Overlap of Mood Disorders and PANS/PANDAS – Implications for Treatment

Kiki D. Chang, M.D.

Private Practice, Menlo Park, CA

Co-Founder, Stanford PANS Clinic

Disclosures of Potential Conflicts 2017-2019

Source	Consul-tant	Advisory Board	Stock or Equity >$10,000	Speakers' Bureau	Research Support	Honorarium for this talk or meeting	Expenses related to this talk or meeting
Impel Neuropharma	X	X					
Sunovion	X			X			
Octopharma	X	X					
Allergan	X						

John Bigjohn (*not his real name*)

- 14 yo boy with onset of intrusive thoughts and depression in September 2017.
- In October 2017, JB experiences racing thoughts, sleeplessness, agitation, and auditory hallucinations. Interview reveals also brief periods of mania, auditory hallucinations. After jumping out his second story window, he is hospitalized in a psychiatric unit and diagnosed with Bipolar I Disorder.
- Next follows 3 months of psychotropic trials: lithium, olanzapine, sertraline, divalproex, none of which significantly stabilize his mood.
- Upon presentation to the clinic, it is learned that prior to the depression, JB experienced intrusive thoughts and images, and met criteria for OCD.

John Bigjohn (continued)

- No infection or other event preceded the OCD. Because of the acute onset and subsequent symptoms (depression, mania, generalized anxiety, urinary urgency) he was diagnosed with PANS.
- Family history revealed that his mother had bipolar II disorder that was caused by a thyroid abnormality (autoimmune thyroiditis). Other family members had histories of depression and anxiety.
- Extensive workup, including bloodwork, MRI, and LP, was negative, except for elevated ANA, anti TPO ab, and positive mycoplasma IgM ab.

John Bigjohn (continued)

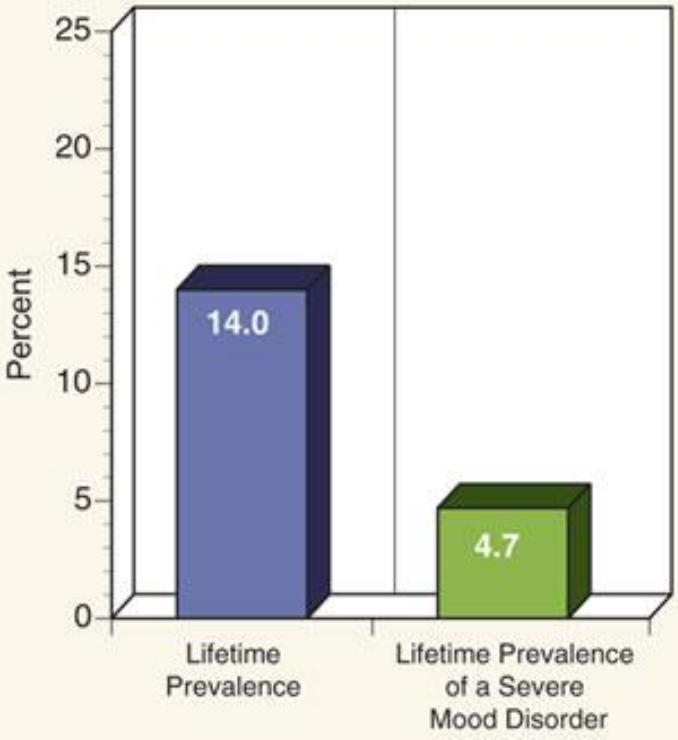
- Medcations:
  - Lithium carbonate ER 900 mg BID
  - Olanzapine 20 mg qhs
  - Divalproex ER 750 mg BID

- JB remained acutely agitated, with high anxiety, intrusive thoughts (SI), auditory hallucinations (AH), and dysphoric mood. He had 2-3 hours of initial insomnia and had gained 25 lbs in the past 3 months.

Any Mood Disorder

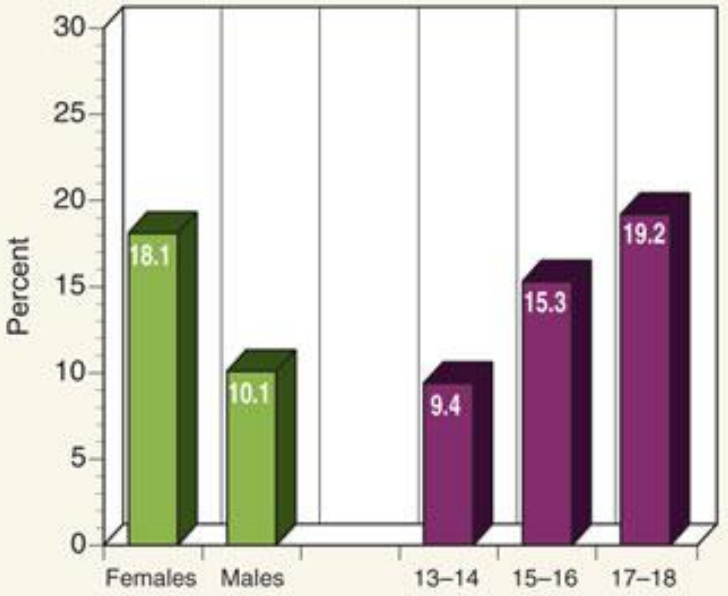
Lifetime Prevalence of 13 to 18 year olds

- **Lifetime Prevalence:** 14.0% of 13 to 18 year olds
- **Lifetime Prevalence of "Severe" Disorder:** 4.7% of 13 to 18 year olds have a "severe" mood disorder



Demographics (for lifetime prevalence)

- **Sex:** Statistically different
- **Age:** Statistically different



- **Race:** No statistically significant differences were found between non-Hispanic whites and other races

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Merikangas KR, He J, Burstein M, Swanson SA, Avenevoli S, Cui L, Benjet C, Georgiades K, Swendsen J. Lifetime prevalence of mental disorders in U.S. adolescents: Results from the National Comorbidity Study-Adolescent Supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry.* 2010 Oct;49(10):980-989.

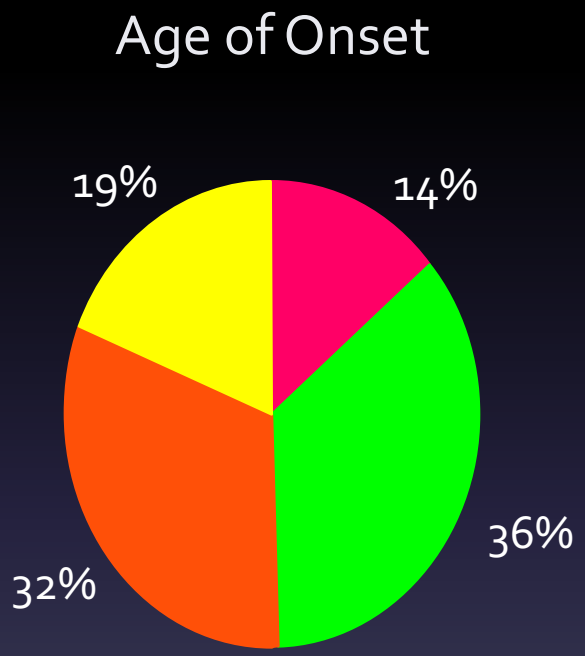
Lifetime Prevalence Rates in Adults

Diagnosis	Number of Studies	Range of Rates (%)
BD-I	19	0.0-2.4
BD-II	10	0.3-2.0
Cyclothymia	5	0.5-2.8
Bipolar spectrum disorders	10	2.6-7.8

Tohen M, Angst J (2002), In: Textbook in Psychiatric Epidemiology, Tsuang MT, Tohen M, eds. New York: Wiley-Liss, pp427-444

Age of Onset and Outcome in BD

480 Adults With Bipolar Disorder

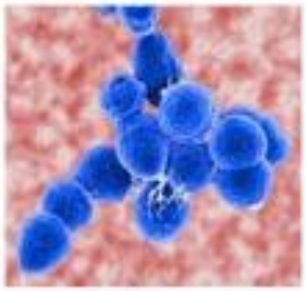


Leverich GS et al. (2007), J Pediatr 150(5):485-490

PANS

- Acute onset OCD or food restriction, and at least two of:
  1) Anxiety
  2) Emotional lability and/or depression
  3) Irritability, aggression,
  severely oppositional behaviors
  4) Behavioral (developmental) regression
  5) Deterioration in school performance
  6) Sensory or motor abnormalities
  7) Somatic signs & symptoms: sleep disturbances, enuresis or urinary frequency

- Tics present in over 50% of cases, but not part of criteria



Pathogen
(eg: GABHS, mycoplasma)

Infects host

Antibacterial antihost

Abs cross-react with basal ganglia

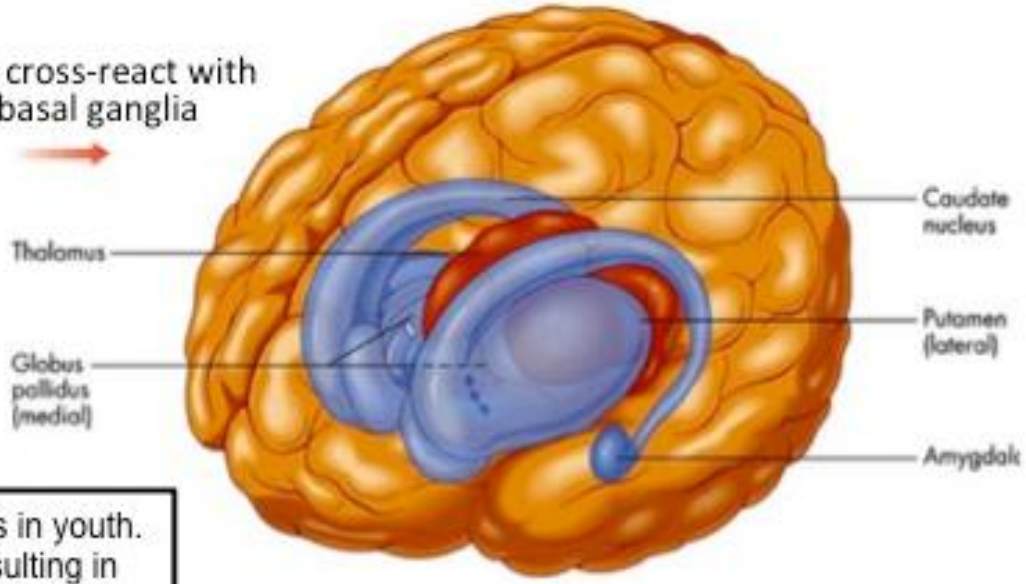
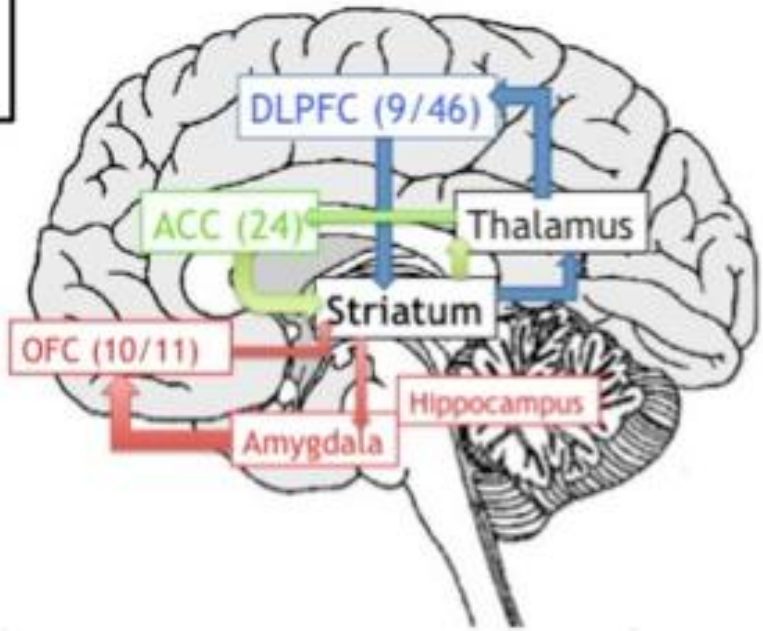


Figure 1. Proposed etiology of PANS symptoms in youth. Pathogens such as bacteria infect the child, resulting in production of antibodies that either cross-react with basal ganglia or lead to inflammation of basal ganglia in other ways. Inflammatory mechanisms allow blood brain barrier to become permeable to antibodies and complement. Inflammation in striatum leads to acute disruption of prefrontal-striato-thalamic circuits, leading to psychiatric symptoms described in youth with PANS.

Disruption of prefrontal-striato-thalamic circuits



Acute Neuropsychiatric Symptoms

Obsessions, compulsions (OCD)

Motor and vocal tics

Cognitive regression, distractibility (ADHD)

Mood dysregulation, anxiety

Moleculera Labs, Inc.

Cunningham Panel™ Testing Results

PATIENT REPORT

Submitting Physician: Jennifer Frankovich, MD
Date of Collection: 12/19/2013
Date of Receipt: 12/20/2013

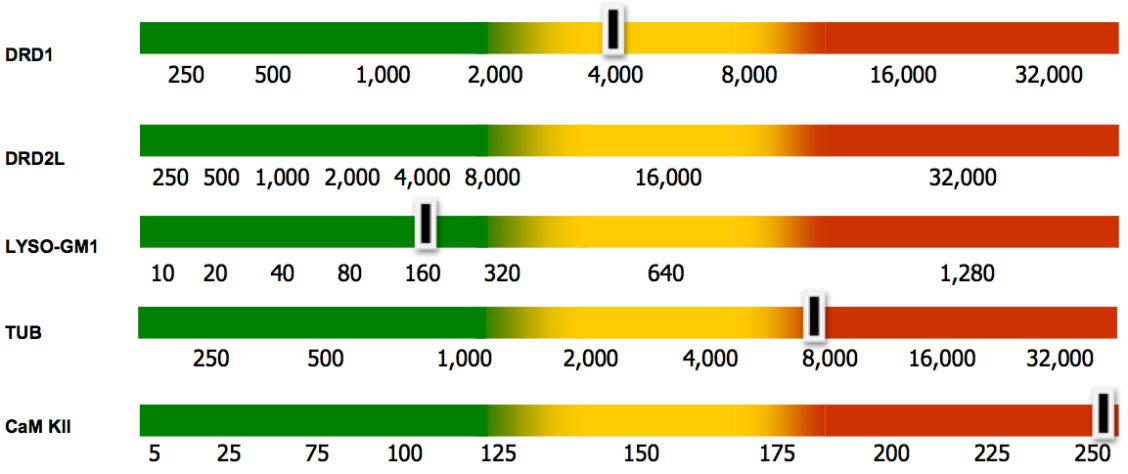
PLEASE NOTE: This report does not contain Dopamine D2L antibody results due to a temporary manufacturing reagent shortage.

LABORATORY TEST RESULTS COMPARED TO NORMAL RANGES

	Dopamine D1 (titer)	Dopamine D2 (titer)	Lysoganglioside (titer)	Tubulin (titer)	CaM Kinase II (% of baseline)
Patient Result	4,000	0	160	8,000	270
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53 to 130
Normal Mean	1,056	6,000	147	609	95

The Cunningham Panel measures human serum Immunoglobulin G (IgG) levels by Enzyme-Linked ImmunoSorbent Assay (ELISA) directed against: Dopamine D_1 Receptor (DRD1), Dopamine D_{2L} Receptor (DRD2L), Lysoganglioside-GM1 (LYSO-GM1) and Tubulin (TUB). The ELISA assays are performed in duplicate using an assay where the colorimetric intensity at a specific wavelength is directly proportional to the amount of antibody in the sample. The fifth assay of this panel is performed in triplicate and measures the specific activity of calcium/calmodulin-dependent protein kinase II (CaM KII) induced by the patient serum in cultured human neuronal cell lines compared to controls. This panel measures the level of these antibodies, and the ability of the patient's sera to stimulate CaM KII at a single point in time. Results may vary depending on the patient's condition and status, whether they are on immunosuppressive agents, corticosteroids or other immune modulatory therapy, and the length of time post treatment.

LABORATORY TEST RESULTS



PANS Research Consortium

15 PANS/PANDAS academic researchers/clinicians

May 2013 - Stanford University

- Developed expert consensus on PANS symptomatology & recommendations for diagnostic workup

April 2014 - NIMH

- Developed consensus treatment protocols

By-product of these 2 conferences →

- Strong research collaborations
  - GWAS, Exome Sequencing, Microbiome studies
- Development of multi-site clinical trials

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JCAP

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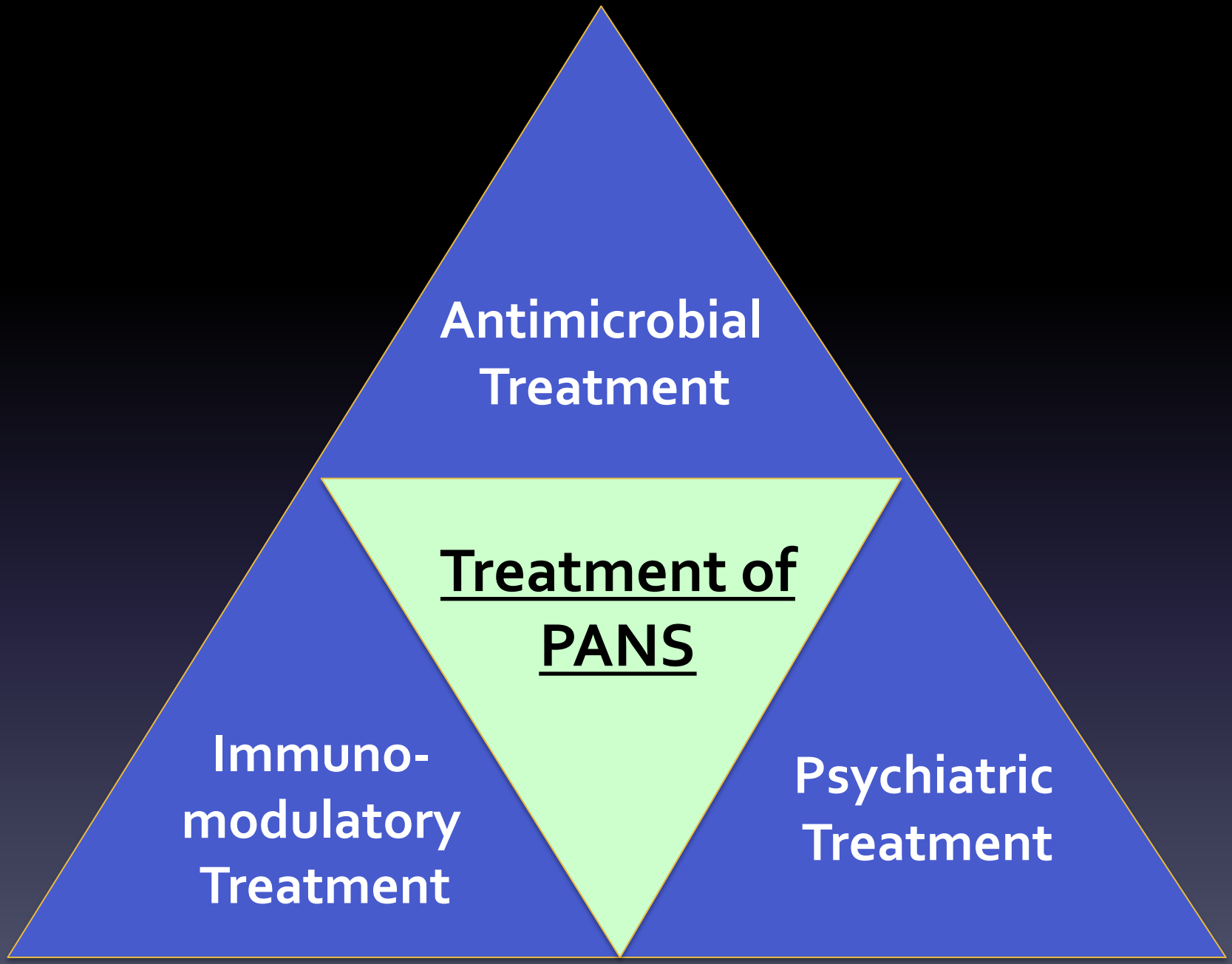
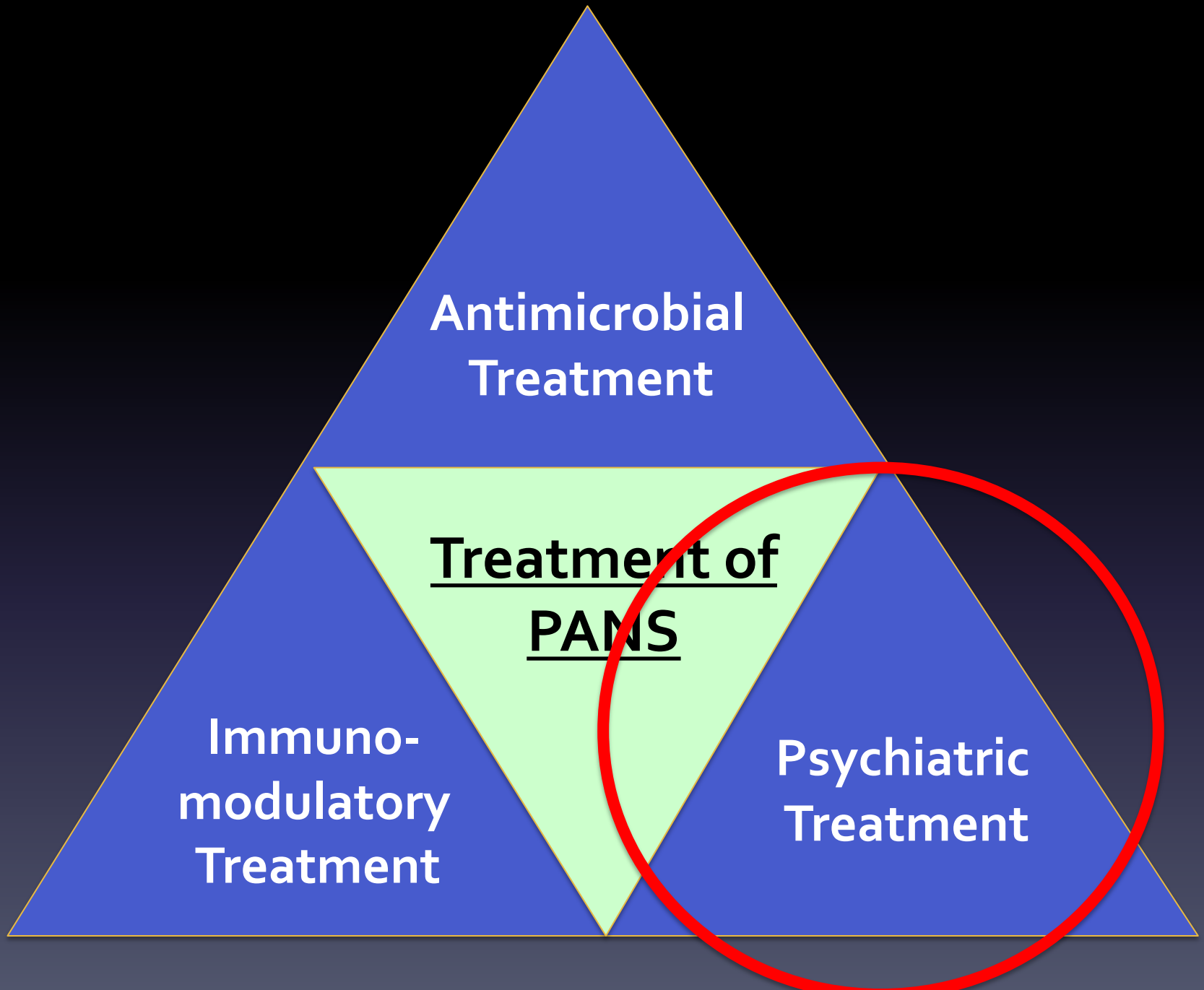

Antimicrobial Treatment
Treatment of PANS
Immuno-modulatory Treatment
Psychiatric Treatment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Pp. 1–8
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Review-Article

Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part I–Psychiatric and Behavioral Interventions

Margo Thienemann, MD,[1] Tanya Murphy, MD,[2] James Leckman, MD,[3] Richard Shaw, MD, PhD,[1] Kyle Williams, MD,[4] Cynthia Kapphahn, MD, MPH,[1] Jennifer Frankovich, MD, MPH,[1] Daniel Geller, MD,[5] Gail Bernstein, MD,[6] Kiki Chang, MD,[1] Josephine Elia, MD,[7] and Susan Swedo, MD[8]

Abstract

Objective: This article outlines the consensus guidelines for symptomatic treatment for children with Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) and Pediatric Autoimmune Neuropsychiatric Syndrome Associated with Streptococcal Infection (PANDAS).

Methods: Extant literature on behavioral, psychotherapeutic, and psychopharmacologic treatments for PANS and PANDAS was reviewed. Members of the PANS Research Consortium pooled their clinical experiences to find agreement on treatment of PANS and PANDAS symptoms.

Results: Current guidelines result from consensus among the Consortium members.

Conclusion: While underlying infectious and inflammatory processes in PANS and PANDAS patients are treated, psychiatric and behavioral symptoms need simultaneous treatment to decrease suffering and improve adherence to therapeutic intervention. Psychological, behavioral, and psychopharmacologic interventions tailored to each child's presentation can provide symptom improvement and improve functioning during both the acute and chronic stages of illness. In general, typical evidence-based interventions are appropriate for the varied symptoms of PANS and PANDAS. Individual differences in expected response to psychotropic medication may require marked reduction of initial treatment dose. Antimicrobials and immunomodulatory therapies may be indicated, as discussed in Parts 2 and 3 of this guideline series.

Overall Principles of Psychiatric Interventions in PANS

- Caregiver and patient burden may be extremely high.
- Minimizing psychiatric symptoms will reduce suffering
- Psychotherapeutic and psychotropic interventions may NOT be curative, but should be considered immediately after diagnosis
- However, proper medical intervention may lessen symptoms to a manageable level, obviating the need for psychotropics

Thienemann et al., 2017; Storch et al., 2015

Psychotherapeutic Interventions

- CBT and ERP for OCD symptoms
- Parent education and participation
- Individual and family supportive therapy
- Support groups

Thienemann et al., 2017; Storch et al., 2015

Psychiatric Treatments for OCD Symptoms

- SSRIs with most documented efficacy:
  - Fluoxetine (may be activating, so usually avoid)
  - Sertraline
  - Citalopram
  - Escitalopram
  - Fluvoxamine
- Second line: Clomipramine, atypical antipsychotics (risperidone)
- SSRIs may worsen symptoms during acute flare of PANS
- Start low, go slow

Thienemann et al., 2017; Murphy et al., 2006

Psychiatric Treatments for Tics

- **Psychotherapy:**
  - Cognitive Behavioral Intervention for Tics (CBIT)
  - Habit Reversal Training (HRT)
- **Medications:**
  - Gunafacine
  - Clonidine
  - Antipsychotics (aripiprazole, risperidone, ziprasione, pimozide, haloperidol))

Thienemann et al., 2017

Psychiatric Treatments for Irritability/Aggression

- **Psychotherapy:**
  - Dialectical Behavioral Therapy (DBT)
  - Family Therapy
- **Medications:**
  - Diphenydramine
  - Lorazepam
  - Antipsychotics (olanzapine, haloperidol)

Thienemann et al., 2017

Psychiatric Treatments for Anxiety

- **Psychotherapy:**
  - Cognitive Behavioral Therapy (CBT)
  - Mindfulness CBT
- **Medications:**
  - SSRIs
  - Benzodiazepines
  - Gabapentin

Thienemann et al., 2017

Psychiatric Treatments for Mood Symptoms

- **Psychotherapy:**
  - CBT
  - Supportive therapy
  - DBT
- **Medications:**
  - Depression: SSRIs, SNRIs, bupropion – be wary of antidepressant induced mania (family history bipolar)
  - Mania: Lithium, lamotrigine, antipsychotics
  - Psychosis: antipsychotics (NB: clozapine)

Thienemann et al., 2017

Psychiatric Treatments for Sleep

- **Psychotherapy:**
  - CBT-I
  - Sleep hygiene (diet, exercise, temperature, sound)
- **Medications:**
  - Melatonin
  - Diphenhydramine
  - Hypnotics (zolpidem)
  - Trazadone

Thienemann et al., 2017

School Accommodations

- **Youth with PANS may have:** cognitive decline, inattention, depression/anxiety, motor/vocal tics, OCD, medication side effects, urinary urgency, handwriting difficulty
- **Individualized Education Plan (IEP)** may be needed

Thienemann et al., 2017

Psychiatric Treatments - Summary

- **Psychotropics:** No empirical evidence for use. Anecdotally SSRIs may be helpful in some cases. Youth may be more sensitive to AEs , including antipsychotics (EPS). Benzodiazepines for management of acute agitation may be safest for risk/benefit considerations. Anecdotal efficacy of lithium in youth with significant mood symptoms. Clozapine with interesting potential MOA
- **Psychotherapy:** Individual (CBT) and family support essential given high stress/burden of illness. Specific therapies may target symptoms (OCD, tics, anxiety, mood, sleep)

Thienemann et al., 2017; Storch et al., 2015

JB –Medical Treatment

- JB was treated with azithromycin for 30 days with no benefit.
- Levo-thyroxine was added and titrated to 125 ug QD.
- Prednisone 1 mg/kg x 5 days = 50% improvement in intrusive thoughts and mood. Prednisone continued at 10 mg qd
- IVIG + methylprednisolone administered monthly x 6 months

JB –Psychiatric Treatment

- Clozapine substituted for olanzapine and gradually titrated to 300 mg qd. Lithium continued.
- Clonazepam 5 mg BID and gabapentin 900 mg BID added for anxiety; metformin added for metabolic control
- After 4 months, JB had 80% improvement in intrusive thoughts, 70% improvement in mood, 50% improvement in anxiety.
- JB attended IOP and received individual therapy (DBT) and group therapy

JB –Psychiatric Treatment

- After 8 months JB was able to return to school (with an IEP, gradually re-introduced), participate in activities with his friends, fly on vacation.
- Prednisone and clonazepam tapered off. JB remains on clozapine, gabapentin, lithium, metformin, and levothyroxine.
- Not currently taking antibiotics or receiving immunomodulatory treatments.

Conclusions

- PANS patients often present with mood disorders, including Depression, and Bipolar Disorder
- There may be overlaps in neurocircuitry as well as etiology in youth with mood disorders and PANS
- Psychiatric interventions should be considered immediately – particularly psychotherapy.
- Psychotropic medications may be useful on an individual basis, but caution is recommended.
- More studies needed in the role of agents such as clozapine in youth with PANS, and conversely, immunomodulators in youth with mood disorders.