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ACTA PÆDIATRICA NURTURING THE CHILD WILEY

REVIEW ARTICLE

Clinical guidance for diagnosis and management of suspected Pediatric Acute-onset Neuropsychiatric Syndrome in the Nordic countries

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Abstract

Pediatric acute-onset neuropsychiatric syndrome is a clinical concept used to describe a subgroup of children with sudden onset of psychiatric and somatic symptoms. The diagnostic term and especially management of children differs depending on the clinical setting to which they present, and the diagnosis and management is controversial. The aim of this paper is to propose a clinical guidance including homogenous diagnostic work-up and management of paediatric acute onset neuropsychiatric syndrome within the Nordic countries. The guidance is authored by a Nordic-UK working group consisting of paediatric neurologist, child psychiatrists and psychologists from Denmark, Norway, Sweden and Great Britain, and is the result of broad consensus.

Conclusion: Consensus was achieved in the collaboration on work-up and treatment of patients with paediatric acute-onset neuropsychiatric syndrome, which we hope

Abbreviations: ACE, angiotensin-converting enzyme; ADHD-RS, ADHD rating scale; ASEBA, Achenbach System of Empirically Based Assessment; BRIEF, Behaviour Rating Inventory of Executive Function; CATS, Child and Adolescent Trauma Screen; C-GAS, Children's Global Assessment Scale; CGI-I, Clinical Global Impression Improvement; CGI-S, Clinical Global Impression-Severity Scale; CNS, central nervous system; CSF, cerebrospinal fluid; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; ESR, Erythrocyte sedimentation rate; GAS, group A Beta-haemolytic streptococcus; IVIG, intravenous immunoglobulin; Kiddie-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia; M.I.N.I.-KID, Mini international neuropsychiatric interview; MOG, Myelin oligodendrocyte glycoprotein; NSAIDs, Non Steroidal Anti-Inflammatory Drugs; OCD, Obsessive Compulsive Disorder; PANDAS, Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections; PANS, Pediatric Acute onset Neuropsychiatric Syndrome; PCR, Polymerase Chain Reaction; PedsQL, Pediatric Quality of Life Inventory; SCARED, The Screen for Child Anxiety Related Disorders; TPO, thyroperoxidase; TSH, thyroid stimulating hormone; WSAS, Work and Social Adjustment Scale; YGTSS, Yale Global Tic Severity Scale.

will improve and homogenise patient care and enable future collaborative research in the field.

KEYWORDS
acute, neuropsychiatric, pediatric, recommendations, syndrome

Key Notes

- International consensus guidelines on treatment and work-up of PANS and PANDAS are most needed, due to the field being highly controversial, with medical decisions being strenuous for implicated parties.
- Guidelines were created among experts from Denmark, Norway, Sweden and the UK, and represent the first attempt to find international consensus.
- This paper will enhance quality of treatment, work-up and regional homogeneity, enabling international collaboration and research.

1 | INTRODUCTION

Pediatric Acute-onset Neuropsychiatric syndrome (PANS) is a clinical concept used to describe children with sudden onset of psychiatric and somatic symptoms.[1] The diagnostic term and especially management of children differs depending on the clinical setting to which they present, and the diagnosis is controversial at the time of writing of this guidance.

The natural course of these acute symptoms from childhood through to adulthood is not well defined. We consider 'PANS' to be an umbrella descriptive term for the symptoms that are the end result of a wide range of possible neurobiological events and pathways,[2] and there is a large overlap in symptomatology with paediatric neurodevelopmental and psychiatric disorders, especially Obsessive Compulsive Disorder (OCD).[3]

The aetiology of the presentations are often unknown and the symptoms may be due to multiple heterogeneous mechanisms.[4] A neuroinflammatory component has been proposed in PANS and its subgroup Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections (PANDAS).[5,6] However, evidence of such is lacking and the work-up often fails to support inflammation,[7–9] although, a recent paper interestingly showed higher average binding to cholinergic interneurons in patients compared with controls, but with a substantial overlap and some methodological disadvantages.[10] Immunopsychiatry is a relatively new field in psychiatry based on the idea that certain psychiatric conditions can be caused by an underlying immunological or inflammatory condition.[11,12] The evidence for the neurobiological treatment options is unclear.[13,14]

According to the health authorities in Sweden, work-up and treatment of these conditions should in general be carried out within a multi-disciplinary team and ideally a research setting.[15] This view is supported by the working group. However, clinical need and management of children presented in this very acute distressing situation, requires some consensus about appropriate management within the constraints of the current knowledge base. Timely access to some of the evidence-based psychological treatments and psychiatric input varies depending on the family's region and country of residence.

This document has been produced as a clinical consensus guidance by the Nordic Pediatric Immunopsychiatry group, a collaboration of child neurologists, psychologists and child and adolescent psychiatrists representative from the Nordic countries and the UK that work with children with acute neuropsychiatric presentations. The aim of this document is to propose a homogenous diagnostic work-up and management of PANS within the Nordic countries and thereby also enabling future collaborative research in field. The following institutions have participated in the work: Department of Child Neurology and Department of child and adolescent mental health in hospital, Oslo University Hospital, the Tourette syndrome Clinic at Herlev University Hospital in Copenhagen, the TANDeM clinic and the 'brain and spine inflammation' service at Evelina London Children's Hospital in London, Astrid Lindgren´s Children's Hospital, Karolinska University Hospital in Stockholm and the Child and Adolescent Psychiatry Research Center, Stockholm.

2 | DEFINITION OF PANS AND PANDAS

The clinical concept of PANS encompasses acute onset (within 72 h) of OCD or restricted eating and presence of at least two neuropsychiatric symptoms with similarly severe and acute onset (Table 1). The proposed diagnostic criteria for PANS [1] have never been evaluated, hence its accuracy cannot be determined. Identifying this subgroup is further complicated by the lack of biomarkers. Nonetheless, we suggest the proposed criteria to be used, since they are widely applied and alternative PANS criteria do not exist. Emphasis is put on the acute nature of the onset. We consider the concept of PANDAS as a subgroup of PANS with a timely connection to a streptococcal infection (Table 2).

TABLE 1 Clinical criteria of Paediatric Acute onset Neuropsychiatric Syndrome (PANS)[a]

1. Abrupt, dramatic onset (culmination within 72 h) of obsessive-compulsive disorder or severely restricted food intake.
2. Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of the following seven categories (see reference for full description): 1. Anxiety, 2. Emotional liability and/or depression, 3. Irritability, aggression and/or severely oppositional behaviours, 4. Behavioural (developmental) regression, 5. Deterioration in school performance, 6. Sensory or motor abnormalities and 7. Somatic signs and symptoms, including sleep disturbances, enuresis or increased urinary frequency.
3. Symptoms are not better explained by a known medical disorder, such as Sydenham's chorea, systemic lupus erythematosus, Tourette disorder or others.[1]

[a]The diagnostic work-up of patients suspected of Paediatric Acute onset Neuropsychiatric Syndrome must be comprehensive enough to assess for other relevant disorders. The nature of the co-occurring symptoms will dictate the necessary assessments, which may include MRI scan, lumbar puncture, electroencephalogram or other diagnostic tests.

TABLE 2 Diagnostic criteria for Paediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections (PANDAS)[5]

1. Presence of Obsessive Compulsive Disorder and/or a tic disorder: The patient must meet lifetime diagnostic criteria (DSM-III-R or DSM-IV) for Obsessive Compulsive Disorder or a tic disorder.
2. Paediatric onset: Symptoms of the disorder first become evident between 3 years of age and the beginning of puberty[a]
3. Episodic course of symptom severity: Clinical course is characterized by the abrupt onset of symptoms or by dramatic symptom exacerbations. [b]Symptoms usually decrease significantly between episodes and occasionally resolve completely between exacerbations.
4. Association with group A Beta-haemolytic streptococcus infection: Symptom exacerbations must be temporally related to group A Beta-haemolytic streptococcus infection, that is associated with positive throat culture and/or significantly elevated anti- group A Beta-haemolytic streptococcus antibody titres[c]
5. Association with neurological abnormalities: During symptom exacerbations, patients will have abnormal results on neurological examination. Motoric hyperactivity and adventitious movements (including choreiform movements or tics) are particularly common[d]

[a]As is generally true for rheumatic fever.

[b]Often, the onset of a specific symptom exacerbation can be assigned to a particular day or week, at which time the symptoms seemed to "explode" in severity.

[c]The temporal relationship between the group A Beta-haemolytic streptococcus (GAS) infection and the symptom exacerbation may vary over the course of the illness. In rheumatic fever, there is often a delay of 6–9 months between the last documented GAS infection and the appearance of symptoms of Sydenham's chorea; however, recrudescence follow the GAS infections at a much shorter interval, often with a time lag of only several days to a few weeks. It appears that the pattern is similar for PANDAS. It should be further noted that because fever and other stressors of illness are known to increase symptom severity, the exacerbations should not occur exclusively during the period of acute illness. Furthermore, as in Sydenham's chorea and rheumatic fever, some symptom recurrences may not be associated with documented GAS infections, so the child's lifetime pattern should be considered when making the diagnosis.

[d]Children with primary Obsessive Compulsive Disorder may have normal results on neurological examination, particularly during periods of remission. Further, the presence of chorea would suggest a diagnosis of Sydenham's chorea, rather than PANDAS. It is particularly important to make this distinction, since Sydenham's chorea is a known variant of rheumatic fever and requires prophylaxis against GAS; PANDAS does not.

3 | DIAGNOSTIC EVALUATION FOR PAEDIATRIC ACUTE NEUROPSYCHIATRIC SYMPTOMS

Pediatric acute neuropsychiatric symptoms, including PANS and PANDAS encompass both psychiatric and somatic symptoms as well as affected functioning.[16] To date, there are no valid instruments nor biomarkers which help detect and measure immunopsychiatric conditions, such as PANS and PANDAS. In addition, studies indicate profound difficulties in separating cases from non-cases using the diagnostic criteria of PANS and PANDAS.[17–19] Therefore, clinical evaluation for patients referred with acute neuropsychiatric symptoms should preferably be made by a multi-professional team consisting of at least a child neurologist, a child and adolescent psychiatrist, and a clinical psychologist. The extensive diagnostic evaluation serves to (1) identify treatable components of any of the underpinnings of the presentation, (2) explore other causes of the symptoms and (3) differentiate immunopsychiatric conditions from somatic conditions such as Sydenham's chorea, autoimmune encephalitis and systemic autoimmune disease and as far as possible from psychiatric disorders, such as non-PANS OCD, tics and Tourette syndrome.[3] PANS and PANDAS are considered as conditions of exclusion; hence it is implicit that the symptomatology is not better explained by a different label.

The work-up might differ slightly to accommodate regional differences, but should include a comprehensive family history, medical, developmental and psychiatric history covering prior and present symptoms, including symptoms related to psychiatric, neurologic, neurodevelopmental, infectious, autoimmune and rheumatic diseases. A detailed somatic and neurologic examination by a child neurologist must be performed in all patients and should include motor and cognitive abilities as well as evaluation for dyskinesia. We recommend filming the child with dyskinesia, since this enables longitudinal assessment. Dyskinesia is difficult to quantify and recognize correctly, and video filming will enhance accuracy in diagnostics enabling differentiation between tics, chorea, choreiform movements or other movement disorders, which is often challenging in these patients. This is especially important in order to assess treatment response and fluctuations. Consider genetic analyses (ranging from array CGH to exome/whole genome sequencing) depending on presentation and family history.

TABLE 3 Standard clinical work-up for patients referred with pediatric acute neuropsychiatric symptoms

Examination		Instrument/analysis	Description
Psychiatric	General[a]	Achenbach System of Empirically Based Assessment (ASEBA),[19] Mini international neuropsychiatric interview (M.I.N.I.-KID)[36] or equivalent	General assessment of psychiatric conditions
		Child and Adolescent Trauma Screen (CATS)[37]	Trauma screening
		Children's Global Assessment Scale (C-GAS)[38]	Assessment of general functioning
		Clinical Global Impression- Severity Scale (CGI-S)[39]	Clinician-rated severity of the patient's illness at time of assessment
		Paediatric Quality of Life Inventory (PedsQL)[40]	Assessment of quality of life
		Optional: Work and Social Adjustment Scale (WSAS)[26]	Measure of impaired functioning
		Optional: KIDSCREEN[41]	Assessment of subjective health and well-being
	Symptom-specific[a]	Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)[42]	OCD inventory
		The Screen for Child Anxiety Related Disorders (SCARED)[43]	Screening for child anxiety related disorders
		Yale Global Tic Severity Scale (YGTSS)[44]	Tics inventory
		Kiddie Schedule for Affective Disorders and Schizophrenia (Kiddie-SADS)[45]	Interview screening for psychiatric diagnoses
		ADHD rating scale (ADHD-RS) [46]	Questionnaire related to inattention, hyperactivity and impulsivity
		Behaviour Rating Inventory of Executive Function (BRIEF)[47]	Behaviour Rating Inventory of Executive Function
Infectious	General	Throat: Bacterial culture	
		Blood: Complete blood cell count with differential count, antistreptolysin-O and anti-deoxyribonuclease B antibodies	
	Symptom-specific	Throat: Mycoplasma Polymerase Chain Reaction (PCR)	
		Nasopharynx: Aspirate PCR panel	Common viral airway infections such as influenza virus and enterovirus
		Urine analysis and culture	
Immunological	General	Blood: Erythrocyte sedimentation rate (ESR), antiphospholipid antibodies (anticardiolipin and beta2 glycoprotein 1 antibodies), antinuclear antibodies (anti-dsDNA, ANA IIF, anti-ENA screen: Anti-SSA, anti-SSA, anti-SSB, anti-Sm, anti-Scl–70, anti-Jo1, anti-Centromer B (-CENP-B) and anti-U1-RNP), immunoglobulins subclasses, tissue-transglutaminase IgA and deamined gliadinpeptide IgG (Celiac disease), neuronal antibodies, Myelin oligodendrocyte glycoprotein (MOG) antibodies, anti-thyroperoxidase (TPO), thyroid stimulating hormone (TSH) receptor antibodies, TSH, T3 and free T4, complement C3 and C4, angiotensin-converting enzyme (ACE), Vitamin-D, Vitamin B12, ferritin, cupper, ceruloplasmin, cytokines	
Toxicological	Symptom-specific	Drug screening	
Metabolic	Symptom-specific	Urine metabolic screening	

[a]Analyses listed as "general" are recommended for all patients whereas "symptom-specific" analyses can be selected according to individual symptom presentation.

Standardized assessment scales and screening tools which are internationally recognized and nationally accredited are recommended. Table 3 lists the assessment scales, screening tools and analyses which we consider as part of the standard clinical work-up. We recommend that instruments and analyses listed as "general" are used for all patients whereas "symptom-specific" analyses can be selected according to individual symptom presentation.

For evaluation of ongoing group A Beta-haemolytic streptococcus (GAS) infection, we suggest doing a throat culture and, as per the judgement of the physician, supply with anti-GAS antibodies. Anti-GAS antibodies are unreliable indicators of ongoing infection and could reflect infection long resolved before disease onset. Hence, we recommend that titres are evaluated with care and according to local laboratory references. Throat cultures are reliable for detection of GAS-throat infection and are recommended[20] in order to identify infections, however, may reflect carrier state of streptococcus.[21]

Although results from different studies are contradictory, we do not advocate the use of the "Cunningham Panel" (Moleculara labs), since the panel has shown low positive and negative predicting values when used in a clinical setting.[22,23]

In case of profound deterioration of adaptive functioning and/or abnormal neurological signs such as focal neurological symptoms, chorea, encephalopathy or epilepsy, extended clinical work-up should be undertaken (Table 4). Pediatric consultation and/or acute referral to a paediatric clinic should be considered.

In case of relapsing/remitting symptomatology and no previous assessment, consider the extended clinical work-up as described above. Otherwise, retest with the most care, especially in the case of invasive or demanding examinations.

4 | MANAGEMENT AND FOLLOW UP

4.1 | General considerations

The decision to treat medically depends on an individual and overall evaluation and condition of the child. Immunomodulatory and anti-inflammatory treatment is controversial and experimental, and therefore, the decision to treat should always rely on a highly specialized team. Immunomodulatory treatment is regarded as auxiliary to the psychiatric treatment including psychotropic medication, according to current guidelines for child and adolescent psychiatric illnesses. We would not recommend the consideration of immunomodulatory treatment unless the children with neuropsychiatric symptoms fulfil the proposed diagnostic criteria for PANS or another identified autoimmune disorder. However, in highly specialized PANS/PANDAS clinics and in the context of research, immunomodulatory treatment might be used in selected cases. The treatment regimen must be balanced to the severity of the symptoms of the child. There remains very little robust evidence to support the recommendations of the internationally proposed medical treatment regiments, and many are adopted from treatments of well-known inflammatory or autoimmune diseases in central nervous system (CNS).[13,14,24]

If the work-up reveals a specific differential diagnosis, the treatment will follow relevant specific treatment regimens.

In general, the treatment aims at:

- Treating mental health symptoms,
- Treating ongoing verified infections and
- Treating a suspected inflammation. However, note that if clinical work-up reveals significant CNS inflammation, differential diagnoses should be considered and *the PANS diagnosis should likely be revised*.

The child must always receive direct referral to access psychological and psychiatric assessment, independent of ongoing diagnostic work-up. This is important in order to receive treatment for the psychiatric symptoms according to the evidence-based guidelines and regional psychiatric treatment regimens. Upon diagnosis, the multidisciplinary team is responsible for setting up a good treatment plan in collaboration with local child and adolescent mental health service, including psycho-education and psychotherapy dependent on the age and symptoms of the child. It is important to include the parents in the planning at an early stage, as well as providing parental psycho-education and strategies. Psychopharmacological treatment in addition to psychological management will need evaluation by the child and adolescent psychiatrist and should follow regional guidelines, depending on symptoms identified.

We recommend objectively following treatment response with clinical assessment tools as described above and include all members of the multidisciplinary team. In addition, we recommend that the clinician uses the Clinical Global Impression-Improvement (CGI-I)[25]

TABLE 4 Extended clinical work-up for patients referred with pediatric acute neuropsychiatric symptoms

Infectious	Cerebrospinal fluid	-Cell count, protein, glucose, lactate -Epstein-Barr-virus/cytomegalovirus/varicella zoster virus/ herpes simplex virus/Mycoplasma/ enterovirus/influenza virus IgG and IgM +Polymerase Chain Reaction (PCR) -*Borrelia burgdorferi* IgG and IgM (paired with serum)
Immunological	Cerebrospinal fluid	-Lumbar opening pressure -Neuronal antibodies (standard panel) -IgG index and electrophoresis for oligoclonal bands (paired with serum) -Cytokines
Radiological		Cerebral MRI including contrast: structural, diffusion and FLAIR sequences
Neuro-physiological		Standard or sleep electroencephalogram

and Pediatric Quality of Life Inventory (PedsQL)[26] following to overall grade response.

In a patient with longstanding disease it can be informative to count the annual relapses and the duration of relapses. These data can be used to describe disease course.

All treatments should be preceded by a careful discussion with the families about the potential risks.

If symptoms resolve or stabilize and one considers the immunomodulatory/antibiotic treatment options sufficiently tried, we recommend that the patient be followed up at 1, 3, 6 and 12 months. The patient should be offered the opportunity to contact the responsible hospital department in case of exacerbations. It might sometimes be relevant to repeat some of the work-up; however, invasive or very demanding tests should be ordered with care.

In the case of an exacerbation one must consider the same treatment options as described below, however, it is only rarely recommended to use intravenous immunoglobulin (IVIG) treatment for more than a total of six doses. Alternative diagnoses might be suspected later in the disease course and the treatment regimen should then be changed accordingly.

It is important to keep in mind that a lack of response to the treatment might be due to misdiagnosis, since clinical criteria for PANS are not validated. If a patient does not respond satisfactory to the auxiliary immunotherapy, the multidisciplinary team must consider exploring other treatment possibilities within the child psychiatry domain and ensure that compliance with treatments (medical and non-medical) is good.

4.2 | Specific treatments

4.2.1 | Antibiotics

We recommend treating verified or strongly suspected ongoing bacterial infections at the discretion of the clinician and following regional guidelines with a maximum duration of 14 days. We do not recommend prophylactic antibiotic treatment or tonsillectomy, since high quality data does not support an effect.[27,28] Also the use of Azithromycin[29] or Cefdinir[30] as an anti-inflammatory agent in PANS is not scientifically supported. Side effects and long-term microbial effects of the use of antibiotic should be kept in mind.

The following treatments are not recommended outside the frames of ongoing research or within highly specialized and dedicated national centres:

4.2.2 | Non Steroidal Anti-Inflammatory Drugs (NSAIDs)

If the child has persistent symptoms affecting daily functioning, and symptoms do not resolve on psychiatric care and elimination of infection alone, our clinical experience is that a treatment trial of oral NSAID (for example, Ibuprofene 10–15 mg/kg/dose, three times a day, maximum 500 mg/dose or Naproxene 10–20 mg/kg/day split in two doses, max 500 mg twice a day) might be considered after the end of antibiotic treatment up to the point of full resolution. We recommend evaluation of the effect after 4 weeks, and if positive effect, treatment might be continued up to maximum 12 weeks. The treatment should always be accompanied by oral proton pump inhibitor in standard dosing to prevent gastritis.

4.2.3 | Steroids

If the child is severely affected (Table 5) after the treatment trial with NSAID and the work-up gives strong suspicion of inflammation, we recommend monthly oral dexamethasone pulses for 3 months (each pulse being 10(–15) mg/m^2 daily in two doses on three consecutive days). Blood pressure and glycosuria should be controlled monthly. Evaluation of treatment effect is recommended after 1 and 3 months. If there is a moderate to full response of the treatment, however, the child relapses in the weeks to months after treatment is stopped, another three pulses can be considered.

4.2.4 | Intravenous immunoglobulin

If the child is severely affected (Table 5) and there is no sustainable effect of the course of steroids or if there are contraindications for treatment with steroid, treatment with IVIG might be considered after discussion in the multidisciplinary team and in national and international fora: boost 2 g/kg over 2 days and thereafter every month (1 g/kg over two consecutive days) for 3 months. Thereafter treatment response should be evaluated and if some effect, but one suspect improvement could still be achieved with ongoing therapy, treatment can be extended to a maximum of 6 months. This treatment is considered experimental and decision to treat with IVIG should always rely on a highly specialized team.

4.2.5 | Plasmapheresis, cytostatic and immunomodulatory drugs

Plasmapheresis is only indicated in patients with clinically probable or definite autoimmune encephalitis as per diagnostic and treatment

TABLE 5 Definition of severe symptoms

At least one major criteria should be present and minimum one of the minor criteria
Major criteria:
Total Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) score ≥24[43]
Reduced intake of food or fluid, leading to less urine production (less than three urinations daily) or weight loss (more than 10%)
Severe tics (Yale Global Tic Severity Scale (YGTSS) total tic severity score ≥40 but <50)[48]
Minor criteria:
School absence 50% during 1 month
Inability to participate in leisure activities or loss of social contact

guidelines published.[31] Cytostatic and other immunomodulatory drugs, such as Rituximab, are only indicated in treatment of clinical possible, probable or definite autoimmune encephalitis as per recommendations [32] and not in PANS/ PANDAS.

5 | CONCLUSION

Broad consensus was achieved in the collaboration on work-up and treatment of patients with PANS as presented in this document. We hope the work will serve as a tool to improve and homogenise patient care as well as enable future collaborative research in the field in the Nordic countries, which is most needed.

6 | DEFINITIONS

1. Responders: 30% reduction in Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) [33,34] *or* CGI-I <= 2 (1 = no illness, 7 = extremely severe) *or* Yale Global Tic Severity Scale (YGTSS) >=35% improvement/ decrease to 6/7 points[35] *or* Achenbach System of Empirically Based Assessment (ASEBA) scores from clinical range to normal range.[36]
2. Relapse: Significant worsening of neuropsychiatric symptoms after improvement: 30% increase in CY-BOCS [33,34] *or* CGI-I > 2 (1 = no illness, 7 = extremely severe) *or* YGTSS >35% reduction/decrease to below 6/7 points[35] *or* ASEBA scores from normal range to clinical range.[36]
3. Non-responders: Unchanged or worsening of core neuropsychiatric symptoms as measured using CY-BOCS, YGTSS, CGI-I and ASEBA and/or continuously fulfilling definition of severe symptoms (Table 5) and/or newly emerged significant impairment in daily functioning for longer than four days, irrespective of treatment given.

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CONFLICT OF INTEREST

The authors all declare no financial or other conflicts of interest with regard to the present work.

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