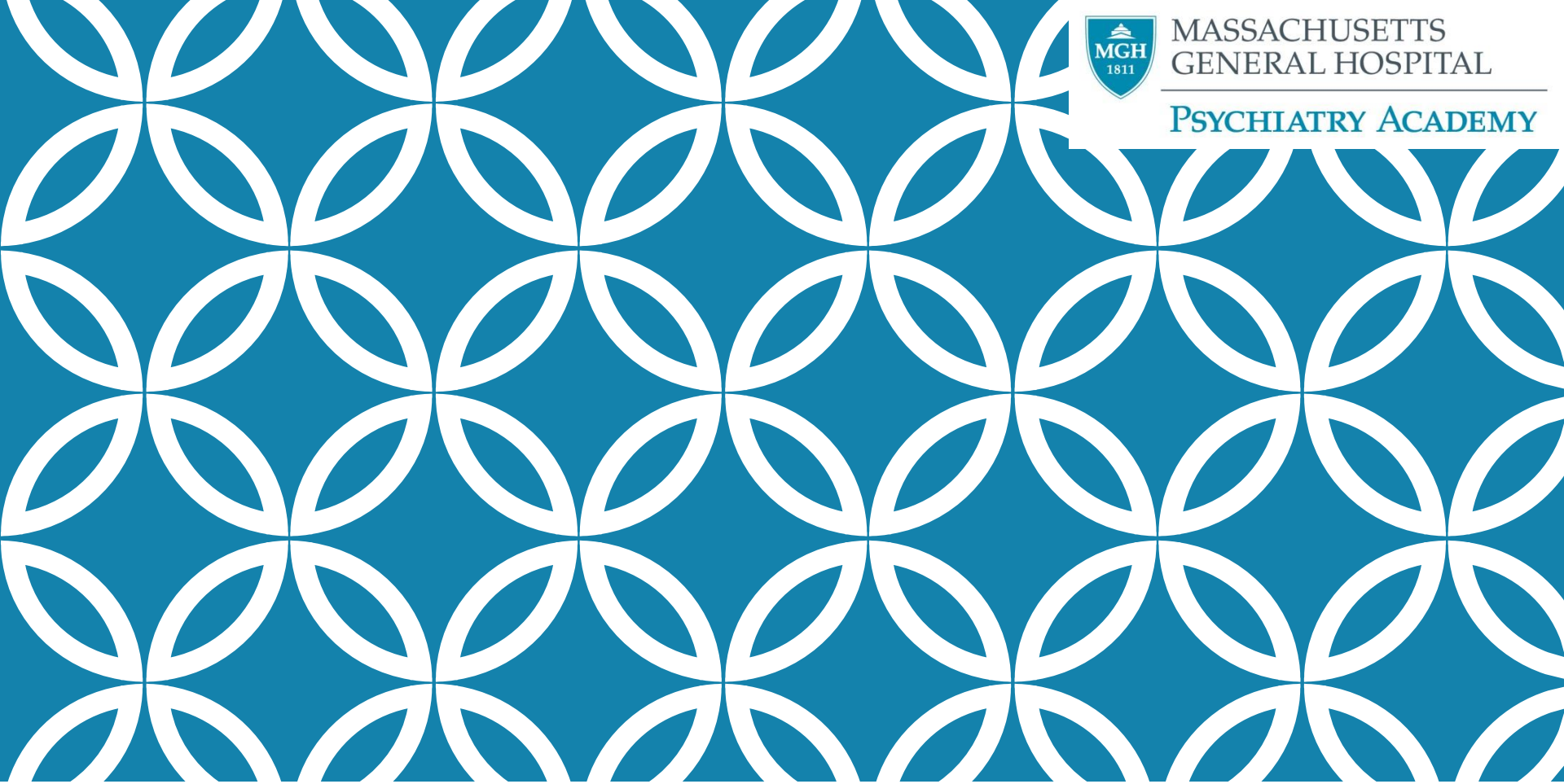


GERIATRICS

Psychopharmacology
Essentials in Geriatric Psychiatry

DISCLOSURES

I have the following relevant financial relationship with a commercial interest to disclose:

Springer Publishing; Book Royalties, for book on late-life depression prevention

CHALLENGES IN GERIATRIC PSYCHOPHARMACOLOGY

- Much more history to gather re: co-morbidities, concomitant medications
- Knowing what the drug-free baseline looks like
- Setting treatment expectations, providing extensive education
- Knowing which medications are still needed, de-prescribing
- Longer time-to-treatment response
- Higher sensitivity to side effects, more potential interactions
- Pill-taking and adherence issues, especially if cognitive impairment present
- PK and PD changes associated with normal physiologic aging

PHARMACOKINETICS

How the **body** affects the **medications**

- **Absorption**
- **Distribution**
- **Metabolism**
- **Elimination**

ABSORPTION CHANGES

- Rate is slowed in normal aging
- Extent tends to be unaffected

DISTRIBUTION CHANGES

- Changes in aging that affect drug distribution
  - ↑ Fat stores
  - ↓ Lean body mass
  - ↑ Volume of distribution for lipophilic drugs
  - ↓ Albumin levels

- Consequences
  - Drugs accumulate in fat stores → longer half-life
  - IM injections may be more painful due to decreased muscle mass
  - Less drug in systemic circulation immediately available
  - More unbound drug may reach brain due to decreased albumin

METABOLISM CHANGES

- PHASE 1
  - Cytochrome P450 enzymes
  - CYP 1A2 and 3A4 are most affected by aging
- PHASE 2
  - Not typically affected by aging

ELIMINATION CHANGES

Elimination determines:

- Time to reach steady-state
- Time to drug elimination – ie, how quickly to titrate the drug

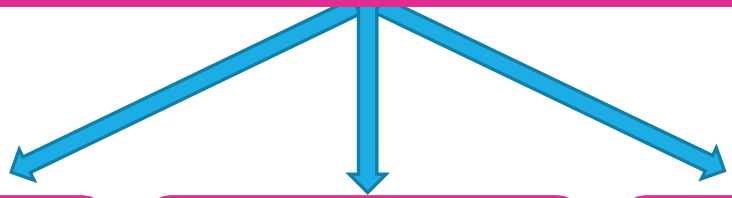
Reduced hepatic blood flow and renal clearance

- Cr may not be an accurate indicator of renal clearance

Can offset these changes by reducing dosing rate. This is the reason to "*start low and go slow*".

PHARMACODYNAMIC CHANGES

Older adults may have greater drug effects than younger people, given the same doses of medication



- Greater sensitivity to drugs
- Higher concentrations of drug at CNS receptors
- Differences in initial levels

PHARMACODYNAMIC CHANGES

☐ In aging, there may be a decrease in ability to up-regulate or down-regulate postsynaptic receptors

☐ Enzyme activity decreases, for example: reduced acetylcholinesterase activity → increased sensitivity to anticholinergic drugs

Overall: Older adults are at much higher risk of having pharmacodynamic drug-drug interactions due to polypharmacy (ie, multiple drugs affecting same neurotransmitters/receptors)

OVERVIEW: GENERAL TIPS

- ☐ Start low, go slow
- ☐ Make just one change at a time – and explain importance of this to patients/family
- ☐ Re-evaluate need for each drug at each visit
  - ☐ Adherence problems increase with the number of prescriptions
  - ☐ Always screen carefully for potential drug-drug interactions
- ☐ Simplify wherever possible
  - ☐ Once daily is optimal
  - ☐ Choose dose strengths that reduce burden of taking the pills (eg, pill sizes, how easy to cut)
  - ☐ Choose liquid formulations/sprinkles/capsules that can be emptied, if swallowing difficult

MEDICATION CLASSES

- ANTIDEPRESSANTS
- MOOD STABILIZERS
- ANTIPSYCHOTICS
- BENZODIAZEPINES
- COGNITIVE ENHANCERS

ANTIDEPRESSANTS

- ☐ Citalopram FDA max dose if > 60 years of age is 20 mg (QTc prolongation and Torsade risk)
- ☐ Fluoxetine & paroxetine: CYP2D6 inhibitors (will interact with many psychotropics)
- ☐ Bupropion also a CYP2D6 inhibitor
- ☐ Mirtazapine: Can help with insomnia
- ☐ Vilazodone: may be less sexual dysfunction (d/t 5T1a partial agonism)
- ☐ Vortioxetine appears safe/efficacious in older adults

ANTIDEPRESSANTS

- TCA
  - Nortriptyline 10-150 mg/d
  - Desipramine 10-250 mg/d
  - Common side effects: mildly anti-cholinergic, minimal orthostasis, needs blood levels, toxicity in overdose

- SSRI
  - Fluoxetine 5-40 mg/d
  - Sertraline 25-200 mg/d
  - Paroxetine* 5-40 mg/d
  - Fluvoxamine 25-250 mg/d
  - Citalopram 5-20 mg/d
  - Escitalopram 5-20 mg/d
  - Common side effects: anxiety/ sedation, agitation, restlessness, GI complaints, headache, rash, sexual dysfunction

    *weakly anti-cholinergic, may lower dosing options

ANTIDEPRESSANTS

- Serotonin/Norepinephrine Reuptake Inhibitors (SNRI)
  - Venlafaxine XR 37.5-225 mg/d
    side effects: increase in BP, confusion, lightheadedness
  - Duloxetine 30-120 mg/d
    side effects: GI, dry mouth, dizziness, sweating, decreased appetite

- Alpha 2 antagonist/Selective Serotonin
  - Mirtazapine 7.5-45 mg/d
    side effects: sedation, weight gain

- Atypical/Other Antidepressants
  - Trazodone 25-250 mg/d
    side effects: sedation, orthostasis, priapism in males (rare)
  - Bupropion 37.5-450 mg/d
    side effects: insomnia (avoid after 4 pm), anxiety, seizures (rare)
  - Vortioxetine 5-20 mg/d
    side effects: N/V, GI, dry mouth, dizziness, caution with CYP 2D6 poor metabolizers (↓ dose)
  - Vilazodone 5-20 mg/d
    side effects: N/V, GI, dry mouth, dizziness, caution with CYP 3A4 inhibitors (↓ dose)

ANTIDEPRESSANTS-PLUS

- Other agents
  - Monoamine oxidase inhibitors: phenelzine, tranylcypromine
  - Psychostimulants: dextroamphetamine, methylphenidate
  - Dopamine agonists: pramipexole, ropinerole
  - Cholinesterase inhibitors: donepezil, rivastigmine, galantamine (in patients with cognitive impairment)
  - Non-amphetamine stimulant-like: modafinil, armodafinil
- Augmentation Strategies
  - Combining antidepressants (eg, SSRI+bupropion)
  - L-thyroxine, lithium, buspirone
  - Atypical antipsychotics

MOOD STABILIZERS

- ☐ Lithium: risk of toxicity due to lower volume of distribution
  - ☐ NSAIDs, ACEIs/ARBs, thiazides, hyponatremia: ↑ levels
  - ☐ Caffeine, high salt intake: ↓ levels
  - ☐ Obtain EKG to rule out cardiac conduction abnormalities
- ☐ Valproic acid: low albumin ↑ free drug levels, risk for toxicity
  - ☐ Obtain CBC, Chem when ordering therapeutic levels (platelets, LFTs)
  - ☐ As with Li+, blood draws may be an issue
- ☐ Carbamazepine: strong CYP3A4 inducer
- ☐ Oxcarbazepine: higher risk for hyponatremia, check Chem
- ☐ Lamotrigine: caution with complex instructions for dose changes if cognitively impaired

ANTIPSYCHOTICS

- ☐ FGA vs. SGA:
  - ☐ History of metabolic disorder, stroke, coronary disease
  - ☐ History of extrapyramidal symptoms, risk profile of older persons
- ☐ Higher risk of tardive dyskinesia → do more frequent AIMS
- ☐ Order lipid panel/A1c at baseline then annually or as indicated
- ☐ Haldol: still in use for acute management of agitated delirium; short-term only! (EPS can be major problem)
- ☐ Black box warning in dementia:
  - ☐ Risperidone, aripiprazole, olanzapine, quetiapine have most evidence for treatment of behavioral disturbances; use of low doses is key

BENZODIAZEPINES

- Drugs with long-lasting active metabolites should be avoided
  - Diazepam (half-life: 44-48; 100 hrs)
  - Chlordiazepoxide (half-life: 30; 36-200 hrs)
- Long-term risks:
  - Worsening memory, dementia risk in epi studies
  - Falls and associated fractures
  - Developing tolerance and dependence
  - Worsening anxiety upon discontinuation
- Tapering should occur over several months if used more than 6 months; consider cross-tapering (eg, alprazolam to clonazepam)
- Generally, best avoided in older adults

KNOW ABOUT THE BEERS CRITERIA

- ☐ Potentially Inappropriate Medication Use in Older Adults:
  - ☐ Anticholinergic medications (diphenhydramine, benztropine, TCAs, paroxetine)
  - ☐ Antihistamines (educate on OTC use!)
  - ☐ BZDs & z-drugs (zolpidem, zaleplon, eszopiclone)
  - ☐ Muscle relaxants (eg, cyclobenzaprine)
  - ☐ NSAIDs (increased GI bleed risk with serotonergic drugs)

- ☐ Avoid ≥ 3 CNS-active drugs whenever possible due to increased risk for falls
  - ☐ Antidepressants
  - ☐ Antipsychotics
  - ☐ Opioids

KNOW ABOUT THE BEERS CRITERIA

☐ Potentially Inappropriate Due to Disease or Disease Risk Interactions

- ☐ **Delirium**: anticholinergics/BZDs/H2 receptor antagonists/z-drugs
- ☐ **Dementia:** anticholinergics/antipsychotics/BZDs/H2 receptor antagonists/z-hypnotics
- ☐ **Fall risk:** anticonvulsants/antipsychotics/BZDs/z-drugs/ TCAs/SSRIs/opioids
- ☐ **Insomnia:** stimulants, modafinil
- ☐ **Parkinson disease:** antipsychotics (quetiapine, clozapine may be lower risk) & antiemetics (eg, promethazine)
- ☐ **Urinary incontinence:** avoid anticholinergic drugs, work to minimize anticholinergic load
- ☐ **SIADH:** antipsychotics, carbamazepine, oxcarbazepine, mirtazapine, SSRIs, SNRIs, TCAs

MANAGING ADVERSE EFFECTS

- Understanding pharmacokinetics
  - Dosing once daily → higher peaks; peaks typically associated with the side effects
  - Splitting dose might reduce side effects (but weigh benefits with risk for nonadherence, especially if cognitive impairment is an issue)

- GI side effects, dizziness, sedation → give dose at bedtime
- Activation → give dose in the morning
- Tremor → use split dosing
- Sexual dysfunction → try switching medications or augmenting with bupropion

MEDICATION TEACHING

- ☐ Use open-ended questions
  - ☐ Emphasize that there are no “bad” or “silly” questions
  - ☐ Identify biases/pre-conceptions about medications, major concerns
  - ☐ Identify and direct focus on target symptom(s)
- ☐ Use read-backs of instructions; print out or write out (easy to do now in EHRs)
- ☐ Include and educate family members whenever possible, but this is essential in cases of cognitive disorders
- ☐ Encourage patient and family to keep medication lists on them at all times and to use pill organizers/med-minders

TREATMENTS FOR COGNITIVE SYMPTOMS

What is available to treat cognitive symptoms of dementia and related functional problems?

COGNITIVE ENHANCERS

- Cholinesterase inhibitors (AChEi): GI side effects most common, affected by speed of titration; vagotonic effects → monitor for bradycardia, use caution or avoid with beta-blockers
- Donepezil
- Galantamine
- Rivastigmine
- Memantine: Initial dose is 5 mg, target dose is 10 mg BID in 4-week starter (5 MG bid if severe renal impairment)
- Aducanumab: new anti-amyloid AD drug

ACETYL CHOLINESTERASE INHIBITORS (ACHEIS)

- Repletion of ACh loss in the brain in AD (eg, nucleus basalis of Meynert)
- Currently available: donepezil, galantamine, and rivastigmine (tacrine not used due to liver toxicity)
- Benefits subtle and time-limited: 30% of patients improve somewhat; overall comparison with placebo shows slower decline over time
- Randomized cross-over study supported very modest cognitive benefits, but no global change
- No evidence for efficacy difference across agents, but some differences in tolerability and convenience
- Long-term benefits are unclear

ACETYL CHOLINESTERASE INHIBITORS (ACHEIS)

- Typically given for mild to moderate AD; notes and cautions:
  - All are approved for mild-moderate AD
  - Rivastigmine also approved for mild-mod dementia of Parkinson disease
  - May be considered for off-label use in DLB and MCI; generally, not recommended for vascular dementia
  - Caution: AChEIs may worsen behavioral symptoms in FTD and not approved for this indication!

ACETYL CHOLINESTERASE INHIBITORS (ACHEIS)

Agent	Start	Target
Donepezil*	5 mg daily	5-10 mg daily
Galantamine	4 mg BID	8-12 mg BID
Rivastigmine**	1.5 mg BID	6 mg BID

**Approved for higher-dose formulation in moderate to severe AD*

***Also available in transdermal patch*

- Side effects: N/V/GI, bradykinesia, bradycardia and syncope (caution with beta-blockers), increased stomach acid, urinary obstruction, distressing dreams
- Use with caution with sick sinus syndrome, conduction deficits, seizures, asthma and COPD

MEMANTINE

- Currently FDA-approved only for moderate to severe AD, but used frequently off-indication at earlier stages, particularly in combination with AChEIs
- Greatest benefit typically seen is in everyday functioning
- Begin at 5 mg per day, and increase to 10 mg BID as tolerated; the 4-week titration pack is typically used
- Use lower doses (5 mg BID max) with renal insufficiency
- Side effects not prominent, but can include: confusion, dizziness, headache, sedation, agitation, falls, and constipation

ADUCANUMAB

- Recently FDA-approved (June 2021)
  - First new class of AD drugs in 20 years (disease-modifying, anti-amyloid Ab-based, monthly IV infusion)
  - Initially approved more broadly in AD
  - Approval revised for early-stage/mild disease
  - Accelerated approval base on surrogate biomarker endpoint
- Concerns, ongoing issues and controversy:
  - High drug cost
  - Questions of efficacy for hard clinical endpoints
  - Potential lack of access, equity and fairness issues
- Medicare coverage determination process is underway

TREATMENTS FOR NON-COGNITIVE SYMPTOMS

What is available to treat the mood, thought, perceptual, psychomotor, and sleep disturbances that frequently accompany dementia?

WHAT ARE BPSD?

Behavioral and psychological symptoms of dementia (BPSD) affect how patients:

- Feel: Disturbances of affect – euphoria, depression, anxiety, irritability, apathy
- Think: Disturbances of thought and perception – delusions, hallucinations
- Act: Disturbances of behavior –

1. Sleep – insomnia, sleep-wake dysregulation
2. Eating – increased or decreased appetite and eating behaviors
3. Physical Activity – hypomotoric behavior or inactivity, vocalizations, pacing, wandering, fidgeting/repetitive movements, disinhibited action, agitation, aggression

COMPREHENSIVE APPROACH TO BPSD

Evaluation of Contributing Factors

- Medical – medication toxicity or toxic interactions; pain or discomfort (eg, constipation, urinary retention); medical illness (eg, infection, respiratory compromise, metabolic or endocrine derangement)
- Environmental – eg, sensory deprivation or over-stimulation
- Psychiatric – exacerbation of prior illness

Individualized Treatment Plan

- Evaluate above factors
- Non-pharmacologic approaches are first-line approach to non-emergency BPSD

Monitoring and Modification of Plan

BPSD PEARLS

- Identify and alleviate the target symptoms
- Reduce patient distress and care partner distress/strain
- Reduce costs of additional care, lengthened stays, premature or complicated long-term placements/institutionalizations
- Remain in compliance with regulatory guidelines – especially important in care of patients with dementia in care facilities/institutions

BPSD PEARLS

- CRITICAL: currently no approved medications for range of BPSD
- Divalproex: often used but limited evidence to support
- Side effects: somnolence, thrombocytopenia, weight gain, tremor, hepatotoxicity, pancreatitis (rare)
- Current dose and titration recommendations
  - Initial dose 125-250 mg twice daily; increase by 125-250 mg/d every 5 days
  - Usual range 500-1,250 mg/d
  - Usual blood depakote level 40-90
  - Clinical response more important than blood level
- Lamotrigine:
  - 12.5-300 mg/d typical range
  - Very slow titration required (eg, start at 12.5 for 2 weeks)
  - Anti-aggressive effects seen
  - Main side effects: Mild tremor, ataxia, sedation, very rare lamotrigine rash – but can be severe
  - **Start low and go even *slower*** (ie, not an option for acute management)

BPSD PEARLS

- Trazodone
  - Shown to reduce agitation among demented patients in 2 controlled trials
  - Typical dosing: 50-250 mg per day (can start with just 12.5-25 mg)
  - Important side effects: sedation (caution re: gait unsteadiness or fall risk), orthostatic hypotension, priapism (very rare)
  - Widely used off-label, potential advantage of substitution for use otherwise of antipsychotic
- Buspirone
  - An azapirone anxiolytic; relative of trazodone
  - Used primarily as an anxiolytic
  - Limited data (case report level)
  - Mild side effects: headache, lightheadedness, nausea
  - Usual dose: 15-30 mg/d in divided doses

ANTIPSYCHOTICS: RECOMMEND DOSES IN BPSD

Atypical agents and characteristics		
Name	Dose range	Common side effects, key features
Olanzapine	Start: 1.25-2.5 mg/d Optimal: 5-10 mg/d	EPS, mildly anticholinergic, sedation, postural hypotension
Risperidone	Start: 0.25-0.5 mg/d Optimal: 0.5-2 mg/d	EPS (dose-related), minimally anticholinergic, prolactin increase, orthostatic hypotension
Quetiapine	Start: 12.5-25 mg/d Optimal: 50-100 mg/d	Lower rate of EPS, more sedation, orthostatic hypotension
Aripiprazole	Start:1-2 mg/d Optimal: 5-10 mg/d	EPS can be significant, low risk of sedation, lower weight gain
Pimavanserin*	10 mg/d tablet or 34 mg/d capsule	Nausea, constipation, confusion; 10-mg tablet if using with CYP 3A4 inhibitors (* PD psychosis approval)
All		Follow ADA/APA consensus guidelines, check QTc, **Note: FDA Black Box warning**

ANTIPSYCHOTICS: CLINICAL RECOMMENDATIONS

- Document use of behavioral and environmental interventions
- Document target symptoms and establish a time frame for assessment of results
- Use lowest doses necessary for the shortest time period
- Plan and implement screening and monitoring of side effects, including labs (ie, fasting glucose, HbA1c, lipids)
- Educate health care agent/care partner about benefits, risks
- Coordinate care with that of other providers
- Note: overall evidence suggests typicals are just as potentially hazardous as atypicals re: Black Box warning

GERIATRIC PSYCHOPHARMACOLOGY

Thank you