Autoimmune Encephalitis: Psychiatric Recognition, Evaluation, and Management

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Learning Objectives

1. **Recognize** clinical trajectories and multidomain findings that should prompt consideration of autoimmune or other inflammatory CNS disease.

2. **Escalate** the evaluation appropriately and know what the workup should include.

3. **Treat** acute and long-term neuropsychiatric symptoms while disease-directed therapy proceeds.

Case: 16-year-old with new-onset psychosis

- Previously high-functioning: history notable only for anxiety
- 3–4 weeks of increasing stress and worsening sleep
- Essentially no sleep for several days before admission
- New AH, religious preoccupation, SI and SIB

INITIAL DIFFERENTIAL

- First episode psychosis?
- Mood disorder?
- Trauma/stress response?

Within 48 hours, the phenotype broadens

PSYCHIATRIC

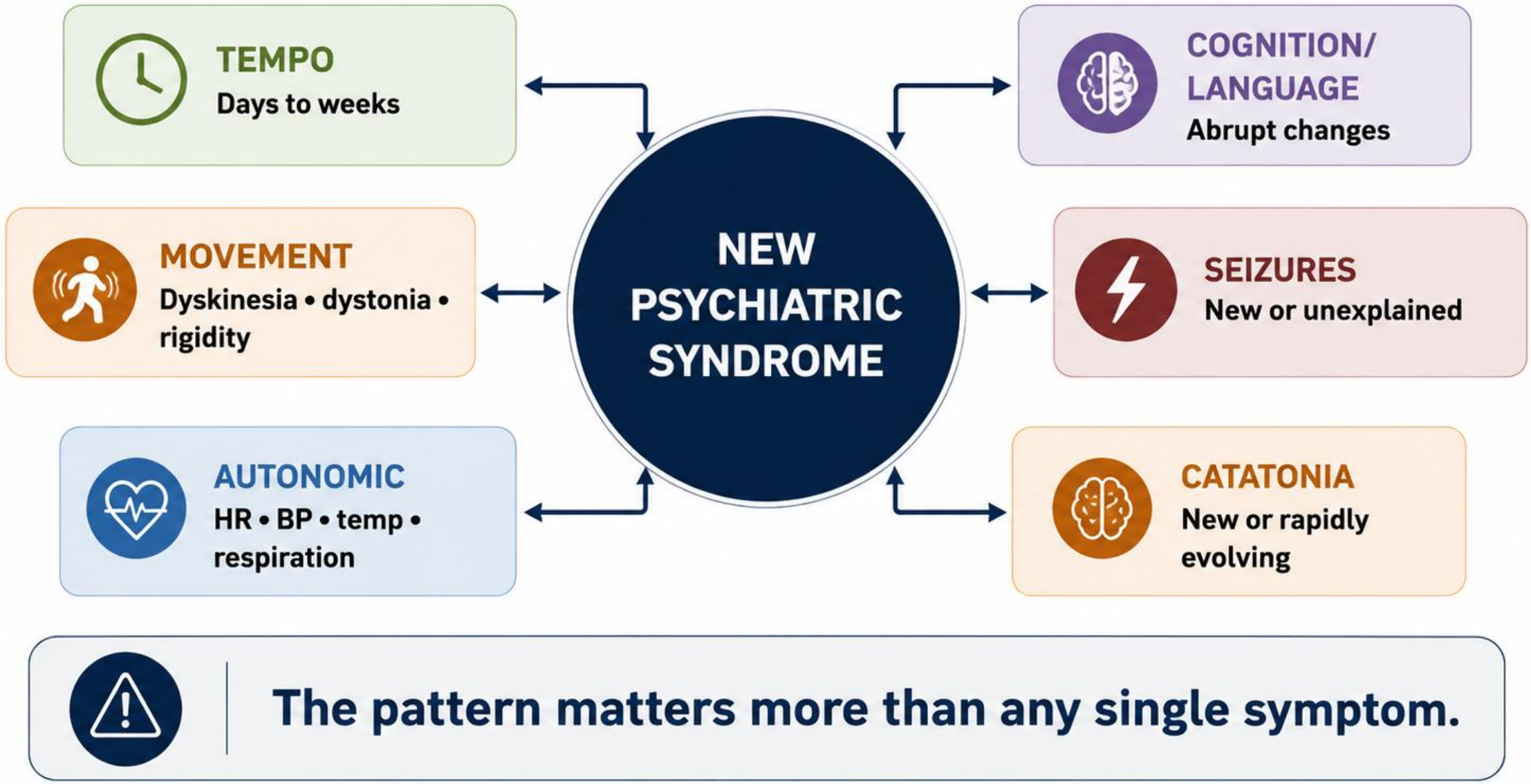
- Increasing agitation and paranoia
- Responding to internal stimuli
- Pressured/ disorganized speech

SOMETHING ELSE?

- Unsteady gait
- Orofacial dyskinesia
- Stuttering and intermittent disorientation

At what point does “first-episode psychosis” or “first-episode mania” stop explaining the whole patient?

When should a psychiatrist think beyond primary psychiatry?



Which features shift the differential?

More typical of primary mood/psychotic illness		Evidence of broader brain dysfunction
Typical psychiatric trajectory (gradual)	→	Rapid progression
Coherent psychiatric syndrome	→	Multidomain evolution
Cognition/language preserved	→	New cognitive/language change
Neurologic exam stable	→	New neurologic findings
No abnormal movements	→	New dyskinesia/rigidity/posturing
Physiology stable	→	Autonomic/LOC abnormalities

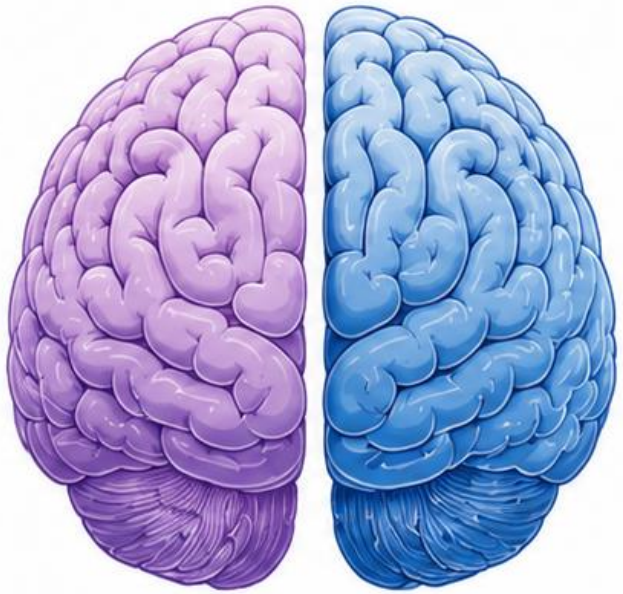
No single feature distinguishes them—
the evolving pattern changes pretest probability.

Pediatric AIE does not always look like Adult AIE

PEDIATRIC AIE

- Less often associated with tumors
- More likely to have movement disorders
- Seizures more common at presentation
- Behavioral dysregulation and insomnia very prominent
- Developmental regression can be a clue

VS



ADULT AIE

- Tumor association more common (especially ovarian teratoma in anti-NMDAR)
- Dyskinesias less prominent
- Seizures less prominent at presentation
- Psychosis prominent
- Memory impairment (anterograde) more prominent

Maintain a high index of suspicion in any child or adolescent with a rapidly evolving neuropsychiatric syndrome.

PANS vs Autoimmune Encephalitis

Overlap exists—but these are not the same syndrome.

	PANS	AUTOIMMUNE ENCEPHALITIS
Onset	**Abrupt: hours to 2–3 days**	**Acute/subacute: days to weeks**
Required features	**New OCD or severe food restriction** + ≥2 acute neuropsychiatric symptom categories Diagnosis of exclusion	**Memory/mental-status or psychiatric syndrome** + neurologic/supportive findings; exclude alternatives
Neurologic findings	**Usually absent or mild** Seizures • focal deficits • altered consciousness → reconsider PANS alone	**Often prominent** Seizures • movement disorder • focal deficits Dysautonomia • altered consciousness
Cognitive impairment	**Often relatively preserved** Attention or school performance may decline	**A cardinal feature** New cognitive/memory impairment or altered mental status
Course without treatment	**Often relapsing–remitting** Flares may remit untreated; chronic courses occur	**Usually persists or progresses** without immunotherapy

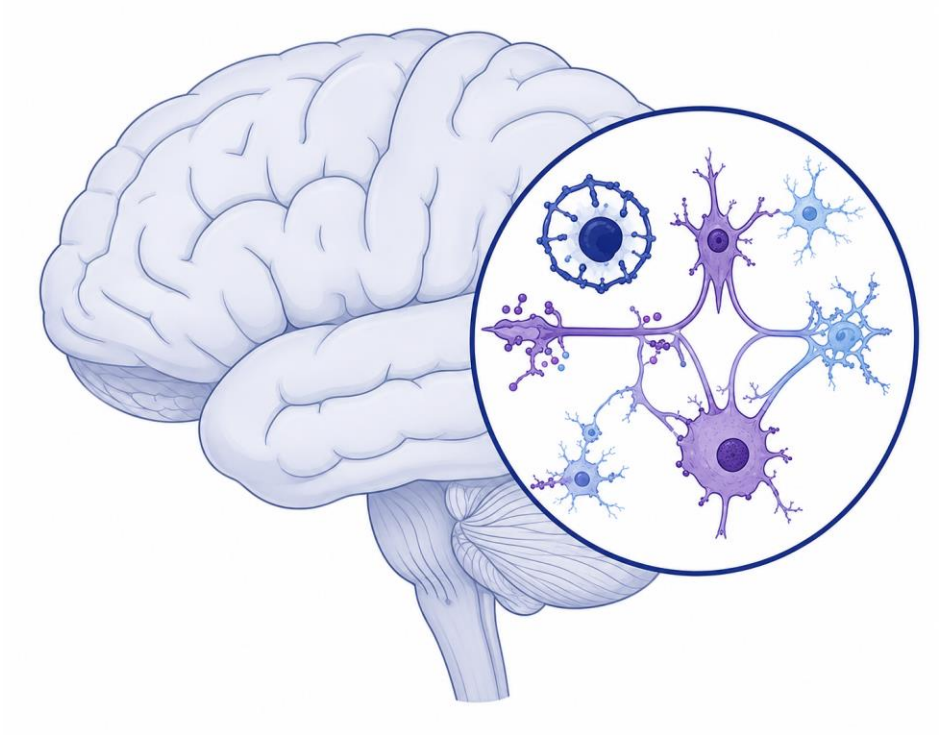
BOTTOM LINE

PANS and AIE can both present abruptly with neuropsychiatric symptoms.
AIE requires evidence of neurologic dysfunction and CNS inflammation.

What is actually happening in the brain?

From syndrome recognition to mechanism

What do we mean by encephalitis?



ENCEPHALITIS

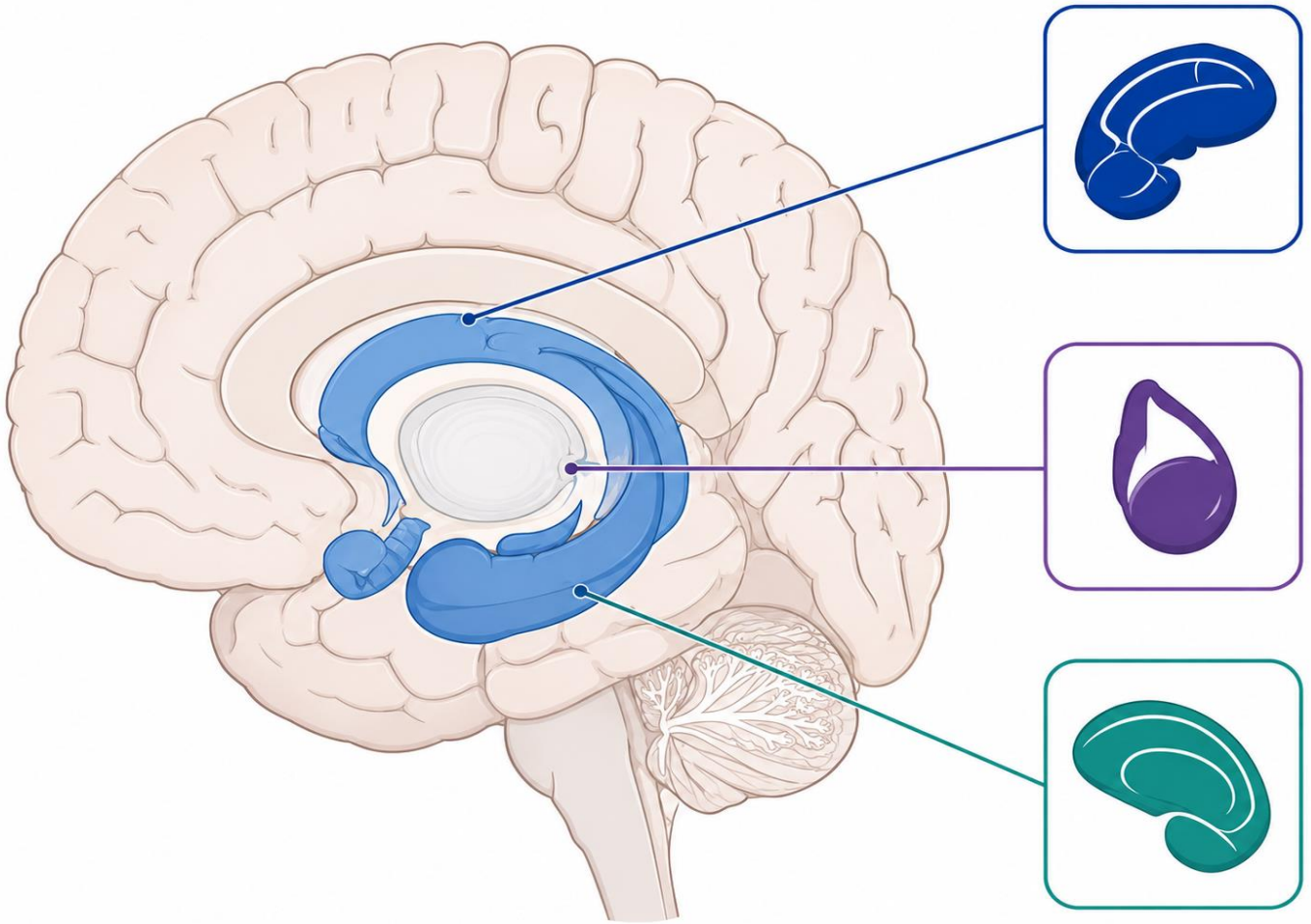
Inflammation of brain parenchyma → neurologic dysfunction

NOT THE SAME AS ENCEPHALOPATHY

Encephalopathy = brain dysfunction without necessarily implying inflammation

Our job is to recognize brain dysfunction–
and then determine whether inflammation is causing it.

Why does limbic inflammation look psychiatric?



HIPPOCAMPUS

New learning

Episodic memory

AMYGDALA / LIMBIC NETWORKS

Threat • Emotion • Salience

MEDIAL TEPMORAL NETWORKS

Memory • Behavior • Seizures

Memory change + psychiatric/behavioral change + seizures
= anatomically coherent syndrome

AIE: one syndrome, multiple mechanisms

ACQUIRED SUBACUTE BRAIN DYSFUNCTION

ANTIBODY POSITIVE

Known antibody associated with AIE

IMMUNE-TRIGGERD/ POSTINFECTIOUS

CNS inflammation not 2/2 known pathogenic neural antibody

ANTIBODY NEGATIVE

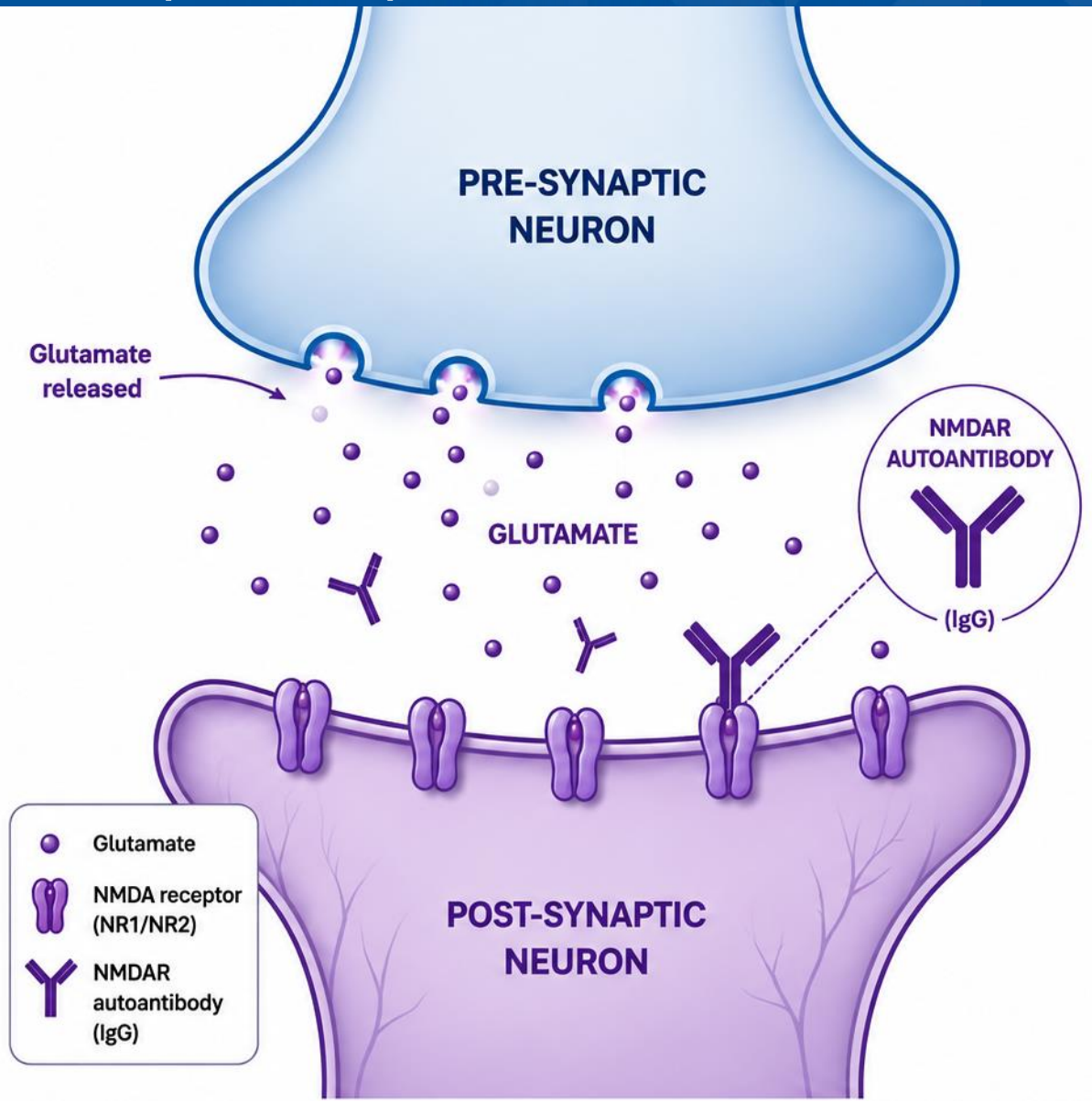
No antibody detected yet clinical syndrome fits AIE

Diagnosis is clinical. Antibody testing supports– but does not define– AIE.

Anti-NMDAR antibody mechanism

Pathogenic IgG disrupts receptor function

1. **Anti-GluN1 binds NR1 subunit**
2. **Cross-linking of receptors**
3. **Internalization of NMDA-Rs**
4. **↓ Surface NMDA-R function**



Anti-NMDAR phenotype: an evolving phenotype

	Prodrome (1–3 days)	Early (1–2 weeks)	Peak (2–6 weeks)	Recovery (months)
 **Psychiatric**	• Anxiety • Irritability • Insomnia	• Agitation • Paranoia • Hallucinations	• Psychosis • Catatonia	• Improving behavior • Residual psychiatric symptoms
 **Cognitive**	• Mild problems with memory • Attention	• Worsening attention • Working memory	• Severe memory deficits	• Gradual recovery • Residual deficits
 **Neurologic**	• Headache	• Seizures • Dyskinesias	• Movement disorder • ↓ Consciousness	• Decreasing deficits • ± Residual seizures
 **Autonomic**	• Mild hyperventilation	• Tachycardia • Labile BP • Fever	• Arrhythmias • Hypotension • Apnea	• Autonomic stabilization

Probable anti-NMDAR encephalitis
(GRAUS ET AL., 2016)

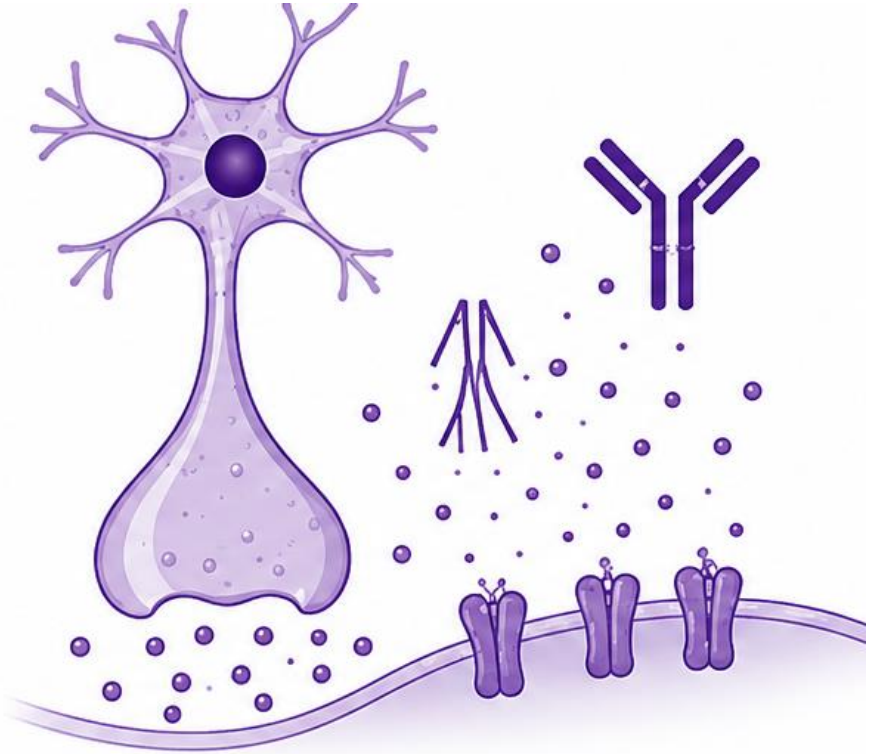
1 **Rapid onset (<3 months) of ≥4 of 6 major symptom groups**

- Abnormal behavior OR cognitive dysfunction
- Speech dysfunction
- Seizures
- Movement disorder, dyskinesias, or rigidity/abnormal postures
- Decreased level of consciousness
- Autonomic dysfunction or central hypoventilation

2 **At least one of the following:**

- Abnormal EEG (focal/diffuse slowing, epileptic activity, or extreme delta brush)
- CSF pleocytosis or oligoclonal bands

3 **Reasonable exclusion of other disorders**



If a **systemic teratoma** is present, only **3 of 6** symptom groups are required.

Case example: crossing multiple domains

PSYCHIATRIC → SPEECH / COGNITIVE → MOVEMENT / GAIT → CATATONIA / CONSCIOUSNESS

OBJECTIVE EVALUATION

MRI BRAIN
Right amygdala
FLAIR abnormality

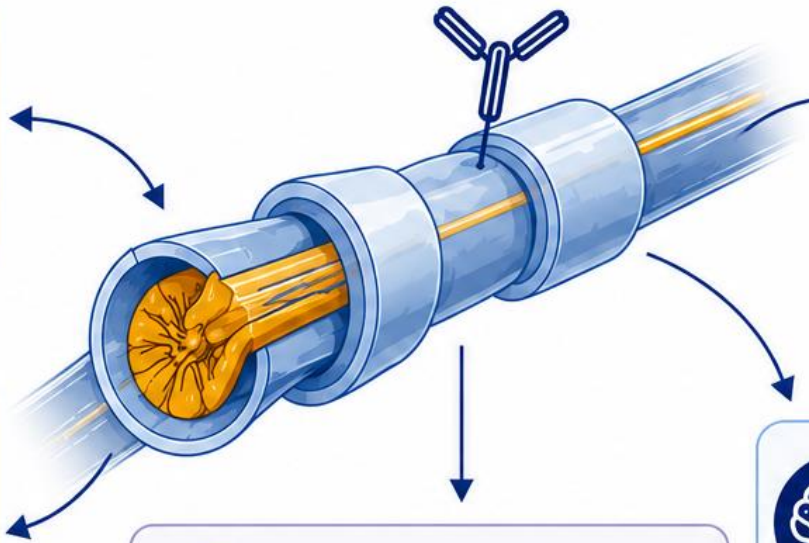
CSF
anti-GluN1 IgG
positive

TUMOR EVALUATION
Ovarian teratoma
identified

The antibody confirmed a syndrome that had already stopped behaving like primary psychosis.

MOG antibody-associated disease (MOGAD)

Demyelinating disease with distinct phenotypes



OPTIC NEURITIS

- Painful vision loss
- Often bilateral

MYELITIS

- Longitudinally extensive cord lesions
- Motor/sensory ± bowel/bladder symptoms

ADEM — *especially younger children*

- Encephalopathy
- Multifocal deficits
- Widespread MRI lesions

BRAINSTEM / CEREBELLAR

- Diplopia / cranial neuropathies
- Ataxia
- Dysarthria / dysphagia

CORTICAL ENCEPHALITIS (FLAMES)

- Seizures • headache
- Encephalopathy
- Cortical FLAIR abnormalities

< 5 YEARS — *INCREASING AGE* — **≥ 11 YEARS**

ADEM particularly common

Optic neuritis increasingly common

GAD-65: different immune mechanism, different course

THE TARGET

GAD65

Enzyme involved in GABA synthesis

INTRACELLULAR ANTIGEN

Antibodies often biomarkers; cytotoxic T-cell–mediated injury contributes

THE PHENOTYPE

- Limbic encephalitis
- Temporal lobe seizures
- Psychiatric symptoms common
- Memory dysfunction
- Cerebellar ataxia
- Stiff-person spectrum

CLINICAL IMPLICATIONS

- Often less robust response to immunotherapy
- Epilepsy and cognitive or psychiatric morbidity may persist
- Relapses can occur
- Persistence and relapses may require longitudinal multidisciplinary care

LOW-TITER SERUM GAD65 ≠ GAD65 NEUROLOGIC AUTOIMMUNITY

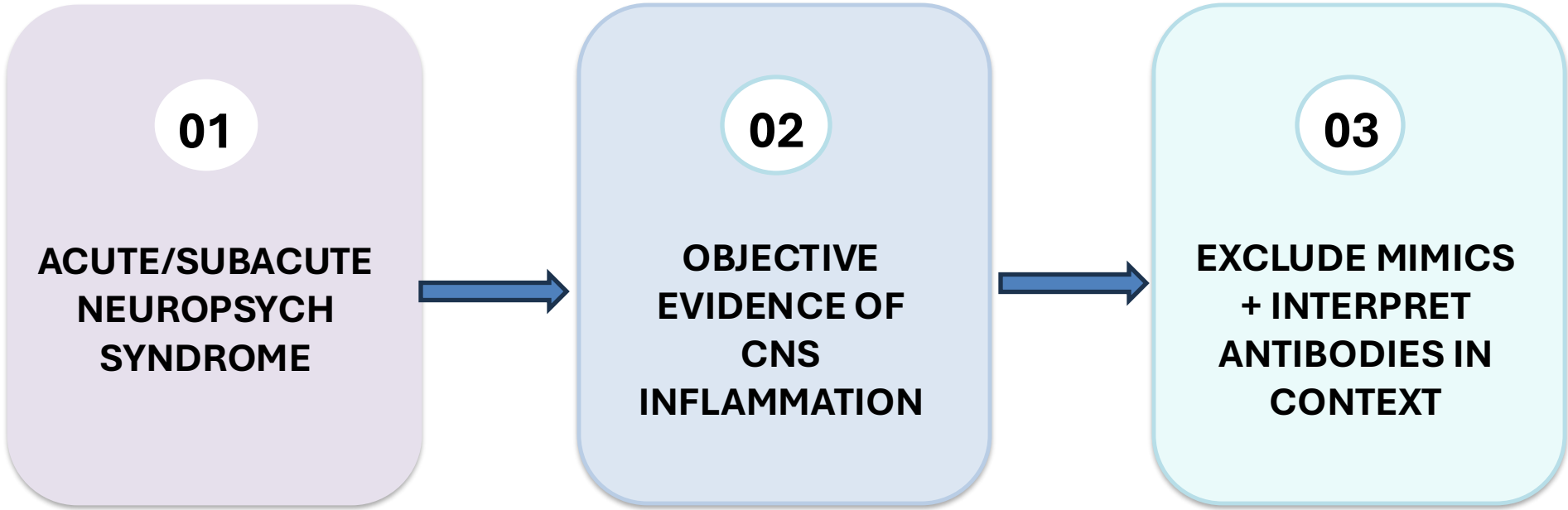
Psychiatric symptoms reported in ~62% of published GAD65 limbic encephalitis cases*

*Adult case literature; not a pediatric prevalence estimate.

EVALUATION & ACUTE MANAGEMENT

Identifying, stabilizing, and treating early

In children, diagnosis integrates phenotype + inflammation



Antibody testing supports the diagnosis; it does not replace the phenotype. Use this framework early– do not wait for definitive antibody results.

Cellucci, Van Mater, et al., 2020.

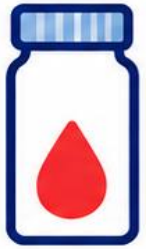
What should the evaluation actually include?

NEUROLOGIC

MRI brain ± contrast
MRI may be normal at diagnosis

EEG
Unusual to have a normal EEG in active disease

CSF



Cell count, protein, glucose

OCBs • IgG index

Infectious studies as indicated

Autoimmune encephalitis antibodies

BLOOD

Inflammatory
ESR CRP Ferritin

ANA and other auto-antibodies as indicated

Infectious studies as indicated

AIE serum antibody panel

PHENOTYPE-DIRECTED

Urine drug screen

Tumor screening

Toxic/metabolic

Genetic evaluation

Evaluate the syndrome—not just the antibody panel.

Two simultaneous treatment tracks run simultaneously

SYMPTOM CONTROL (PSYCHIATRIC + MEDICAL)

- Agitation
- Psychosis / mania
- Sleep disruption
- Seizures
- Autonomic instability
- Catatonia

IMMUNOTHERAPY (TARGET THE DISEASE)

- First-line: steroids, IVIG, plasma exchange
- Second-line: rituximab, cyclophosphamide
- Tumor removal if applicable

Psychiatric treatment supports the patient while underlying immune process is treated.

Agitation is an observation– not a mechanism

Before choosing a medication: identify what is driving the agitation.

The medication that helps one syndrome may worsen another.

PRNs in active encephalitis: familiar drugs, different risks

Use the lowest effective dose. Reassess frequently.

	ANTIPSYCHOTICS	BENZODIAZEPINES	α2 AGONISTS	HYDROXYZINE
CONSIDER FOR	• Psychosis • Severe agitation posing safety risk	• Catatonia • Seizures • Severe anxiety	• Dysautonomia / hyperarousal • Sleep	• Mild–moderate anxiety • Sleep • Adjunct for agitation
WATCH	• EPS / akathisia • Malignant catatonia • Lower seizure threshold • QT prolongation • Neuroleptic sensitivity	• Disinhibition • Delirium ↑ • Respiratory depression • Sedation	• Hypotension • Bradycardia • Sedation	• Anticholinergic burden • QT prolongation • Sedation
PEARL	• **Use low doses** • **Reassess often** • **Watch for neuroleptic sensitivity**	• **First-line for catatonia** • **May worsen delirium**	• **Avoid abrupt stop** • **Monitor BP / HR**	• **Limited efficacy for severe agitation** • **Useful for anxiety/sleep**

So the question is not
‘what is the strongest PRN?’

It is
‘what adverse effect can this particular child’s physiology safely afford?’

Match the medication to the mechanism driving the behavior.

Sleep disruption during active disease

Multifactorial

Disease-related (limbic dysfunction)
Circadian rhythm disruption

Hospital environment
Noise, lights, interruptions

Medications
Steroids, stimulants, anticholinergics

Psychiatric symptoms
Anxiety, mania, delirium

WHAT WE COMMONLY USE

Melatonin

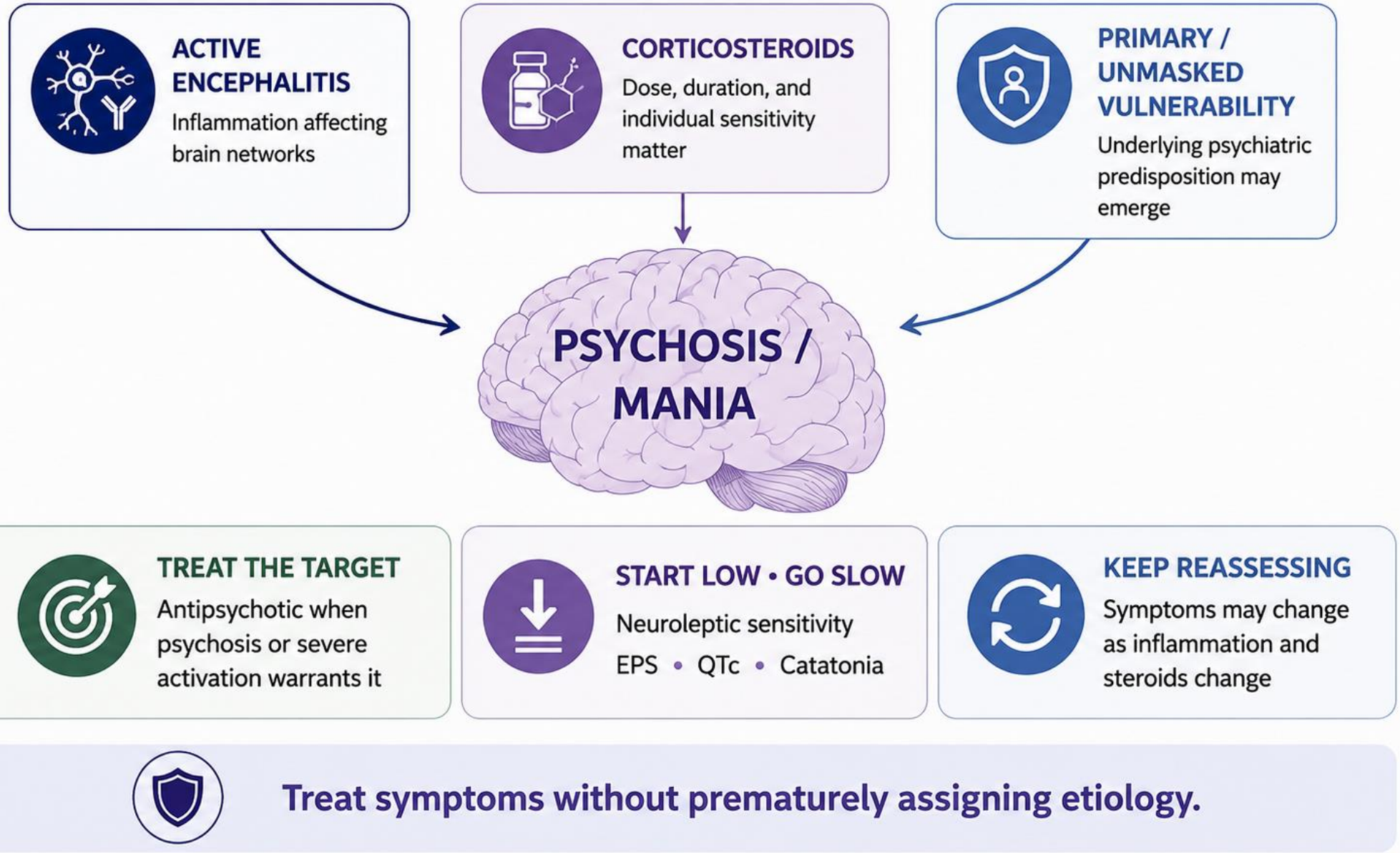
α2-agonist
clonidine > guanfacine for acute HS use

Mirtazapine
selected patients

Low-dose antipsychotic
only when another target justifies it

Optimize sleep hygiene + treat underlying causes.

Treating psychosis/mania during active disease



Catatonia during active disease

1. SUSPECT / CONFIRM CATATONIA

BFCRS + focused exam
Look for hypo- and hyperkinetic features

2. LORAZEPAM CHALLENGE

1–2 mg IV/PO
At least every 4–6 hours
Assess response and titrate to response and tolerability

3. SEVERE OR INADEQUATE RESPONSE

Increase dose
Consider scheduled dosing
Consider ECT for refractory catatonia

4. ECT

When response remains inadequate or rapid resolution is needed

SIMULTANEOUSLY

Treat underlying encephalitis
(immunotherapy as indicated)

Hydration and nutrition

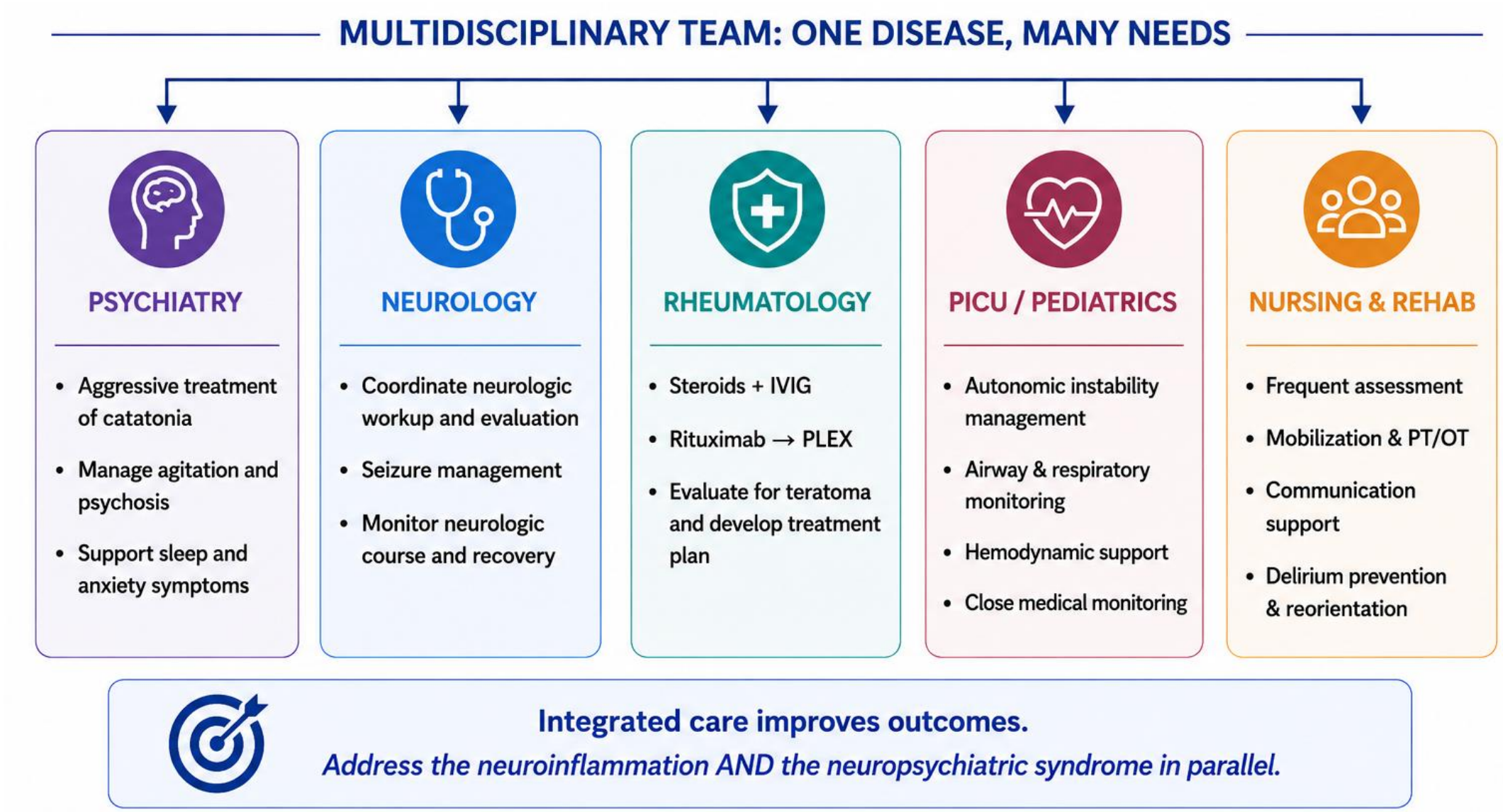
DVT prophylaxis

Monitor autonomic instability
(vitals, temperature, BP, HR)

Prevent medical complications
(aspiration, pressure injuries, infections, rhabdomyolysis, electrolyte disturbances)

Do not wait for immunotherapy alone to resolve severe catatonia.

Our patient: severe disease never belongs to one service



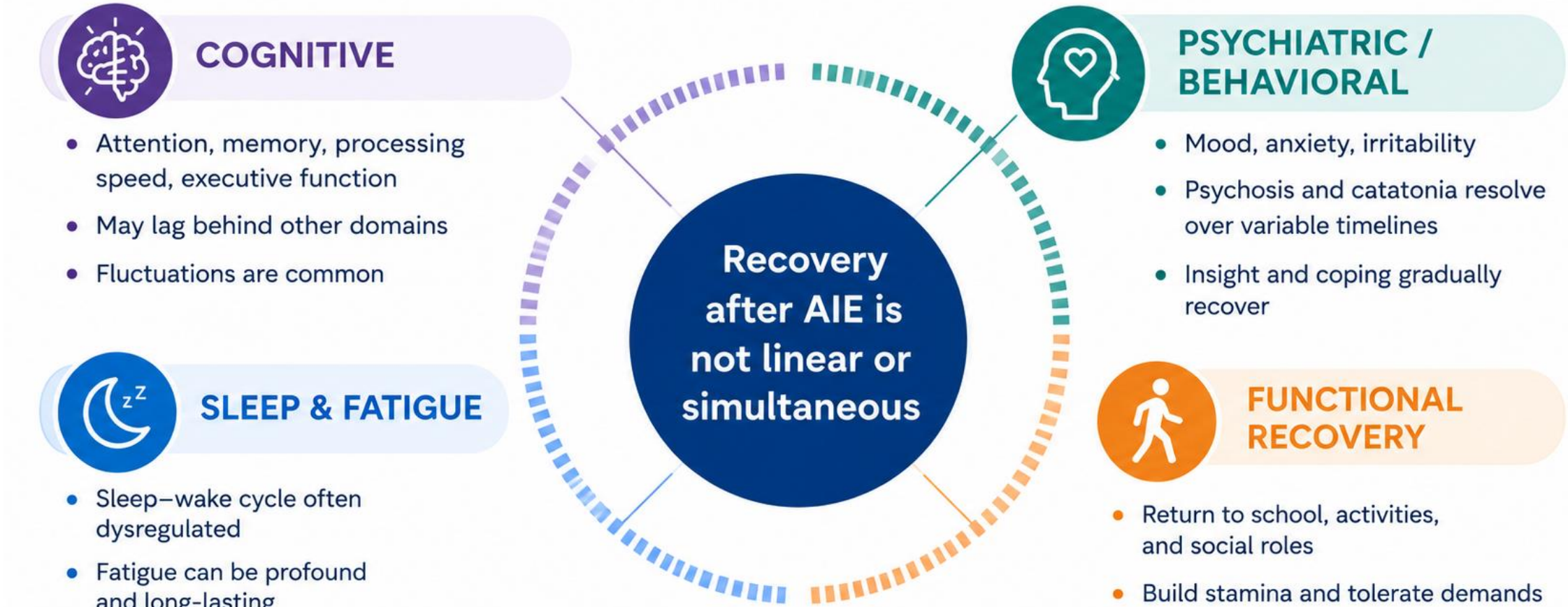
The inflammation improves.

The child may not be recovered.

Long-term neuropsychiatric care

Recovery is multidimensional

Different domains improve at different rates



Set realistic expectations and support gradual progress.

Executive dysfunction after AIE

Common and disabling– improves with time but needs support

PERSISTENT DEFICITS ARE COMMON

≥2 years after pediatric NMDAR encephalitis*

53% Attention impairment

41% Executive dysfunction

70% Academic difficulties

88%
had a "favorable" mRS (0–2)

mRS = modified Rankin Scale
(0 = no symptoms, 2 = slight disability)

**French multicenter cohort, n=81*

ETIOLOGY / PATHOPHYSIOLOGY

Acquired executive–attention deficit after brain inflammation

May unmask underlying vulnerability

TREATMENT DECISION

Do attention problems significantly impair functioning (school, home, social)?

YES (Pause if active inflammation)

TREAT
First line often still a stimulant (with careful collaboration with neurology)

Attention & executive dysfunction are common after AIE.
Treat the functional impairment—based on evaluation, not etiology.

Psychiatric symptoms during recovery

Balance benefit, side effects, and the evolving clinical picture

CATATONIA

- Monitor for persistence or recurrence
- Taper benzodiazepines cautiously
- Re-escalate treatment if symptoms recur

Don't taper too quickly—relapse can occur.

PSYCHOSIS / MANIA

- Symptoms may persist beyond acute inflammation
- Reassess ongoing antipsychotic indication
- Gradually reduce when clinically appropriate and safe

Regularly reassess need, dose, and duration.

MOOD / ANXIETY

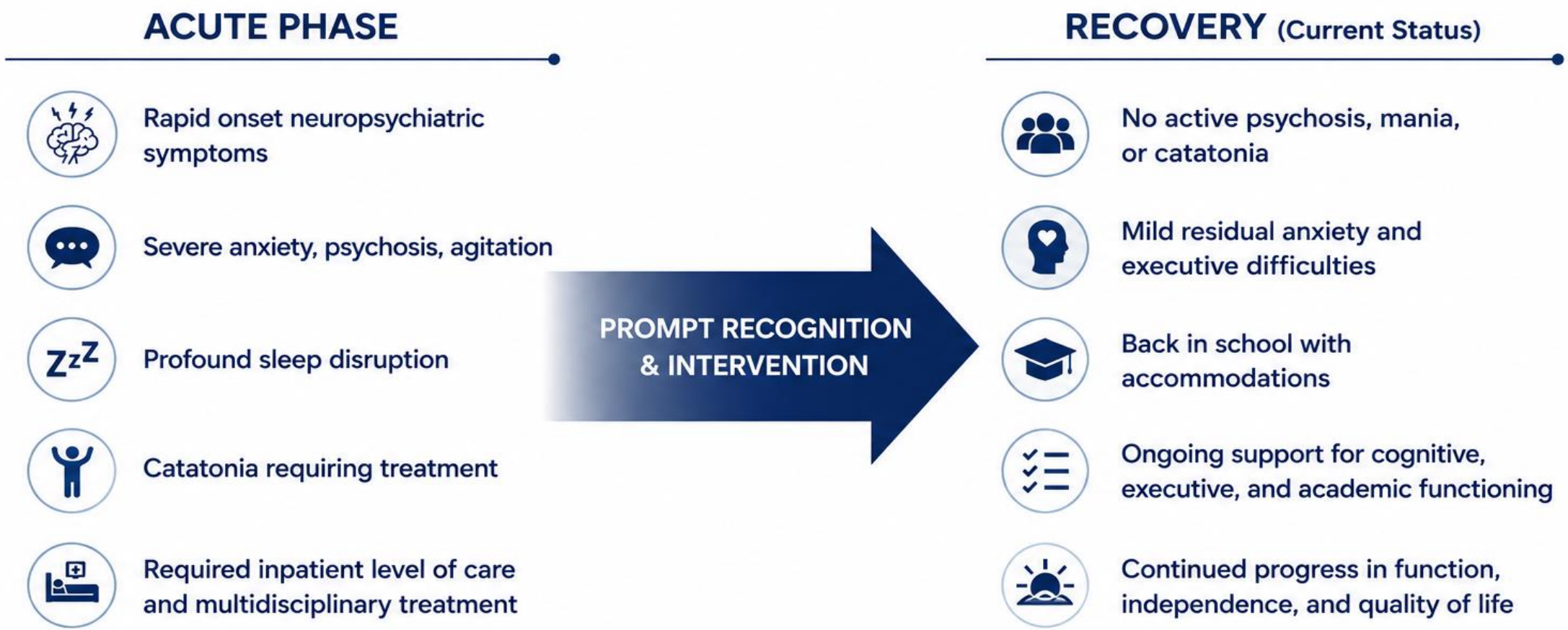
- Treat persistent syndromes when indicated
- Consider cognition, fatigue, sleep, and medication effects
- Avoid prematurely labeling recovery phenomena as a new primary psychiatric disorder

Context matters—interpret symptoms in the recovery trajectory.

KEY PEARL: | Reassess the indication for every psychiatric medication as the underlying disease evolves.

Severe acute psychiatric symptoms ≠ chronic psychiatric illness

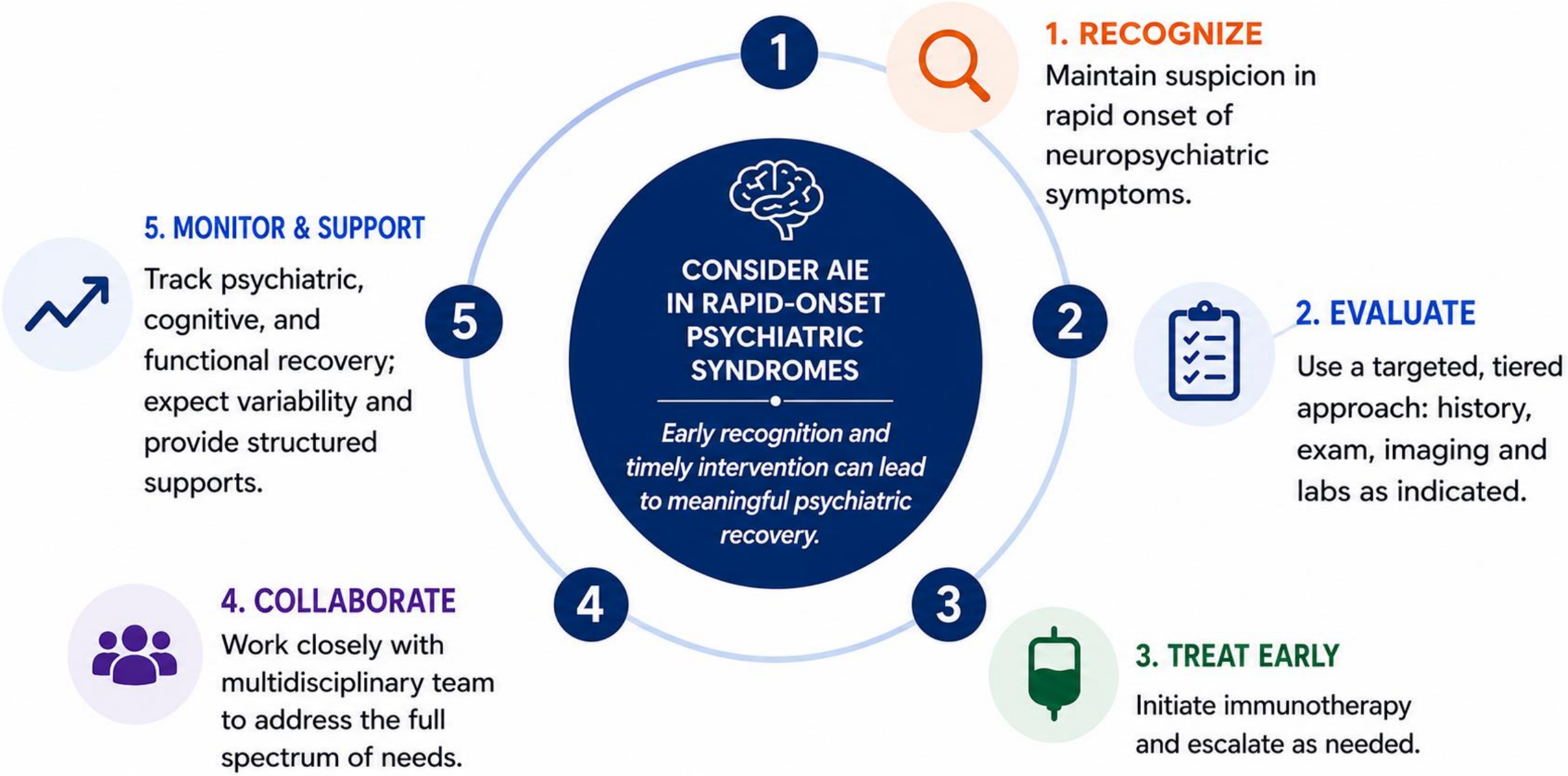
Our patient's psychiatry recovery substantially ourpaced her cognitive and functional recovery.



KEY TAKEAWAY: *Early recognition and timely intervention can lead to meaningful psychiatric recovery.*

Take-home framework

Key principles for CAP psychiatrist and AIE



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Comparison of autoimmune neurologic syndromes

ANTI-NMDAR
Neuronal surface autoimmune encephalitis

TYPICAL AGE
Most common in children and young adults; can occur at any age

THINK
Rapidly evolving multidomain neuropsychiatric syndrome

PSYCHIATRIC CLUE
- Psychosis • agitation • catatonia
- severe sleep disruption

PROGNOSIS
Often substantial recovery with treatment; relapses possible

MOGAD
Inflammatory CNS demyelinating disease

TYPICAL AGE
Any age; about 30% of cases are pediatric

THINK
ADEM • optic neuritis • myelitis; varies with age and anatomy

PSYCHIATRIC CLUE
Behavioral/cognitive change with encephalopathy

PROGNOSIS
Often steroid-responsive; monophasic or relapsing

GAD65
Intracellular-antigen–associated neurologic autoimmunity

TYPICAL AGE
Variable; often adults, but pediatric disease occurs

THINK
Limbic/epileptic or hyperexcitability phenotype

PSYCHIATRIC CLUE
Usually accompanies seizures, memory dysfunction, or other limbic features

PROGNOSIS
Variable/incomplete response; chronic epilepsy or cognitive deficits may persist

Neuropsychological recovery

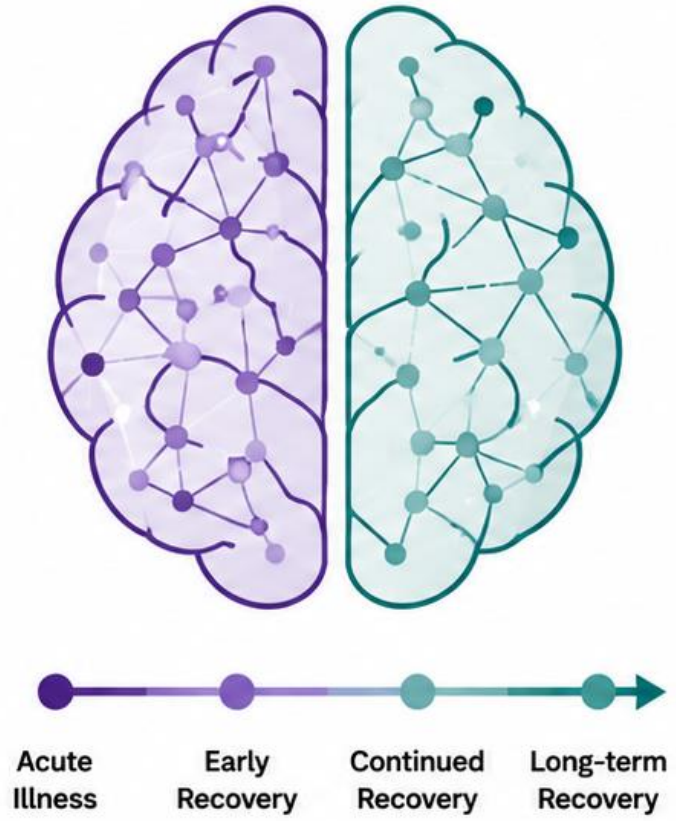
Test function, not just symptoms

WHEN TO TEST

- After medical stabilization, when the patient can participate meaningfully
- When cognitive or functional complaints persist
- Before major school/academic or vocational decisions
- When functional difficulties interfere with daily life

WHAT TO ASSESS

- Attention & processing speed
- Memory (verbal / visual)
- Executive function
- Language
- Visuospatial skills
- Academic achievement
- Emotional / behavioral function



WHY IT MATTERS

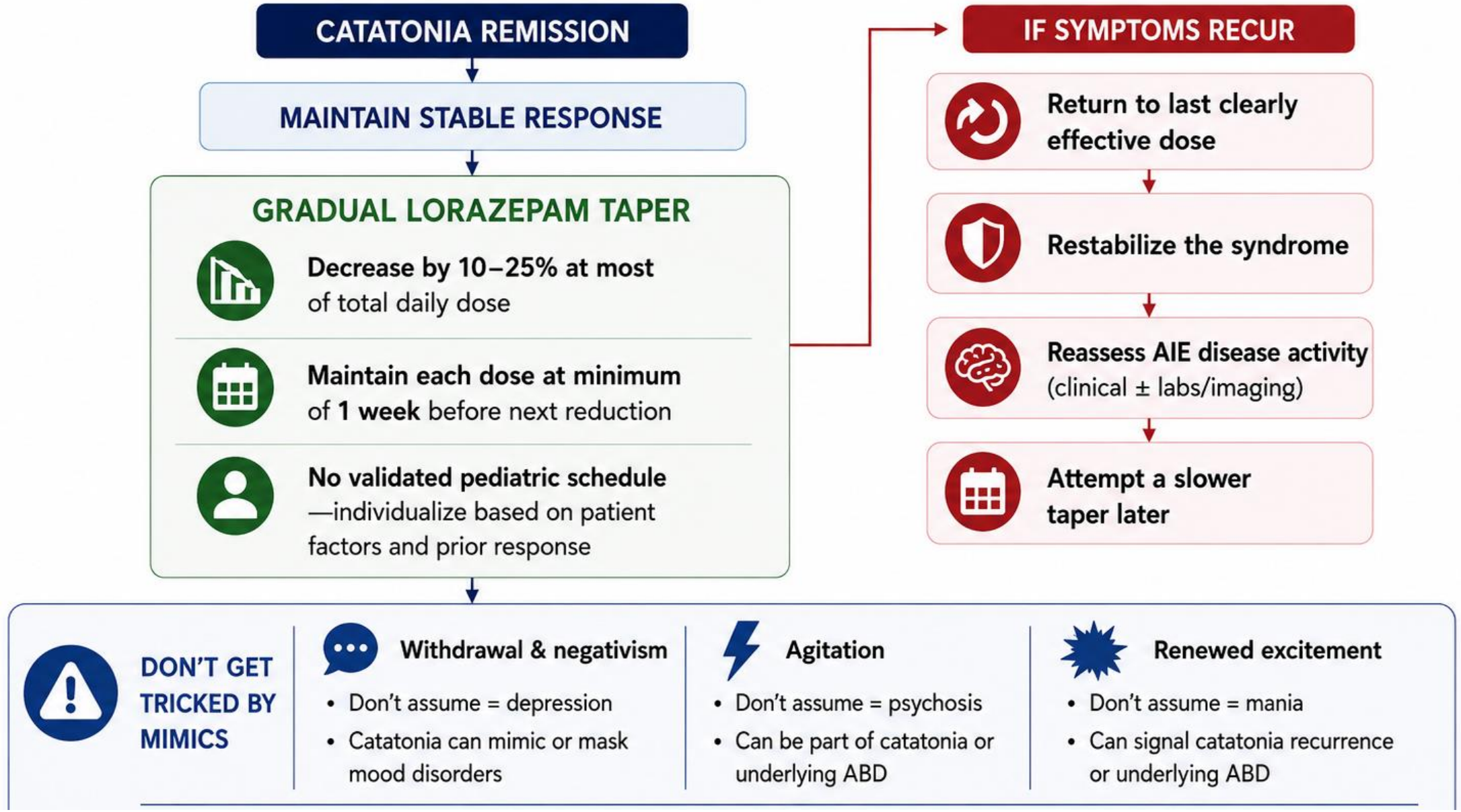
- Differentiates residual disease from other contributors (e.g., meds, mood, sleep, fatigue)
- Reveals strengths and weaknesses
- Guides realistic expectations
- Informs school accommodations and therapy planning
- Provides objective data to track recovery and guide decisions

FOLLOW OVER TIME

- Recovery unfolds over months to years
- Repeat testing when clinically indicated to answer a specific question
- Compare to prior results to detect change
- Adjust supports and interventions based on data

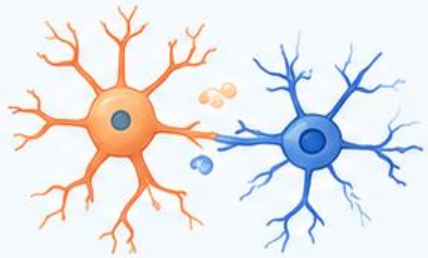
Catatonia in recovery

Goal: Avoid recurrence– don't outrun recovery



Recovery: persistent psychiatric symptoms

RESIDUAL NEUROINFLAMMATION



- Cytokines
- Network dysregulation
- Neurochemical changes
- Ongoing pain / fatigue

PSYCHOLOGICAL SEQUELAE

- Trauma
- Prolonged hospitalization
- Loss of independence
- Adjustment to new baseline

MEDICATION EFFECTS

- Steroids
- Levetiracetam
- Interferons / IVIG
- Other agents (neuropsychiatric side effects)

PREMORBID VULNERABILITY

- Personal / family history
- Anxiety / depression
- Neurodiversity traits

PSYCHIATRIC PHENOTYPE

Anxiety • Depression • Irritability • Psychosis • OCD • Catatonia