Geriatric Psychopharmacology

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Disclosure Information

- Dr. Crocco has served as a consultant in the past year to:
  - i-Function

Objectives

Review the best practices and difficult challenges in providing optimal psychopharmacology to the geriatric population.

Top 5 in Geriatric Psychopharmacology

The Challenges of Polypharmacy

Agitation in Neurocognitive Disorders

Depression

Benzodiazepines/Sedative Hypnotics

Disease Modification in Alzheimer's Disease

There is No "Typical" Older Person

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Geriatric Polypharmacy

More than half of individuals 65 years or older take five or more nonprescription and/or prescription medications per week, and 12% of persons in this age group take 10 or more nonprescription and/or prescription medications per week.

(*US Pharm.* 2019;44(7):33-36).

In a sample of Medicare beneficiaries discharged from an acute hospitalization to a skilled nursing facility, patients were prescribed an average of 14 medications, including over one-third with side effects that could exacerbate underlying geriatric syndromes.

(Saraf AA, et al, *J Hosp Med* 2016; 11:695).

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Geriatric Polypharmacy

How do you optimally mange a geriatric patients when polypharmacy is a major challenge?

Definitions

Pharmacokinetics (effect of the body on the drug)

Vs.

Pharmacodynamics (effect of the drug on the body)

Geriatric Pharmacokinetics and Polypharmacy

- **A**dsorption: Decrease in blood flow and gastric acids

GI motility and GI pH impaired by antacids/H2 blockers

- **D**istribution: Increased VOD of lipid soluble drugs; Decreased VOD of water-soluble drugs, decrease in plasma albumin

Lipid Sol: Typical antipsychotics. Water Sol: Lithium, ETOH

- **M**etabolism: Phase I-CYP 450 Liver Enzymes: oxidation.

Elderly patients have polypharmacy that can induce or inhibit

- **E**limination: Renal Clearance: Loss of renal mass over time, 35% filtration rate decline from age 35 to 90

Lithium, ACEI's

Geriatric Polypharmacy and Pharmacodynamics

- Decrease in baroreceptor responsivity

Worsening orthostatic hypotension

- Decrease in neurotransmitter, neurotransmitter receptors, and neurons

Worsening EPS, anticholinergic side effects

Geriatric Polypharmacy

- Pharmacodynamic drug interactions are more concerning overall than pharmacokinetic drug interactions and lead to more serious problems.
- They are more predictable and are due to the additive burden of similar or contrasting mechanism of action that lead to side effects and troubling outcomes.

Geriatric Polypharmacy and Pharmacodynamics

Serotonin Reuptake Inhibitors (SRI's) and other antidepressants leading to serotonin syndrome

SRI and aspirin or clopidogrel, causing bleeding

Quetiapine and B-blocker leading to worsening orthostatic hypotension

Cholinesterase inhibitor and oxybutynin leading to no cognitive improvements

Red Flag Drugs

- Narrow therapeutic index/toxicity
- Anticholinergic medications
- Powerful inhibitors or inducers of the CYP450, particularly psychotropics such as fluoxetine, fluvoxamine, paroxetine
- Psychotropic medications
- Sedative/Hypnotics

Potential Toxicity

Examples:

- Antithrombotic drugs such as warfarin
- hypoglycemics such as glyburide
- Anti-epileptic drugs such as carbamazepine

Anticholinergic Medications

- Tricyclic and tetracyclic antidepressants
- Low potency typical antipsychotics/clozapine
- Benztropine/diphenhydramine/ trihexyphenidyl/hydroxyzine
- oxybutynin/tolterodine

Many psychotropic drugs have anticholinergic properties!

Psychotropic Medications

Side Effects in the Elderly:

- Orthostatic hypotension
- Falls
- EPS
- Anticholinergic: dry mouth, urinary retention, constipation, blurry vision
- Cognitive impairment
- Metabolic syndrome
- Cardiovascular Risk
- Sedation

Geriatric Polypharmacy: Best Practices

Obtain a complete list of medications including OTC's. Sources: patient/care provider/family vs. pharmacy/medication reconciliation

Consult with PCP/Primary-Care Physician

Avoid polypharmacy

Take note of RED FLAG drugs

Avoid prescribing drugs that have a high potential for drug-drug interactions especially due to pharmacodynamic factors.

Best Practices

Start low, go slow.

Agitation in Major Neurocognitive Disorder (MND)

How do you optimally mange a geriatric patient pharmacologically with agitation and dementia?

Clinical Management of MND

- Cognitive
- Medical/Neurological
- **Psychiatric**
- **Behavioral**
- Care provider support/issues

Psychiatric and Behavioral Symptoms in MND

90% demonstrate behavioral disturbances

- Aggression
- Agitation
- Depression
- Anxiety
- Disinhibition
- Sleep disturbances
- Psychosis

Reisberg 1989; Reisberg 1996; Devanand 1997; Wragg & Jeste 1989; Cohen-Mansfield: Adv Psychosom Med 1989.

Management of Agitation and Aggression in MND

- Non-pharmacologic behavioral interventions are somewhat effective in managing behavioral disturbance and is first line. [1]
- Clinical trials have failed to establish significant efficacy of antipsychotic medications for dementia related behavioral disruption[2]
- Select atypical antipsychotics are modestly effective in the management of psychosis and agitation in the elderly.
- Benefits vs risks/adverse events must be weighed in decision to treat with medications as well as in selection of agent.

[1.] Brodaty, et al; Am J Psych, 2012 [2.] Ballard C. et al; Cochrane Database Syst Rev 2006.

Psychiatric and Behavioral Symptoms in MND

- Consequences:
  - More rapid decline cognitively
  - More rapid decline functionally
  - Increased mortality
  - Increased long term care admissions

Devanand DP, et al. N Engl J Med. 2012;367:1497-1507

Why Behavioral Treatments First?

Medications:
- May not work or may stop working
- Carry significant risk of side effects
- May not be indicated if symptoms are infrequent or mild

Behavioral Treatments are:
- Individualized
- Empower caregivers and patients
- Lower risk than pharmacotherapy

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Pharmacological Treatment of and agitation in MND

- No FDA-approved treatment
- All pharmacological approaches are off-label use for aggression and agitation[1]
- Antipsychotic medications
  - Side effects
  - Black Box Warning - increased mortality with atypical antipsychotics in the elderly[2]
  - 30-60% More recent of NH residents with dementia are prescribed antipsychotics[3] commonly for longer than a year[4]

[1.] Levenson S; Caring for the ages 2003 [2.]Wang et al; N Engl J Med 2005.
[3.]Rochon et al; Arch Intern Med 2007 [4.]Cohen-Mansfield et al; Arch Intern Med 1999.

Management of Agitation and Aggression in MND

- Cholinesterase inhibitors are FDA indicated for the treatment of Alzheimer's and Parkinson's dementia and can be helpful for the prevention of behavioral agitation.
- SSRIs, such as citalopram, escitalopram, and sertraline are useful particularly when agitation is due to depression or anxiety.
- There is incidental evidence only for trazodone at low doses (12.5-50 mg).

DSM-5, APA, 2013; APA: Practice guideline for the treatment of patients with Alzheimer's disease and other dementias of late life. Am J Psych, 2007.

Management of Agitation and Aggression in MND

Cit-AD study:

Double blind placebo-controlled study

Agitation and psychosis in Alzheimer's dementia

Citalopram up to 40 mg had a 40% vs 26% reduction in agitation and psychosis when compared with placebo Porsteinsson, AP, et al. JAMA 2014.

Mirtazapine-open label study only with good results, Phase 3 trial underway (15-30 mg daily dosing)

Research Evidence for Efficacy of Atypical Antipsychotics from Placebo Controlled Trials in Agitation/Psychosis in Dementia

(Adapted from Maglione et al., 2011)

Antipsychotic	Symptom Domain	Confidence	Effect	SMD (95% CI)
Aripiprazole	Overall BPSD	Moderate	Small	0.20 (0.04, 0.35)
Aripiprazole	Agitation	Low	Small	--
Aripiprazole	Psychosis	Low	Non-significant	0.14 (-0.02, 0.29)
Olanzapine	Overall BPSD	Low	Very Small	0.12 (0.00, 0.25)
Olanzapine	Agitation	Moderate	Very small	0.10 (0.07, 0.31)
Olanzapine	Psychosis	Insufficient	Non-significant	0.05 (-0.07, 0.17)
Quetiapine	Overall BPSD	Low	Non-significant	0.13 (-0.03,
Quetiapine	Agitation	Insufficient	Non-significant	0.06 (-0.14, 0.25)
Quetiapine	Psychosis	Insufficient	Non-significant	0.04 (-0.11, 0.19)
Risperidone	Overall BPSD	Moderate	Very Small	0.19 (0.00, 0.38)
Risperidone	Agitation	Moderate	Small	0.22 (0.09, 0.35)
Risperidone	Psychosis	Moderate	Small	0.20 (0.05, 0.36)
SGAs Overall	Overall BPSD	High	Very Small	--
SGAs Overall	Agitation	Moderate	Small	--
SGAs Overall	Psychosis	Low	Very small	--

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Atypical Antipsychotics in MND Agitation

- Risperidone has most evidence and has gained regulatory approval in UK
- Olanzapine, aripiprazole
- Quetiapine demonstrated no better than placebo

Crossover /discontinuation study demonstrates that stopping risperidone in dementia patients results in a significant recurrence of agitation and psychosis

(Devanand, DP et al, NEJM, 2012)

Atypical Antipsychotics in MND Agitation

Brexpiprazole demonstrated efficacy in 3 recent phase 3 RCTs as well as tolerability

- First 2 trials, 12 week randomized, double-blind, placebo-controlled parallel-arm studies mg dosing, 0.5-2mg dosing respectively.
- Benefits observed at 2mg maximum daily
- CMAI and CGI-S showed statistically significant improvements from placebo
- Headache, insomnia, dizziness and UTI were most common adverse events

(Grossberg GT, et al. *Am J Geriatr Psychiatry*. 2020;28(4):383-400).

Agitation and Psychosis Dementia with Lewy Bodies (DLB)

DLB agitation and psychosis managed with atypical antipsychotics with less dopaminergic blockade activity- such as quetiapine, clozapine-less risk of EPS

What about Pimavanserin?

Inverse agonist and antagonist Serotonin 5HT2A

FDA approved for Parkinson's psychosis, but not DLB. –

In this cohort, 741 deaths seen in retrospective study. Most likely risk of death greater than 1-2% seen in atypical antipsychotics with dementia. (Hwang YJ, et al, Neurology 2021).

Ongoing current RCT in AD agitation and psychosis.

Other Pharmacologic Treatments

Mood Stabilizers/anti-epileptics: no demonstrated efficacy

divalproex sodium

lamotrigine

carbamazepine

gabapentin-Most commonly prescribed medication in US for agitation in MND

Lithium-documented neuroprotective effects, RTC Phase 2 completed, demonstrated safety in short term use, efficacy trends towards patient with manic symptoms but no improvement in agitation and psychosis.

(Devanand, Crocco, et al. AJGP, 2021).

Efficacy vs. Tolerability

In geriatric psychopharmacology, tolerability is often chosen over efficacy.

Prazosin

- Alpha-1 adrenergic receptor antagonist, mediates post synaptic norepinephrine effects and decreases Norepinephrine effects.
- Doses 1-6 mg/d, but only one very small RCT.
- Currently Phase 2 trial underway

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Dextromethorphan/Quinidine Formulations

Combination of dextromethorphan and quinidine which blocks CYP450 2D6 enzyme metabolism of DM.

NMDA antagonist, sigma 1 agonist and Norepinephrine (NE), serotonin (5HT) reuptake inhibitor FDA indicated for pseudobulbar affect (PBA) dysregulation only.

Phase 2 10-week RTC for AD and agitation:

- 30/10 mg BID dosing, NPI agitation and aggression scores reduced significantly
- Falls, diarrhea, and UTI most common side effects
- No worsening sedation or cognitive loss

(Cummings, et al. JAMA 2015)

Cannabinoids

- No major evidence for cannabinoids (CBD, THC) for MND agitation or other psychiatric conditions in the elderly.

May have neuroprotective effects.

Geriatric Depression

What is the best pharmacotherapy for geriatric depression?

Geriatric Depression

- Most clinical trials comparing SRI's to placebo, demonstrated high placebo response rates and often no superiority in the drug.

55-81% will fail to remit especially those with late-life onset

May be due to:

-Under-dosing antidepressants: start low and go slow, but do not under-dose

-Neurodegenerative disease/dementia may lead to depression with different mechanisms of action: vascular causes of depression, cholinesterase inhibitors/NMDA antagonist.

(Alexopoulos, 2011)

Geriatric Depression: Acute Treatment

SRI's have the best safety profile

First-line SSRI's[1]: Escitalopram, citalopram, sertraline, QTc prolongation in patients over 60 taking greater than 20mg of citalopram daily

- Paroxetine not recommended in elderly due to anticholinergic effects and potent inhibition of multiple CYP450 isoenzymes
- Fluoxetine not recommended in elderly due to long half-life (up to 21 days in geriatrics) and potent inhibition of multiple CYP450 isoenzymes
- SNRI's: Venlafaxine, duloxetine, desvenlafaxine

(Marcum Z, et al.. Am J G Psychopharm. 2012;10(4):264-271; 2. Anderson I, J Affective Dis. 2000;58(1):19-36;

Geriatric Depression: Acute Treatment

Vortioxetine demonstrated efficacy and tolerability in elderly (64-88 years, n=300) depressed patients at 5mg vs. placebo.

(Katona C, et al.. Int Clin Psychopharm. 2012;27(4):215-223).

Geriatric Depression: Acute Treatment

SRI adverse effects: GI distress, insomnia, sexual side effects, somnolence, headache

Seen more in geriatric patients: Abnormal GI bleeding, Osteopenia, fractures, risk of falls, syndrome of inappropriate secretion of antidiuretic hormone (SIADH) leads to hyponatremia

SNRI's have similar adverse reactions.

Additionally, may have transient hypertension or orthostatic hypotension

Start at ½ the recommended daily dose. *In dosing remember always start low and go slow, but don't under dose!*

Incomplete Response in Geriatric Depression

Augmenting agents

Non-MAOI antidepressant in another class (buproprion, mirtazepine)

Atypical antipsychotics: FDA approved for augmentation of depression are **aripiprizole**, olanzapine, quetiapine, brexpiprazole

Non-FDA approved augmenting agents

- Thyroid hormone/triiodo-thyronine (T3)
- Lithium
- Stimulants/Methylphenidate

Treatment Resistant Depression

Esketamine approved by the FDA but failed to produce statistically significant improvement in the elderly with treatment resistant depression.

(Ochs-Ross R, et al. Am J Geriatric Psychiatry. 2020;28(2):121–141).

Geriatric Depression: The Maintenance Phase

- Depression tends to reoccur in the elderly
- Rates of recurrence of 50-90 percent over a period of 2-3 years
- Studies indicate that preventing the recurrence of depression in geriatric patients require continued treatment with antidepressants for at least 2 years (Reynolds, et al, NEJM, 2006)
- Continuous Maintenance treatment for at least 2 years is recommended in over 65 patients, despite the number of previous episodes.

Benzodiazepines/Sedative Hypnotics

Can benzodiazepines be used safely in geriatric patients?

Benzodiazepines/Sedative Hypnotics

- Falls, with increased risk of fractures/head injuries, impairment in motor coordination and speed, AMS and disinhibition in long term use

- Safer to use in elderly, but in short term use, less than 3 months:

Lorazepam
Oxazepam
Temazepam
Alprazolam

No Phase I metabolism, no active metabolites and shorter half-lives

Benzodiazepines/Sedative Hypnotics

2 case control retrospective studies and a large prospective population-based study revealed "no evidence of a causal association between benzodiazepine use and dementia".

(Bierman, et al. 2007; Imfeld , et al, 2015; Gray SL, et al. **BMJ** 2016;352(i90):i90).

Benzodiazepines/Sedative Hypnotics

- Z drugs such as zolpidem, zaleplon, eszopiclone may be better than benzodiazepines in sleep disturbances, but can lead to excessive drowsiness, blackouts sleep walking: recommend use half doses.
- Ramelteon, a melatonin receptor antagonist, suvorexant an orexin receptor antagonist may be better options

Benzodiazepines/Sedative Hypnotics

- Sleep-behavioral interventions work better
- Short term use, less than 4 weeks
- Z drugs or ramelteon

Disease Modification in Alzheimer's Disease (AD)

Are the new FDA approved drugs that target Amyloid effective in AD?

Symptomatic Treatment in AD

Pharmacological Approaches:

- Cholinesterase inhibitors (CI): FDA indicated for mild and moderate to severe AD
  - Donepezil (5mg, 10mg, 23 mg tablets)
  - Rivastigmine (oral: 1.5, 3, 4.5, 6 mg; Patch: 4.6, 9.5, 13.3 mg)
  - Galantamine (oral: 4, 8, 12 mg; XR 8, 16, 24 mg)
- N-methyl D-aspartate (NMDA) receptor inhibitors: FDA indicated for Moderate to Severe AD only

  Memantine (oral 5, 10 mg; XR: 7, 14, 21, 28 mg)

DSM-5, APA, 2013; APA: Practice guideline for the treatment of patients with Alzheimer's disease and other dementias of late life. Am J Psych, 2007.

Symptomatic Treatment in AD

Cholinesterase inhibitors common side effects: GI distress, fatigue, bradycardia.

Less common: seizures, CAD, worsening COPD

When given with NSAIDS, increased risk of GI bleed, should no be given with anticholinergic medications.

Memantine common side effects: diarrhea, constipation, dizziness, headache, hallucinations, somnolence

Symptomatic Treatment in AD

- Combination treatment of CI with memantine demonstrated mixed results.

Yes cognitive benefit

Gauthiera & Molinuevo, 2013.

No cognitive benefit

Howard, et al. 2012.

Disease Modification in Alzheimer's Disease (AD)

- 2 FDA approved drugs for the treatment of AD: aducanumab and lecanemab
- Clinical trials of anti-amyloid therapies have not been ideal
- AB neuritic plaque clearance is very effective, not clinical benefit, trials only in very early AD/MCI or mild dementia
- efficacy not convincing
- Need for diagnosing for neuritic plaques, such as amyloid CT/PET, CSF or blood biomarkers
- 2 phase 3 trials with aducanumab: EMERGE and ENGAGE. Improvement in only one study with 23% reduction in decline on the CDR sum or boxes and 27% reduction in the ADAS-COG after 12 months Contrastly, nearly half the patients who received the higher does no longer had amyloid plaques as measure on Amyloid PET scan.

Overall Summary

- Follow your medical decision-making process-weighing strongly the risk/benefit profile.
- Use psychotropics when absolutely necessary in the elderly.
- Start low but titrate up slowly and consistently to the lowest dose that is effective and tolerated.
- Stop the medication when no longer needed or no significant benefit.
- Monitor symptoms closely.
- Provide clearly both the risks and benefits with patient and their care providers/family members.