ECHO IDAHO

Alzheimer's Disease and Related Dementias

An Examination of Medications Used in Dementia Care: Addressing Common Prescribing Practices

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University of Idaho
School of Health and Medical Professions

Project ECHO

Learning Objectives

- What is BPSD?
- What is considered best therapy for BPSD?
- Discuss evidence for FDA-approved medications for:
  - Sleep
  - Agitation
- Identify what is not recommended

Background

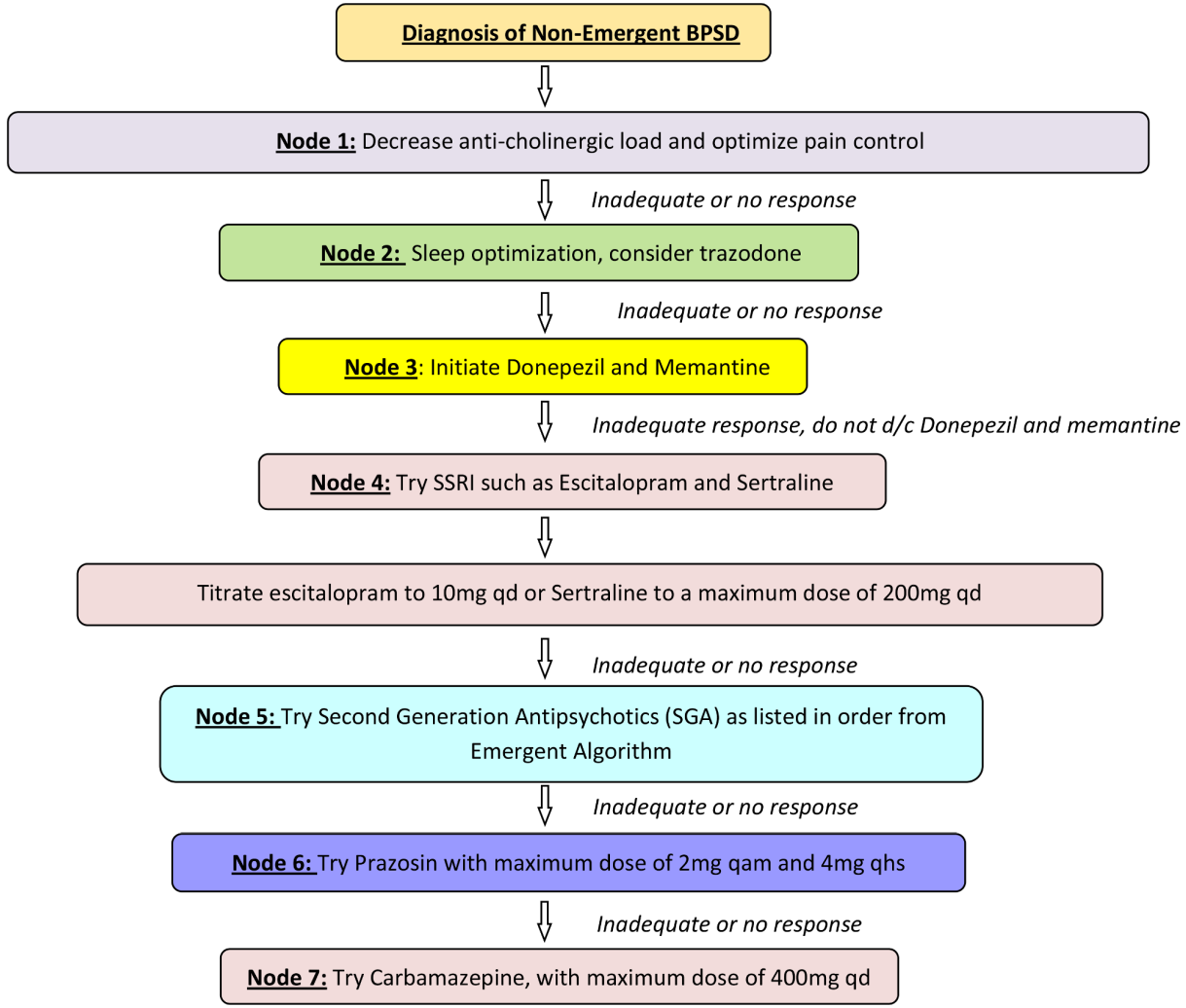
BPSD

BPSD: Behavioral and Psychosocial Symptoms in Dementia

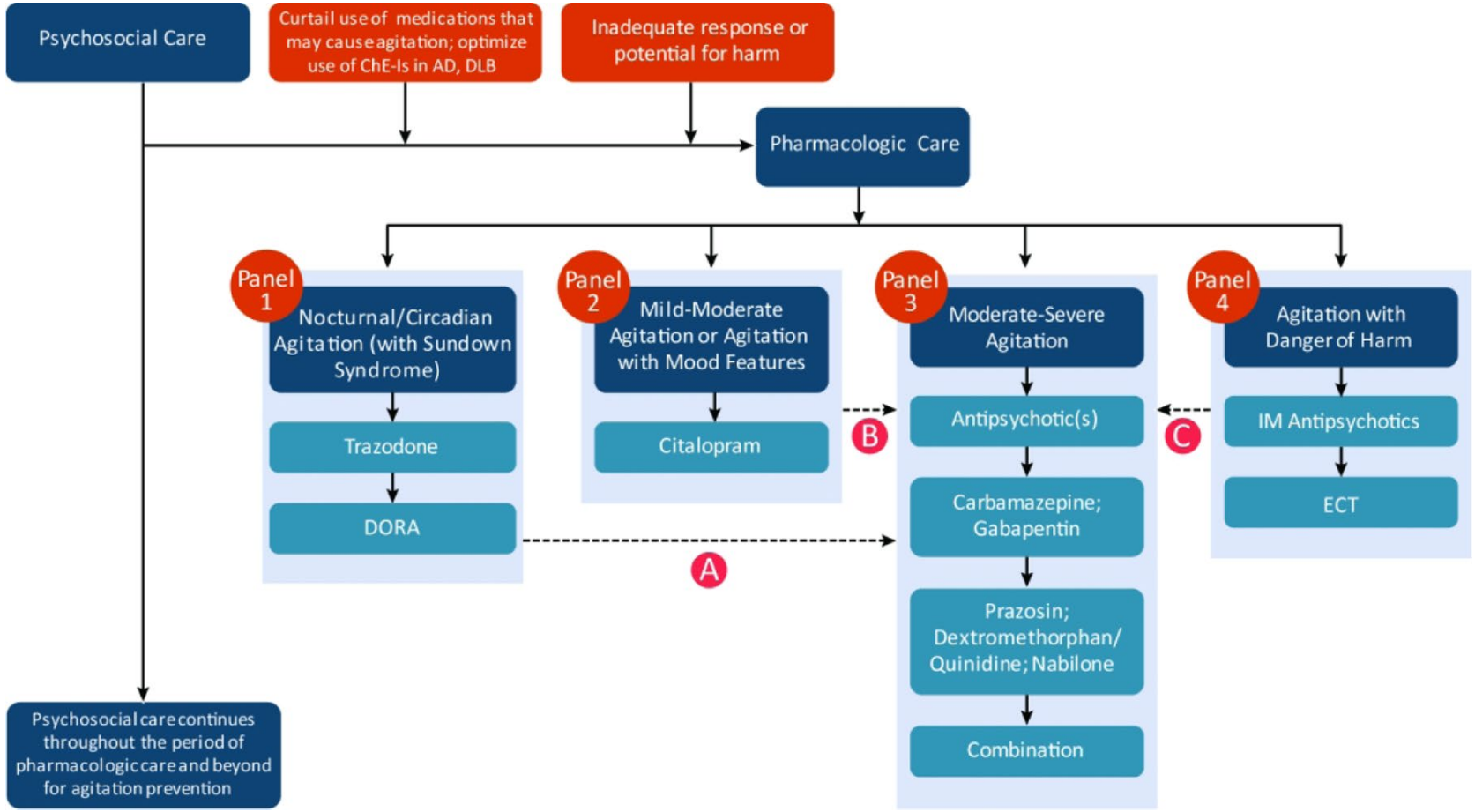
- Aggression
- Agitation
- Psychosis
- “Mood symptoms”

    - Also: screaming, calling out, verbal and physical aggression, agitation, apathy, sexual disinhibition, defiance, wandering, hostility, intrusiveness, repetitive behavior and/or vocalization, hoarding, nocturnal restlessness, emotional lability, paranoid behaviors, psychosis (hallucinations and/or delusions)

BPSD Therapy – Harvard South Shore



BPSD Therapy – International Pschogeriatric Association



Saint Alphonsus Memory Center

Immense focus on the caregivers

- Identify greatest concerns
- Barriers to care
- Connect with emotional support
- Education, disease process
- Education, improving interactions with and care for the patient
- Connect with resources within the community

General Philosophy

Lowest effective dose of every medication

- Optimize benefit
- Minimize risk

Optimize nonpharmacologic interventions

- Environment
- Caregivers
- Other disease states

General Philosophy

Guides

- Beer's List
- STOPP-START
- Anticholinergic Burden
  - Calculator at acbcalc.com
- Deprescribing.org
- Sleepwell at mysleepwell.ca

AGS BEERS CRITERIA® 2023

deprescribing.org

Sleepwell mysleepwell.ca

Step 1

What medications may contribute to BPSD?

Step 1: Meds that make BPSD worse

- Anticholinergics
- “Skeletal Muscle Relaxants”
- Antipsychotics
- Benzodiazepines
- “Z-hypnotics”
- Opioids
- Stimulants
- Bupropion
- Dopamine-blocking agents
- Serotonergic

Step 1: Meds that make BPSD worse

To Deprescribe:

- Consider a Taper:
  - Especially for medications that affect the brain
  - Slower taper for benzodiazepines and opioids

- Generic Taper:
  - Half the dose every 1-2 weeks until you reach the lowest commercially available dose
  - At this point, you should be able to discontinue the medication

- For Sleep Medications:
  - Try cutting the tablet in half. They can still take the other half if they are still awake in 1 hour

Step 2

What other disease states can make BPSD worse?

Step 2 – Diseases that make BPSD worse

- Pain
- Anxiety/Depression/Agitation
- Dizziness/“Queasiness”
- Constipation/GI distress
- Loneliness/Isolation

Pain Assessment in Advanced Dementia (PAINAD) scale

Items*	0	1	2	Score
Breathing independent of vocalization	Normal	Occasional labored breathing. Short period of hyperventilation.	Noisy labored breathing. Long period of hyperventilation. Cheyne-Stokes respirations.	
Negative vocalization	None	Occasional moan or groan. Low-level speech with a negative or disapproving quality.	Repeated troubled calling out. Loud moaning or groaning. Crying.	
Facial expression	Smiling or inexpressive	Sad. Frightened. Frown.	Facial grimacing.	
Body language	Relaxed	Tense. Distressed pacing. Fidgeting.	Rigid. Fists clenched. Knees pulled up. Pulling or pushing away. Striking out.	
Consolability	No need to console	Distracted or reassured by voice or touch.	Unable to console, distract, or reassure.	
			Total¶:	

This pain assessment score can be used to assess pain in patients with dementia. Patients should be observed for 5 minutes prior to performing the assessment. Total scores range from 0 to 10, with 10 representing severe pain.

* 5-item observational tool.

¶ Total scores range from 0 to 10 (based on a scale of 0 to 2 for 5 items), with a higher score indicating more severe pain (0 = "no pain" to 10 = "severe pain").

Step 2 – Diseases that make BPSD worse

It is okay to question reported pain

- Is it pain?
  - Those with dementia may struggle to interpret stimuli
  - Family/Caregivers may start by asking about pain

- Exercise caution when using pain scales
  - May consider using PAINAD

- It is not uncommon for those with chronic pain to be able to taper or discontinue their opioids as dementia progresses

Patient Case 1: Is It Pain?

DM, 73 yo F

- Multiple trips to the ED for uncontrolled pain (22 times in 30 days)
- Regimen:
  - Acetaminophen 500 mg, 1-2 tablets 3 times every day as needed for pain
  - Duloxetine 60 mg, 1 capsule every morning
  - Ibuprofen 200 mg, 3 tablets (600 mg) 2 times every day
  - Meloxicam 15 mg, 1 tablet every morning
  - Pregabalin 50 mg, 2 capsules (100 mg) every evening
  - Tramadol 50 mg, 1 tablet every 6 hours while awake

- MoCA 9/30

Step 2 – Diseases that make BPSD worse

Recommended therapy for presumed pain

- Physical therapy (if appropriate)
- Topicals
  - Diclofenac, Lidocaine, other muscle rubs
- Acetaminophen
  - “Arthritis Strength” 650 mg ER, 2 tablets (1300 mg) 2 times every day

- Further AGS recommendations for pain:
  - Morphine, up to 20 mg
  - Buprenorphine transdermal patch, up to 10 mcg/hr
  - Pregabalin, up to 300 mg daily

Step 2 – Diseases that make BPSD worse

- "Brain fog" is sometimes described as:
  - Dizziness – has the person fallen?
  - Nausea, "Queasiness" – Does the person vomit? Have they lost weight?
  - Depression, Daytime fatigue, "Laziness"

- Agitation/Anxiety Trigger
  - Person – often the spouse
  - Large life event

- Loneliness
  - Lack of social engagement

Patient Case 2: Can We Reduce Triggers?

CC, 82 yo F

- Delusions of parasitosis
- Medications that affect the brain:
  - Aripiprazole 2 mg, 1 tablet daily
  - Mirtazapine 7.5 mg, 1 tablet every evening
  - Sertraline 100 mg, 1 tablet every evening
  - Trazodone 50 mg, 1 tablet every evening

- Realized she was lonely

Step 3

Are the medications for Alzheimer's Dementia optimized?

Step 3 – Optimize ChE-I and Memantine

- ChE-I (Cholinesterase Inhibitor)
  - Typically Donepezil, but also Rivastigmine, Galantamine
  - Evidence for acute treatment of BPSD is limited
    - Any benefit is likely very small
    - NOT effective for severe agitation
    - May work better for some and not others
  - *Can make BPSD worse*
  - Start Donepezil at 5 mg every evening, typically in the evening
  - In 2 weeks, can increase to Max dose 10 mg
- Memantine
  - NMDA receptor antagonist
  - Start at 5 mg daily . . . Increase by 5 mg daily every week
  - Max dose 20 mg daily – as a single dose or twice daily

Patient Case 3: How Do We "Optimize" Medications?

LM, 79 yo F

- Presumed Alzheimer's dementia
- MoCA 16/30 in December 2023
- Long history of anxiety/agitation, with history of diazepam at bedtime
- Medications that affect the brain:
  - Donepezil 10 mg, 1 tablet every day
  - Memantine 5 mg, 1 tablet 2 times every day
  - Sertraline 25 mg, 2 tablets (50 mg) every day

Step 4

Is pharmacotherapy for anxiety/agitation optimized?

Step 4 – SSRI

Selective Serotonin Reuptake Inhibitor (SSRI)

- Citalopram
  - CitAD trial used 30 mg daily
  - The FDA reduced recommended max dose to 20 mg daily on those at least 65 years
- Escitalopram
  - The active isomer of citalopram
  - Increases QTc, but much less so than citalopram . . . no FDA warning
  - No large studies evaluating treatment for BPSD
  - Most experts agree escitalopram is a “suitable alternative” to citalopram
  - Start at 5 mg daily
  - Takes 4-6 weeks for full effect – After 2-4 weeks may increase by 5 mg daily
  - Max dose 20 mg daily

Step 4 – SSRI

Selective Serotonin Reuptake Inhibitor (SSRI)

- Sertraline
  - No QT concern
  - Efficacious for BPSD
  - Start at 25 mg daily (50 mg daily for non-frail)
  - Takes 4-6 weeks for full effect – After 2-4 weeks may increase by 25 mg daily
  - Most get benefit between 50 mg and 250 mg daily
  - Max dose 200 mg daily

Step 4a – SSRI Alternatives

- Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)
  - Duloxetine: Start at 20-30 mg daily . . . Max 60-120 mg daily
  - Venlafaxine

- Buspirone
  - Start at 10 mg 2-3 times daily . . . Max 20 mg 3 times daily

- Mirtazapine
  - Start at 7.5 mg nightly . . . Max 15 mg nightly

Step 5

Are there medications that can be used for sleep?

Step 5 – Nocturnal/Circadian Agitation

Why are sleeping medications such a big concern?

- Daytime Fatigue
- Confusion
- Falls
- Hallucinations, Vivid Dreams
- Can make BPSD worse

Step 5 – Nocturnal/Circadian Agitation

What is behind lack of sleep?

- Poor sleep hygiene
- Daytime Napping
- Anxiety/Agitation
  - Loneliness – especially at night
- Stimulating activities before bed
- Lack of daytime activity
- Staying in room, or in bed most of the day

Step 5 – Nocturnal/Circadian Agitation

How severe is reported insomnia?

- Is the insomnia new?

- What are the hours of sleep?
  - Many people get 7-8 hours of sleep

- Normalize that it is common to sleep less as you age

Step 5 – Nocturnal/Circadian Agitation

- Our clinic does everything we can to avoid prescribing for sleep
  - Sleep hygiene
  - Set expectations for sleep duration and timing
  - Address disrupted sleep-wake cycle
  - Light therapy

- Melatonin
  - Start at 3-5 mg … recommend to not exceed 10 mg
  - Can take if needed for nighttime awakening too
  - Ramelteon (Rozerem) is synthetic melatonin

Step 5 – Nocturnal/Circadian Agitation

- Trazodone
  - Or Trazodon't?
  - " . . . is commonly used . . . and may be tried . . ."
  - " . . . is known for its sedating properties . . ."
  - Recommended dose 12.5-25 mg (1/4- to ½-tablet)
  - Max dose 50 mg nightly
  - Fall risk similar to benzodiazepines

Step 5 – Nocturnal/Circadian Agitation

- DORA: Dual Orexin Receptor Antagonists
  - Suvorexant (Belsomra)
  - Lemborexant (DayVigo)

- The International Psychogeriatic Association references a 2020 paper . . .

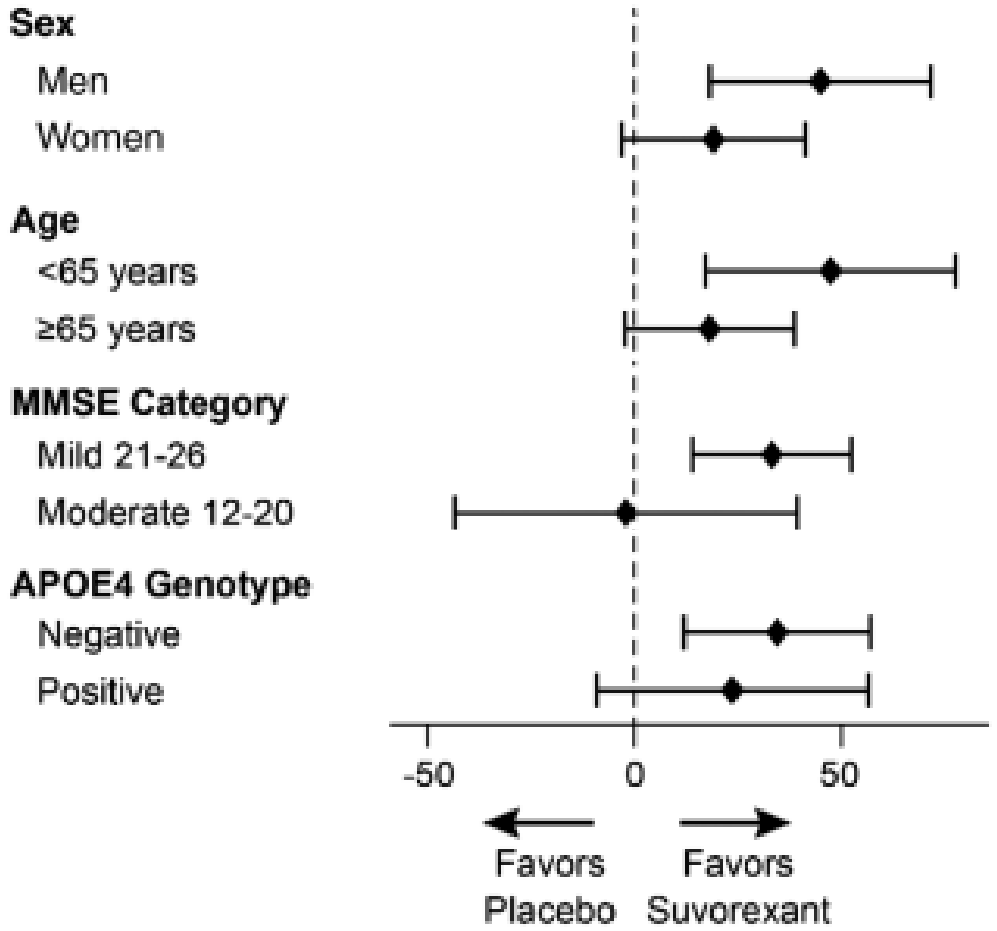
Suvorexant (Belsomra)

Suvorexant in patients with probable Alzheimer's disease dementia and insomnia

- Used polysomnography
- Total Sleep Time (TST) improved
- REM sleep not improved between treatment and placebo
- Concerning Side Effects:
    - Somnolence: 6 (4.2%) vs. 2 (1.4%)
    - Falls/Ataxia/Worsening of balance: 3 (2.1%) vs. 0
    - Dry Mouth: 3 (2.1%) vs. 1 (0.7%)

Suvorexant (Belsomra)

Suvorexant in patients with probable Alzheimer's disease dementia and insomnia



Patient Case 4: Is The Sleep Med Helping?

JC, 75 yo F

- Depression, Fatigue, Anxiety, reported PTSD
- MoCA 20/30 on 8/21/2018
- Medications that affect the brain:
  - Aripiprazole (Abilify) 5 mg daily
  - Caffeine (Vivarin) every morning
  - Fluoxetine (Prozac) 40 mg daily
  - Hydroxyzine (Atarax) 25 mg 3 times every day as needed for anxiety (using twice weekly)
  - Suvorexant (Belsomra) 10 mg nightly
  - Topiramate (Topamax, for headaches) 200 mg every morning

Patient Case 4: Is The Sleep Med Helping?

JC, 75 yo F … SUVOREXANT

- November 2017 – Suvorexant 10 mg nightly
  - Sleeping 10 hours per night
- December 2017 – Suvorexant 5 mg nightly
  - Realized she was struggling to function during the day
  - No longer napping during the day … now making plans
  - Now make plans for things to do during the day
- January 2018 – Stopped Suvorexant
  - Much more awake during the daytime and engaged in life
  - MoCA 25/30
- March 2018
  - No more concerns for sleep at night

Step 6

What are the options for severe symptoms?

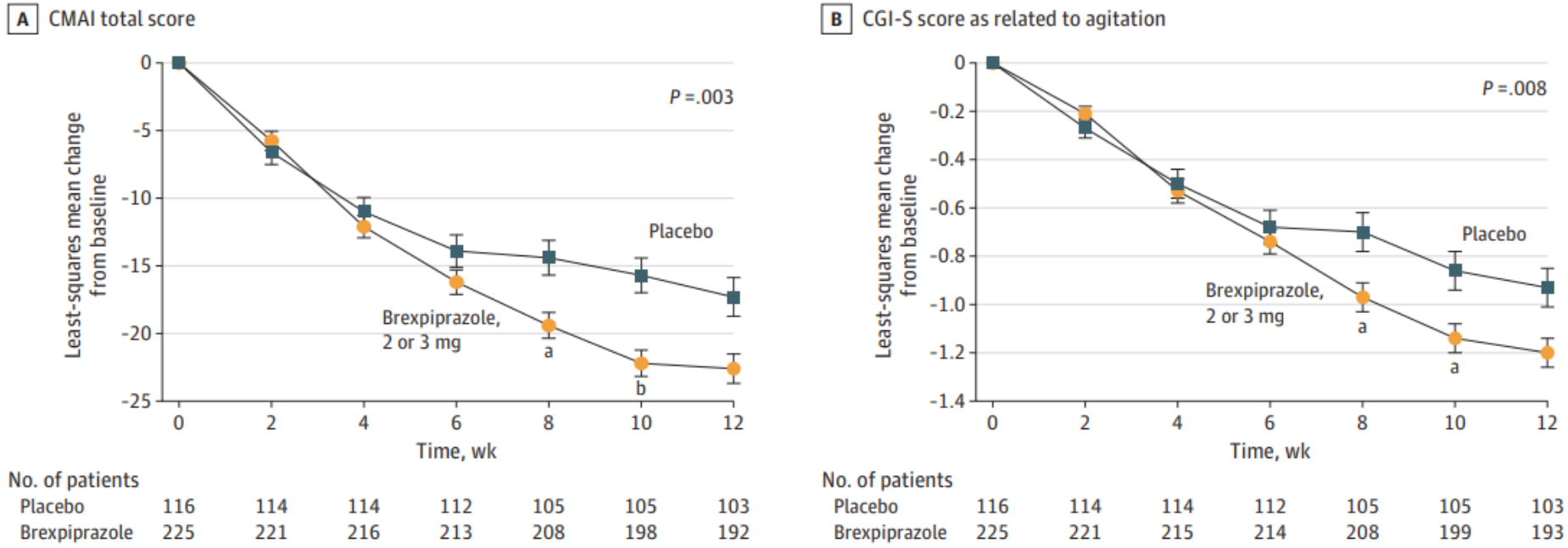
Step 6 – Moderate-Severe Agitation

- Harvard South Shore
  1) Antipsychotic: Aripiprazole, then Risperidone
  2) Prazosin
  3) Carbamazepine

- International Psychogeriatric Association
  1) Antipsychotic: Risperidone, Olanzapine, Aripiprazole, or Brexpiprazole
  2) Carbamazepine; Gabapentin
  3) Prazosin

Brexpiprazole (Rexulti)

Figure 2. Change From Baseline in Cohen-Mansfield Agitation Inventory (CMAI) Total Score (Primary End Point) and Clinical Global Impression–Severity of Illness (CGI-S) Score as Related to Agitation (Key Secondary End Point): Efficacy Sample



Baseline mean CMAI total scores: brexpiprazole, 80.6; placebo, 79.2. Baseline mean CGI-S scores: brexpiprazole, 4.7; placebo, 4.7. Footnotes indicate nominal *P* values with no adjustment for multiplicity.

[a] $P < .01$ vs placebo, mixed model for repeated measures.

[b] $P < .001$ vs placebo, mixed model for repeated measures.

Brexpiprazole (Rexulti)

Table 3. Summary of Treatment-Emergent Adverse Events (Safety Sample)

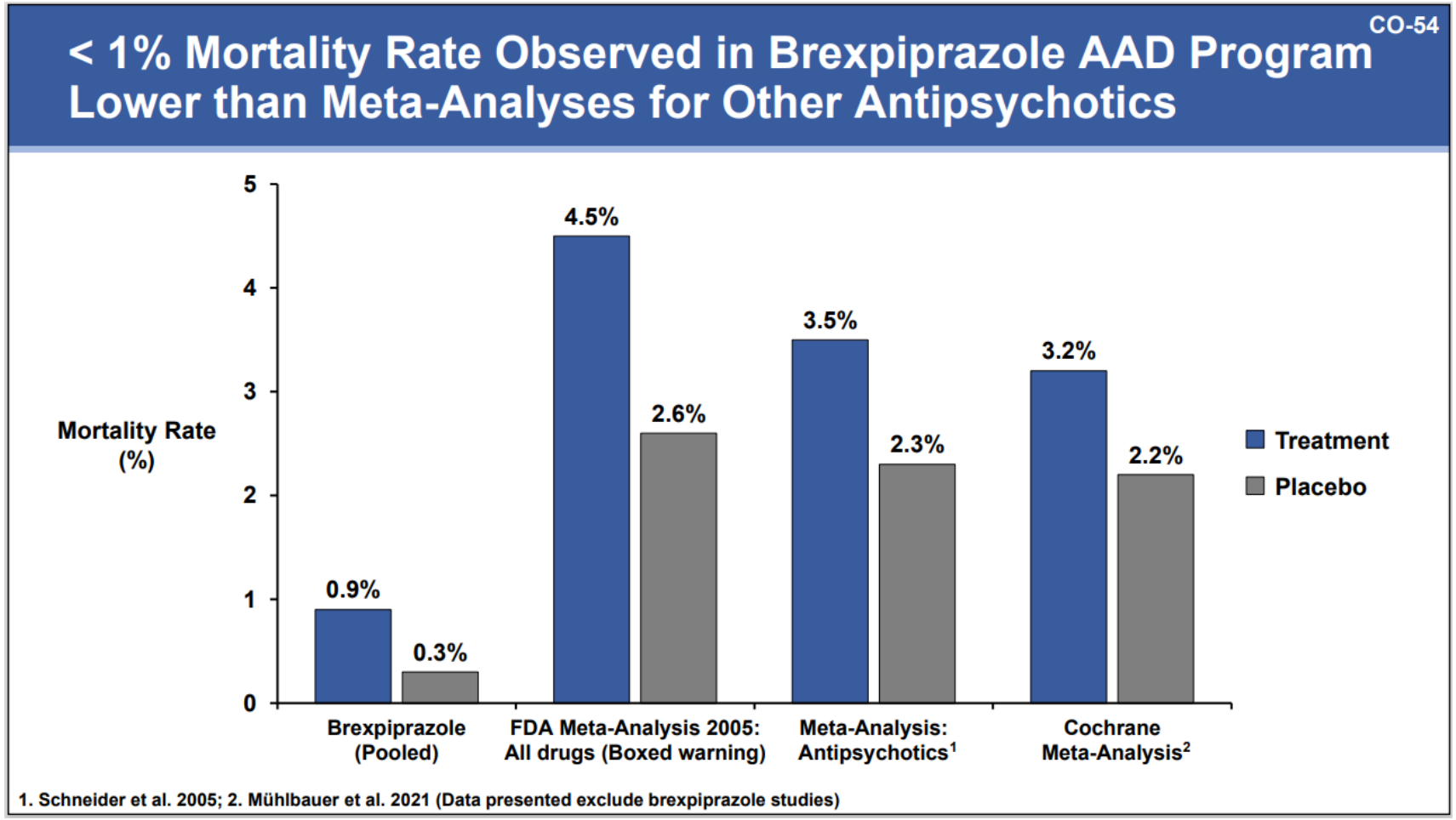
Event	Placebo (n = 116), No. (%)	Brexpiprazole, No. (%)		
		2 or 3 mg (n = 226)	2-mg Subgroup (n = 73)	3-mg Subgroup (n = 153)
At least 1 TEAE	36 (31.0)	92 (40.7)	28 (38.4)	64 (41.8)
At least 1 serious TEAE	3 (2.6)[a]	6 (2.7)[b]	0	6 (3.9)
Discontinuation due to adverse event	5 (4.3)[c]	12 (5.3)[d]	1 (1.4)	11 (7.2)
Death	0	1 (0.4)[e]	0	1 (0.7)
TEAEs with an incidence ≥2% in the brexpiprazole, 2 or 3 mg, group and an incidence greater than placebo				
Somnolence	1 (0.9)	8 (3.5)	3 (4.1)	5 (3.3)
Nasopharyngitis	2 (1.7)	7 (3.1)	3 (4.1)	4 (2.6)
Dizziness	2 (1.7)	6 (2.7)	1 (1.4)	5 (3.3)
Asthenia	0	5 (2.2)	0	5 (3.3)
Diarrhea	1 (0.9)	5 (2.2)	3 (4.1)	2 (1.3)
Urinary tract infection	1 (0.9)	5 (2.2)	0	5 (3.3)
Other TEAEs of interest				
Fall	2 (1.7)	4 (1.8)	2 (2.7)	2 (1.3)
Akathisia	0	2 (0.9)	0	2 (1.3)
Extrapyramidal disorder	0	2 (0.9)	1 (1.4)	1 (0.7)
Hip fracture	1 (0.9)	1 (0.4)	0	1 (0.7)
Sedation	0	1 (0.4)	0	1 (0.7)

Brexpiprazole (Rexulti)

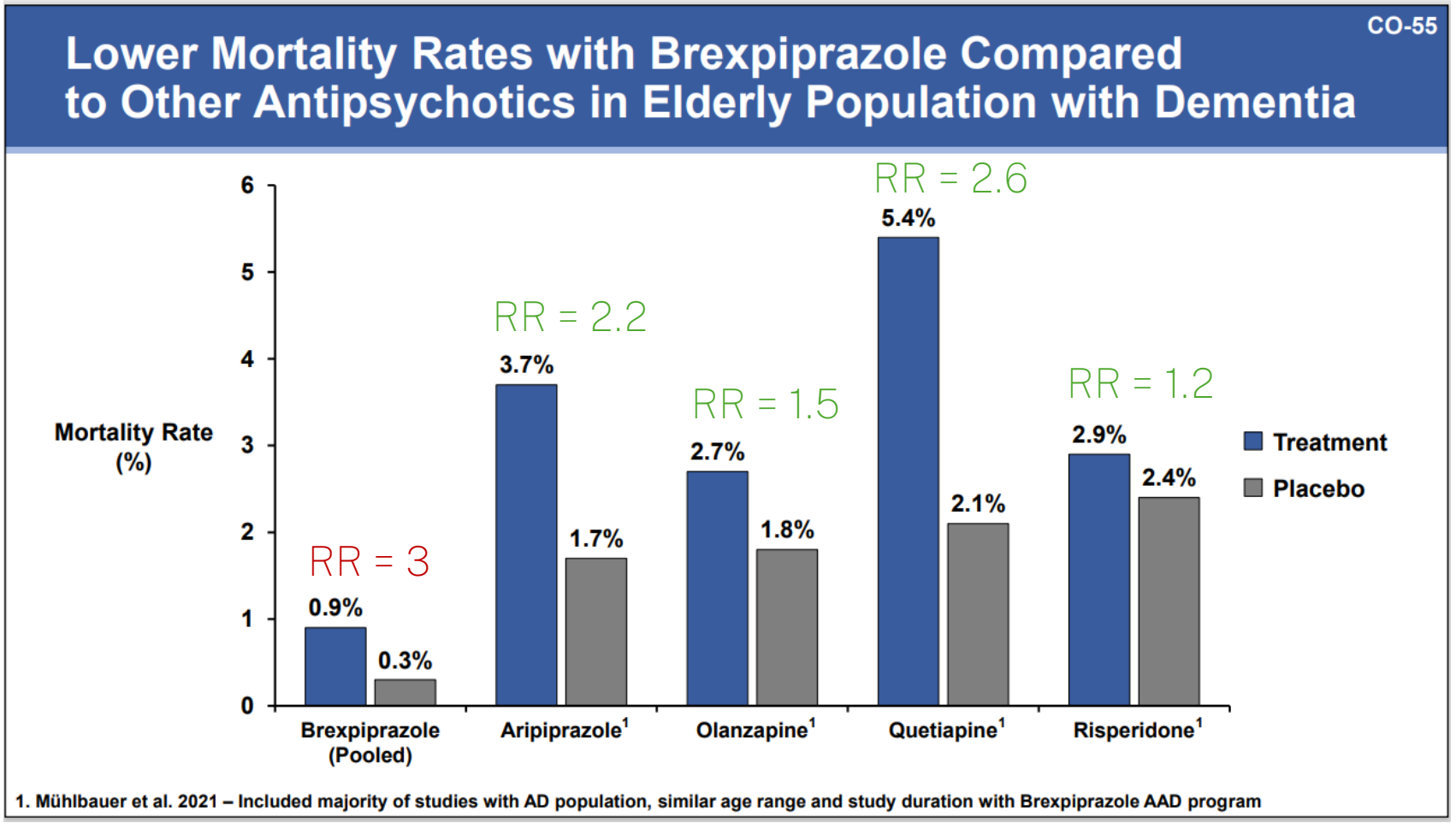
Mortality

Brexpiprazole reports a higher mortality rate compared with placebo [0.9% (n = 6) vs 0.3% (n = 1)] from its clinical trials for agitation associated with dementia due to AD.[21] Two deaths were reported in the brexpiprazole 0.5-mg group, 2 in the brexpiprazole 1-mg group, 1 in the brexpiprazole 2-mg group, and 1 in the brexpiprazole 3-mg group.[21] There were 2 additional deaths with brexpiprazole beyond the protocol-specified safety follow-up period: 1 death occurring 2 days after the 30-day follow-up period and another occurred more than 100 days after the last brexpiprazole dose.[21]

Brexpiprazole (Rexulti)



Brexpiprazole (Rexulti)



Brexpiprazole (Rexulti)

Assertions from the JAMDA article:

- "There may be financial barriers . . . Although costs should be considered . . ."
- "With brexpiprazole's FDA approval . . . providers may consider the medicolegal implications of prescribing or administering an off-label drug . . ."
- "Off-label drug use generally lacks evidence of clinical efficacy or scientific support and is associated with higher rates of adverse events . . ."
- "Physicians have also been involved in legal claims related to prescribing or promoting off-label medications."

Brexpiprazole (Rexulti)

- Article Conclusions for Brexpiprazole:
  - Brexpiprazole is FDA-approved for reduction in agitation in setting of Alzheimer's
  - Doses less than 2 mg daily seem to be ineffective

- Pharmacist Thoughts on Brexpiprazole:
  - FDA-Approval does not mean it is safer or more effective than other therapies (e.g. SSRIs)
  - Think of it as similar to aripiprazole
  - We do not know that it is better than other antipsychotics
  - Too soon to say if it's less risk than other second-generation antipsychotics
  - Cost is around $1,400 per month

Step 6 Moderate-Severe Agitation

- First, ensure nonpharmacologic interventions have been optimized

- Risperidone
  - Start at 0.2 mg to 0.5 mg daily
  - May increase by 0.25 mg daily
  - Max 2 mg daily
  - Adequate trial time is 3 weeks
  - Less sedating than other antipsychotics

- Often started in setting of crisis
  - Recommend to readdress after crisis has passed
  - Readdress pharmacologic & non-pharmacologic measures

Step 6 Moderate-Severe Agitation

- Aripiprazole
  - Start at 2 mg to 2.5 mg daily . . . Target 5 mg daily at the end of 2 weeks
  - Increase dose by 5 mg daily every 2 weeks to max dose 15 mg daily
- Prazosin
  - Start at 1 mg at bedtime
  - Increase by 1-2 mg daily every 3-7 days . . . Max 2 mg every morning and 4 mg every evening
- Mood-Stabilizing Anticonvulsants:
  - Gabapentin
  - Carbamazepine
  - But NOT (outside of bipolar):
    - Lamotrigine
    - Valproic acid
    - Lithium

Patient Case 5: Will More Medications Help?

DA, 68 yo M

- At initial visit, dx with FTD v. AD w/ concerns for mobility
- Increased hallucinations, requesting more medication
- Medications that affect the brain:
  - Bupropion 300 mg XL, 1 tablet daily
  - Donepezil 10 mg, 1 tablet every evening
  - Lamotrigine 25 mg, 2 tablets (50 mg) 2 times every day
  - Memantine 10 mg, 1 tablet 2 times every day
  - Propranolol 40 mg, ½ tablet (20 mg) 2 times every day
  - Quetiapine 25 mg, 2 tablets (50 mg) every evening
  - Risperidone 0.5 mg, 1 tablet 2 times every day
  - Trazodone 50 mg, 1 tablet every evening

What is absent from the algorithms?

Medications NOT Recommended

- Antihistamines, Anticholinergics
  - Hydroxyzine, Diphenhydramine, Doxylamine
- Benzodiazepines
  - Alprazolam, Clonazepam, Lorazepam
- Z-Hypnotics
  - Zolpidem, Eszopiclone, Zaleplon
- “Skeletal Muscle Relaxants”
  - Methocarbamol, Cyclobenzaprine, Baclofen, Carisoprodol
- Tricyclic Antidepressants (TCAs)
  - Doxylamine, Amitriptyline, Nortriptyline
- Alpha-2-Adrenergic Agonists
  - Clonidine, Tizanidine
- Valproic acid

Key Points

- Algorithms exist to help guide treatment of BPSD
- Before adding medicines, look for causes of BPSD
  - Other medications
  - Under treated disease states
  - Other people … Or loneliness
  - Lack of routine, including vacations
- All medications carry risks
  - Especially sleep medications and antipsychotics
  - If possible, start with an SSRI
  - Goal is Lowest Effective Dose of every medication

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