Important Message from our Medical Advisory Committee

November 7, 2022

Catatonia and Neuroleptic Malignant syndrome (NMS)

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Dear families affected by Phelan-McDermid syndrome (PMS),

The PMS Medical Advisory Committee and the PMS Neuropsychiatric Consultation Group provide support to families and to physicians caring for people with PMS with complex behavioral presentations. Based on our experience with more than 100 affected individuals, and knowing the difficulty that families encounter in accessing appropriate psychiatric care, we have developed this information sheet for you to share with your providers as relevant.

PMS is a rare genetic disorder which usually involves changes in a critical gene (SHANK3) on the long arm of chromosome 22. The SHANK3 protein is a scaffolding protein in glutamatergic synapses, including among other functions the positioning of the NMDA receptor. Clinical features often include intellectual disability, autism, epilepsy, sensory seeking behaviors, pica, chronically disrupted sleep, and severe constipation with related behavioral disturbances.

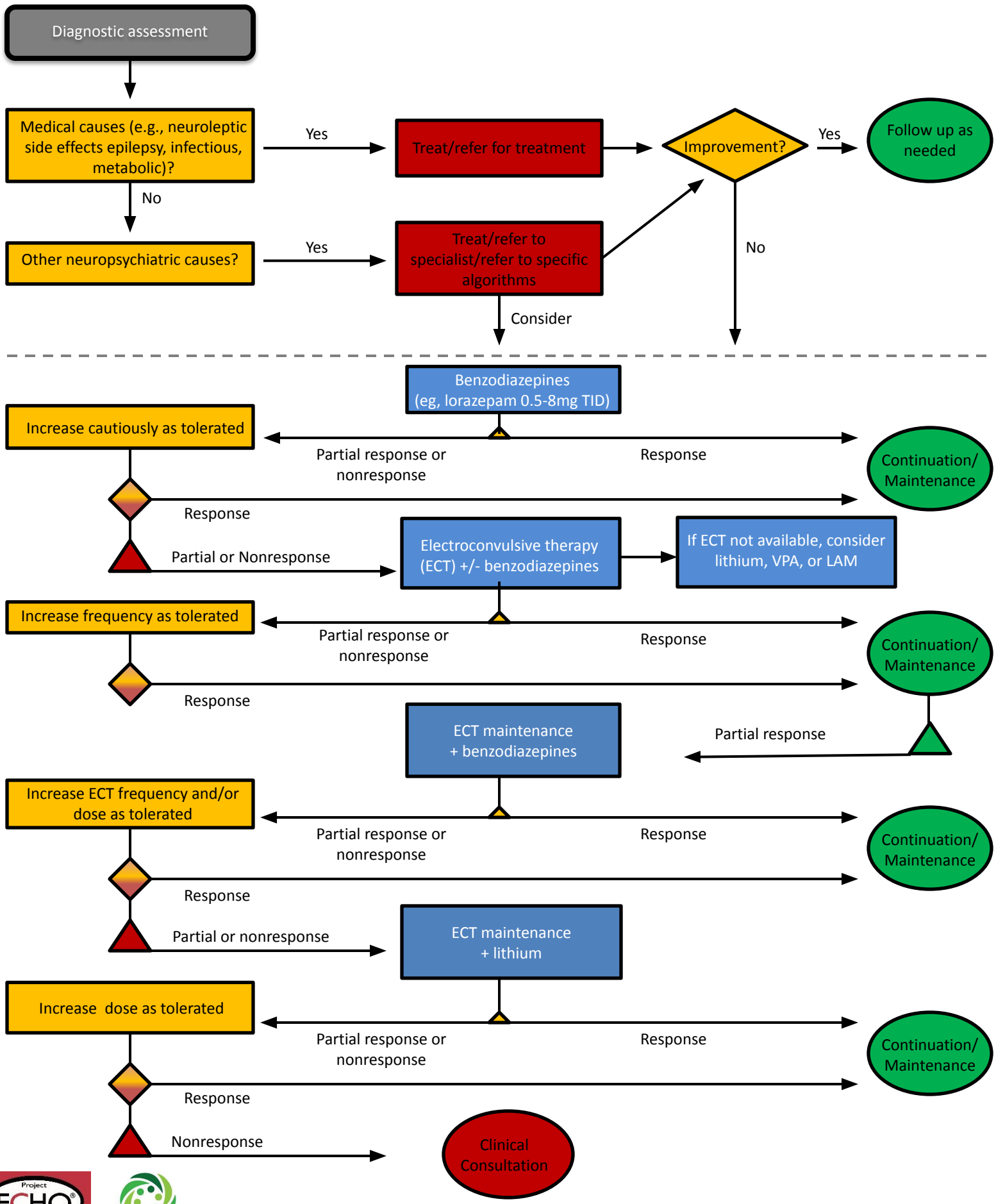
Around puberty or in early adulthood, some people with PMS are prone to develop bipolar disorder, associated psychotic features, and severe anxiety or obsessive compulsive symptoms. When distressed, some may develop new aggression or self-injurious behaviors, or try to run away.

Emergency Department and Urgent Care providers must be aware that:

- People with PMS are extremely sensitive to antipsychotics, with high rates of extrapyramidal symptoms, medication-induced catatonia, and neuroleptic **malignant syndrome (NMS)**.
- Antipsychotics should be used only when alternative medications to manage difficult symptoms have been explored, and then at only low doses.
- Intramuscular doses of medications like haloperidol have triggered NMS in some people with PMS, and repeated doses of antipsychotics can induce catatonia.
- The use of more than one antipsychotic medication at a time is strongly discouraged.
- Catatonia occurs in roughly 50% of PMS patients who develop psychiatric symptoms.
- Catatonia itself can be the first episode of psychiatric disturbance.
- When catatonia occurs, it may be stuporous, but hypermotoric catatonia with prominent, purposeless restlessness, agitation, and atypical aggression resembling manic delirium is also well described in PMS.
- If catatonia is suspected, PMS patients tend to respond well to lorazepam TID, sometimes requiring increases to high doses (see Pharmacological Treatment Guidelines attached below).

Details about requesting a consult from the PMS Neuropsychiatric Consultation Group can be found here: https://pmsf.org/neuropsychiatric-consultation-group/

Expert Consensus Recommendations* for the Pharmacological Management of Catatonia** in Phelan-McDermid Syndrome



*These recommendations are not established as "evidence-based."

**** Notes for the Treatment Algorithm for the Pharmacological Management of Catatonia in Phelan-McDermid Syndrome**

- Would recommend starting lorazepam 0.5-1 mg TID, and increasing by 0.5 mg TID every few days, based on response.
- Track frequency of catatonia symptoms objectively to carefully guide titration; increase lorazepam until symptom improvement plateaus, or until the point of over-sedation.
- Monitor vital signs closely and if unstable, expedite to urgent referral for ECT.
- If no response to benzodiazepines, ECT alone is the next step assuming symptom severity warrants it. If the patient is simply prompt dependent with psychomotor retardation, ECT may not be indicated.
- If only PARTIAL response to benzodiazepines, consider ECT while remaining on the benzodiazepine, and using flumazenil reversal. It is NOT necessary to taper the benzodiazepine.
- If there is PARTIAL response to benzodiazepines, and the remaining symptoms do not warrant ECT, consider adjunctive antidepressant or mood stabilizer, depending on the underlying psychopathology.
- Acute ECT needs to be delivered at least three times weekly with BILATERAL electrode placement and monitoring for seizure quality.
- If inadequate response to bilateral ECT, consult with an expert to address ECT technical parameters and associated medications to improve seizure quality.
- Every patient who responds to ECT requires medication to decrease maintenance ECT frequency while maintaining clinical stability.
- Once the patient is on twice weekly ECT, start lithium and titrate to a therapeutic serum level as you decrease ECT frequency.

****Clinical Guidelines to Initiate Treatment of Catatonia in Phelan-McDermid Syndrome**

Any person with PMS who is in their usual state of health and experiences the onset of at least three of the following symptoms according to the Diagnostic and Statistical Manual for Mental Disorders Fifth Edition (DSM-5, APA, 2013):

(1) stupor (i.e., no psychomotor activity; not actively relating to environment);
(2) catalepsy (i.e., passive induction of a posture held against gravity);
(3) waxy flexibility (i.e., slight, even resistance to positioning by examiner);
(4) mutism (i.e., no, or very little, verbal response);
(5) negativism (i.e., opposition or no response to instructions or external stimuli);
(6) posturing (i.e., spontaneous and active maintenance of a posture against gravity);
(7) mannerisms (i.e., odd, circumstantial caricature of normal actions);
(8) stereotypy (i.e., repetitive, abnormally frequent, non-goal-directed movements);
(9) agitation, not influenced by external stimuli;
(10) grimacing;
(11) echolalia (i.e., mimicking another's speech);
(12) echopraxia (i.e., mimicking another's movements)

*The Diagnostic Manual - Intellectual Disability, Second Edition (DM-ID2; Barnhill et al., 2017) notes that mutism, mannerisms, stereotypies, and grimacing can also be features of intellectual disability, and that echolalia can be a feature of ASD, so the history and time of onset of these symptoms is critical to delineate.

*****Clinical Guidelines to Initiate a Laboratory-Based Assessment to rule out <u>Encephalitis</u> in Phelan-McDermid Syndrome**

Presence of encephalopathy defined as:

(1) depressed of altered level of consciousness lasting 24 hours OR
(2) lethargy OR
(3) personality change

PLUS at least 1 of the following:

(a) fever;
(b) seizure;
(c) focal neurological findings;
(d) CSF pleocytosis;
(e) EEG or neuroimaging findings "consistent with encephalitis"

Any person with PMS who is in their usual state of health and experiences the onset of several of the following symptoms accompanied by new focal neurological signs, or in the absence of focal neurological signs, any person whose psychiatric symptoms fail to respond to appropriate trials of psychiatric medications *may* warrant a work-up to exclude encephalitis:

-A marked change in sleep patterns;

-Symptoms characteristic of mania or depression;

-New, intense anxiety (obsessive compulsive symptoms, separation anxiety, phobias);

-Loss of previous abilities; general confusion; disorientation;

-New and unusual motor patterns, such as changes in gait, difficulty making transitions across visual borders, and loss of hand skills;

-New incontinence;

-Note that multiple recurrent episodes may occur.

*****Protocol for the Laboratory-Based Assessment of Catatonia and/or Encephalitis in Phelan-McDermid Syndrome**

Blood Tests:
Comprehensive metabolic panel (CMP)
Complete blood count (CBC) and Differential
Serum Iron, Total Iron Binding Capacity (TIBC), Iron saturation
Erythrocyte sedimentation rate (ESR)
C-reactive protein (CRP)
Vitamin B12 level
Vitamin B6 level
Vitamin D level
Folate level
Free T4 and Thyroid Stimulating Hormone
Serum homocysteine, total
Celiac serology
Fluorescent ANA
Strep titer - if not done in the past three months or history of recurrent strep throats
Anti-thyroid antibodies: Thyroglobulin Ab and Thyroid Peroxidase (TPO) Ab
[a]Serum Autoimmune Encephalopathy Evaluation (*profile + reflex tests*)

Cerebral spinal fluid studies using lumbar puncture are recommended if the patient has: (1) seizures; (2) no response to standard treatment of catatonia; (3) new onset movement disorder (e.g., choreiform movements)

Cerebral Spinal Fluid Studies:
[b]Neopterin (HPLC Fluorescence)
[a]Serum and CSF: IgG, albumin, Oligo bands (Mayo Clinic Multiple Sclerosis Panel)
[c]Routine CSF measures: gram stain, culture cell counts, glucose, and protein
[a]Spinal Autoimmune Encephalopathy Evaluation (*profile + reflex tests*)

Other studies:
Brain MRI with or without contrast (must be done prior to lumbar puncture)
Electroencephalogram (EEG) - overnight if possible or extended if indicated. Routine EEG Is adequate if clinical suspicion is low and there is no evidence of clinical seizures

[a]Mayo Clinic Laboratories - https://www.mayocliniclabs.com/
[b]MNG Laboratories - https://mnglabs.com/
[c]If any evidence of CNS infection, follow standard of care procedures

Useful References

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