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Restoring Neurotransmitter Balance in Agitation Associated with AD: An Antipsychotic Approach

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Outline

- Major Neurocognitive Disorder and Agitation
- The Burden of Agitation
- Guidelines for the Treatment of Agitation
- Antipsychotic Treatment of Agitation in Patients with Major Neurocognitive Disorder

Major Neurocognitive Disorder and Agitation

Agitation-IPA Agitation Workgroup

- The patient meets criteria for a cognitive impairment or dementia syndrome (e.g. AD, FTD, DLB, vascular dementia, other dementias, a pre-dementia cognitive impairment syndrome such as mild cognitive impairment or other cognitive disorder).
- The patient exhibits at least one of the following behaviors that are associated with observed or inferred evidence of emotional distress (e.g. rapid changes in mood, irritability, outbursts). The behavior has been persistent or frequently recurrent for a minimum of two weeks and represents a change from the patient's usual behavior.
  - (a) Excessive motor activity (examples include: pacing, rocking, gesturing, pointing fingers, restlessness, performing repetitious mannerisms).
  - (b) Verbal aggression (e.g. yelling, speaking in an excessively loud voice, using profanity, screaming, shouting).
  - (c) Physical aggression (e.g. grabbing, shoving, pushing, resisting, hitting others, kicking objects or people, scratching, biting, throwing objects, hitting self, slamming doors, tearing things, and destroying property).
- Behaviors are severe enough to produce excess disability, which in the clinician's opinion is beyond that due to the cognitive impairment and including at least one of the following:
  - (a) Significant impairment in interpersonal relationships.
  - (b) Significant impairment in other aspects of social functioning.
  - (c) Significant impairment in ability to perform or participate in daily living activities.
- While co-morbid conditions may be present, the agitation is not attributable solely to another psychiatric disorder, suboptimal care conditions, medical condition, or the physiological effects of a substance.

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Impact of behavioral and psychological symptoms of Alzheimer's disease on caregiver outcomes

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This study was to determine the prevalence of behavioral and psychological symptoms of dementia (BPSD) and its association with dementia severity and to explore the association between specific BPSD and caregiver stress, burden, and depression. A cross-sectional study involving the interviewing of the primary caregivers of patients with Alzheimer's disease (AD) was conducted. Multivariable analysis was used to analyze the associations between specific symptoms of BPSD and caregiver outcomes. A total of 102 AD patients (age 79.4 ± 7.9 years, 70.6% female) and their caregivers were included. Nearly 46% had moderate-to-severe AD. Nearly all patients (99.0%) had at least one BPSD. Apathy was among the most common symptoms (74.5%), and hallucination was the only symptom associated with severity of AD ($p = 0.017$). After adjustment, agitation was associated with Patient Health Questionnaire-9 (PHQ-9) and Zarit Burden Interview (ZBI-22) ($p = 0.021$ and 0.007, respectively); sleep disorders were associated with only PHQ-9 ($p = 0.049$). In conclusion, the BPSD, especially agitation and sleep disorders, can give rise to difficulties for both patients and their caregivers. The prevalence of BPSD is high (99.0%), and the symptoms can start early. Routine screening of BPSD in all AD patients is advocated.

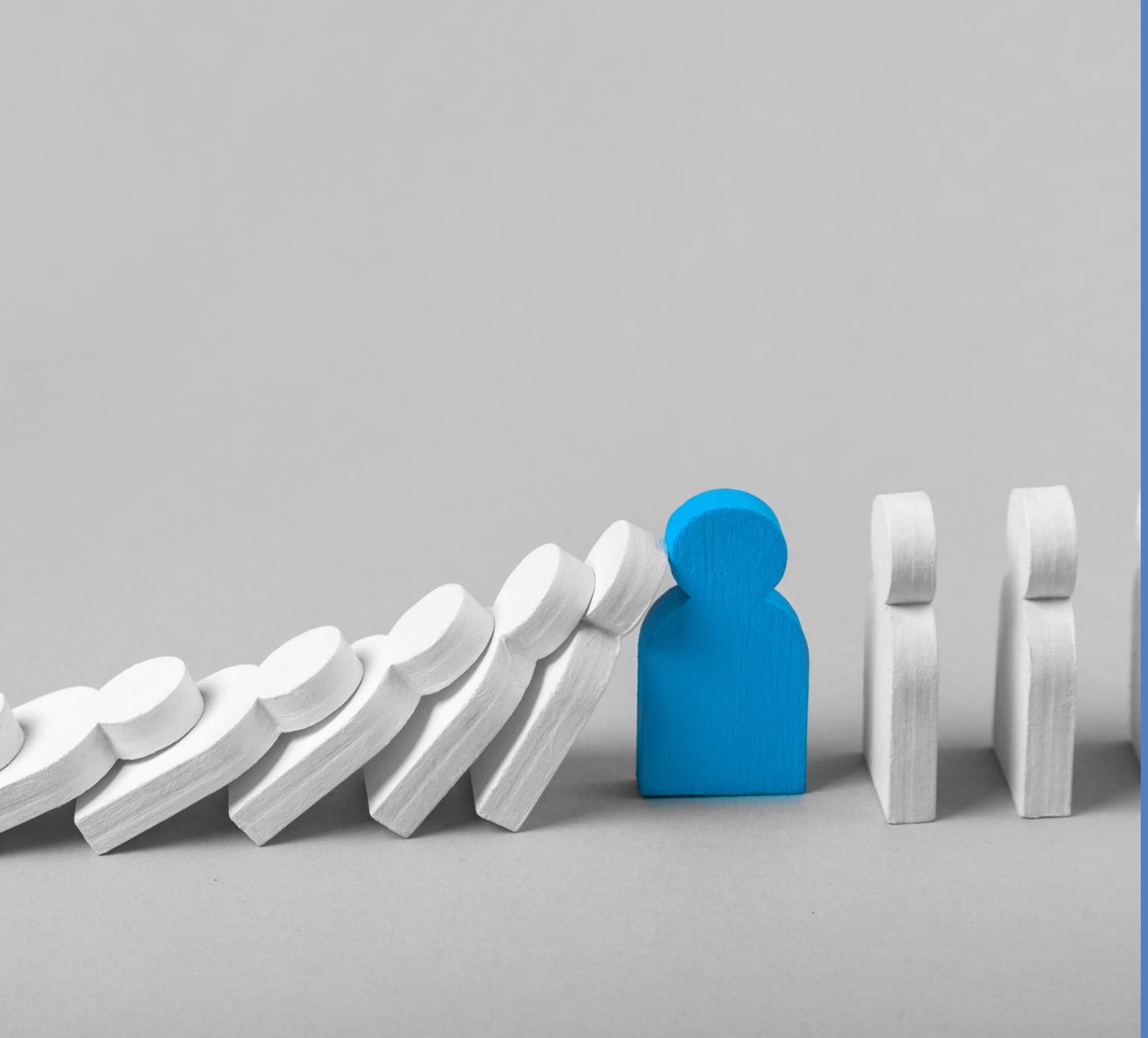
Pinyopornpanish et al. Sci Rep. 2022.

BPSD	Severity of BPSD	Total n = 102 (%)	Mild AD n = 56 (%)	Moderate-to-Severe AD n = 46 (%)	*p*-value
Delusions	Mild	10 (9.80)	4 (7.14)	6 (13.04)	
n = 40 (39.2%)	Moderate	17 (16.67)	6 (10.71)	11 (23.91)	0.166[b]
	Severe	13 (12.75)	9 (16.07)	4 (8.70)	
Hallucinations	Mild	13 (12.75)	7 (12.50)	6 (13.04)	
n = 34 (33.3%)	Mod	16 (15.69)	6 (10.71)	10 (21.74)	0.017[b]
	Severe	5 (4.90)	0 (0)	5 (10.87)	
Agitation	Mild	28 (27.45)	17 (30.36)	11 (23.91)	
n = 56 (54.9%)	Mod	18 (17.65)	7 (12.50)	11 (23.91)	0.485[b]
	Severe	10 (9.80)	5 (8.93)	5 (10.87)	
Dysphoria	Mild	27 (26.47)	18 (32.14)	9 (19.57)	
n = 42 (41.2%)	Mod	10 (9.80)	5 (8.93)	5 (10.87)	0.514[b]
	Severe	5 (4.90)	2 (3.57)	3 (6.52)	
Anxiety	Mild	17 (16.67)	8 (14.29)	9 (19.57)	
n = 47 (46.1%)	Mod	19 (18.63)	10 (17.86)	9 (19.57)	0.873[a]
	Severe	11 (10.78)	6 (10.71)	5 (10.87)	
Euphoria	Mild	9 (8.82)	4 (7.14)	5 (10.87)	
n = 16 (15.7%)	Mod	2 (1.96)	2 (3.57)	0 (0)	0.411[b]
	Severe	5 (4.90)	4 (7.14)	1 (2.17)	
Apathy	Mild	23 (22.55)	15 (26.79)	8 (17.39)	
n = 76 (74.5%)	Mod	24 (23.53)	15 (26.79)	9 (19.57)	0.296[a]
	Severe	29 (28.43)	12 (21.43)	17 (36.96)	
Disinhibition	Mild	16 (15.69)	10 (17.86)	6 (13.04)	
n = 38 (37.3%)	Mod	14 (13.73)	7 (12.50)	7 (15.22)	0.860[b]
	Severe	8 (7.84)	5 (8.93)	3 (6.52)	
Irritability	Mild	21 (20.59)	11 (19.64)	10 (21.74)	
n = 71 (69.6%)	Mod	30 (29.41)	18 (32.14)	12 (26.09)	0.918[a]
	Severe	20 (19.21)	11 (19.64)	9 (19.57)	
Aberrant motor behavior	Mild	18 (17.65)	11 (19.64)	7 (15.22)	
n = 52 (51.0%)	Mod	13 (12.75)	7 (12.50)	6 (13.04)	0.947[a]
	Severe	20 (19.61)	11 (19.64)	9 (19.57)	
Sleep disorders	Mild	14 (13.73)	7 (12.50)	7 (15.22)	
n = 68 (66.7%)	Mod	30 (29.41)	13 (23.21)	17 (36.96)	0.363[a]
	Severe	24 (23.53)	11 (19.64)	10 (21.74)	
Appetite/eating behavior	Mild	11 (10.78)	6 (10.71)	5 (10.87)	
n = 51 (50.0%)	Mod	22 (21.57)	15 (26.79)	7 (15.22)	0.374[a]
	Severe	18 (17.65)	11 (19.64)	7 (15.22)	
Total NPI-Q mean ± SD		11.19 ± 6.22	10.89 ± 5.85	11.54 ± 6.69	0.602[c]

Table 3. Prevalence of BPSD and severity of AD by FAST. *AD* Alzheimer's disease, *BPSD* behavioral and psychological symptoms of dementia, *FAST* functional assessment staging test, *NPI-Q* neuropsychiatric inventory questionnaires. [a]Chi-square test. [b]Fisher's exact test. [c]student t-test.

Prevalence of BPSD and severity of AD by FAST

Pinyopornpanish et al. Sci Rep. 2022.



The Burden of Agitation

Correlation between variables

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1. Severity of AD	–																	
2. NPI-Q score	0.052	–																
3.Delusion	0.045	0.483**	–															
4.Hallucination	0.298**	0.546**	0.563**	–														
5.Agitation	0.109	0.668**	0.214*	0.261**	–													
6.Dysphoria	0.001	0.437**	0.191	0.318**	0.204*	–												
7.Anxiety	0.043	0.504**	0.249*	0.242*	0.218*	0.232*	–											
8. Euphoria	−0.125	0.288**	0.123	0.124	0.083	0.015	0.074	–										
9.Apathy	0.098	0.484**	0.072	0.176	0.409**	0.299**	0.205*	−0.086	–									
10.Disinhibition	−0.033	0.478**	0.166	0.141	0.389**	−0.027	0.106	0.128	0.075	–								
11. Irritability	−0.046	0.624**	0.167	0.211*	0.359**	0.117	0.339**	0.173	0.173	0.475**	–							
12. Motor	−0.015	0.506**	0.173	0.276**	0.296**	0.095	0.103	0.073	0.128	0.157	0.224*	–						
13. Sleep	−0.086	0.528**	0.046	0.173	0.327**	0.227*	0.086	0.067	0.238*	0.141	0.196*	0.204*	–					
14.Eating	−0.152	0.344**	−0.123	−0.135	0.159	0.046	0.062	0.204*	0.066	0.103	0.098	0.138	0.287**	–				
15. Age(c)	0.220*	−0.029	−0.103	0.071	−0.034	−0.031	0.009	0.081	−0.055	−0.111	−0.023	−0.135	0.168	0.018	–			
16. Sex(c)	0.020	−0.047	−0.316**	−0.132	0.114	0.069	−0.058	−0.066	0.141	0.000	−0.087	−0.047	−0.036	0.126	0.112	–		
17. PSS(c)	0.246*	0.311**	0.135	0.148	0.339**	0.082	0.145	0.027	0.256**	0.231*	0.253*	0.000	0.222*	−0.008	−0.000	−0.102	–	
18. PHQ–9(c)	0.215*	0.254*	0.080	0.120	0.333**	0.248*	0.025	−0.065	0.186	0.052	0.102	0.023	0.290**	0.084	0.052	0.009	0.490**	–
19.ZBI-22(c)	0.255*	0.369**	0.083	0.220*	0.460**	0.189	0.083	0.041	0.223*	0.285**	0.256**	0.047	0.284**	0.025	−0.662	−0.066	0.557**	0.510**

Table 4. Correlation between variables. *AD* Alzheimer's disease, *BPSD* behavioral and psychological symptoms of dementia, *NPI*-Q neuropsychiatric inventory questionnaires, *PSS* perceived stress scale, *PHQ-9* patient health questionnaire-9, *ZBI-22* 22-item Zarit Burden Interview. *p-value < 0.05, **p-value < 0.01, c caregiver.

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Severity of BPSD and caregivers' outcome

	PSS		PHQ-9		ZBI-22	
	Coefficient* (SE)	*p*-value	Coefficient* (SE)	*p*-value	Coefficient* (SE)	*p*-value
Delusion	0.133 (0.742)	0.858	0.010 (0.449)	0.981	−0.652 (1.573)	0.679
Hallucinations	0.179 (0.959)	0.853	−0.163 (0.581)	0.780	0.769 (2.033)	0.706
Agitation	1.350 (0.823)	0.105	1.173 (0.499)	**0.021**	4.792 (1.738)	**0.007**
Dysphoria	−0.725 (0.840)	0.391	0.728 (0.509)	0.157	1.645 (1.770)	0.356
Anxiety	0.259 (0.676)	0.703	−0.329 (0.409)	0.424	−0.758 (1.429)	0.597
Euphoria	−1.339 (0.912)	0.884	−0.350 (0.552)	0.528	0.427 (1.923)	0.825
Apathy	0.500 (0.669)	0.457	−0.096 (0.405)	0.814	0.067 (1.415)	0.962
Disinhibition	0.799 (0.754)	0.293	−0.129 (0.457)	0.778	2.115 (1.614)	0.194
Irritability	1.068 (0.724)	0.144	0.253 (0.439)	0.565	1.285 (1.540)	0.407
Aberrant motor behavior	−0.726 (0.563)	0.201	−0.317 (0.341)	0.355	−1.280 (1.191)	0.286
Sleep disorders	1.009 (0.629)	0.112	0.735 (0.381)	**0.049**	1.805 (1.362)	0.189
Appetite/eating behavior	−0.212 (0.591)	0.721	0.093 (0.358)	0.795	−0.849 (1.283)	0.510

Table 5. Severity of BPSD and perceived stress, depression, and burden reported by caregivers (multivariable linear regression analysis). *AD* Alzheimer's disease, *BPSD* behavioral and psychological symptoms of dementia, *PSS* perceived stress scale, *PHQ-9* patient health questionnaire-9, *SE* standard error, *ZBI-22* 22-item Zarit Burden Interview. Adjusted for caregiver age, sex, severity of AD, and other domains of BPSD. Bold values indicate statistical significance ($p \leq 0.05$). *Unstandardized coefficients.

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Guidelines for the Treatment of Agitation in Patients with Major Neurocognitive Disorder

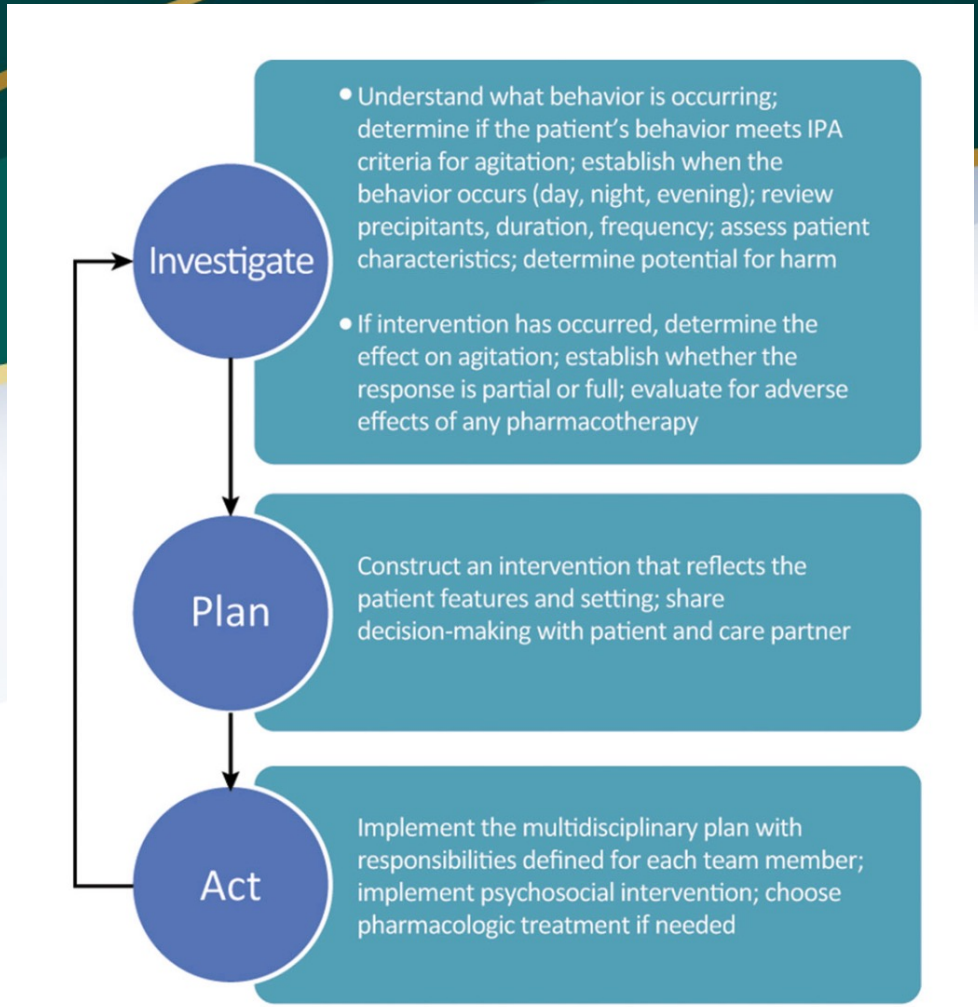

Figure 1. Investigate, Plan, Act (IPA) approach to agitation evaluation, management, and prevention. The process is repeated until the agitation is reduced to an acceptable level and prevention of recurrent episodes is optimized. The approach builds on the IPA definition of agitation in cognitive disorders (M de la Flor, PhD, illustrator).

Cummings et al. Int Psychogeriatr. 2024.

WHAT IS THE TRIGGER FOR AGITATION?

Treating the underlying cause is the best way to manage agitation. If the cause for agitation is not clear, it is essential to carry out a proper assessment:

PINCH ME

P Pain: Is the person in any pain? Has urinary retention been excluded?

I N Infection: Chest/ urine/ CNS/ skin/ joint. Refer to sepsis pathway as appropriate.
Intracranial: Is there a focal neurological deficit? Head injury?

C Constipation: When was the last bowel movement? Could there be faecal impaction? (Consider DRE and disimpaction).

H Hydration & Nutrition: Does the patient seem dehydrated? Is there any major electrolyte imbalance or metabolic disturbance? Consider hypoxia, hypotension, hypoglycaemia.

M Medication: Omission of regular medication (esp benzodiazepines/ alcohol), addition of new medication (steroid, anticholinergic, opioid).

E Environment: Overstimulation (noise/ activity), understimulation (boredom, reduced social contact and activity), break in established routine, fear/ uncertainty associated with change in care setting, restrictions on movement.

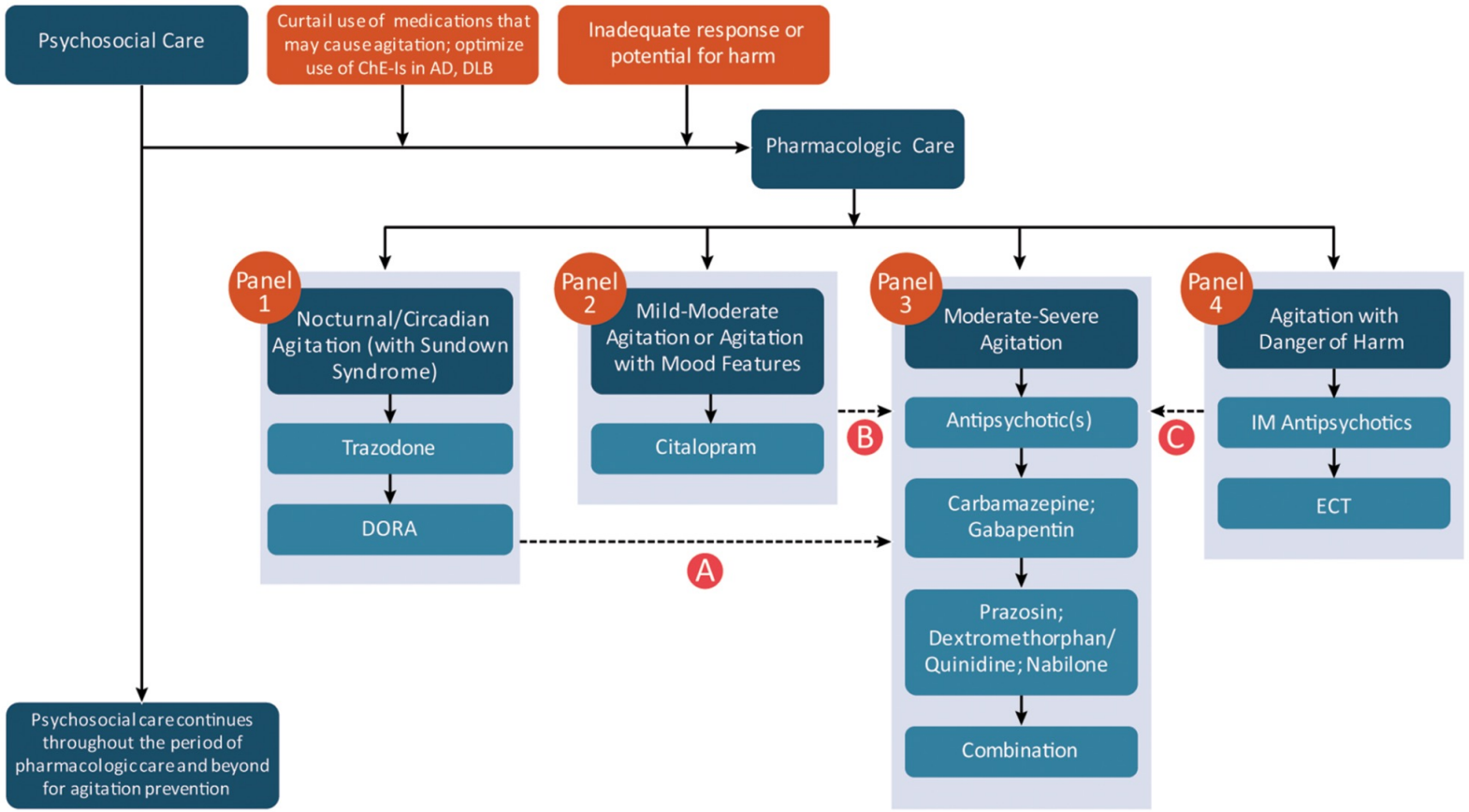

Figure 2. IPA agitation treatment algorithm. Psychosocial care is considered first and continued throughout the agitation episode with plans to curtail future agitation. Pharmacologic care is personalized and guided by the major features of the agitation including whether it has a circadian pattern or occurs mostly at night (Panel 1), is mild to moderate or has mood changes (Panel 2), is of moderate or severe severity but does not present a danger to self or others (Panel 3), or is severe and represents a treat of harm (Panel 4). Pharmacologic strategies progress from Panel 1 to Panel 3 if the first treatments fail (arrow A). Pharmacologic strategies advance from Panel 2 to Panel 3 if the first treatments fail (arrow B). Pharmacologic strategies are adjusted to Panel 3 once the very severe agitation addressed in Panel 4 is controlled (arrow C) (DORA – dual orexin receptor antagonist; ECT – electroconvulsive therapy; IM – intramuscular) (M de la Flor, PhD, Illustrator).

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Treatment	Study	Findings
Brexpiprazole for Agitation in Alzheimer's Dementia	Grossberg et al. [12]	Significant improvements in CMAI scores for patients treated with brexpiprazole at a dosage of 2 mg/day compared to placebo. Lower doses were not effective, indicating the dose-dependent efficacy of brexpiprazole [12].
Mirtazapine for Agitated Behaviors in Dementia	Banerjee et al. [13]	No significant benefit of mirtazapine over placebo and a higher mortality rate in patients treated with mirtazapine, suggesting caution in its use for agitation in dementia [13].
Escitalopram for Agitation in Alzheimer's Disease	Ehrhardt et al. [14]	Provided a study design but no outcome data, limiting its applicability [14].
Music Therapy and Audiobooks	Harrison et al. [5]	found that both music and audiobooks decreased agitation in three of four subscales, although audiobooks increased overall agitation in one subscale. This highlights the importance of the type and duration of auditory stimulation [5].
Personalized Music Intervention	Sitsi et al. [8]	Showed that personalized music interventions reduced verbally agitated behaviors and increased experiences of pleasure, without affecting physical agitation or negative emotions [8].
High-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) Combined with Cognitive Training	Zhang et al. [15]	reported significant reductions in neuropsychiatric behaviors, including agitation, following four weeks of rTMS-CT treatment [15].
Tailored Lighting Intervention	Figueiro et al. [6]	Significant improvements in sleep, mood, and behavior, with greater reductions in CMAI scores for those in the active lighting intervention group [6].
Digital Person-Centered Care Program (iWHELD)	McDermid et al. [16]	The iWHELD program decreased the use of psychotropic medications without worsening agitation, suggesting the benefits of digital interventions in dementia care [16].

Choudry et al. Int J Emer Med. 2025.

Antipsychotics Treatment of Agitation in Patients with Major Neurocognitive Disorder

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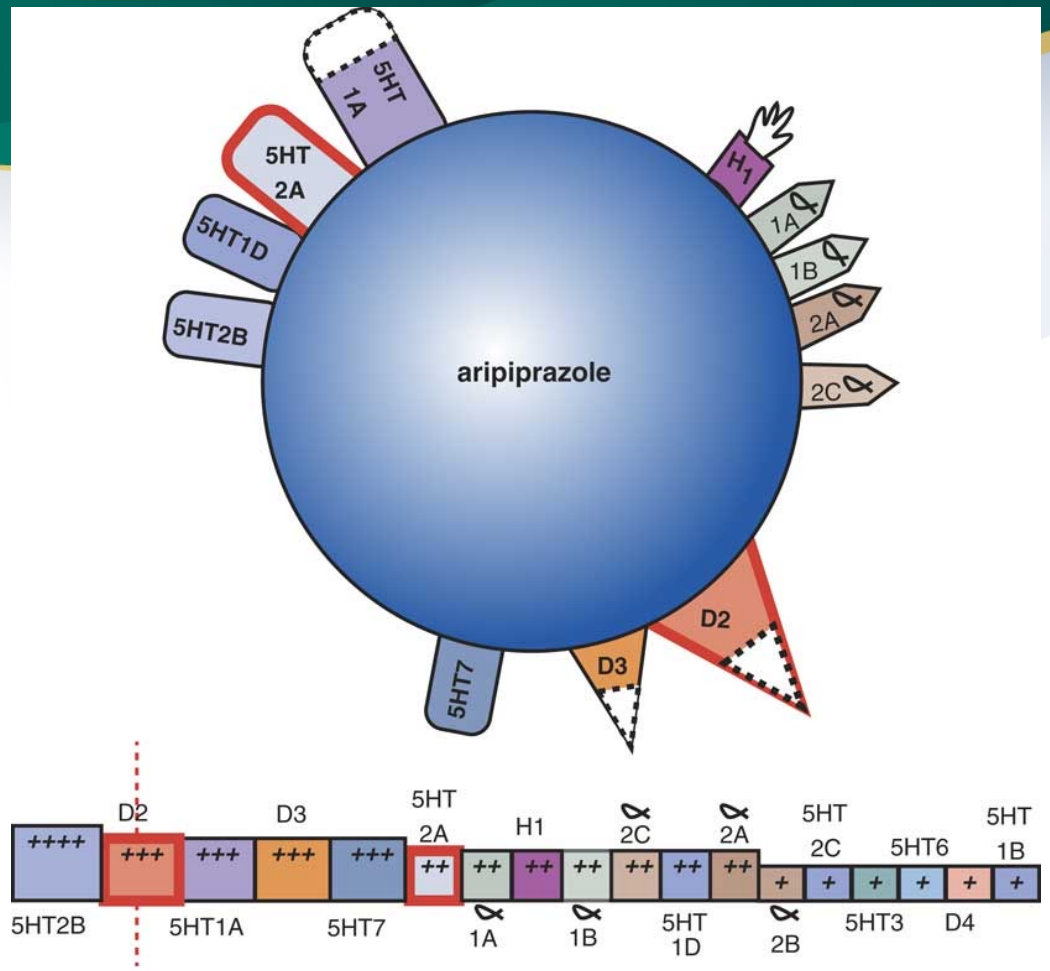
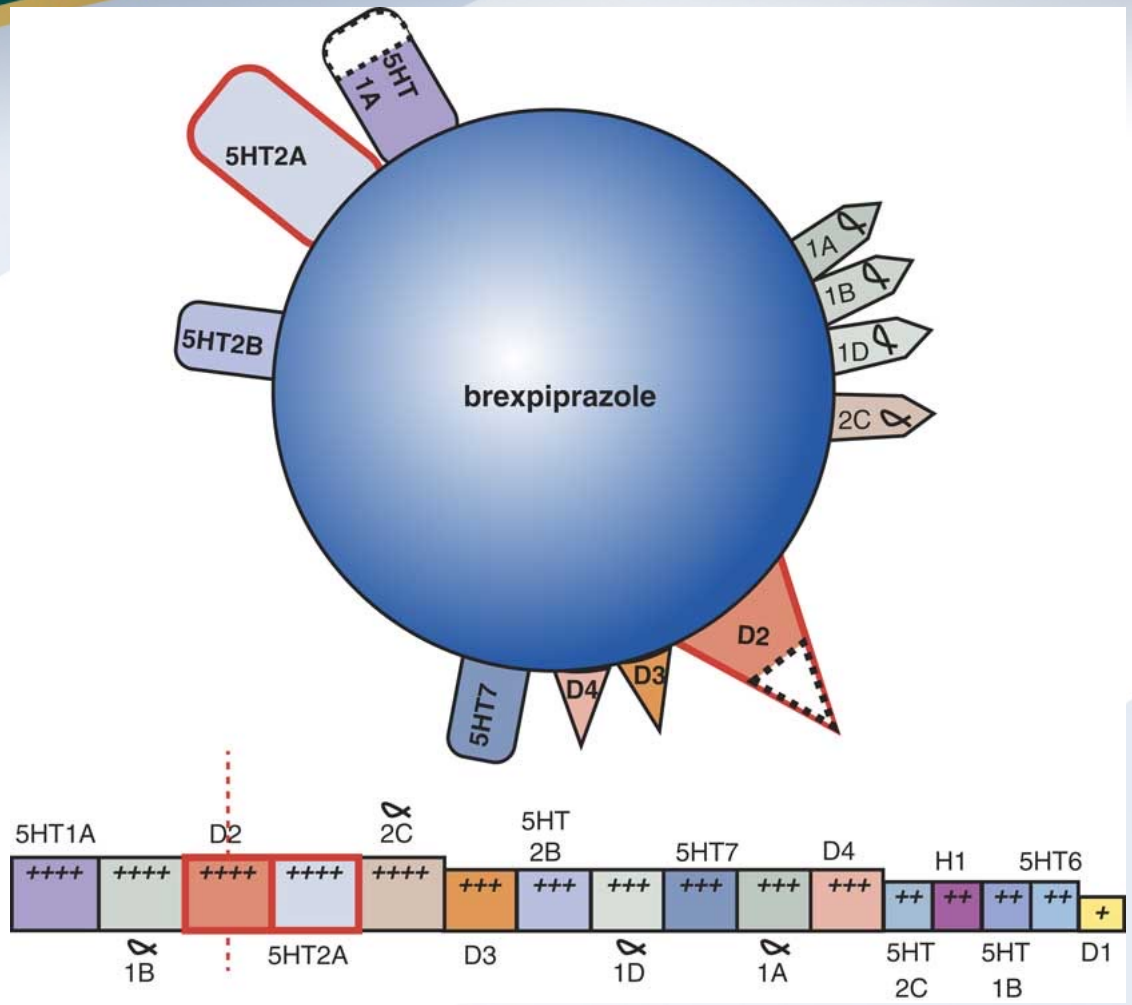
Medication Recommendations by the IPA Agitation Workgroup

- Risperidone
- Olanzapine
- Aripiprazole
- Brexpiprazole
- Quetiapine

Cummings et al. Int Psychogeriatr. 2024.





https://www.cambridge.org/core/journals/cns-spectrums/article/mechanism-of-action-of-brexpiprazole-comparison-with-aripiprazole/410BABD1B670F753928441063F16D61B

- 1. Brexpiprazole, like aripiprazole, is a dopamine multifunctional agent. Both have dopamine and serotonin receptor partial agonism as their pharmacological mechanism of action. Both are also known as "atypical antipsychotics" and as "adjunctive antidepressants."
- 2. No head-to-head studies compare the efficacy or the safety of brexpiprazole versus aripiprazole, so comparisons can only be made on the basis of their pharmacologic properties, or by comparing separate clinical studies of each drug versus placebo.
- 3. Pharmacologically, brexpiprazole has **less intrinsic activity** (ie, is less of a partial agonist and more of an antagonist) at D2 receptors than aripiprazole. Brexpiprazole also has much more potent actions at 5HT2A, 5HT1A, and alpha 1B receptors than aripiprazole.
- 4. Clinical differentiation appears to be mainly improved tolerability (eg, potentially less akathisia and extrapyramidal symptoms with brexpiprazole than aripiprazole) but similar efficacy for the 2 compounds both in schizophrenia and as adjunctive treatments in major depression.

Brexpiprazole

Fig. 1.

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Kim et al. Clin Psychopharmacol Neurosci. 2025.

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Q & A

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