

A New Treatment for an Old Problem: Brexpiprazole for the Treatment of Agitation in Dementia

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Disclosures:

- Dr. Fraser has no financial disclosures to report.
- Dr. Sun has no financial disclosures to report.
- We will be discussing off label use of medications during this presentation.

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presentation.

Objectives:

By the completion of this session,
participants should be able to:



Identify pharmacological approaches for
agitation in patients with dementia



Identify the safety profile of the newly
approved brexpiprazole for agitation
associated with dementia



Understand the challenges/barriers to
brexpiprazole's use for agitation
associated with dementia in practice



BEHAVIORAL AND
PSYCHIATRIC SYMPTOMS
ARE OFTEN COMMON
PRESENTATIONS IN
PATIENTS WITH DEMENTIA



NON-PHARMACOLOGICAL
THERAPIES ARE FIRST LINE



PHARMACOLOGICAL
APPROACHES NEED TO
BE REASSESSED



BASIC SAFETY PRINCIPLES
APPLY-IF IMMINENT DANGER
TO SELF OR OTHERS-ED
EVALUATION
IS RECOMMENDED

You should know...

Identify

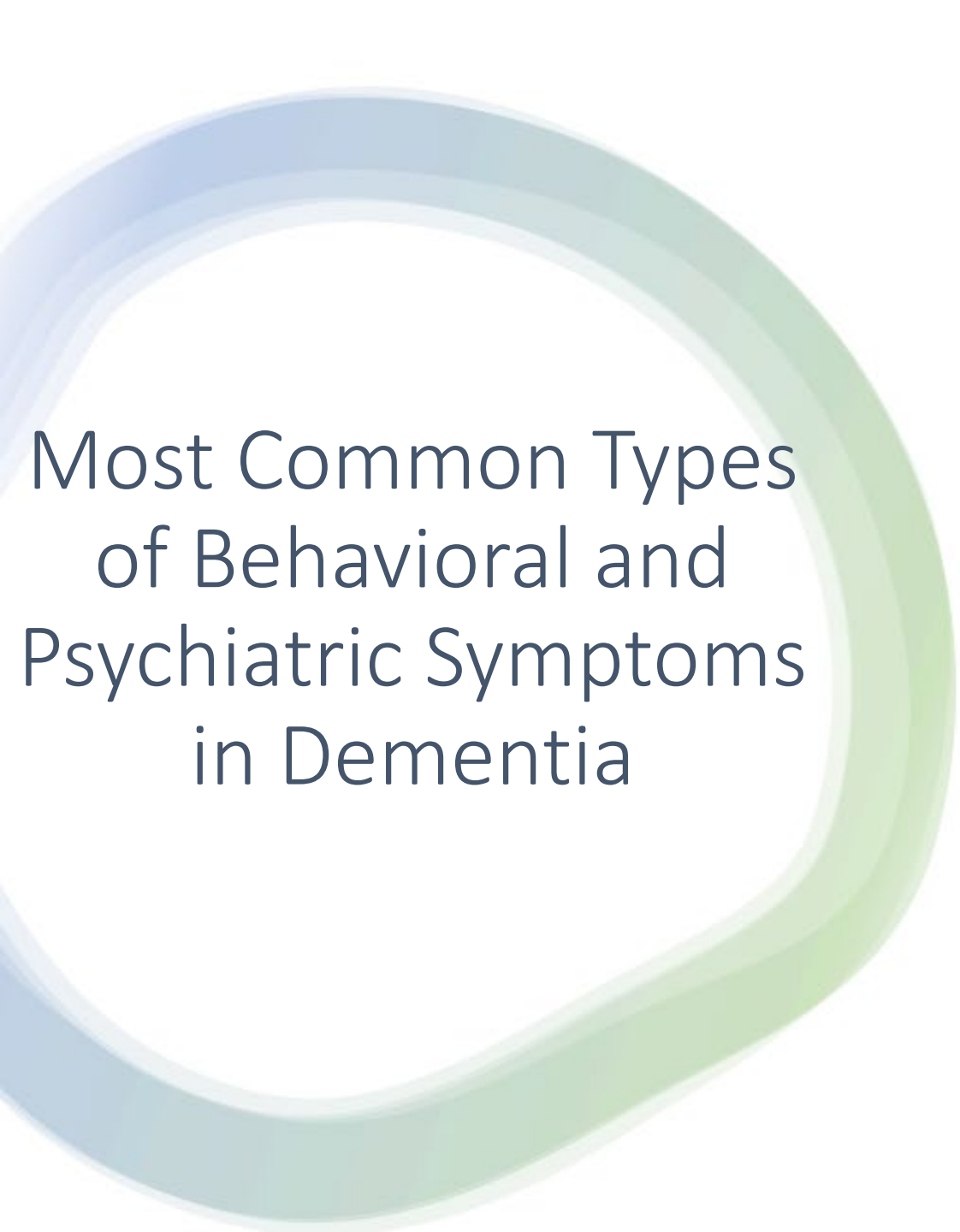
- Identify dosing strategies for brexpiprazole for agitation in AD

Name

- Name 2 side effects common in older adults with brexpiprazole


Identify

- Identify 3 studied medication options for agitation in AD




Most Common Types of Behavioral and Psychiatric Symptoms in Dementia

- Depression
 - Apathy
 - Irritability
 - **Agitation**
 - Anxiety
-
- Most likely to get calls about anxiety and agitation.
 - We will focus on agitation management and review of treatments.



When to Use Pharmacological Approach

- Can and should be exploring non-pharmacological options while using medications. ie: DICE (Describe, Investigate, Create, Evaluate)
- Any time symptoms are escalating to risk of harm to patient or others.
- When nonpharmacological interventions are not improving symptoms.
- When patient is in distress with symptoms-sleep, depression, anxiety and aggression.



Key Points With Medication Interventions

- Antipsychotics have best evidence/most studied for severe agitation (though this is limited)
- Start low and go slow
- Use lowest dose possible for shortest duration
- Trial a discontinuation of medication if symptoms improve
- FDA Black Box warning
- Risks vs Benefits vs QOL



Medication Options

- We have been using several medications "off label" for many years to manage behavioral symptoms associated with dementia
- There is data available regarding use of these medications.
- None of the following medications are FDA approved for treatment of agitation in dementia.



Considerations With Medication Options

- Consider individual patient and their preferences and risks
- May consider starting at lower doses given patient characteristics
- Some clinicians prefer quetiapine due to lower risk of EPS
 - Doses 12.5 mg daily up to 200 mg
- Or olanzapine
 - Doses 1.25 mg up to 10 mg
- SNRIs (venlafaxine and duloxetine)
 - Potential benefit for pain
- Sleep issues and day/night reversal:
 - Mirtazapine (consider 7.5 mg at bedtime to start)
 - Light box therapy
- Recommend avoiding:
 - Fluoxetine, fluvoxamine, paroxetine



Medication Options

- Non-emergent situations-have time (weeks) to evaluate medication responses
 - Decrease anticholinergic load, optimize pain control (scheduled Tylenol as first line)
 - Optimize sleep-->consider Trazodone (12.5-25 mg)
 - Fall risk same as benzodiazepines
 - Can have some help with anxiety
 - Donepezil and memantine
 - Can delay symptom onset
 - Small benefit for symptoms
 - Typically tolerated
 - SSRIs: escitalopram and sertraline
 - Start (5mg) 10 mg daily for escitalopram and 25 mg daily for sertraline
 - Takes several weeks to work
 - Need to check Na levels



Algorithm Options

- Several studies and groups have proposed algorithms for pharmacological management of BPSD
- We will review a few here

Treatment Algorithms

Psychopharmacology Algorithm Project at the Harvard South Shore Program

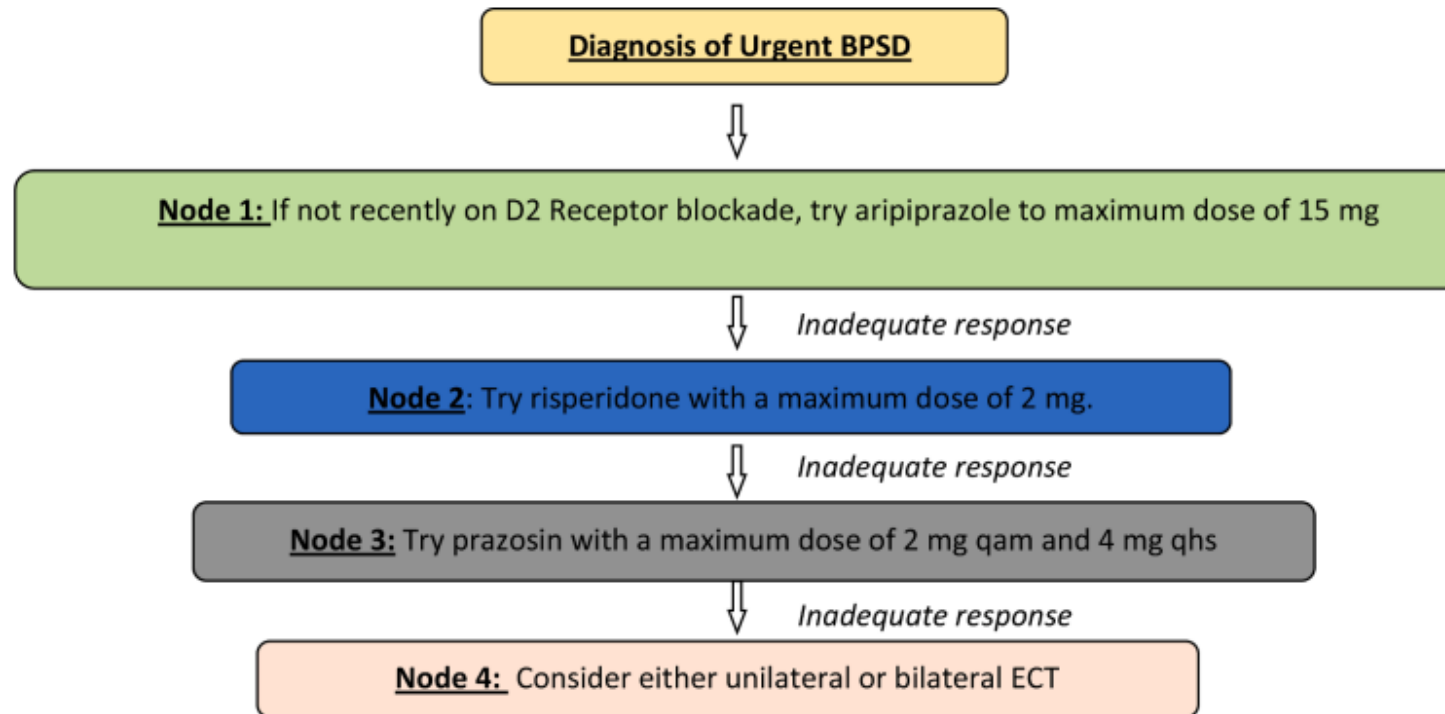


Figure 3. Flowchart for Urgent BPSD Management

Urgent BPSD (behavioral and psychological symptoms of dementia) = agitation needs to be treated but there is space to wait a few days-weeks for improvement



Medication Options

- For urgent situations (able to take oral, have some time to evaluate):
 - Aripiprazole up to 15 mg daily (start at 2-2.5 mg daily)
 - Risperidone up to 2 mg daily (start at 0.25-0.5 mg daily)
 - Avoid in LBD and vascular dementia
 - Prazosin up to 2 mg am and 4 mg qhs (start at 1mg at bedtime)
 - Small evidence base



Medication Options

- For emergent situations (and not able to take oral):
 - IM olanzapine (Doses: 1.25-5 mg q 30-60 min up to three times a day, I usually space out farther in practice, usually 2-4 hours)
 - --> not effective can trial IM haloperidol (Doses: in my practice, typically 2-5 mg q 2-4 hours, up to three times per day)
 - -->not effective can trial IM benzodiazepines (Doses: 0.5 mg lorazepam q 4hours, up to 2 mg in a day)



Medication Options

- Non-emergent situations-have time (weeks) to evaluate medication responses (continued)
 - Second generation antipsychotics
 - Could trial SGA that worked in past or those reviewed previously
 - Prazosin
 - Carbamazepine
 - Can start 100 mg daily
 - Needs monitoring (CBC, CMP)

Treatment Algorithm

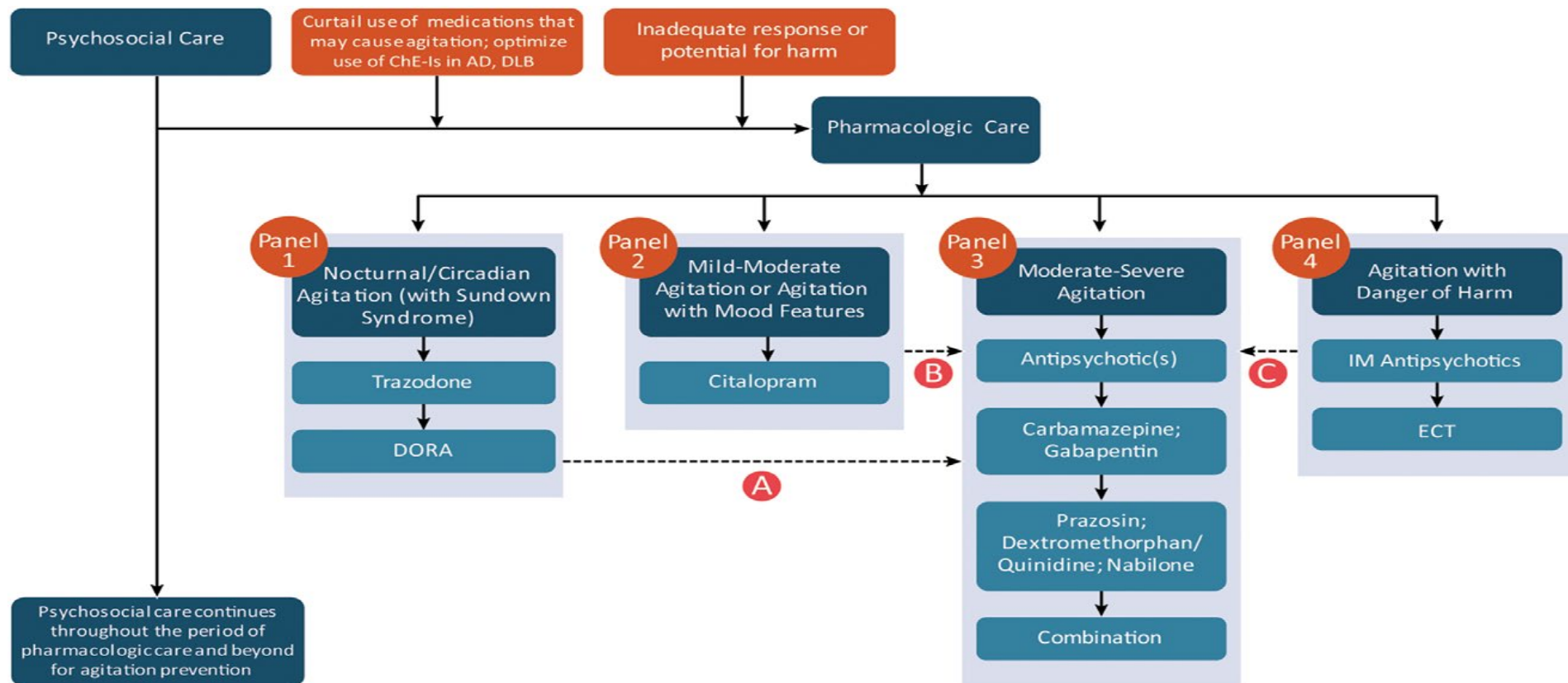
From University of Ontario group

Sequential Drug Treatment Algorithm for Agitation and Aggression in Alzheimer's and Mixed Dementia

	STEP	EFFICACY	TIME TO ONSET	TOLERABILITY	EASE OF USE	EFFICACY/ OTHER
RISPERIDONE	1					
QUETIAPINE	2					
ARIPIPRAZOLE	2					
CARBAMAZEPINE	3					
CITALOPRAM	4					
GABAPENTIN	5					
PRAZOSIN	6					

Treatment Algorithm

International Psychogeriatric Association Consensus Algorithm



Black Box Warning

- Increased risk of mortality in elderly patients
- Associated with ***all* antipsychotics**
- Analyses of 17 placebo-controlled trials, largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6-1.7x the risk of death in placebo-treated patients
- Although the causes of death were varied, most of the deaths appeared to be **cardiovascular** (heart failure, sudden death) or **infectious** (pneumonia)

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

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. REXULTI is not approved for the treatment of patients with dementia-related psychosis without agitation associated with dementia due to Alzheimer's disease. [\(5.1\)](#)
- Antidepressants increased the risk of suicidal thoughts and behaviors in patients aged 24 years and younger. Monitor for clinical worsening and emergence of suicidal thoughts and behaviors. Safety and effectiveness of REXULTI have not been established in pediatric patients with MDD. [\(5.2, 8.4\)](#)

There is a New Medication in Town...

FDA NEWS RELEASE

FDA Approves First Drug to Treat Agitation Symptoms Associated with Dementia due to Alzheimer's Disease


For Immediate Release: May 11, 2023

Today, the U.S. Food and Drug Administration is announcing the supplemental approval of **Rexulti (brexpiprazole)** oral tablets for the treatment of agitation associated with dementia due to Alzheimer's disease. This is the first FDA-approved treatment for this indication.

"Agitation is one of the most common and challenging aspects of dementia for patients with dementia due to Alzheimer's disease. 'Agitation' symptoms ranging from pacing or restlessness to verbal and physical aggression," said Tiffany Farchione, M.D., director of the Division of Neurology and Psychiatry in the FDA's Center for Drug Evaluation and Research. "These symptoms are leading causes of assisted living or nursing home placement and have been associated with accelerated disease progression."

MEDICALNEWS TODAY Health Conditions Health Products

FDA approves antipsychotic drug brexpiprazole for dementia — is it safe?




USNews 29TH NEWS

FDA Approves First Drug Meant to Ease Alzheimer's-Linked Agitation

May 11, 2023

HealthDay Reporter

1, 2023 (HealthDay News) — The first drug to treat agitation in Alzheimer's disease now has approval from the U.S. Food and Drug Administration.



Overview of Brexpiprazole

- Partial D₂ and serotonin 5HT_{1A} receptor agonist, serotonin 5HT_{2A} antagonist
- Tablet strengths available:
 - 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg
- Brand only - \$56.76/tablet



Brexpiprazole Indications

- Adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults
- Treatment of schizophrenia in adults and pediatric patients (≥ 13)
- **Treatment of agitation associated with dementia due to Alzheimer's disease** (approved 5/2023)*

****Not** indicated as an as needed ("prn") treatment for agitation associated with dementia due to Alzheimer's disease*

Brexpiprazole Dosing

Indication	Starting Dosage	Recommended Target Dosage	Maximum Dosage
MDD adults	0.5 mg or 1 mg/day	2 mg/day	3 mg/day
Schizophrenia in adults	1 mg/day	2-4 mg/day	4 mg/day
Schizophrenia in pediatric patients	0.5 mg/day	2-4 mg/day	4 mg/day
Agitation associated with dementia due to Alzheimer's disease*	0.5 mg/day	2 mg/day	3 mg/day

**Trials showed no significant efficacy over placebo for doses < 2 mg/day*

Brexpiprazole Pharmacokinetics

- Peak plasma concentrations reached within 4 hours
- Can be administered with or without food
- Metabolized through **CYP3A4 and CYP2D6**

Lower doses of Brexpiprazole may be required if taking:	Higher doses of Brexpiprazole may be required if taking:
Fluoxetine, paroxetine, bupropion	Phenytoin, phenobarbital, carbamazepine
Ketoconazole, voriconazole	Rifampin
Clarithromycin, erythromycin	Primidone
Amiodarone	St. John's Wort

- Dose adjustments for renal and hepatic impairment
 - CrCl < 60 mL/min: max dose 2 mg
 - Moderate-severe hepatic impairment: max dose 2 mg

Efficacy and Safety of Brexpiprazole for the Treatment of Agitation in Alzheimer's dementia: Two 12-week, Randomized, Double-Blind, Placebo-Controlled Trials

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



Patient Population

Patients 55-90 years of age with a diagnosis of probable AD with symptoms of agitation or aggression



Intervention (Study 1)

Randomized 1:1:1 to receive **brexpiprazole 2 mg/day**, **brexpiprazole 1 mg/day**, or **placebo** for 12 weeks (n=433)



Intervention (Study 2)

Randomized 1:1 to received **flexibly dosed brexpiprazole (0.5 mg-2 mg/day)** or **placebo** for 12 weeks (n=270)

Efficacy and Safety of Brexpiprazole for the Treatment of Agitation in Alzheimer's dementia: Two 12-week, Randomized, Double-Blind, Placebo-Controlled Trials

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

Name: _____ Dates: From _____ to _____

Cohen-Mansfield Agitation Inventory (CMAI)¹ – Short

Instructions: For each of the behaviours below, check the rating that indicates the average frequency of occurrence over the last 2 weeks.

	1- Never	2- Less than once a week	3- Once or twice a week	4- Several times a week	5- Once or twice a day	6- Several times a day	7- Several times an hour
Physical/Aggressive							
1. Hitting (including self)	1	2	3	4	5	6	7
2. Kicking	1	2	3	4	5	6	7
3. Grabbing onto people	1	2	3	4	5	6	7
4. Pushing	1	2	3	4	5	6	7
5. Throwing things	1	2	3	4	5	6	7
6. Biting	1	2	3	4	5	6	7
7. Scratching	1	2	3	4	5	6	7
8. Spitting	1	2	3	4	5	6	7
9. Hurting self or others	1	2	3	4	5	6	7
10. Tearing things or destroying property	1	2	3	4	5	6	7
11. Making physical sexual advances	1	2	3	4	5	6	7
Physical/Non-Aggressive							
12. Pace, aimless wandering	1	2	3	4	5	6	7
13. Inappropriate dress or disrobing	1	2	3	4	5	6	7
14. Trying to get to a different place	1	2	3	4	5	6	7
15. Intentional falling	1	2	3	4	5	6	7
16. Eating/drinking inappropriate substance	1	2	3	4	5	6	7
17. Handling things inappropriately	1	2	3	4	5	6	7
18. Hiding things	1	2	3	4	5	6	7
19. Hoarding things	1	2	3	4	5	6	7
20. Performing repetitive mannerisms	1	2	3	4	5	6	7
21. General restlessness	1	2	3	4	5	6	7
Verbal/Aggressive							
22. Screaming	1	2	3	4	5	6	7
23. Making verbal sexual advances	1	2	3	4	5	6	7
24. Cursing or verbal aggression	1	2	3	4	5	6	7
Verbal/Non-aggressive							
25. Repetitive sentences or questions	1	2	3	4	5	6	7
26. Strange noises (weird laughter or crying)	1	2	3	4	5	6	7
27. Complaining	1	2	3	4	5	6	7
28. Negativism	1	2	3	4	5	6	7
29. Constant unwarranted request for attention or help	1	2	3	4	5	6	7

Cohen-Mansfield Agitation Inventory (CMAI)

- 29-item scale
- Each item rated 1 (never) through 7 (several times an hour)
- Total score out of 203
- Score > 45 generally regarded as clinically significant agitation

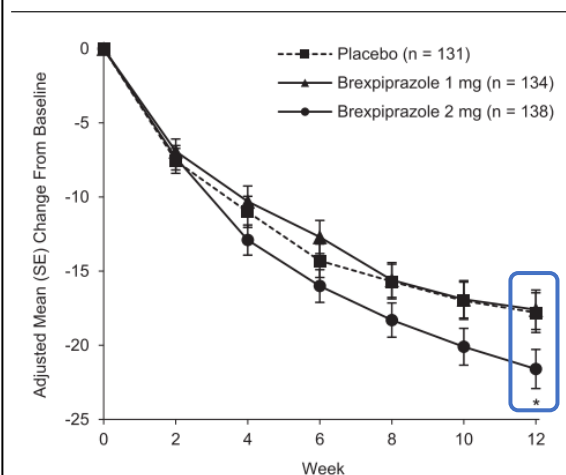
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Study 1 Efficacy:

- Brexpiprazole 2 mg demonstrated **statistically significantly greater improvement** compared to the placebo group. Brexpiprazole 1 mg did *not*

FIGURE 3. Primary endpoint in Study 1: effects of brexpiprazole on symptoms of agitation (CMAI Total).



Change from baseline to week 12 in CMAI score:

Brexpiprazole 2 mg: -21.6

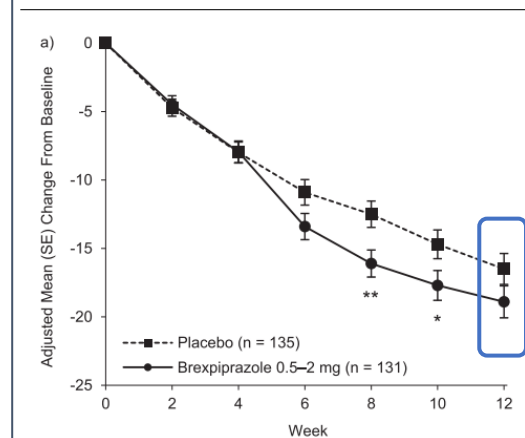
Brexpiprazole 1 mg: -17.6

Placebo: -17.8

Study 2 Efficacy:

- Brexpiprazole 0.5-2 mg did *not* achieve statistical superiority relative to the placebo group

FIGURE 5. Primary endpoint in Study 2: effects of brexpiprazole on symptoms of agitation (CMAI Total) in a) total efficacy sample and b) subgroup titrated to 2 mg (or equivalent placebo) at Week 4 (post hoc analysis).



Change from baseline to week 12 in CMAI score:

Brexpiprazole: -18.9

Placebo: -16.5

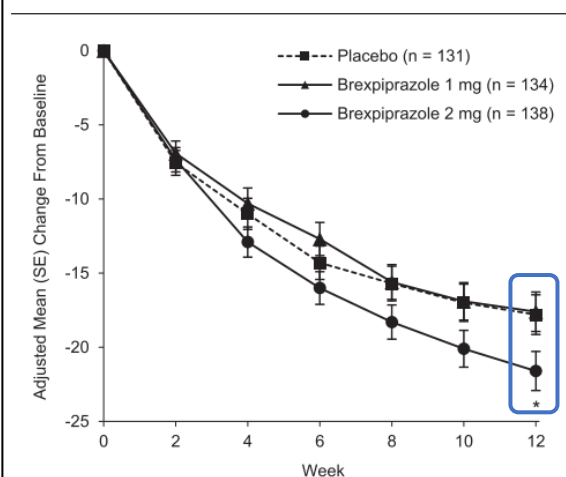
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Change from baseline to week 12 in CMAI score:

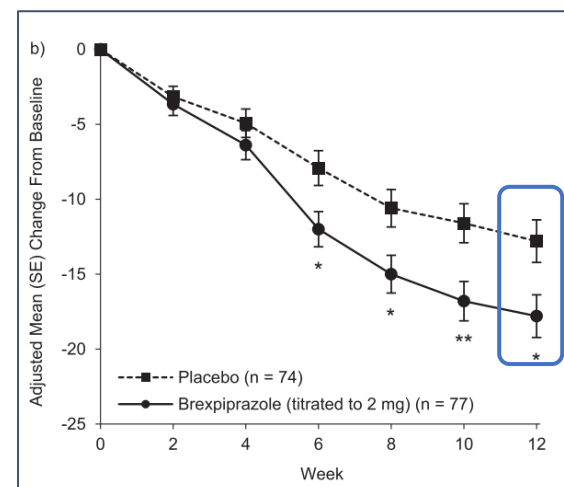
Brexpiprazole 2 mg: -21.6

Brexpiprazole 1 mg: -17.6

Placebo: -17.8

Study 2 Efficacy:

- Post hoc efficacy analysis: subgroup of patients who were titrated to max brexpiprazole dose (2 mg) at week 4 showed improvement in CMAI score



Change from baseline to week 12 in CMAI score:

Brexpiprazole 2 mg: -17.8

Placebo: -12.8

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Study 1 Safety:

- Treatment-emergent adverse effects (TEAE):
 - 65% in brexpiprazole 2 mg arm
 - 49% in brexpiprazole 0.5-1 mg arm
 - 45.9% in placebo arm
- Most common: [headache, insomnia, dizziness, UTI](#)
- 5 deaths during the study (all in brexpiprazole group) - [none considered related to treatment](#)
- [No clinically meaningful difference between groups in other safety assessments](#)

Study 2 Safety:

- [No notable difference](#) in TEAE between brexpiprazole group and placebo group
- Most common: [headache, somnolence](#)
- 3 patients on brexpiprazole experienced seizure
- 1 death in placebo group, 1 death in brexpiprazole group – none considered related to study drug
- [No clinically meaningful difference between groups in other safety assessments](#)

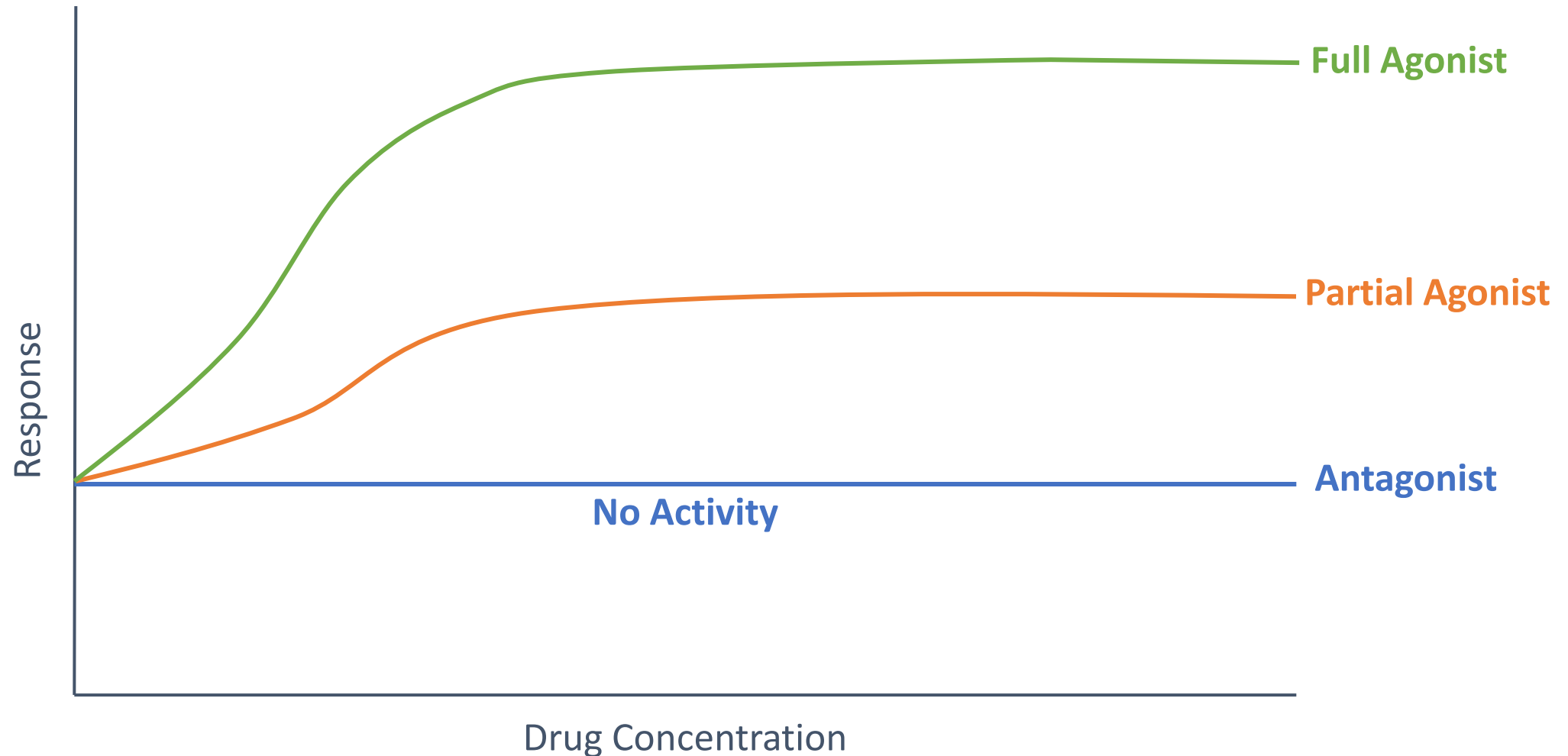
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Conclusion: Brexpiprazole
2 mg/day has the potential to be an
efficacious, safe, and well-tolerated
treatment for **agitation associated with**
Alzheimer's disease.

Agonist vs. Antagonist vs. Partial Agonist?



The ABC's of D₂ Partial Agonists

Receptor Activity and Clinical Effects of **Aripiprazole**, **Brexpiprazole**, and **Cariprazine**:

Receptor	Aripiprazole	Brexpiprazole	Cariprazine	Clinical Effects
Dopamine D ₂ partial agonism	////	///	///	Antipsychotic effect, EPS
Serotonin 5-HT _{1A} partial agonism	///	////	///	Antidepressant and anxiolytic effect, pro-cognitive effect, less risk of EPS
Serotonin 5-HT _{2A} antagonism	+++	++++	++++	Less risk of EPS, weight gain

/ = partial agonism
+ = antagonism

Other Antipsychotics

Receptor Activity of Antipsychotics:

Receptor	Aripiprazole	Brexipiprazole	Olanzapine	Quetiapine (IR)	Risperidone
Dopamine D ₂	////	///	++	+	+++
Serotonin 5-HT _{1A}	///	////	0	/	+
Serotonin 5-HT _{2A}	+++	++++	+++	+	++++
Histamine H ₁	++	++	+++	+++	++

/ = partial agonism
+ = antagonism

- **Dopamine D₂**: Antipsychotic effect, EPS
- **Serotonin 5-HT_{1A}**: Antidepressant and anxiolytic effect, pro-cognitive effect, less risk of EPS
- **Serotonin 5-HT_{2A}**: Less risk of EPS, weight gain
- **Histamine H₁**: Sedation and weight gain

Other Antipsychotics

	Aripiprazole	Brexpiprazole	Olanzapine	Quetiapine (IR)	Risperidone
Time to peak	3-5 hours	4 hours	6 hours	1.5 hours	1 hour
Effect of food	With or without food	With or without food	With or without food	Without food or with a light meal	With or without food
Half-life	75 hours	91 hours	21-54 hours	6 hours	20 hours
Formulations	Tablet, ODT tablet, solution, long-acting injectable	Tablet	Tablet, ODT tablet, short- acting injectable, long- acting injectable	Tablet, extended- release tablet	Tablet, ODT tablet, solution, long-acting injectable

Formulary Status

Insurance Plan	Aripiprazole	Brexipiprazole	Olanzapine	Quetiapine (IR)	Risperidone
UPMC For Life (Medicare)	✓	Tier 5: Prior Authorization Required	✓	✓	✓
Aetna Medicare	✓	High Tier: ✓	✓	✓	✓
Highmark Medicare	Prior Authorization for New Starts	Prior Authorization for New Starts, Specialty Product	✓	✓	✓
United Health Medicare	✓	Tier 5: ✓	✓	✓	✓

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REXULTI® (brexpiprazole)

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Want to know what your prescription may cost?
Let's start with your insurance.

The list price, also known as the Wholesale Acquisition Cost (WAC), of REXULTI is \$1,419 per month,* but most patients pay less with their prescription drug plan.

COMMERCIAL
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MEDICAID

VA OR TRICARE

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With Medicare, out-of-pocket costs for REXULTI prescriptions average about \$21.37 per month.† Of course, out-of-pocket costs vary throughout the year,



Food for Thought

Considering SNF regulations now that brexpiprazole is approved for ongoing treatment vs need for dose reduction (per CMS regulations)

Considering use in outpatient settings; approval and potential PA and med trials with insurance

What to do about prescribing meds that have "worked for years" but now we have an approved medication

How to review with patients and families *new and approved* vs "tried and true"

Will brexpiprazole's approval increase antipsychotic use among patients with agitation in dementia?

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