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Medications for Management of Behavioral Disorders and their Side Effects: Pros and Cons

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Cost of AD*

- 5.4 million Americans (2011)
- 16 million Americans (2050)
- 6th leading cause of death in United States
- Only one among top 10 that cannot be prevented, cured, or even slowed

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Behaviors... "Do Something!"

- Physicians
 - Burden to prescribe a "fix"
- Pharmacists
 - Burden to recommend a "fix"



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Acute to LTC¹

- Prevalence of potentially inappropriate medications (PIMs) in community: 60%
- Post critical illness – potential and *actual* or *overtly* inappropriate medications (AIMs) increased by 20%
 - Half of these started in ICU

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Acute to LTC¹

- Clinical context
 - Antipsychotics for delirium
- Fear of interference with primary care physician relationship
 - Med reconciliation at discharge needs to address PIMs and AIMs

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STOPP²

- Screening Tool of Older Person's potentially inappropriate Prescriptions
 - STOPP criteria PIMs associated with ADEs
 - Beers criteria PIMs less reliably associated with ADEs

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Off-label Use: Evidence Based? ³

- Archives of Internal Medicine (2006)
 - Highest rates of off-label use were for anticonvulsants (74%), antipsychotics (60%), and antibiotics (41%)
 - Driven by mistaken belief in FDA-approval???
 - Lorazepam for chronic anxiety
 - Quetiapine for dementia with agitation

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Antipsychotic Profile ⁸

- Chemical Class
 - Butyrophenone
 - Dibenzoxazepine
 - Dihydroindolone
 - Diphenylbutylpiperidine
 - Phenothiazines
 - Aliphatic
 - Piperazine
 - Thioxanthenes
- 1st Generation: FGA
 - Haloperidol
 - Loxapine
 - Molindone
 - Pimozide
 - Chlorpromazine
 - Trifluoperazine
 - Thiothixene

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Antipsychotic Profile ⁸

- Chemical Class
 - Benzisoxazole
 - Dibenzodiazepine
 - Dibenzothiazepine
 - Thienobenzodiazepine
 - Benzothiazolylpiperazine
- 2nd Generation: SGA
 - Risperidone
 - Clozapine
 - Quetiapine
 - Olanzapine
 - Ziprasidone

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Antipsychotic Profile ⁸

- Chemical Class
 - Dihydrocarbostyryl
- 3rd Generation: TGA
 - Aripiprazole

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Effects on ⁸ NT/Receptors

- Dopamine blockade
 - D1Blockade
 - May mediate antipsychotic effect
 - D2 Blockade
 - Mesolimbic area:
 - Antipsychotic effect
 - Nigrostriatal area:
 - Extrapramidal SE
 - Tuberinfundibular area:
 - Prolactin elevation

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Effects on NT/Receptors

- Dopamine Blockade
 - D3 Blockade
 - May mediate antipsychotic effect
 - D4 Blockade
 - Effect unclear
- H1 Blockade
 - Anti-emetic effect
 - Sedation, postural hypotension, weight gain
 - Potentiation of other CNS medications

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Effects on NT/Receptors

- ACh Blockade
 - Mitigation of extrapyramidal SE
 - Dry mouth, blurred vision, constipation, urinary retention and incontinence, sinus tachycardia, memory disturbance, sedation

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Effects on NT/Receptors

- A1 Blockade
 - Postural hypotension, dizziness, reflex tachycardia, sedation, hypersalivation, urinary incontinence
 - Potentiation of antihypertensives acting via alpha-1 blockade (e.g. prazosin)

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Effects on NT/Receptors

- A2 Blockade
 - Increased release of ACh
 - Sexual dysfunction
 - Antagonism of antihypertensives acting as alpha-2 stimulants (e.g. clonidine)

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Effects on NT/Receptors

- 5-HT_{1A} Blockade
 - Antidepressant, anxiolytic and anti-aggressive action
- 5-HT₂ Blockade
 - Anxiolytic (5HT_{2c}), antidepressant, anti-aggressive, anti-agitation (5HT_{2a}), antipsychotic effect
 - Hypotension, sedation, weight gain (5HT_{2c})

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Effects on NT/Receptors

- Dopamine Reuptake Blockade
 - Antidepressant, antiparkinsonian
 - Psychomotor activation, aggravation of psychosis

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MOA⁸

- FGA: primary D2 blockade
- SGA and TGA:
 - Affect D3 and D4 receptors. Serotonin, glutamate
 - Facilitate dopamine transmission in frontal cortex and striatum
- SGA (clozapine, olanzapine, quetiapine, risperidone, ziprasidone):
 - 5HT2 blockade greater than D2 blockade
 - Lower affinity to D2 receptors b/c of faster dissociation
 - Selectively block mesolimbic (A10) dopamine neurons; other antipsychotics block both A10 and A9 (nigrostriatal neurons)

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ADR⁸

- Determined by:
 - Differences in receptor affinity
 - Rate of dissociation from receptor
- The faster an antipsychotic dissociates from D2 receptor the lesser the risk of EPS, prolactin elevation, tardive dyskinesia

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Geriatric⁸ Considerations

- Start low – go slow
- CYP3A4 (quetiapine, ziprasidone, haloperidol, etc.)
- Monitor CNS and anticholinergic effects
- Increased sensitivity to EPS
- Higher incidence of tardive dyskinesias
 - Risk per year: 30% over age 45 (FGA)
 - 5.3% with novel agents

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Geriatric⁸ Considerations

- Orthostatic hypotension (FGA, SGA, TGA)
- Increased weight and triglycerides
 - Higher risk of CAD and CVA

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Geriatric⁸ Considerations

- Dementia patients with multiple risk factors:
 - Age >80
 - Malnutrition
 - Use of benzodiazepines
 - Pulmonary conditions and/or treatment emergent sedation
- Mortality risk 1.6 to 1.7 times placebo

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Geriatric⁸ Considerations

- TIA and stroke reported in elderly patients with:
 - Pre-existing cerebrovascular risk factors
 - Use of antipsychotics (FGA and SGA) for dementia-related psychosis
- Risk of death from CV or infectious causes
 - 1.6 to 1.7 times placebo

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Risks Associated with Antipsychotics ⁴

- Boost Pneumonia Risk
 - Antipsychotics with highest affinity to H1-histaminergic receptor (atypicals and phenothiazines)
 - Sedation – ↓ swallowing – ↑ aspiration
- Need for more research and discussion around drawing “conclusions” regarding risk of these agents

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FDA Black Box Warning ⁵

- April 2005
 - ...the FDA determined that the treatment of behavioral disorders in elderly patients with dementia with atypical antipsychotic medications is associated with increased mortality...
- June 2008
 - The warning was extended to conventional or “typical” antipsychotics

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Are Alternative Therapies Safe? ⁸

- Benzodiazepines
 - Bind to GABA receptors
 - Inhibitory NT
 - Facilitate action of GABA on CNS excitability
 - Clonazepam has 5-HT potentiating properties

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Are Alternative Therapies Safe? ⁸

- Benzodiazepines
 - Geriatric considerations
 - Medications metabolized by oxidation (e.g. diazepam, estazolam) can accumulate
 - Higher risk of CNS effects
 - Balance, gait, memory, cognition, behavior
 - Fall risk increases 2 to 3 times
 - Higher with larger doses
 - Higher in females

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Are Alternative Therapies Safe? ⁸

- Benzodiazepines
 - Relieve behavioral or somatic symptoms of anxiety
 - Little effect on psychic or cognitive symptoms
 - Not recommended long-term

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Are Alternative Therapies Safe? ⁸

- Antidepressants
 - SSRI: citalopram, sertraline, etc.
 - NDRI: bupropion
 - SNRI: venlafaxine, duloxetine
 - SARI: trazadone
 - NaSSA: mirtazapine
 - Non-Selective Cyclic Antidepressants: TCAs
 - MAOIs
 - Psychostimulants: methylphenidate

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Are Alternative Therapies Safe? ⁸

- Antidepressants
 - NE reuptake block
 - 5-HT reuptake block
 - DA reuptake block
 - 5-HT1 blockade
 - 5-HT2 blockade
 - M1(ACh) blockade
 - α_1 and α_2 blockade
 - D2 blockade

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Are Alternative Therapies Safe? ⁸


- Antidepressants
 - Must consider unique characteristics of agents
 - Multiple drug-drug interactions
 - Tachyphylaxis (“poop-out” syndrome) in 10-20% of patients
 - Require adequate trial period (up to 6 weeks at a reasonable dose)

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Lancet Article ⁷

“Antidepressants of Little Use in Dementia Patients”



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Are Alternative Therapies Safe? ⁸

<p>Anticonvulsants for...</p> <ul style="list-style-type: none"> • 1st Generation <ul style="list-style-type: none"> – Clonazepam • 2nd Generation <ul style="list-style-type: none"> – Carbamazepine – Divalproex sodium – Valproic acid 	<p>Mood Stabilization</p> <ul style="list-style-type: none"> • 3rd Generation <ul style="list-style-type: none"> – Gabapentin – Lamotrigine – Oxcarbazepine – Topiramate
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Are Alternative Therapies Safe? ⁸

- Important to monitor renal and hepatic function
- SE can usually be managed with slower dosage titration
- Common ADRs
 - GI
 - Lethargy, sedation, behavior changes
 - Dose-related tremor
 - Ataxia
 - Changes in appetite and weight gain
 - Dysarthria, incoordination
 - Diplopia, nystagmus

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Are Alternative Therapies Safe? ⁸

- Anticonvulsants
 - Baseline biochemical workups
 - Except lamotrigine
 - Periodic labs
 - Except lamotrigine
 - Plasma level monitoring
 - Carbamazepine
 - Valproate

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Are Alternative Therapies Safe? ⁸

- Anticonvulsants
 - Geriatric considerations
 - Slow dosing titration
 - Confusion, cognitive impairment, falls
 - Multiple drug-drug interactions
 - High risk for delirium
 - Hepatic impairment
 - Reduced protein binding
 - ClCr < 60 (gabapentin) ClCr < 30 (oxcarbazepine)

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SOM ⁹

- Physicians regulatory responsibility per the State Operations Manual
- §483.25(1) Unnecessary Drugs
“...documented the clinical rationale...”

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What is GDR – Really? ⁹

- *Within the first year in which a resident is admitted on an antipsychotic medication or after the facility has initiated an antipsychotic medication, the facility must attempt a GDR in two separate quarters (with at least one month between the attempts), unless clinically contraindicated. After the first year, a GDR must be attempted annually, unless clinically contraindicated.*

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What is GDR – Really? ⁹

- *For as long as a resident remains on a sedative/hypnotic that is used routinely and attempt to taper the medication quarterly unless clinically contraindicated.*

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What is GDR – Really? ⁹

- *During the first year in which a resident is admitted on a psychopharmacological medication (other than an antipsychotic or a sedative/hypnotic), or after the facility has initiated such medication, the facility should attempt to taper the medication during at least two separate quarters (with at least one month between the attempts), unless clinically contraindicated. After the first year, a tapering should be attempted annually, unless clinically contraindicated.*

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New Treatment: PBA

- Pseudobulbar Affect (PBA)
- At risk population:
 - MS
 - ALS
 - Stroke
 - Traumatic brain injury

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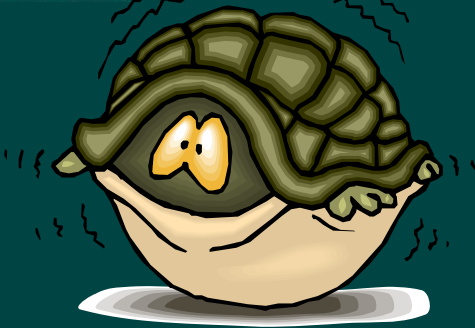
New Treatment: PBA

- Dextromethorphan HBr 20mg
 - Uncompetitive NMDA receptor antagonist and sigma-1 agonist
- Quinidine Sulfate 10mg
 - CYP450 2D6 inhibitor
- *Nuedexta™*
 - 1 cap PO daily x 7 days, then 1 cap PO q 12 hrs

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Questions?



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Resources:

- * Burden of Alzheimer's Disease High and Growing: Report
 - Alzheimer's & Dementia: The Journal of the Alzheimer's Association, March 2011
- 1. Inappropriate Medications Commonly Prescribed to the Elderly in the ICU
 - Society of Critical Care Medicine (SCCM) 40th Critical Care Congress: Abstract 569. Presented January 17th, 2011

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Resources:

2. New Criteria Define Inappropriate Meds in Older Inpatients
 - Arch Intern Med. 2011; 1013-1019, 1019-1020, 1032-1034.
3. Off-label use: Oft not evidence-based
 - Medscape: G. Caleb Alexander, MD, MS, Assistant Professor of Medicine at the University of Chicago Medical Center. September 1, 2009

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Resources:

4. Antipsychotic Drugs May Boost Pneumonia Risk in Elderly Outpatients
 - Ann Intern Med. 2010; 152:418-425
5. Impact of FDA Black Box Advisory on Antipsychotic Medication Use
 - Arch Intern Med. 2010; 170(1):96-103

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Resources:

6. Alternative Agents No Safer Than Atypicals in the Elderly
 - Medscape Medical News. March 28, 2011
7. Antidepressants of Little Use in Dementia Patients
 - Lancet. July 18, 2011
8. Clinical Handbook of Psychotropic Drugs
 - 17th Rev Edition; KZ Butler, JJ Jeffries, AS Virani. Hogrefe & Huber Publishers 2007©
9. CMS Manual System, Pub. 100-07 State Operations Provider Certification (Dec 15, 2006)

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