

Neuropsychiatric Symptoms of Dementia: Clinical Applications

COMMUNITY-WIDE GERIATRIC MEDICINE GRAND ROUNDS

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Disclosures

I have no financial interests or relationships to disclose

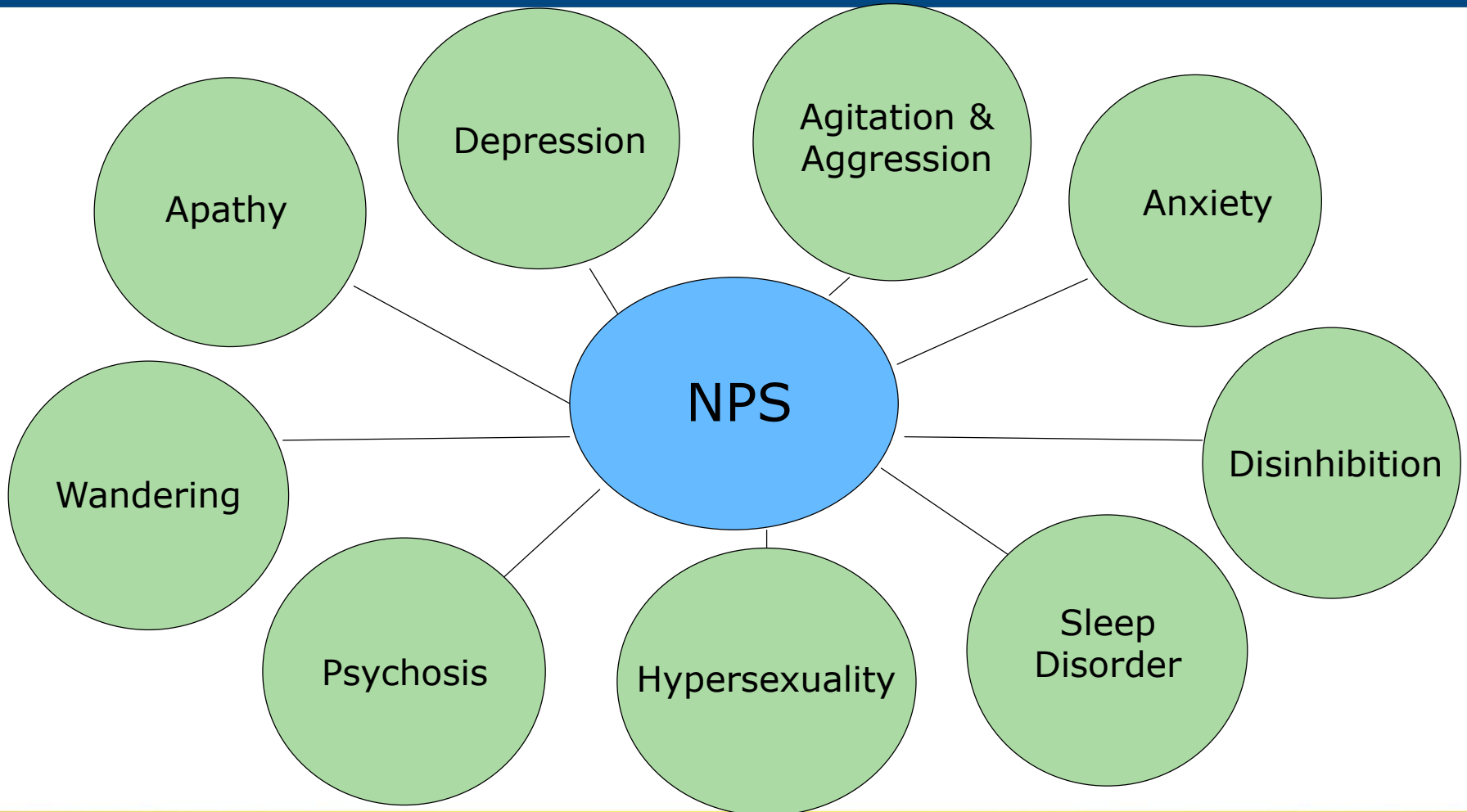
OBJECTIVES

1. Recognize the emergence of neuropsychiatric symptoms (NPS) in patients with dementia
2. Utilize a systematic approach to address NPS with non-pharmacologic interventions prior to the addition of medications
3. Understand when to use pharmacologic interventions for NPS and special considerations for their use
4. Introduce current clinical trials and emerging medications

EPIDEMIOLOGY

- WHO estimates that more than 50 million people have dementia worldwide, with 10 million new cases each year
- In 2019 dementia cost 1.3 trillion US dollars globally
- Alzheimer Disease is currently the 7th leading cause of death
- Alzheimer's disease is most common type of dementia, accounting for 60-80% of cases
- About 60-90% of patients with dementia will have one or more neuropsychiatric symptoms

Common Neuropsychiatric Symptoms of Dementia



APA Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia

- Judicious use of antipsychotics with careful consideration of risks v benefits
 - Minimizing risk of violence, patient distress, improve quality of life, and reduce caregiver burden
- Based in current literature and with consideration that the potential benefits of an intervention outweigh the harms
- Recommendation (1), Suggestion (2)
- Ratings for strength of supporting research evidence (A, B, C)

APA Practice Guideline

15 Guideline Statements

1. Assessment of Behavioral/Psychological Symptoms of Dementia
2. Development of a Comprehensive Treatment Plan
3. Assessment of Benefits and Risks of Antipsychotic Treatment
4. Dosing Duration and Monitoring of Antipsychotic Treatment
5. Use of Specific Antipsychotic Medications, Depending on Clinical Context

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DICE Approach: Describe Investigate Create Evaluate

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Regular Research Article

Moving Evidence-Informed Assessment and Management of Behavioral and Psychological Symptoms of Dementia into the Real World: Training Family and Staff Caregivers in the DICE Approach

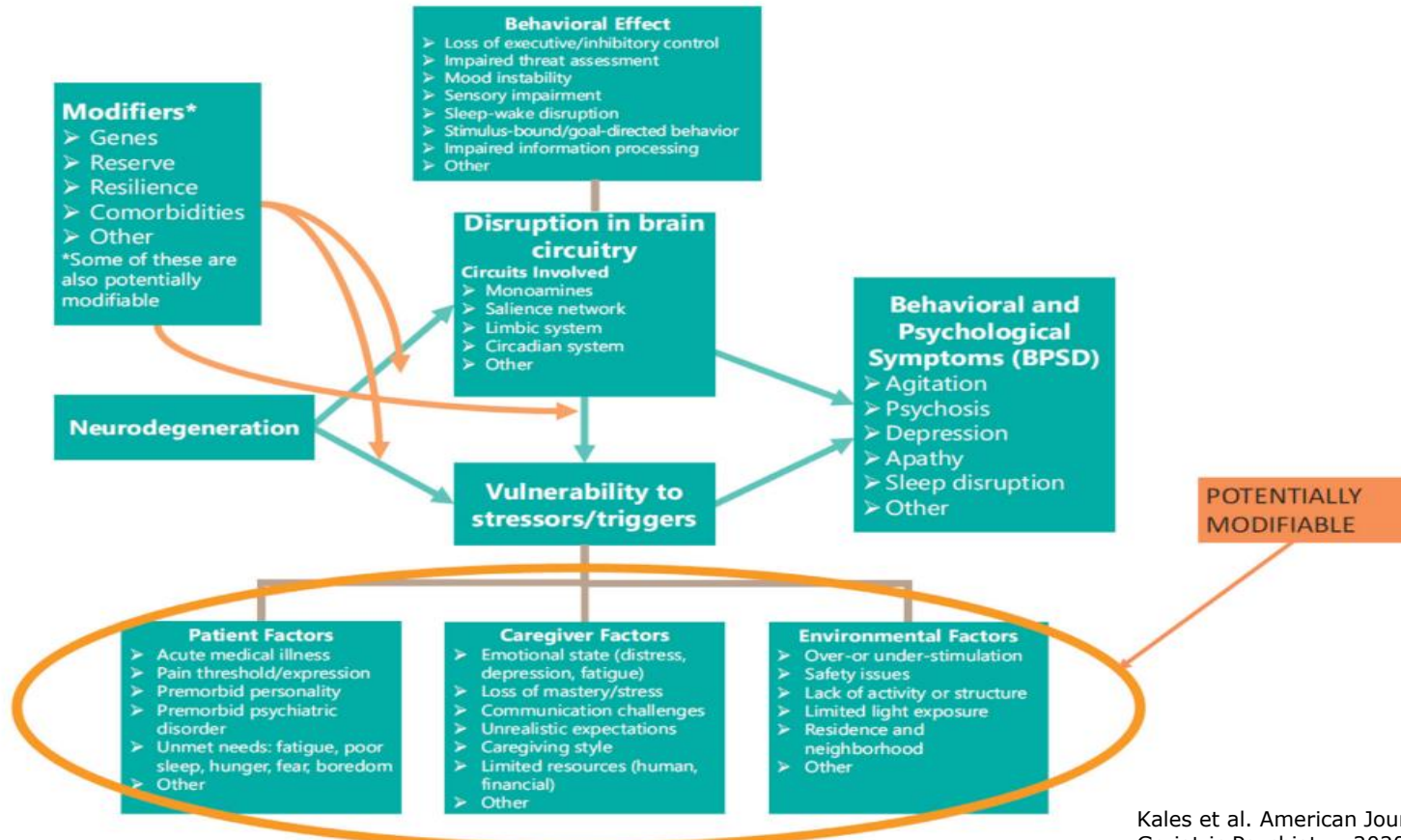
*Helen C. Kales, MD, Vincent Kern, BA, H. Myra Kim, ScD,
Mary C. Blazek, MD MEd*

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DICE Approach: Describe Investigate Create Evaluate

FIGURE 1. Proposed model of causal contributors to BPSD in persons with Alzheimer's and related dementias.



Kales et al. American Journal of Geriatric Psychiatry 2020

DICE Approach: Describe Investigate Create Evaluate

FIGURE 2. The DICE approach.



- **Describe** a behavior that challenges; who, what, where, when, and how the behavior occurs
- **Investigate** thinking like a detective and explore the person with dementia, the caregivers, and environment for possible clues to triggers underlying possible causes of behavior
- **Create** a prescription in collaboration with your team to help prevent and manage behaviors
- **Evaluate** and review prescription effectiveness, and modify or restart the process as needed

Pharmacologic Interventions

Pros

- Safety considerations
- More immediate/fast acting
- Underlying psychiatric condition requiring treatment
- Giving medication is “doing something”

Cons

- May not understand (or may cover up) underlying cause
- Side effects/interactions with other medications
- Paradoxical effect
- Off-label use

The Psychopharmacology Algorithm Project at the Harvard South Shore Program

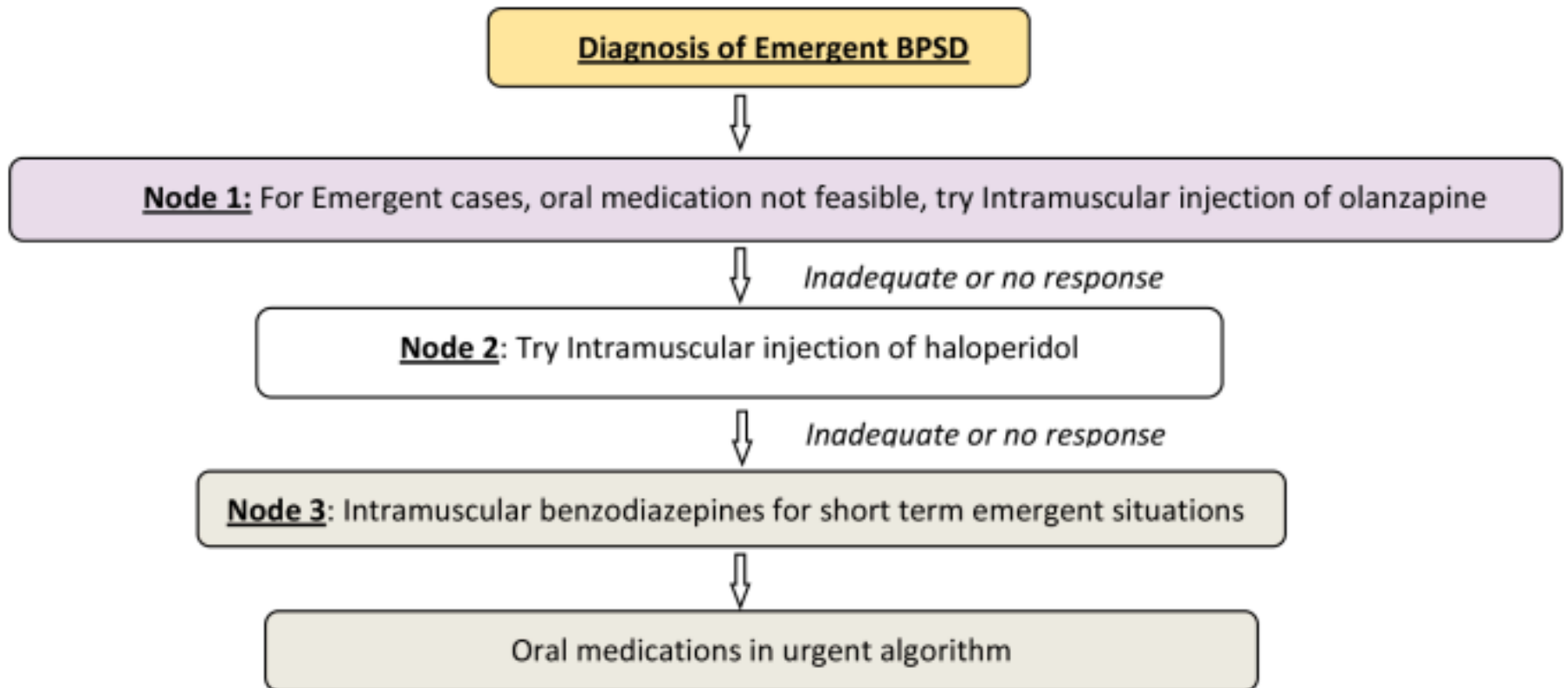


Figure 2. Flowchart for Emergent BPSD Management

Chen et al. Psychiatry Research 2021

The Psychopharmacology Algorithm Project at the Harvard South Shore Program

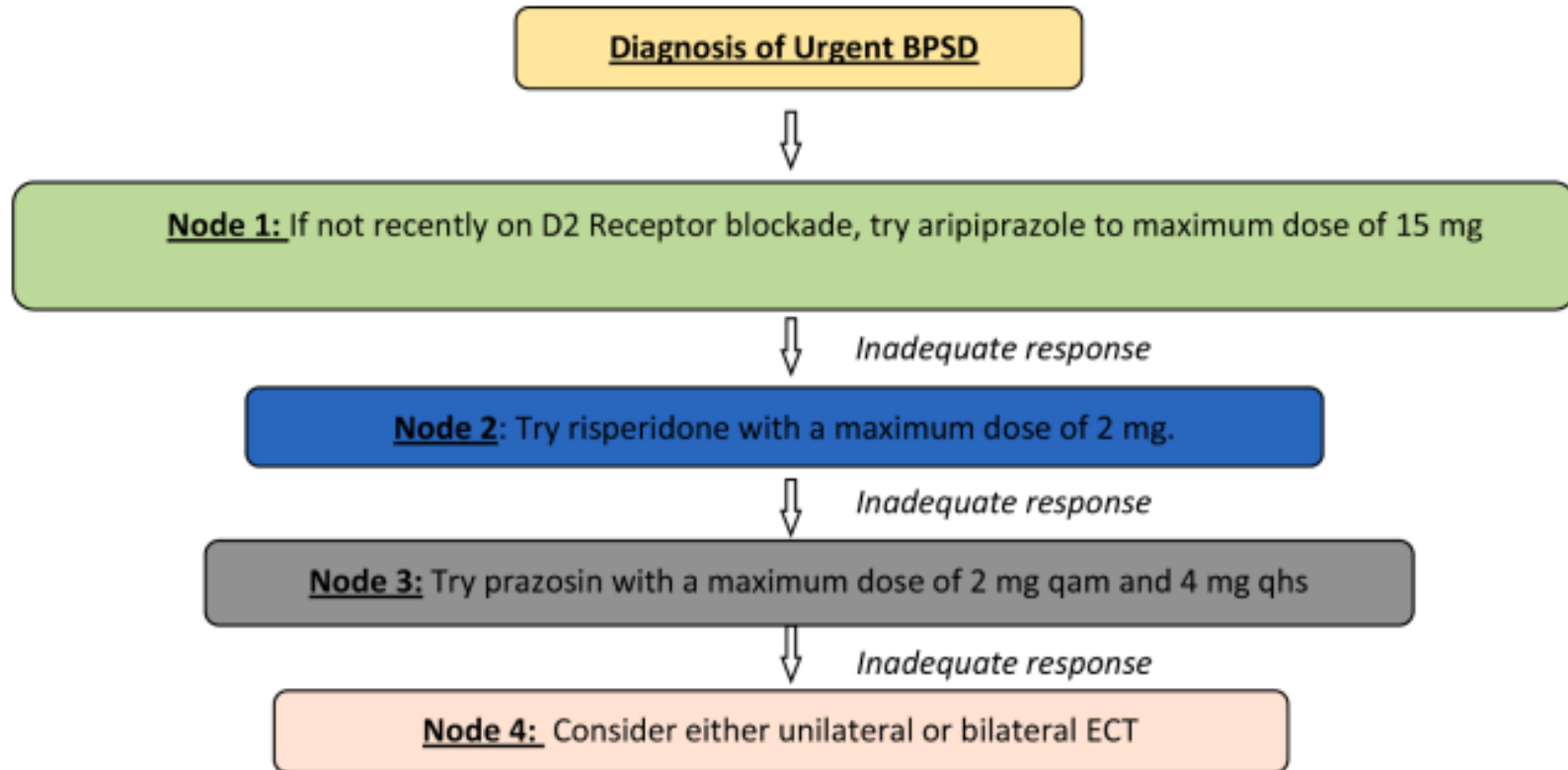


Figure 3. Flowchart for Urgent BPSD Management

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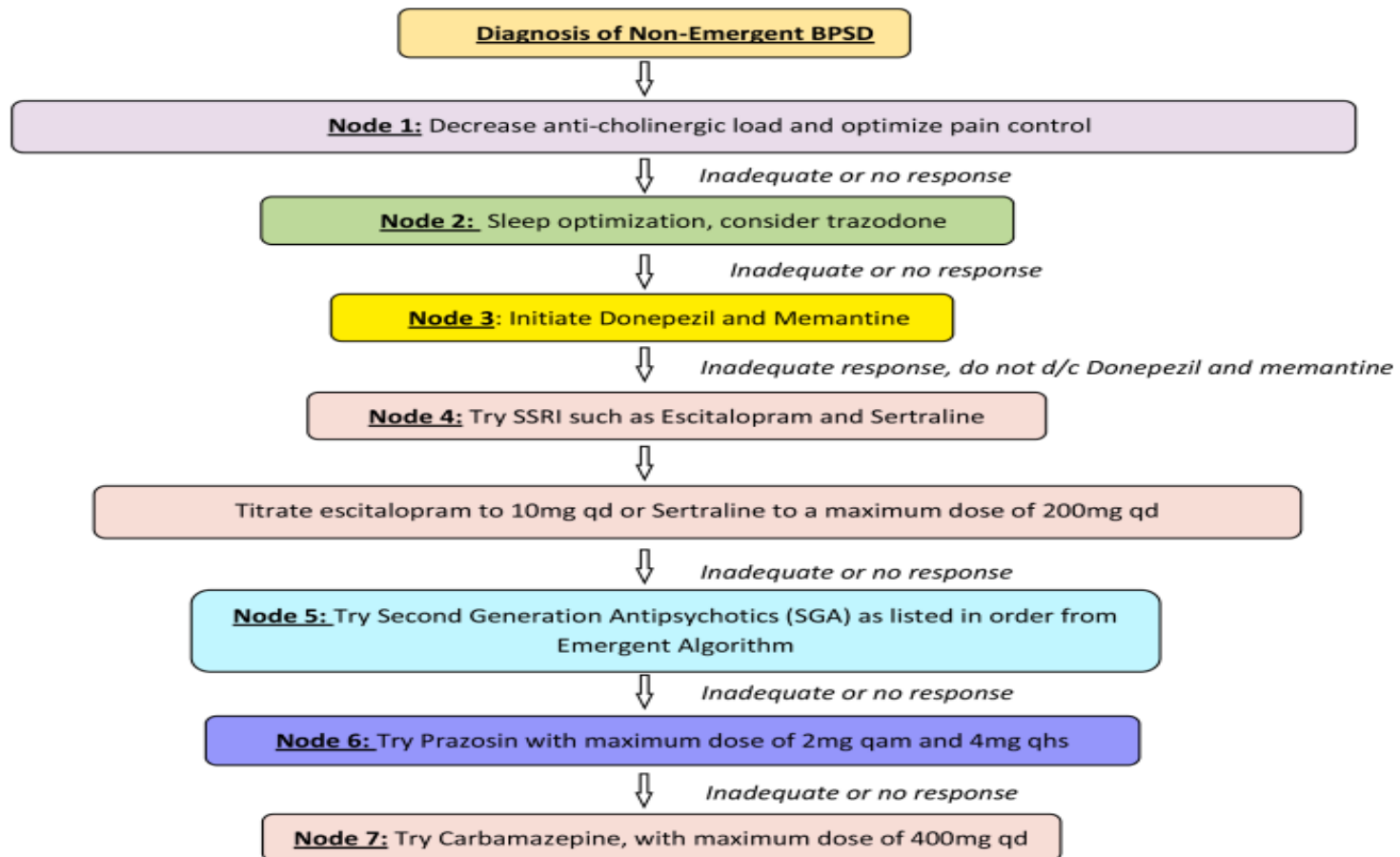


Figure 4. Flowchart for Non-Emergent BPSD

Chen et al. Psychiatry Research 2021

Pharmacologic Interventions

Symptom	Intervention Considerations
Apathy	Methylphenidate Acetylcholinesterase Inhibitors Memantine
Depression	SSRI Mirtazapine Bupropion SNRI Atypical Antipsychotic
Anxiety/Irritability	SSRI Trazodone Mirtazapine Benzodiazepine
Agitation/Aggression	SSRI Trazodone Mood Stabilizer Antipsychotics

Pharmacologic Interventions

Symptom	Intervention Considerations
Insomnia	Trazodone Ramelteon Dual orexin receptor antagonists (DORAs)
Disinhibition	Mood Stabilizer
Hypersexuality	SSRI
Psychosis	Atypical Antipsychotics Brexpiprazole Pimavanserin

Black Box Warning – Antipsychotics

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. SEROQUEL is not approved for elderly patients with dementia-related psychosis [\(5.1\)](#)

Suicidal Thoughts and Behaviors

- Increased risk of suicidal thoughts and behavior in children, adolescents and young adults taking antidepressants [\(5.2\)](#)
- Monitor for worsening and emergence of suicidal thoughts and behaviors [\(5.2\)](#)

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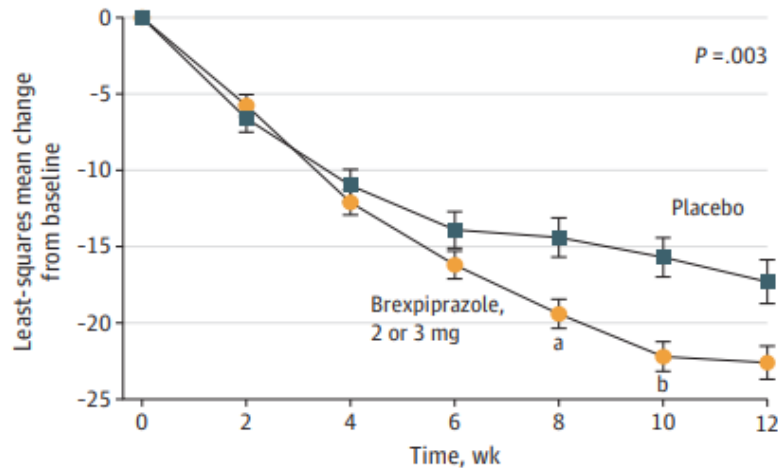
Black Box Warning – Antipsychotics

- Schneider et al 2005 meta-analysis of atypical antipsychotic drug trials to assess evidence of mortality associated with their use in older adult patients with dementia (1.7 fold)
- Wang et al 2005 retrospective cohort study examined risk of death in older adult patients started on typical vs atypical antipsychotics (17.9% typical vs 14.6% atypical)
- Most deaths were cardiovascular or infectious in nature
- Although use of atypical APS in dementia patients increases risk of mortality, the absolute increased risk to a given individual with a short term course of APS is 1-2%

Brexpiprazole (Rexulti)

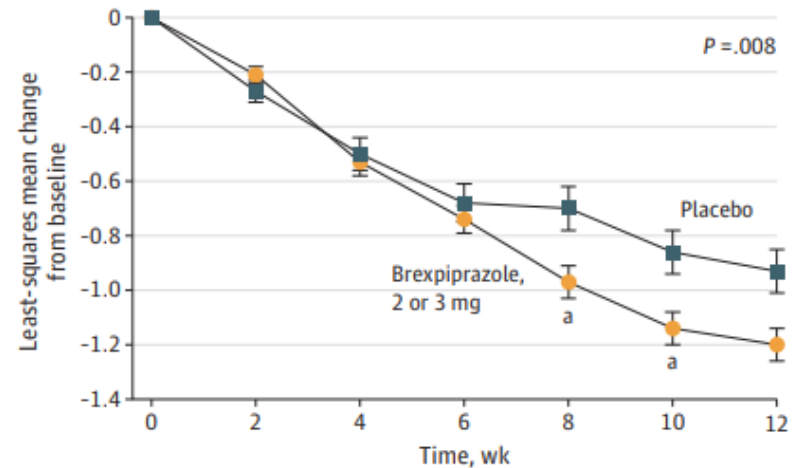
Figure 2. Change From Baseline in Cohen-Mansfield Agitation Inventory (CMAI) Total Score (Primary End Point) and Clinical Global Impression–Severity of Illness (CGI-S) Score as Related to Agitation (Key Secondary End Point): Efficacy Sample

A CMAI total score



No. of patients	
Placebo	116 114 114 112 105 105 103
Brexpiprazole	225 221 216 213 208 198 192

B CGI-S score as related to agitation



No. of patients	
Placebo	116 114 114 112 105 105 103
Brexpiprazole	225 221 215 214 208 199 193

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.

Lee et al. JAMA Neurology 2023

Current Research and Future Directions

- **Dexmedetomidine**
- **Escitalopram**
- **Xanomeline-trospium**
- **Cannabinoids**
- **Dextromethorphan**
- **Masupiridine**
- **Prazosin**





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