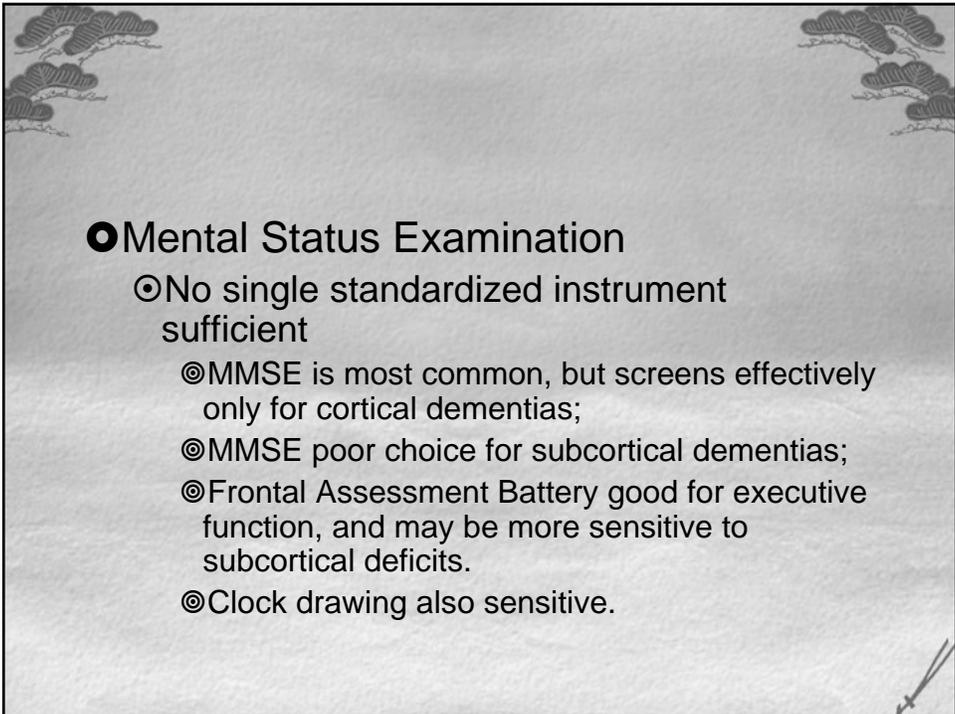
Diagnosis & Differential

- Early diagnosis important in vascular dementia, as it (theoretically) can be prevented with proper interventions;
- Where cerebrovascular disease exists--so does cardiovascular disease and peripheral vascular disease--surrogate markers for risk.



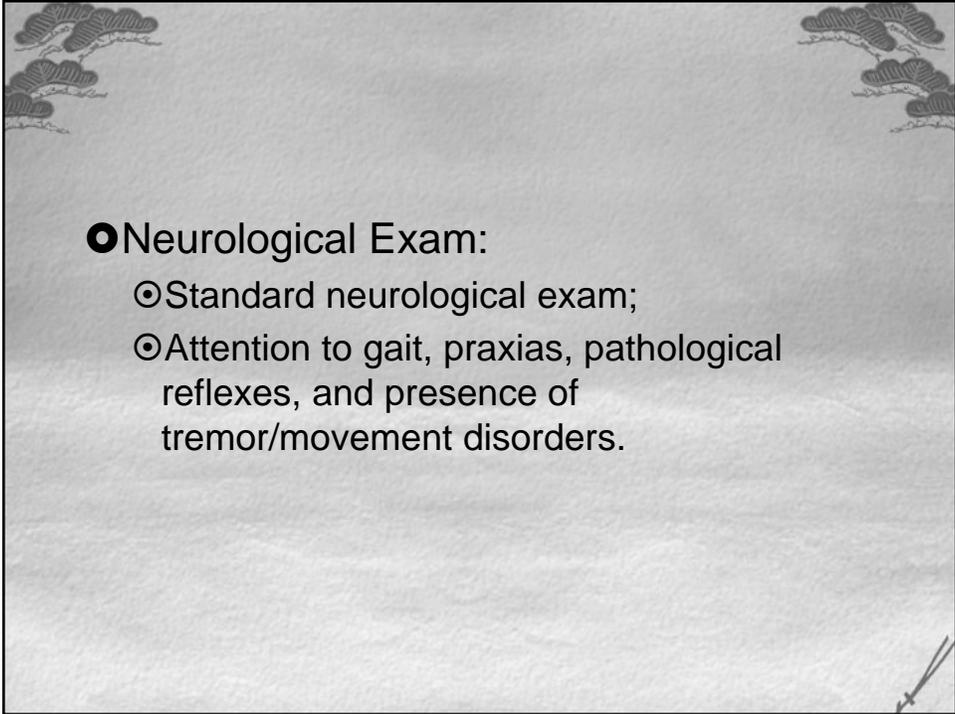
● Clinical history--most important part of the evaluation:

- ⊙ Search for deterioration in memory, cognition, and function;
- ⊙ Convincing specific examples needed;
- ⊙ Outside informant is essential;
- ⊙ Screening questionnaires for informants may be helpful.



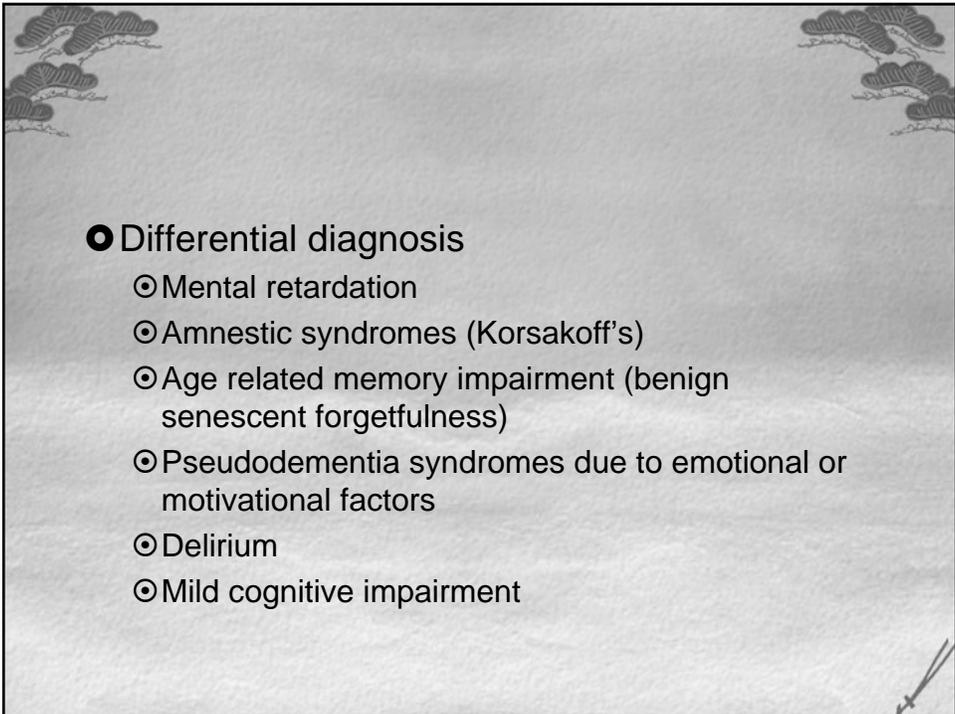
● Mental Status Examination

- ⊙ No single standardized instrument sufficient
 - ⊙ MMSE is most common, but screens effectively only for cortical dementias;
 - ⊙ MMSE poor choice for subcortical dementias;
 - ⊙ Frontal Assessment Battery good for executive function, and may be more sensitive to subcortical deficits.
- ⊙ Clock drawing also sensitive.



● Neurological Exam:

- ⊙ Standard neurological exam;
- ⊙ Attention to gait, praxias, pathological reflexes, and presence of tremor/movement disorders.



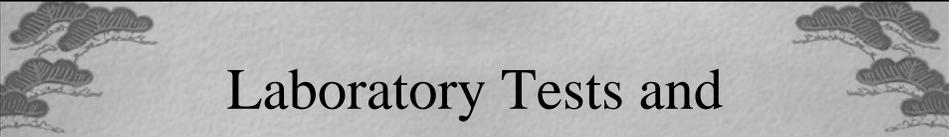
● Differential diagnosis

- ⊙ Mental retardation
- ⊙ Amnestic syndromes (Korsakoff's)
- ⊙ Age related memory impairment (benign senescent forgetfulness)
- ⊙ Pseudodementia syndromes due to emotional or motivational factors
- ⊙ Delirium
- ⊙ Mild cognitive impairment



● Clinical features suggesting vascular dementia

- ⊙ Mixed cortical-subcortical features;
- ⊙ Preservation of insight/judgment;
- ⊙ Abrupt onset, stepwise course;
- ⊙ Emotional incontinence, lability;
- ⊙ History of vascular disease
- ⊙ Focal neurological signs, symptoms.



Laboratory Tests and Diagnostic Procedures

- Screening battery
 - ⊙ CBC
 - ⊙ Serum chemistries
 - ⊙ TSH, fT4
 - ⊙ VDRL/RPR
 - ⊙ B12/folate/methylmalonic acid
 - ⊙ Fasting lipid panel



● Other selected tests for new dementia:

- ⊙ HIV
- ⊙ Blood/urine screens for EtOH, drugs, heavy metals--based on history;
- ⊙ ANA, C3, C4, anti-ds-DNA Ab, anticardiolipin antibody if rheumatologic factors considered possible;
- ⊙ Disease specific tests (Wilson's disease)



● Tests of questionable clinical utility

- ⊙ Presenilin 1--predicts early-onset DAT, but very low sensitivity;
- ⊙ APOE--associated with late onset DAT, but marker of poor resilience overall;
- ⊙ EEG--limited utility due to non-specific changes that only occur in late stages.
 - ⊙ More likely useful in Creutzfeldt-Jacob

Neuroimaging

● MRI with/without contrast

- ⊙ Effectively screens for most features of dementia safely and with high sensitivity;
- ⊙ Detects vascular lesions, space occupying lesions, hydrocephalus, lobar/structural atrophy, and demyelination;
- ⊙ Biggest “bang for buck” neuroimaging procedure, but lengthy, requires cooperation, and costly.

● CT with/without contrast

- ⊙ Less sensitive but less expensive than MRI;
- ⊙ Requires iodinated contrast--more difficult in patients with renal impairment.

● Positron Emission Tomography (PET)

- ⊙ Most specific and sensitive neuroimaging test for early DAT
 - ⊙ Temporoparietal hypometabolism with relative sparing of visual and sensorimotor cortex;
 - ⊙ Relatively little assistance in characterizing vascular disease, and typically requires concurrent MRI technique.
 - ⊙ Perhaps helpful with differential of frontal dx.



- SPECT (Single photon emission computed tomography)

- ⊙ May assist with characterization of fronto-temporal dementias and vascular dementia, but any positive finding typically requires MRI/CT follow-up.

- ⊙ Not terribly effective for screening and has low sensitivity/specificity.



Vascular Dementia--Prognosis

- Considerable individual variation in survival--highly dependent upon total burden of vascular disease.

- ⊙ Typical cause of death is cardiovascular morbidity--so addressing co-morbid CV disease is paramount to improving survival.

- In contrast:

- ⊙ Huntington's disease: 10-15 years

- ⊙ Parkinson's disease: ~15 years

- ⊙ Wilson's disease: normal survival if early.



VaD: Treatment Options

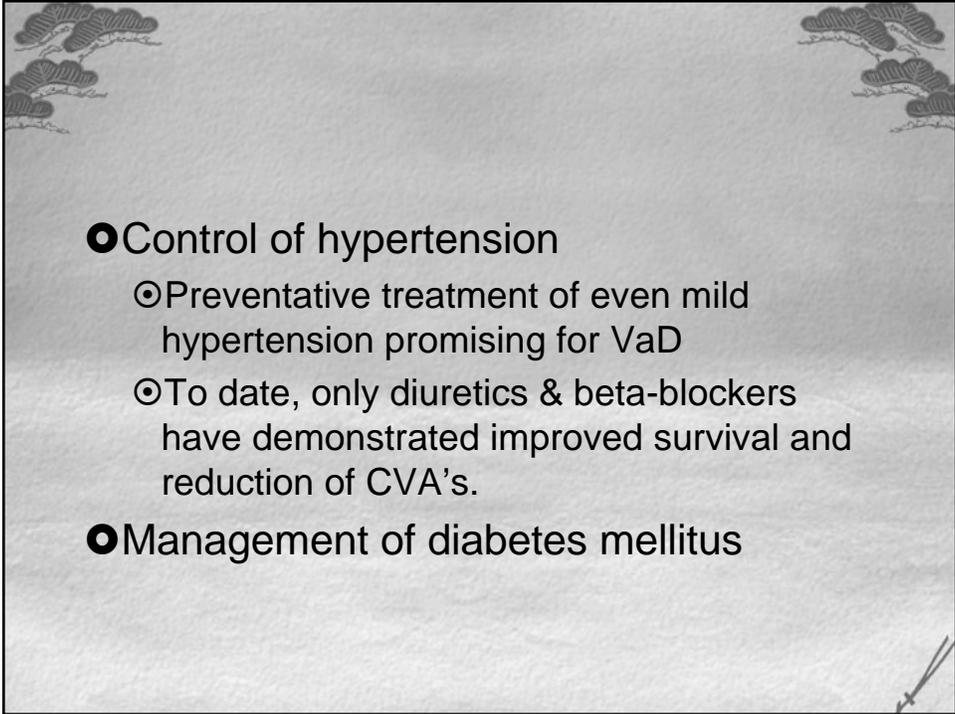
● Address underlying vasculopathic risk factors:

◎ Cardiovascular optimization

- Lipid panel with attempted correction of underlying lipid abnormalities;
- Baseline EKG;
- Consider stress studies if EKG abnormalities or concurrent symptoms suggestive of CAD.
- ASA
- Beta-blockers
- Statins

◎ Anticoagulation

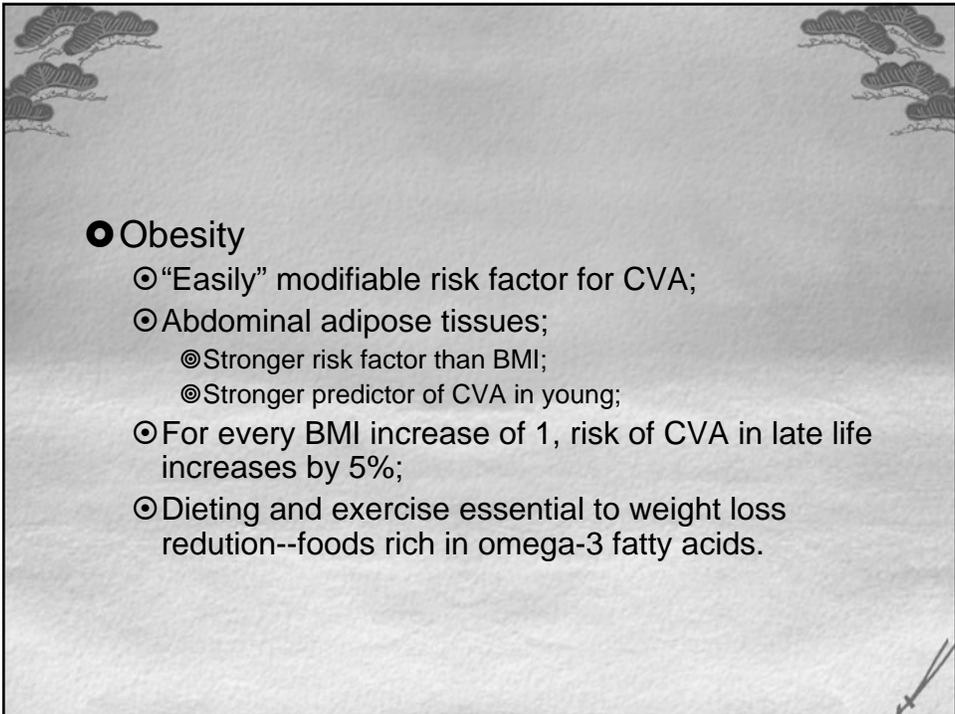
- ◎ ASA to start--remains the backbone of anticoagulation therapy for both cardiovascular and cerebrovascular disease;
- ◎ If cerebrovascular disease progresses, then alternatives include:
 - High dose aspirin;
 - Combination dipyridamole/aspirin;
 - Ticlopidine, clopidogrel (ADP receptor inhibitors);
 - Warfarin.



- Control of hypertension

- ⊙ Preventative treatment of even mild hypertension promising for VaD
- ⊙ To date, only diuretics & beta-blockers have demonstrated improved survival and reduction of CVA's.

- Management of diabetes mellitus



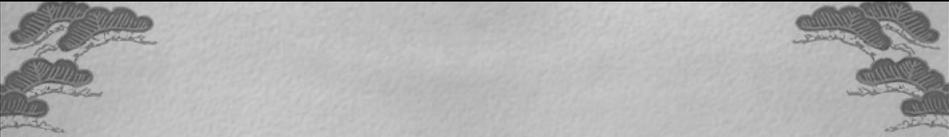
- Obesity

- ⊙ "Easily" modifiable risk factor for CVA;
- ⊙ Abdominal adipose tissues;
 - ⊙ Stronger risk factor than BMI;
 - ⊙ Stronger predictor of CVA in young;
- ⊙ For every BMI increase of 1, risk of CVA in late life increases by 5%;
- ⊙ Dieting and exercise essential to weight loss reduction--foods rich in omega-3 fatty acids.



● Obstructive sleep apnea

- ◎ Closely correlated with obesity typically, but is an independent risk factor for CVA even when controlling for BMI;
- ◎ Other problems include congestive heart failure, daytime sleepiness, and sudden death.
- ◎ Various treatments:
 - ◎ UPPP (50%) success rate;
 - ◎ CPAP
 - ◎ Tracheostomy for severe, refractory cases.



● Nicotine dependence

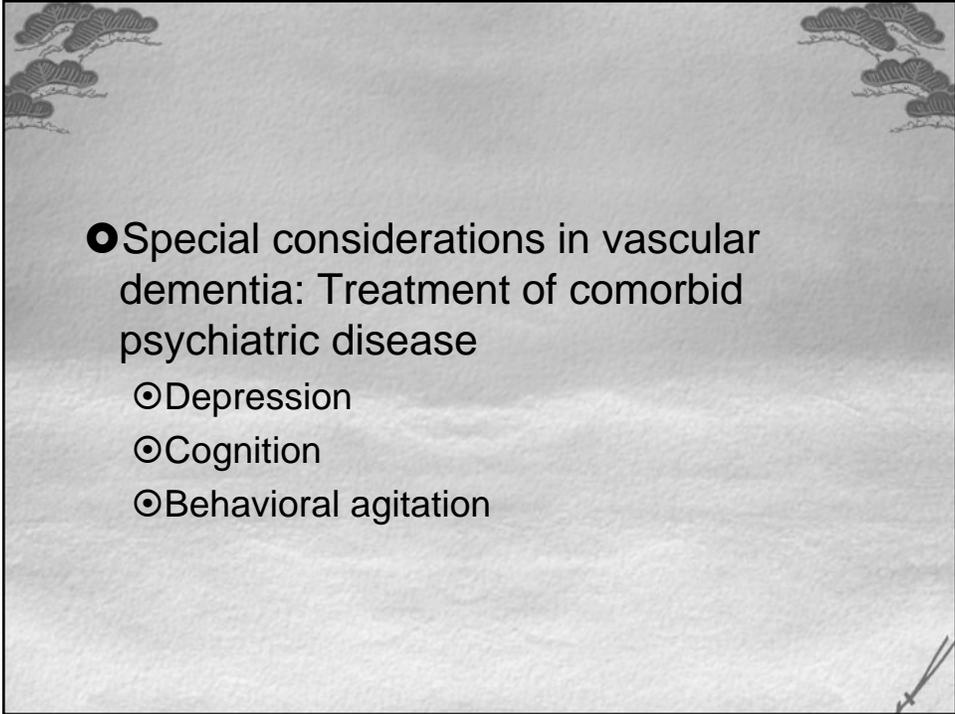
- ◎ Historic meta-analysis addressed risk of CVA due to smoking (Shinton & Beevers 1989)
 - ◎ Disproportionately increased CVA in those less than 55 years of age by OR 2.9;
 - ◎ Risk of hemorrhagic CVA increased by OR 2.9;
 - ◎ Risk of ischemic CVA increased by OR 1.9.
- ◎ Framingham heart study (1988)
 - ◎ Risk of CVA proportionate to amount of smoking;
 - ◎ >2ppd increased risk of CVA by OR 2.0;
 - ◎ Relationship present after controlling for age & HTN;
 - ◎ CVA risk drops soon after stopping (2-5 years).

● Alcohol dependence

- ⊙ Data somewhat confusing--the “middle way” seems correct with this. (1 drink = 12 g EtOH)
- ⊙ Meta analysis (Reynolds et al., 2003)
 - ⊙ Compared with ND, use of >60g EtOH/daily increased risk of total CVA (OR 1.64), ischemic CVA (OR 1.69), and hemorrhagic CVA (OR 2.18).
 - ⊙ Compared with ND, use of 12-24g/day was associated with reduced risk of ischemic CVA (OR 0.72);
 - ⊙ Compared with ND, use of less than 12g/day associated with reduced risk of total (OR 0.83) and ischemic CVA's (OR 0.82).

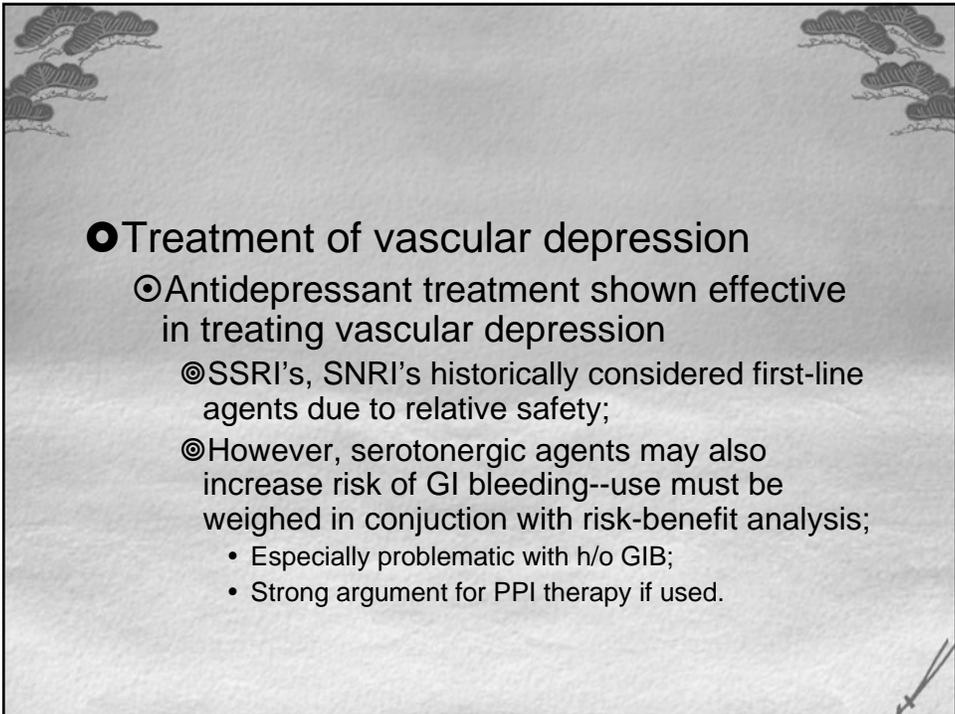
● Alcohol

- ⊙ Data confirmed by other studies (Mukamal et al., 2005) that showed moderate drinking of 1-3 drinks/daily on 3-4 days/week was associated with lowest risk of ischemic CVA (OR 0.68);
 - ⊙ Heavier EtOH use associated with increased hemorrhagic and embolic CVA subtypes;
- ⊙ Modifiable risk factor--screen for EtOH history and those with higher EtOH use, encourage dietary modification or referral to substance abuse treatment.



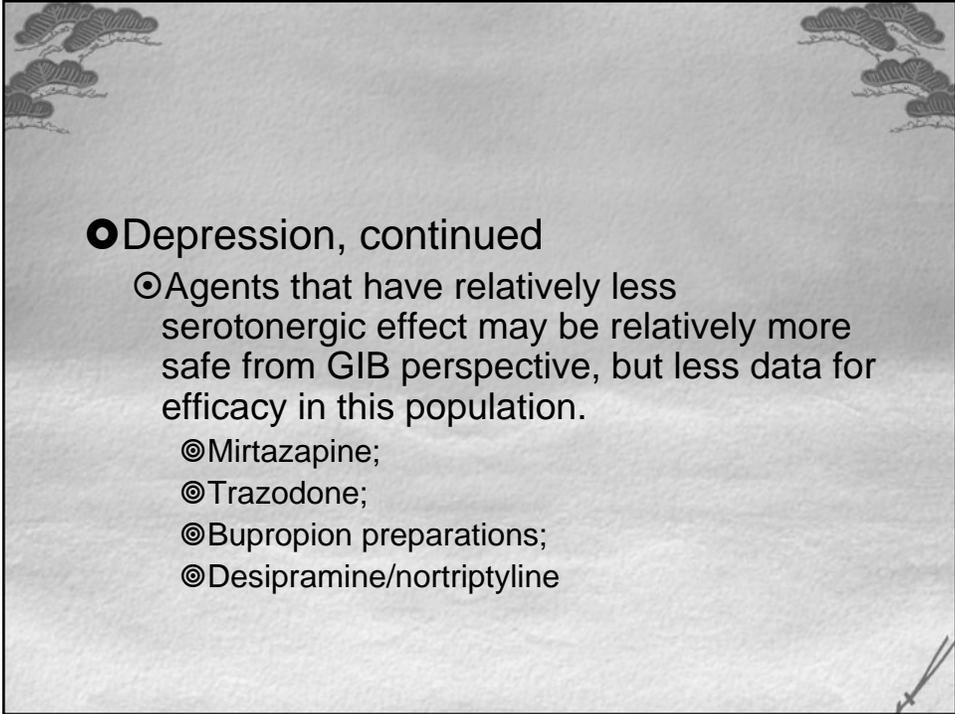
● Special considerations in vascular dementia: Treatment of comorbid psychiatric disease

- ⊙ Depression
- ⊙ Cognition
- ⊙ Behavioral agitation



● Treatment of vascular depression

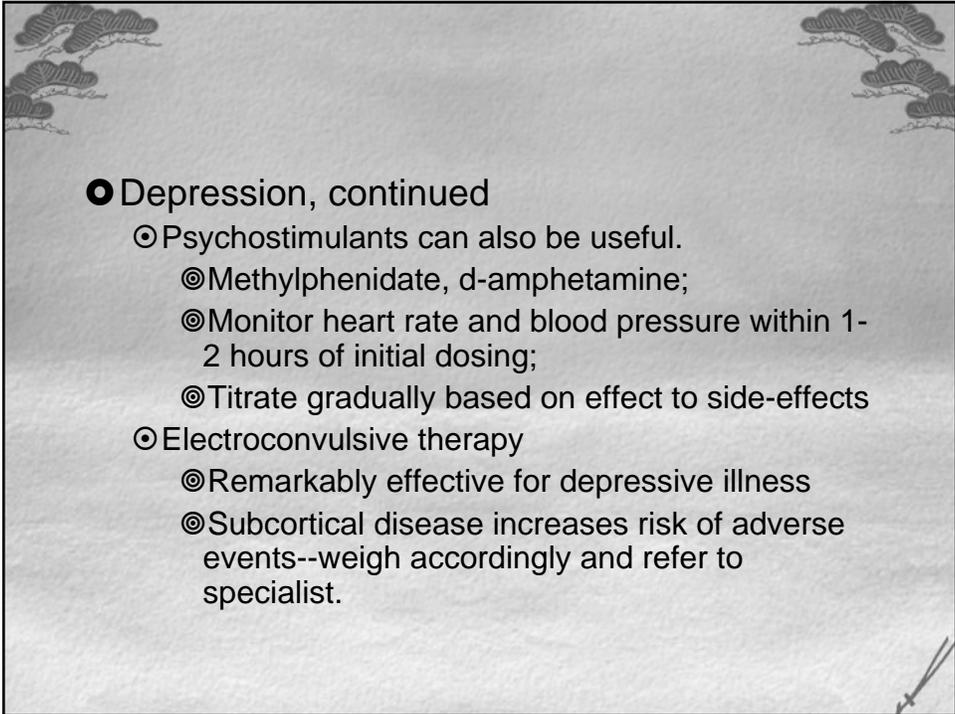
- ⊙ Antidepressant treatment shown effective in treating vascular depression
 - ⊙ SSRI's, SNRI's historically considered first-line agents due to relative safety;
 - ⊙ However, serotonergic agents may also increase risk of GI bleeding--use must be weighed in conjunction with risk-benefit analysis;
 - Especially problematic with h/o GIB;
 - Strong argument for PPI therapy if used.



● Depression, continued

⊙ Agents that have relatively less serotonergic effect may be relatively more safe from GIB perspective, but less data for efficacy in this population.

- ⊙ Mirtazapine;
- ⊙ Trazodone;
- ⊙ Bupropion preparations;
- ⊙ Desipramine/nortriptyline



● Depression, continued

⊙ Psychostimulants can also be useful.

⊙ Methylphenidate, d-amphetamine;

⊙ Monitor heart rate and blood pressure within 1-2 hours of initial dosing;

⊙ Titrate gradually based on effect to side-effects

⊙ Electroconvulsive therapy

⊙ Remarkably effective for depressive illness

⊙ Subcortical disease increases risk of adverse events--weigh accordingly and refer to specialist.



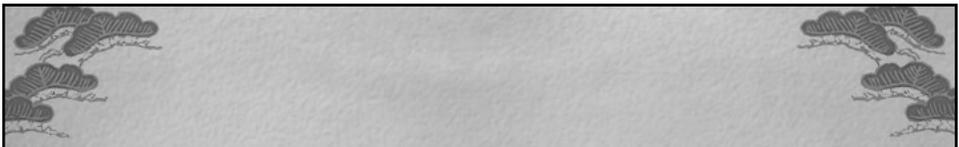
● Treatment of cognition

- ⊙ Overall, remarkably disappointing options;
 - ⊙ Anticholinesterase inhibitors
 - ⊙ Approved for DAT, not for VaD.
 - ⊙ Limited benefit in DAT, but generally safe.
 - ⊙ In VaD, mild-moderate evidence of benefit.
 - ⊙ Memantine--supported by systematic reviews.
 - ⊙ Nimodipine--mixed and VaD.
- 



● Agitation

- ⊙ Agitation and behavioral disturbances present in up to 90% of patients with dementia across the course of their disease;
 - ⊙ Increased risk of nursing home placement;
 - ⊙ Increased risk of hospitalization;
 - ⊙ Inability to maintain a least restrictive environment for their well-being and care.
- 



● Agitation

- ⊙ Interpersonal, social, and environmental interventions can be useful in mild to moderate agitation;
- ⊙ Severe agitation that threatens the integrity of patients and staff requires pharmacological treatment AFTER diagnosis;
- ⊙ Differential includes constipation, urinary retention, pain, delirium, sensory deprivation, depression, etc.
 - ⊙ Antidepressants--may be useful with impulsivity. Very effective with regards to depression and pseudobulbar affect.
- ⊙ Antipsychotics have the best data for treatment of non-specific agitation--they also enjoy black box warnings.



● Agitation

- ⊙ Meta-analysis (Schneider et al, 2006)
 - ⊙ Efficacy noted for risperidone and aripiprazole
 - ⊙ Smaller effects for less severe dementia, outpatients, and patients selected for psychosis
 - ⊙ Cognitive test scores worsened with drugs
 - ⊙ No evidence for increased injury, falls, or syncope;
 - ⊙ Significant risk for cerebrovascular events, especially with risperidone .



● Agitation

◎ Meta-analysis (Ballard & Waite, Cochrane Review, 2006).

- ◎ Risperidone & olanzapine significantly improved aggression compared to placebo;
 - ◎ Risperidone significantly improved psychosis;
 - ◎ Risperidone and olanzapine both showed significantly higher incidence of serious adverse cerebrovascular events (including stroke), extra-pyramidal side effects and other adverse outcomes;
 - ◎ Risperidone and olanzapine had increased numbers of dropouts in trial;
 - ◎ Data were insufficient to examine impact upon cognitive function.
- 



● Agitation

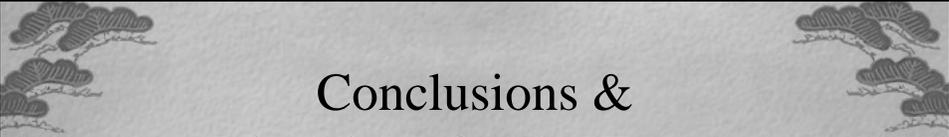
◎ Risk of death/AE meta-analysis (Schneider et al., JAMA, 2005)

- ◎ Death occurred more often among patients randomized to drugs (118 [3.5%] vs 40 [2.3%]).
 - ◎ The OR by meta-analysis was 1.54; 95% confidence interval [CI], 1.06-2.23; P = .02
 - ◎ Sensitivity analyses did not show evidence for differential risks for individual drugs, severity, sample selection, or diagnosis.
- 



● Agitation—conclusions

- ◎ Efficacy data exist for atypicals in control of aggression in dementia patients—HOWEVER
 - ◎ Significant risk of stroke and serious adverse events exist—especially in patients with history of vascular disease;
 - ◎ Use should be individualized and based upon severe aggression or aggression that limits patient's ability to remain in the least restrictive environment after other agents tried;
 - ◎ Document rationale!



Conclusions & Directions for the Future

- Poor prognosis
- Primary intervention is best—prevention is key to limiting progression of disease;
- Anticoagulation may have role—weigh in relation to risk of falls and AE's;
- Few data exist regarding role of pharmacology in significantly improving cognition and VaD;
- May be at special risk for stroke/AE's with use of neuroleptics;
- Transition to palliative care model focusing on quality of life rather than longevity.