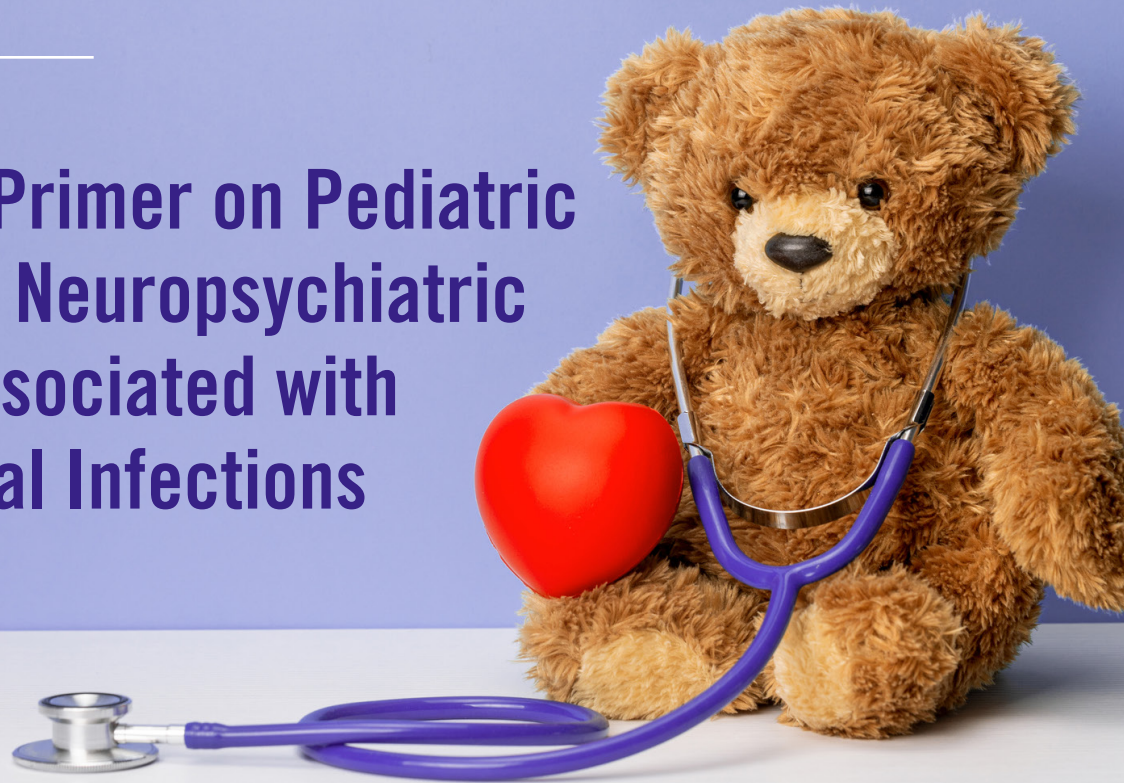


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# Pharmacist Primer on Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)

by Taylor Easey, PharmD



**S**treptococcal infections among the pediatric population are common. Group A Streptococcus (GAS), otherwise known as *Streptococcus pyogenes*, is the number one cause of bacterial sore throat for pediatric patients and accounts for up to 30% of sore throats in children.<sup>1</sup> Possible physiological complications of these infections, such as scarlet or rheumatic fever, are well known, but neuropsychiatric complications may also present. First described in the 1990s, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is a reaction to streptococcal infections that produces alterations to an individual's mood and behavior.<sup>2</sup> Symptoms of PANDAS are consistent with symptoms of obsessive-compulsive disorder (OCD) and tic disorders that develop suddenly following GAS exposure and infection. More recently, PANDAS has been recategorized as a sub-type of pediatric acute-onset neuropsychiatric syndrome (PANS).<sup>3</sup> PANS is the abrupt onset of OCD and tic disorder symptoms in pediatric patients and is non-specific in regard to origin.

Our understanding of the pathophysiology of PANDAS has evolved significantly over the past three decades,

but some aspects are still hotly contested. Similar to the Sydenham chorea that can occur with rheumatic fever, PANDAS is generally believed to be the result of autoimmune activity following a response to GAS infection. Specifically, it is thought that anti-GAS antibodies cross-target areas of the basal ganglia, a region of the brain where dysfunction has been implicated in the pathophysiology of OCD and tic disorders. Investigations have found antibody activity at neuronal targets such as lysoganglioside, tubulin, and D1 and D2 receptors.<sup>4</sup> A 2018 study found that children with clinically confirmed PANDAS possessed IgG antibodies with higher binding affinity to cholinergic interneurons compared to the binding affinity in matched healthy subjects.<sup>5</sup> Additionally, the authors of this study observed an improvement in PANDAS symptoms following administration of intravenous immunoglobulin (IVIG). Children in particular are believed to be prone to the disorder due to their frequent exposure to streptococcal bacteria and their robust immune responses to them.

The first study to characterize the disease also provided five working diagnostic criteria that are still used today. Those criteria are: presence of OCD or tic disorder, onset of age of between 3 and 12

years old, rapid onset of symptoms and an episodic pattern, temporal association with GAS infection, and presence of neurological abnormalities.<sup>2</sup> The abrupt onset is often the most striking feature and what many patients and parents will note most. Some of the most common symptoms are irritability; obsessive-compulsive thoughts and behaviors such as frequent hand washing; difficulty sleeping; and abnormal or involuntary motor movements. Although not exclusive to this patient population, many PANDAS patients have pre-existing psychiatric conditions, which can be exacerbated as a result of their PANDAS. Other common comorbid symptoms include depression, difficulty sleeping, and ADHD-like symptoms. As far as the timing of onset is concerned, research has found that most patients will become symptomatic within 7 to 14 days following the beginning of infection. Although overlap of PANDAS symptoms and active infection is the typical presentation, there remains the possibility for patients to develop neuropsychiatric symptoms after clearing the infection.<sup>6</sup> It is also possible for patients to have otherwise asymptomatic infections, in which case, anti-streptococcal titers can be useful to aid diagnosis. Symptoms of PANDAS appear suddenly, over 24 to 48 hours, and slowly subside over the course of weeks to months.

Recurrences are common and follow the same pattern as the initial episode, with subsequent GAS infections being associated with new recurrences.<sup>7</sup> Early patient characterization of PANDAS reported that the frequency of tic disorder symptoms appeared to equal the frequency of OCD symptoms, but more recent literature has suggested that OCD-like symptoms may be more prevalent.<sup>2,8</sup> The demographics seen with PANDAS are similar to what would be found in patients with more common OCD and tic disorders, including a predominance in males and age averaging 6 to 7 years old upon presentation.

Optimal treatment of PANDAS remains to be determined, but numerous interventions have been investigated with varying levels of success. The clearest recommendation is that patients with GAS infections receive appropriate antibiotic therapy. There are no randomized controlled trials regarding antibiotic selection for PANDAS, but prospective descriptive research has shown that standard antistreptococcal antibiotics are effective at resolving neuropsychiatric symptoms.<sup>6</sup> Preferred antibiotics are penicillin and amoxicillin, but in the case of a penicillin allergy, a cephalosporin or azithromycin can be used.<sup>9</sup> Conventional treatment used for typical OCD and tic disorders, such as cognitive behavioral therapy (CBT) and psychopharmacotherapy, has been shown to be effective. PANDAS-related OCD in particular was found to respond well to CBT.<sup>10</sup> Selective serotonin reuptake inhibitors (SSRIs) can be considered for children with persistent OCD symptoms, but extra care must be given to monitor for paradoxical activation, which may be more common in this population.<sup>11</sup> For this reason, SSRIs should be initiated at low doses and titrated carefully. Alpha-2 adrenergic agonists such as clonidine or guanfacine may be useful in the management of particularly bothersome tics. Use of other treatments, including immunomodulatory agents, non-steroidal anti-inflammatory drugs (NSAIDs), and prophylactic or suppressive antibiotics, remain controversial. As mentioned earlier, IVIG as part of an investigation into PANDAS pathophysiology was found to improve symptoms.<sup>5</sup> However, results from randomized controlled trials are mixed with one early 1999 study showing benefit

**TABLE 1. All About PANDAS**

<b>Pathophysiology</b>	<ul style="list-style-type: none"> <li>• Autoimmune activity in the basal ganglia and other brain regions is activated by streptococcal infection</li> </ul>
<b>Characteristics</b>	<ul style="list-style-type: none"> <li>• Symptoms of PANDAS are most consistent with OCD and tic disorders <ul style="list-style-type: none"> <li>» Irritability, restlessness, insomnia, and anxiety are also common</li> </ul> </li> <li>• Typically begins 7-14 days after onset of streptococcal infection</li> <li>• Recurrence upon reinfection or re-exposure is common</li> </ul>
<b>Treatment</b>	<ul style="list-style-type: none"> <li>• Antibiotics are the standard treatment and have the greatest level of evidence</li> <li>• SSRIs and alpha-2 adrenergic agonists can be useful for OCD and tic specific symptoms</li> <li>• Other treatment modalities, such as NSAIDs, corticosteroids, and IVIG, have had mixed results</li> <li>• Antibiotic prophylaxis is not routinely recommended and supporting evidence is low</li> </ul>
<b>Role of the Pharmacist</b>	<ul style="list-style-type: none"> <li>• Provide guidance and support to patients and parents</li> <li>• Offer test and treat services in allowed states</li> <li>• Spread awareness to other healthcare providers</li> </ul>

and a more recent 2016 study showing no advantage over placebo.<sup>12,13</sup> Both of these studies included approximately 30 patients and used the Children’s Yale-Brown Obsessive Compulsive Scale and Clinical Global Impressions-Improvement ratings to assess for improvement in OCD and tic related symptoms. Both trials also used the same treatment of 1mg/kg IVIG for two days. Corticosteroids, such as prednisone, and NSAIDs have shown some promise in retrospective studies, but higher-quality, more robust trials are needed.<sup>14,15</sup> There is at least one ongoing clinical trial assessing the effect of naproxen on PANDAS symptoms. Lastly, antibiotic prophylaxis has been proposed, but evidence supporting the use of this treatment modality for the prevention of GAS infections is conflicting.<sup>16,17</sup> One 1999 trial that followed 37 patients for eight months did not find any difference between prophylactic penicillin and placebo but another 2005 trial of 23 patients followed for one year found patients treated with prophylactic penicillin or azithromycin had lower rates of recurrent PANDAS.

Pharmacists have the ability to be important members of the treatment team when managing PANDAS. Given that knowledge of PANDAS is rare, even among healthcare providers, pharmacists can help provide resources or guidance on treatment. Community pharmacists are in the unique position to help parents recognize some of the hallmark signs and

symptoms of PANDAS and refer patients for formal work-up and treatment. As mentioned earlier, one of the most remarked upon features by parents is the very abrupt onset of behavioral problems. Picking up on these behavioral changes can help expedite treatment and ultimately lead to resolution of symptoms. Additionally, more and more states are allowing pharmacists to participate in “test and treat,” either through direct prescriptive authority provided by the state or through a collaborative practice agreement. This allows for pharmacists to administer point-of-care tests for select infectious diseases and prescribe appropriate antimicrobials.<sup>18</sup> These services can help expand access to care and provide quick treatment for patients in need.

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