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Treatment of PANDAS and PANS: a systematic review

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ABSTRACT

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) are a subtype of acute-onset obsessive-compulsive disorder (OCD) thought to be caused by an autoimmune response to group A streptococcal infection. Based on this proposed pathophysiology, alternative treatments for acute-onset OCD have been introduced, including antibiotics and immunomodulatory interventions. However, the literature on treatment of PANDAS is diverse, and clinical consensus regarding optimal treatment strategy is lacking. We conducted a systematic review of articles in PubMed, Cochrane Library, and Scopus that addressed treatment for PANDAS and related disorders. Twelve research studies involving the following treatments met inclusion criteria: penicillin, azithromycin, intravenous immunoglobulin, plasma exchange, tonsillectomy, cognitive behavior therapy, NSAID and corticosteroids. In addition, 65 case reports in which patients received immunomodulatory treatments, antibiotics, and/or psychotropics were identified. We determined that rigorously conducted research regarding treatments for PANDAS is scarce, and published studies have a high risk of bias. Further research is needed in which promising treatment strategies for PANDAS and other variants of OCD with proposed autoimmune etiology are rigorously investigated.

1. Introduction

1.1. Potential autoimmune etiology of acute-onset OCD

The first 50 cases of a subtype of pediatric obsessive compulsive disorder (OCD) with acute onset of symptoms and episodic course were described by Swedo et al. (1998); these authors coined the term PANDAS, or “pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.” OCD is characterized by obsessive thoughts and compulsive rituals. OCD has an estimated lifetime prevalence of 2.3% and is associated with substantial comorbidity (Ruscio et al., 2010). Among children, OCD is a common psychiatric illness (Stewart et al., 2004), and early-onset OCD is associated with high familial load (Browne et al., 2015) and often with tic disorders (do Rosario-Campos et al., 2005). The etiology of OCD is unknown, but some evidence suggests that certain cases of OCD may be autoimmune in nature or triggered by streptococcal infection (Perez-Vigil et al., 2016; Orlovskaya et al., 2017).

The pathogenesis of PANDAS is thought to be similar to that of Sydenham’s chorea, which is also triggered by streptococcal infections (Swedo et al., 1989; Swedo et al., 1993; Swedo et al., 1998). Specifically, antibodies raised in response to infection with group A β -hemolytic *Streptococcus* (GABHS) cross-react with autoantigens in the basal ganglia and cortical structures and yield the motor and behavioral abnormalities associated with PANDAS (Aron et al., 1965; Giedd et al., 1995; Husby et al., 1976).

Patients with a clinical picture similar to PANDAS but with a non-streptococcal infectious trigger are described as having PITAND, or “pediatric infection-triggered autoimmune neuropsychiatric disorders” (Allen et al., 1995). The term “childhood acute neuropsychiatric symptoms (CANS)” was proposed as a broader term for patients with PANDAS symptoms unaccompanied by GABHS infection (Singer et al., 2012). The term “pediatric acute-onset neuropsychiatric syndrome” (PANS) was suggested to describe children with acute-onset OCD or eating disorders in combination with multiple psychiatric or neurological symptoms (Swedo et al., 2012). Diagnostic criteria for PANDAS,

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Table 1
Diagnostic criteria for PANDAS, PANS and CANS.

PANDAS (Swedo et al., 1998)	PANS (Swedo et al., 2012)	CANS (Singer et al., 2012)	PITAND (Allen et al., 1995)
OCD and/or tic syndrome (DSM-IV) Prepubertal symptom onset Episodic course, abrupt onset of symptoms or of symptom exacerbation Association with GABHS infection (positive throat culture and/or elevated anti-GABHS antibody titers) Association with neurological abnormalities	Abrupt, dramatic onset of OCD or severely restricted food intake Additional neuropsychiatric symptoms, ≥ 2 of the following: - Anxiety - Emotional lability and/or depression - Irritability, aggression and/or severely oppositional behavior - Behavioral regression - Deterioration in school performance - Sensory or motor abnormalities - Somatic symptoms, including sleep disturbances, enuresis or urinary frequency - Symptoms not better explained by neurological or medical disorder	Acute dramatic onset of symptoms Primary criterion: OCD Secondary criterion: tics, dysgraphia, hyperactivity, clumsiness, anxiety, psychosis, emotional lability, developmental regression, sensitivity to sensory stimuli Mono/polyphasic course	Pediatric onset Lifetime OCD or tic disorder Sudden onset, or a pattern of sudden, recurrent, clinically significant symptom exacerbations and remissions Exacerbations not exclusively related to stress or illness. Un treated exacerbations last at least 4 weeks. Exacerbations severe enough to suggest treatment modification. During OCD and/or tic exacerbations, the majority of patients will have an abnormal neurological examination, frequently with adventitious movements Evidence of an antecedent or concomitant infection. Patients may or may not continue to have clinically significant symptoms between episodes of OCD and/or tic disorder.

PANDAS: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

PANS: Pediatric acute-onset neuropsychiatric syndrome.

CANS: Childhood acute neuropsychiatric symptoms.

PITAND: Pediatric Infection-triggered autoimmune neuropsychiatric disorders.

PANS, CANS, and PITAND are summarized in Table 1. All of these clinical entities involve recurrent episodic acute exacerbations of tics or obsessive-compulsive symptoms along with neuropsychiatric or neurological symptoms. All of the definitions also underscore the possible autoimmune etiology of these disorders, and the difference between these cases and cases of non-autoimmune OCD. However, the diagnostic criteria are based not on signs of autoimmunity, but on clinical presentation and psychiatric symptoms.

Diagnosis of PANDAS and related disorders is challenging, owing to the wide variation in the presentation of symptoms and course. The symptomatology of these disorders may overlap with almost any other psychiatric condition, thereby complicating differential diagnosis. The patient's family may observe a brief period of subtle obsessive-compulsive symptoms that emerges gradually and regresses spontaneously. Families often note that these behaviors would have been forgotten if not for the sudden and dramatic subsequent onset of symptoms.

1.2. Treatments

Cognitive behavior therapy (CBT) including exposure and response prevention (ERP), and selective serotonin reuptake inhibitors (SSRIs) are the primary evidence-based therapies for OCD (Team POTSP, 2004). Approximately 50%–80% of patients with OCD respond to these treatments (Grant, 2014), but a substantial proportion of patients subsequently experience lifelong treatment resistance (Grant, 2014). Behavioral interventions, such as habit reversal training, and psychopharmacological treatment strategies are the recommended treatments for tic disorders (Hollis et al., 2016). In contrast to the recommended treatments, when an infectious or autoimmune etiology is suspected, these treatments for OCD and tics may be insufficient.

Supplemental or alternative treatment options when suspecting PANDAS include antibiotics or tonsillectomy to treat and/or prevent GABHS infection (Pavone et al., 2014). To suppress the immune system in patients with putative autoimmune-based OCD corticosteroids (Frankovich et al., 2015), therapeutic plasma exchange (TPE) (Latimer et al., 2015; Perlmutter et al., 1999), intravenous immunoglobulin (IVIG) (Perlmutter et al., 1999), or anti-CD20 monoclonal antibodies (rituximab) (Frankovich et al., 2015) have been given. Administration of nonsteroidal anti-inflammatory drugs (NSAIDs) to ameliorate psychiatric symptoms of PANDAS and PANS also has been suggested and is

in line with the autoimmune etiology theory (Chiarello et al., 2017). Recently, a consortium of clinicians and researchers have authored three consensus papers regarding treatment of PANDAS and PANS using psychiatric and behavioral interventions (Thienemann et al., 2017), immunomodulatory therapies (Frankovich et al., 2017) and antibiotics (Cooperstock et al., 2017). These guidelines of the clinical management of PANDAS and PANS are based on clinical experience and on research, and support use of immunomodulatory treatment and antibiotics, beside standard psychiatric treatment.

2. Objective

Our objectives were to evaluate studies in which patients with PANDAS, PANS, CANS, or PITAND were given treatment and to determine whether there was sufficient evidence to recommend adoption of specific therapies for these patients.

3. Methods

3.1. Information sources and search strategy

This study was designed as a systematic review of research studies and case reports in which patients with PANDAS, PANS, PITAND, or CANS received treatment. The study was carried out in accordance with PRISMA guidelines (Moher et al., 2009). PubMed, Cochrane Library, and Scopus databases were searched from the earliest start date available for the databases to February 15, 2017 (Scopus), February 20, 2017 (Cochrane Library), or February 20, 2017 (PubMed). Additional searches of PubMed, Scopus, and Cochrane Library were conducted on May 31, 2017 and October 27, 2017. No MeSH (i.e., medical subject headings) terms were found for PANDAS, PANS, PITAND or CANS. Therefore, the following free text search words were used: (1) “pediatric autoimmune neuropsychiatric disorders associated with strep*.” (2) “pediatric acute-onset neuropsychiatric syndrome.” (3) “childhood acute neuropsychiatric symptoms.” and (4) “pediatric infection-triggered autoimmune neuropsychiatric disorders.” In Scopus, the document type was set to “article.” No filters were applied in searches of Cochrane Library or PubMed.

3.2. Eligibility criteria and study selection

Article abstracts were screened by either of the investigators (E.H. or S.S.) for relevant content, and articles with empirical data regarding treatments were accessed for further review. Articles were included that (1) applied diagnostic criteria for PANDAS, PANS, CANS, or PITAND; (2) presented treatment and outcome data; and (3) were written in English. Articles then were categorized as a study or a case report. A study was defined as an analytic article of defined treatments with prospectively defined outcome measures. A case report was defined as a retrospective presentation of treatment outcomes presented in a descriptive article. Case report articles could contain data from single or multiple cases.

3.2.1. Quality assessment of treatment-related studies

All articles defined as studies were assessed for possible bias using standardized forms prepared by the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU, 2014a,b). Types of bias assessed included selection bias, performance bias, detection bias, attrition, reporting bias and other bias. Following evaluation, each study was categorized as having an overall low, moderate, or high risk of bias. The overall risk was determined to be the highest score given at least twice in the scoring tool.

3.2.2. Data extraction

The full texts of all included studies were read, and the following data were extracted: study design, number of participants, diagnosis, treatment given, control condition, main outcome measure, time to follow-up, and main results. Full texts of included case reports also were read, and the following data were extracted: number of cases, gender, age, diagnosis, presence of tics and OCD, OCD subtype, presence of aggression, treatments, treatment outcome, follow-up time, and follow-up outcome. Treatment outcomes were rated on a 4-point scale, in which 1 indicated no improvement, and 4 indicated that the authors stated in the text that symptoms were in “full remission.” or “completely resolved.” Two investigators (E.H. and S.S.) independently read and extracted data from all articles.

4. Results

4.1. Available literature

The literature searches returned 234 articles from PubMed, 15 articles from Cochrane Library, and 837 articles from Scopus. After removing duplicates, 973 articles were compiled for abstract screening. A total of 811 articles failed to meet inclusion criteria, and 162 articles were included for full-text review. Seventy-seven of the 162 articles met inclusion criteria after full-text review. Of these, 11 were treatment studies, one was a survey study and 65 were case series or case reports. Our systematic approach for selection of articles is summarized in Fig. 1.

4.1.1. Treatment studies

Of the 11 treatment studies, 4 were double-blind randomized controlled studies (RCTs) (Murphy et al., 2017; Perlmutter et al., 1999; Snider et al., 2005; Williams et al., 2016), one was a cross-over trial (Garvey et al., 1999), 2 were open trials (Nadeau et al., 2015; Storch et al., 2006) and 4 were observational studies (Brown et al., 2017a,b; Murphy et al., 2013; Pavone et al., 2014). The 11 studies included a total of 529 patients; the 4 RCTs included a total of 90 patients. At least two studies were based on the same study population (Brown et al., 2017a,b). Treatments evaluated in the 11 studies were penicillin, azithromycin, IVIG, TPE, tonsillectomy, CBT, corticosteroids and NSAID. In addition to the 11 treatment studies, one large survey study was also included. The survey study was based on parent reports of 698 cases with PANS, reporting treatment frequency and effect of antibiotics,

anti-inflammatory medications, IVIG, TPE, psychotropic medications, psychotherapy and complementary and alternative medicines (Calaprice et al., 2017). All studies are listed in Table 2.

4.1.1.1. Quality assessment of the treatment studies. Eleven of the 12 studies had a high or moderate risk of bias. Three treatment studies had no control group. Randomization was inadequately described in 2 of the 4 RCTs. Only 1 study—in which IVIG was evaluated (Williams et al., 2016)—had a low overall risk of bias. The eleven treatment studies had small sample sizes, ranging from 7 to 37 participants in the RCTs, cross over study and open trials; and 43 to 120 participants in the 4 observational studies. The survey study had a larger sample ($n = 698$), but these participants were self-selected and the outcomes self-reported, resulting in a high risk of bias (Calaprice et al., 2017). In Table 3, results of our bias assessment are presented.

4.1.2. Case reports

The 65 case reports involved a total of 240 patients. In 6 of the articles, the authors presented data in summarized form as case series. Treatments noted in the case reports included antibiotics and tonsillectomy to address the infectious agent; IVIG, TPE, corticosteroids, NSAID and anti-CD20 monoclonal antibodies for immunomodulation; and psychotropic medications and CBT for psychiatric symptoms. In the 6 case series, the authors evaluated the response to antibiotics (Murphy and Pichichero, 2002), antibiotics in combination with tonsillectomy (Demesh et al., 2015), TPE alone or in combination with antibiotics (Beşiroğlu et al., 2007; Latimer et al., 2015), treatment of sinusitis (Mahony et al., 2017) and NSAID (Spartz et al., 2017). Our systematic review of case reports is presented in Supplementary Table S1.

4.2. Treatments for PANS, PANDAS, PITAND, and CANS

4.2.1. Antibiotics

Various antibiotics have been used to treat patients with PANDAS and related conditions. These include penicillin, macrolides (e.g., azithromycin), and cephalosporins (e.g., cefdinir). In 2 studies, the prophylactic effect of antibiotics on PANDAS was determined (Snider et al., 2005; Garvey et al., 1999). In another study, the effect of antibiotics on PANS was assessed (Murphy et al., 2017). Garvey et al. (1999) found that penicillin prophylaxis was not superior to placebo to prevent streptococcal infection and thereby avoid exacerbation of psychiatric symptoms, nor did it lead to fewer symptom exacerbations. Because this was a prophylaxis study aimed at preventing exacerbations rather than treating existing symptoms the results of this study should not be interpreted as a failure of penicillin to treat current PANDAS symptoms. Snider et al. (2005) evaluated frequency of streptococcal infections and psychiatric exacerbations as outcome measures in a trial of penicillin versus azithromycin; a placebo arm was not included in this study. The authors demonstrated that the treatments were equally effective in preventing exacerbations, but the absence of a placebo arm limited the conclusions that could be drawn from the study.

Murphy et al. (2017) conducted a study in which children with PANS and current psychiatric symptoms were treated with azithromycin or placebo. These authors found no significant treatment effect of azithromycin based on the CY-BOCS, but this treatment produced a modest effect as assessed by CGI-S (Guy and ECDEU, 1976), a seven point global measure of functioning which may be more sensitive to change than CY-BOCS. In the study by Snider et al. (2005), 500 mg of azithromycin was given per week as prophylaxis for PANDAS; in the study by Murphy et al. (2017), the dose was much higher (10 mg/kg up to 500 mg per day; i.e., 3500 mg per week).

In the large survey study, 97% of 698 patients reported that they had been treated with antibiotics for PANS-associated infections (Calaprice et al., 2017). The most commonly received antibiotics were amoxicillin, azithromycin and amoxicillin-clavulanate. Out of 235 patients receiving amoxicillin, 20% reported treatment to be “very

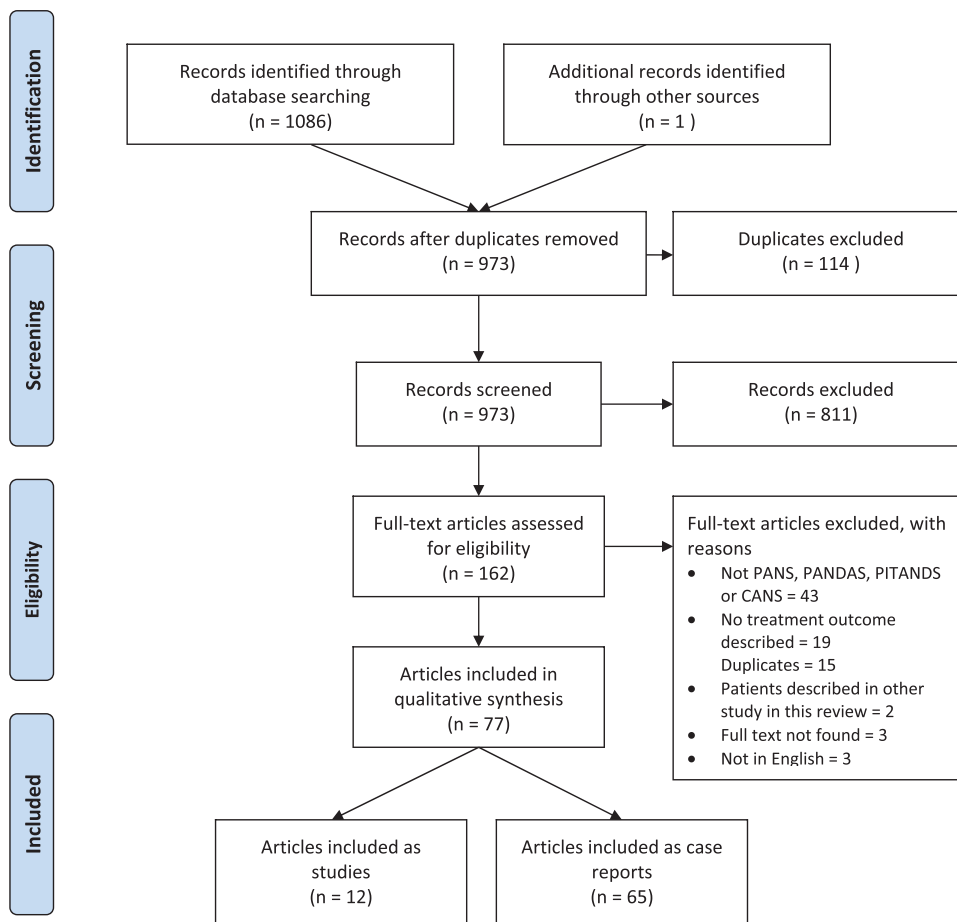


Fig. 1. Flowchart of literature search and inclusion of articles. The flowchart follows the PRISMA guidelines.

effective” whereas 28% chose to discontinue treatment due to lack of efficacy. Corresponding proportions for azithromycin ($n = 216$) were 26% reported as “very effective” and 23% discontinuation due to lack of efficacy. 30% of patients treated with amoxicillin-clavulanate ($n = 184$) reported the treatment to be “very effective”, and 22% chose to discontinue due to lack of efficacy.

In contrast to the modest effects described in the 3 treatment studies (Brown et al., 2017a,b; Murphy et al., 2013), results of several case reports indicate that antibiotics have a positive effect on psychiatric symptoms of PANDAS and related disorders. We have identified case reports comprising a total of 130 patients treated with antibiotics. Twenty-seven patients were treated only with antibiotics, and 5 of these patients indicated complete remission of symptoms after treatment. In general, the case reports varied in terms of type of antibiotics given and dosage. Supplementary Table S2 summarizes data from the case reports involving antibiotics as treatment.

To summarize, antibiotics have been described in 130 case reports. Moreover, antibiotics have been reported to be effective in 8–52% of treated cases in a large survey study, depending on dose and type. Antibiotics have been tested in two RCTs and one cross-over study with mixed results and outcome measures. Therefore, the evidence for using antibiotics for PANS, PANDAS, PITAND and CANS is inconclusive.

4.2.2. Therapeutic plasma exchange

One study of TPE for treatment of PANDAS was identified in the literature review. In this study, the authors examined the effect of TPE in 10 children with PANDAS in an open-label placebo-controlled setting (Perlmutter et al., 1999). (A third arm in this study was double-blind treatment with IVIG, described herein in Section 4.2.3 Intravenous immunoglobulin.) The 3 treatments (TPE, IVIG, and placebo-IVIG) were compared at the 1-month follow-up visit. The authors found a striking

improvement in the TPE group compared to placebo, and symptoms remained improved from baseline on all measures at the 1-year open follow-up assessment.

In the survey study only 25 out of 698 patients received TPE. 15 of these reported a positive response but only 6 patients experienced an enduring positive effect (Calaprice et al., 2017).

In addition to the above studies a total of 7 case reports and case series comprising 45 patients treated with TPE were identified in the literature review.

Latimer et al. (2015) conducted a retrospective case series of all 40 patients treated with TPE on psychiatric indication at Georgetown University Hospital; 5 of these patients were lost to follow-up. Of the remaining 35 patients, an average duration of 4.2 years of illness was observed, and all had been treated with antibiotics without improvement. Five patients were non-responders to oral corticosteroids and 17 to IVIG. After TPE, a 78% reduction in symptom severity was reported during follow-up (6 months to 5.4 years post-treatment). Notably, improvement was not associated with duration of illness (Latimer et al. 2015).

Another case series included 4 adults with both tics and OCD (Beşiroğlu et al., 2007). Symptoms were assessed prospectively and in a systematic manner. All patients had been treated previously with SSRIs and neuroleptics without favorable results. Following TPE, these patients experienced remarkably positive effects, with a mean reduction in Y-BOCS score of 20 points. All patients also had improvement in tics.

In 1 case report, a patient with PANDAS had symptoms “fully resolved” with TPE treatment (Elia et al., 2005). One case was treated with combination of TPE and rituximab, following treatment with both corticosteroids with mycophenolate mofetil and IVIG, resulting in symptom remission (Frankovich et al., 2015). Results described in 2 other case reports were modest (Giedd et al., 1996; Sadhasivam and

Table 2
Study design, study population, follow-up, intervention and outcome measures of included studies.

First author	Study design, follow-up (m), treatment type	Study population (age)	Intervention S = subject, C = control	Outcome measures	Results
Garvey et al. (1999)	Balanced cross-over study, double-blinded (8) antibiotics	37 children meeting criteria for PANDAS (9.61 ± 2.59 yrs.)	S: PcV (250 mg) twice daily during 4 months C: Placebo (250 mg) twice daily during 4 months	Symptom severity using YGTSS, CY-BOCS and NIMHRS, Number of streptococcal infections	PcV = Placebo
Snider et al. (2005)	RCT, double-blinded (12), antibiotics	23 children meeting criteria for PANDAS (7.9 ± 1.3 yrs.)	S: Azithromycin (250 mg) twice daily 1 d/week, placebo capsule 6 d/week (n = 12) during 12 months C: S: PcV (250 mg) twice daily 1 d/week, placebo capsule 6 d/week (n = 11) during 12 months	Primary: number of GAS infections Secondary: number of neuropsychiatric exacerbations	Azithromycin = PcV
Murphy et al. (2017)	RCT, double-blinded (1), antibiotics	31 children meeting criteria for PANS (mean 8.26 yrs.)	S: Azithromycin (10mg/kg up to 500mg per day) and probiotic for 4 weeks (n = 17) C: Placebo and probiotic for 4 weeks (n = 14) S: IVIG (1g/kg/d for 2 d) (n = 9) TPE (1 plasma volume/procedure, 5 or 6 procedures) (n = 10) C: saline solution (1g/kg/d for 2 d) (n = 10) Placebo non-responders offered IVIG	Primary: Severity of OCD using CGI-S OCD and CY-BOCS Secondary: CGI-I, C-GAS, YGTSS, SNAP-IV, CALS, SCARED Severity of neuropsychiatric symptoms using TSURS, CY-BOCS, CGI-S, GAS, and NIMHRS	Azithromycin > Placebo. However, effects were small and there was no reduction in CY-BOCS, only in OCD-CGIS
Perlmutter et al. (1999)	RCT, double-blinded to IVIG- and placebo group, not blinded to TPE group (12), IVIG and TPE	29 children meeting criteria for PANDAS (TPE 10.3 ± 2.8 yrs.; IVIG 9.1 ± 2.4 yrs.; placebo 9.4 ± 0.8 yrs.)	S: IVIG (1 gm/kg/d on 2 consecutive days, total dose 2 gm/kg) (n = 17) C: IV placebo (n = 18) Non-responders to blinded infusion were offered open-label IVIG at week 6 (n = 24)	Primary: CY-BOCS and CGI-I	IVIG = Placebo
Williams et al. (2016)	RCT, double-blinded (6), IVIG	35 children meeting criteria for PANDAS (IVIG 8.99 ± 2.37; placebo 9.61 ± 2.32 yrs.)	S: Previous tonsillectomy and/or adenoidectomy (n = 32) C: No surgery (n = 76)	Symptom severity using CY-BOCS and YGTSS	Tonsillectomies and Adenoidectomies = No surgery
Murphy et al. (2013)	Observational study, prospectively assessed (> 12), tonsillectomy	43 children meeting criteria for PANDAS, 69 children with OCD and/or tics not meeting PANDAS criteria (9.2 ± 2.4 yrs.)	S: Previous tonsillectomy (n = 25) or adenotonsillectomy (n = 31) C: No surgery (n = 64)	Symptom severity using CY-BOCS and YGTSS	Tonsillectomies and Adenoidectomies = No surgery
Pavone et al. (2014)	Observational study, prospectively assessed (> 24), tonsillectomy	120 children meeting criteria for PANDAS (11.05 ± 1.2 yrs.)	S: Previous tonsillectomy (n = 25) or adenotonsillectomy (n = 31) C: No surgery (n = 64)	Symptom severity using CY-BOCS and YGTSS	Tonsillectomies and Adenoidectomies = No surgery

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Table 2 (continued)

First author	Study design, follow-up (m), treatment type	Study population (age)	Intervention	Outcome measures	Results
Storch et al. (2006)	Waitlist controlled open trial, blind to rater (3), CBT	7 children meeting criteria for PANDAS (11.1 ± 1.4 yrs.)	S: 14 CBT sessions over 3 weeks (up to 4 booster sessions) (n = 7) C: Waitlist (n = 7)	Primary: CY-BOCS, CGI-S, ADIS-IV-P, CGI-I and remission status Secondary: TODS-PR, CDI and MASC-10	CBT ameliorated OCD symptoms, but not depression or anxiety. No comparison group
Nadeau et al. (2015)	Open trial, intervention study, not controlled (1-4), CBT	11 children meeting PANDAS or PANS criteria (9.4 ± 2.7 yrs.)	S: Maximum of 14 CBT session in person or via webcam on a twice-weekly schedule (n = 11)	Primary: CY-BOCS, CGI-S and CGI-I Secondary: SCARED and COIS-C/P	Treatment ameliorated OCD symptoms (CY-BOCS) and general function (CGI-S). No comparison condition.
Brown et al. (2017a-b)	Observational retrospectively assessed, NSAID	95 patients meeting criteria for PANS and/or PANDAS with 390 flares in total	S: Prophylactic (n = 76) or early (n = 43) NSAID treatment C: No NSAID treatment (n = 271)	Primary: PANS flare duration Secondary: Impact of timing of NSAID introduction on PANS flare duration	NSAID > Control
Brown et al. (2017a-b)	Observational study, retrospectively assessed, corticosteroids	98 patients meeting criteria for PANS and/or PANDAS with 403 flares in total	S: Oral corticosteroid burst treatment (n = 85) C: No corticosteroid burst treatment (n = 318)	Primary: PANS flare duration Secondary: Impact of timing of corticosteroid introduction on flare duration and effect of course length on duration of symptom improvement	Corticosteroids > Control
Calaprice et al. (2017)	Observational study, retrospectively assessed, self-reported, mixed treatments	698 patients with self-reported PANS	S: various treatments for PANS	Primary: Frequency of treatment Secondary: Self-reported effect of treatment	N/A

PANDAS = Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections; PANS = Pediatric acute-onset neuropsychiatric syndrome; RCT = Randomized controlled trial; IVIG = Intravenous Immunoglobulin; TPE = Therapeutic plasma exchange; OCD = Obsessive-compulsive disorder; YGTSS = Yale Global Tic Severity Scale; TSURS = Tourette Syndrome Unified Rating Scale; CY-BOCS = Children's Yale-Brown Obsessive-Compulsive Scale; CGI-S = Clinical Global Impression Severity scale; CGI-I = Clinical Global Impression Improvement scale; ADIS-IV-P = Anxiety Disorders Interview Schedule Parent version; GAS = Global Assessment Scale; C-GAS = Child-Global Assessment Scale; TODS-PR = Tourette's Disorder Scale-Parent Rated version; CDI = Children's Depression Inventory; COIS-C/P = Child Obsessive Compulsive Impact Scale-Child/Parent versions; CBCL = Child Behavior Checklist; MASC-10 = Multidimensional Anxiety Scale for Children-10; SCARED = Screen for Childhood Anxiety Related Emotional Disorders; NIMHRS = National Institute of Mental Health Rating Scales for global functioning, anxiety and depression; CALS = Children's Affective Liability Scale; NSAID = Nonsteroidal Anti-Inflammatory Drugs.

Table 3
Results and quality assessment of included studies.

First author (intervention)	Results	Risk of bias						Support for judgement	
		Select-ion B1	Perform-ance B2	Detect-ion B3	Attrit-ion B4	Report-ing B5	OtherB6		Over-all
Garvey et al. (1999) (PcV)	NIMH depression and anxiety scales showed significant improvement during active phase, no significant difference between the two phases regarding OCD and tic severity or exacerbations was seen. Fewer streptococcal infections during the active phase (n = 14) than in the placebo phase (n = 21) but the difference was not statistically significant.	2	2	1	1	2	2	2	B1: randomization procedure not reported. B2: lack in compliance, difference in off-study antibiotics. B3: validated scales, acceptable follow-up. B4: low drop-out rate. B5: primary/ secondary outcome and AE not reported. B6: information missing.
Snider et al. (2005) (Azithromycin/ PcV)	Number of neuropsychiatric exacerbations decreased in PcV group, 23 to 6, and in azithromycin group, 21 to 11, (p < 0.01), non-significant between groups. Streptococcal infections decreased in both groups (p < 0.01), but no significant difference between groups.	3	1	2	1	2	1	2	B1: randomization and baseline differences not stated. B2: double-blind study, good compliance. B3: all scales not validated. B4: low drop-out rate. B5: AE not reported. B6: funding reported
Murphy et al. (2017) (Azithromycin)	No significant difference in CY-BOCS scores between groups was seen. There was a significant reduction in CGI-S OCD in the azithromycin group compared to placebo; 21.76 % and 0.95 % in average respectively. Tic severity moderated treatment response in the azithromycin group.	1	1	2	2	3	1	2	B1: randomization by pharmacy. B2: double-blind design B3: validated scales, unclear statistics. B4: 1 randomized person not in analysis. B5: pre-published protocol deviate from outcomes reported. B6: financial disclosures complete
Perlmutter et al. (1999) (IVIG/ TPE)	1-month follow-up: IVIG and TPE showed significant improvement of all neuropsychiatric scores except GAS and tic severity compared to placebo, TPE also showed significant improvement in tic severity compared to placebo. 1-year follow-up: Symptoms remained improved from baseline for both IVIG and TPE.	2	2	1	1	2	2	2	B1: randomization procedure not reported, difference in tic severity between groups. B2: TPE group not blinded, difference in off-study medication. B3: validated scales, short and long term follow-up. B4: low drop-out rate. B5: primary/ secondary outcome not reported. B6: information missing

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Table 3 (continued)

First author (intervention)	Results	Risk of bias			Support for judgement			
		Select-ion B1	Perform-ance B2	Detect-ion B3	Attrit-ion B4	Report-ing B5	OtherB6	Over-all
Williams et al. (2016) (IVIG)	Week 6: Mean decrease in CY-BOCS was 24% in the IVIG group and 12% in the placebo group, difference not statistically significant. CGI-I scores did not differ significantly between the groups either. CY-BOCS total scores at end of follow-up (week 24) were improved by 62%.	1	1	1	1	1	1	1
Murphy et al. (2013) (Tonsillectomy)	Most participants had surgery before onset of symptoms and surgery did not affect symptomology, no difference in CY-BOCS or YGTSS scores was seen between the groups	1	1	2	1	2	2	2
Pavone et al. (2014) (Tonsillectomy)	Surgery did not increase number of patients with resolution of symptoms (RR = 1.39; p = 0.29). No difference in CY-BOCS or YGTSS scores was seen between the groups.	2	2	2	2	2	2	2
Storch et al. (2006) (CBT)	Clinician severity ratings (CY-BOCS, ADIS-P) decreased significantly after CBT-intervention, maintained at follow-up, 71% and 50% was considered not having an OCD diagnosis on the ADIS-P post treatment and follow-up, respectively. Self-reported anxiety and depression was not significantly reduced. Significantly lower CY-BOCS score post treatment (13.2) compared to pretreatment (25.8). Significant decrease in CGI-S score pre- to post treatment (3.8 to 2.1). Significant difference in COIS-P, no significant difference in COIS-C or SCARED.	3	3	1	1	1	1	3
Nadeau et al. (2015) (CBT)		3	3	2	3	1	1	3

(continued on next page)

Table 3 (continued)

First author (intervention)	Results	Risk of bias					Support for judgement		
		Select-ion B1	Perform-ance B2	Detect-ion B3	Attrit-ion B4	Report-ing B5	OtherB6	Over-all	
Brown et al. (2017a,b) (NSAID)	Prophylactically treated flares were about 4 weeks shorter, and early treated flares about 2.5 weeks shorter than flares not treated with NSAID (12.2 weeks long). In early treated flares, each day that NSAID treatment was delayed was associated with an increase in flare duration of 0.18 weeks; this relationship however was nonsignificant when adding all covariates ($p = 0.06$). Flares treated with corticosteroids were significantly shorter (6.4 ± 5.0 weeks) than flares not treated with corticosteroids (11.4 ± 8.6 weeks). Treatment initiated early in flare was associated with shorter flare duration, and longer corticosteroid course generated longer duration of symptom improvement.	2	2	2	1	1	1	2	B1: difference in baseline characteristics. B2: difference in off-study medication. B3: evaluator not blinded, unvalidated scales. B4: low drop-out rate. B5: AE reported, relevant outcome measures. B6: financial disclosure complete
Brown et al. (2017a, b) (Corticosteroid)	Flares treated with corticosteroids were significantly shorter (6.4 ± 5.0 weeks) than flares not treated with corticosteroids (11.4 ± 8.6 weeks). Treatment initiated early in flare was associated with shorter flare duration, and longer corticosteroid course generated longer duration of symptom improvement.	2	2	2	1	1	1	2	B1: difference in baseline characteristics. B2: difference in off-study medication. B3: evaluator not blinded, unvalidated scales. B4: low drop-out rate. B5: AE reported, relevant outcome measures. B6: financial disclosure complete.
Calaprice et al. (2017) (various treatments)	97% had any type of antibiotics, 63% had any type of anti-inflammatory treatment and 54% reported any type of psychotropic treatment. Broad-spectrum antibiotics and courses > 30 days produced best results among antibiotics. 31% had received IVIG, and of these 49% reported it to be “very effective”.	3	3	3	3	1	1	3	B1: self-selected sample. B2: observational study, multiple treatments given. B3: self-reported outcomes, survey study. B4: non-responders not reported. B5: adequate study protocol and outcome measures. B6: financial disclosure complete.

Risk of bias: 1 = low risk, 2 = moderate risk, 3 = high risk; OCD = Obsessive-compulsive disorder; IVIG = Intravenous immunoglobulin; TPE = Therapeutic plasma exchange; PcV = Penicillin V; CBT = Cognitive behavior therapy; GAS = Global Assessment Scale; CY-BOCS = Children's Yale-Brown Obsessive-Compulsive Scale; YGTSS = Yale Global Tic Severity Scale; CGI-S/I = Clinical Global Impression-Severity/Improvement scale; COIS-C/P = Child Obsessive Compulsive Impact Scale-Child/Parent version; SCARED = Screen for Childhood Anxiety Related Emotional Disorders; ADIS-P = Anxiety Disorders Interview Schedule Parent version; AE = adverse events; NSAID = Nonsteroidal Anti-Inflammatory Drugs.

Litman, 2006). Two patients with PITAND who underwent TPE also had improvement in symptoms (Allen et al., 1995).

TPE has been described in multiple case reports and case series. In the survey study, only 6 out of 25 treated patients reported enduring improvement following TPE. In contrast, the two systematically performed case series reported positive outcomes. Furthermore, TPE has been tested in a controlled setting but the available literature has several limitations, most notably that no study involved blinding. Therefore, the evidence for TPE is inconclusive.

4.2.3. Intravenous immunoglobulin

Contradictory results of IVIG treatment were found in 2 double-blinded RCTs (Perlmutter et al., 1999; Williams et al., 2016). In the study by Perlmutter et al. (1999), 9 children with PANDAS treated with IVIG improved considerably compared to a placebo group at 1 month of follow-up. However, these patients were assigned to open-label IVIG after 1 month, which precluded any long-term placebo comparison. Williams et al. (2016) applied a similar study design but did not demonstrate an effect of IVIG versus placebo during the double-blind phase. In the subsequent open-label phase, the majority of patients improved on IVIG. These authors did not determine a factor that predicted favorable treatment response, but elevated baseline levels of serum calcium calmodulin-dependent protein kinase II (CaMKII) and anti-nuclear antibody (ANA) were associated with treatment response in a post hoc analysis (Williams et al., 2016).

In the survey study treatment with IVIG was reported for 206 patients; however, therapeutic impact was only reported for 191 patients (Calaprice et al., 2017). IVIG was reported “very effective” for 49% of the treated patients, “somewhat effective” for 25% and “not very effective” for 11%.

An additional 6 case report papers (Allen et al., 1995; Frankovich et al., 2015; Gerardi et al., 2015; Hachiya et al., 2013; Kovacevic et al., 2015; Murphy et al., 2014) involving a total of 19 patients addressed treatment of patients with PANDAS, PITAND, or PANS using IVIG. Ten of these patients were presented in a case series of a combination treatment of IVIG and corticosteroids (Kovacevic et al., 2015). Eleven of the 19 patients experienced full remission of symptoms following IVIG (Frankovich et al., 2015; Kovacevic et al., 2015; Murphy et al., 2014).

IVIG has been described in multiple case reports and case series. Results from the self-reported survey study provides some support for IVIG being perceived as an effective treatment for PANS. IVIG has been tested in two double-blind RCTs, with the higher quality study indicating low support. Therefore, the evidence for using IVIG is inconclusive.

4.2.4. Tonsillectomy and adenoidectomy

Outcomes of tonsillectomy and/or adenoidectomy were reported in 2 prospective observational studies (Murphy et al., 2013; Pavone et al., 2014). Authors of these studies came to the same conclusion: symptom severity was not dependent of having a tonsillectomy or adenoidectomy. However, Murphy et al. (2013) observed a significantly higher number of previously conducted tonsillectomies in the PANDAS group compared with children unaffected by PANDAS, OCD or tics. This finding could be due to a confounding by indication, e.g. that previous strep infections could increase the risk both for PANDAS and for a tonsillectomy.

Another 24 patients who underwent tonsillectomy and/or adenoidectomy were identified in the reviewed literature (Alexander et al., 2011; Batuecas Caletro et al., 2008; Boseley et al., 2007; Calkin and Carandang, 2007; Chmelik et al., 2004; Demesh et al., 2015; Frankovich et al., 2015; Fusco et al., 2010; Heubi and Shott, 2003; Lynch et al., 2006; Orvidas and Slattery, 2001). In 1 case series, 9 patients with PANDAS were treated with antibiotics and tonsillectomy and all improved (Demesh et al., 2015).

Tonsillectomy and/or adenoidectomy has been described in multiple case report and case series. It has not been tested in a controlled

setting, but two observational studies indicate no support. In line with this, the evidence for treating PANDAS with tonsillectomy and/or adenoidectomy is weak.

4.2.5. Cognitive behavior therapy

In 2 studies (Nadeau et al., 2015; Storch et al., 2006), authors evaluated the effect of CBT on symptoms of OCD in patients with PANDAS and PANS. Results of both studies showed a significant decrease in OCD symptom severity. However, these studies were preliminary and limited by lack of an active control group and small sample sizes (7 and 8 participants, respectively). Furthermore, Nadeau et al. (2015) had an over 40% drop-out rate, leaving only 6 patients evaluated at follow-ups ranging from 1 to 4 months. The use of antibiotics also may have influenced the outcome of this study (Nadeau et al., 2015).

The survey study reported 473 out of 698 patients receiving some form of psychotherapy (Calaprice et al., 2017). Patients who had received the recommended treatment for OCD (exposure with response prevention, ERP) reported the treatment to be “very effective” in 39% of treated cases.

CBT techniques, including psychoeducation and ERP, were applied in 7 case reports of patients with PANDAS (Calkin and Carandang, 2007; Frankovich et al., 2015; Gabbay and Coffey, 2003; Giedd et al., 1996; Kuluva et al., 2008; Lawrence and Baggott, 2017; Sharma et al., 2012) and 2 case reports of patients with PANS (Frankovich et al., 2015; Muir et al., 2013). No case report involved CBT as the main treatment of PANS or PANDAS symptoms. Although CBT is an evidence-based treatment for OCD, few authors have examined patients with OCD of potential autoimmune etiology.

CBT as treatment for PANS or PANDAS has been described in several case reports. The survey study lends some support for treating PANS-related OCD with ERP. Two uncontrolled studies indicated that CBT ameliorated OCD symptoms in patients with PANS or PANDAS. Hence, it is possible that patients who fulfill PANS or PANDAS criteria could benefit from CBT treatment, but this has not been tested in a controlled setting. Therefore, the evidence for CBT is inconclusive.

4.2.6. Nonsteroidal anti-inflammatory drugs

One observational study of NSAID as treatment for PANS was identified in the review (Brown et al., 2017b). This study was a retrospective assessment on the duration of flares in PANS patients following treatment with or without NSAID. Of the first 218 consecutive patients at a PANS clinic, 95 patients treated with NSAID were evaluated. A total of 390 flares experienced by the patients were evaluated. Flares not treated with NSAID had a mean duration of 12.2 weeks. Flares treated with NSAID were shortened by 4 weeks (95% CI 1.85–6.24 weeks) when patients were on prophylactic NSAID, and 2.6 weeks (95% CI 0.43–4.68 weeks) when flares were treated within 30 days of flare onset. This study excluded 17 patients who required treatments with rituximab, cyclophosphamide, mycophenolate mofetil or chronic immunomodulatory therapy. Whether or not these patients were treated with NSAID, and how they responded, is unclear. It is also unclear in the study if all untreated flares at the clinic were included. Transient side effects were experienced by 19% of the patients.

One large case series has evaluated the use of NSAID in PANS (Spartz et al., 2017). This study was based on the same sample of the first 218 consecutive patients treated at the Stanford PANS clinic as Brown et al., (2017b). Seventy-seven patients experiencing a total of 109 occurrences of change in treatment regime consisting of only addition ($n = 52$) or removal ($n = 57$) of NSAID were described. The patients were regarded as responders to NSAID treatment if they improved after addition of NSAID or deteriorated after removal of NSAID. In total, 42% of the included patients were responders to NSAID treatment. Notably, 39% of patients experienced side effects of NSAIDs.

In addition to the study and the case series, 2 case reports describing treatment with NSAID were identified (Greenberg, 2014; Ray et al.,

2013). Greenberg et al. state that ibuprofen in addition to antibiotics helped to speed improvement of psychiatric symptoms (Greenberg, 2014).

In the survey study (Calaprice et al., 2017), Ibuprofen was received by 302 out of 698 included patients, with 23% reporting the treatment to be “very effective” and 10% discontinuing due to lack of efficacy.

To conclude, NSAID has been described in one large case series, in which 32 out of 77 patients were considered responders. One observational study (based on the same study population as the case series) indicated that NSAID may shorten PANS flare duration. No trial of NSAID has been conducted and therefore the overall evidence is inconclusive.

4.2.7. Corticosteroids

One observational study evaluating the effect of corticosteroids on flare duration in PANS was identified in the literature review (Brown et al., 2017a). This study is also from the Stanford PANS clinic and the study population is the first 178 consecutive patients of the clinic. Ninety-eight patients, experiencing a total of 403 flares, who were treated with oral corticosteroids were evaluated. Flares not treated with corticosteroids ($n = 318$) had a mean duration of 11.4 weeks. Flares treated with corticosteroids ($n = 85$) were shortened by 3.5 weeks (95% CI $-1.05 - 5.95$ weeks). Early treatment with oral corticosteroids was associated with shorter flare duration. A longer treatment course was associated with a longer duration of improvement. Side effects of oral corticosteroids were reported in 44% of treatment courses, most commonly escalation of psychiatric symptoms. Limitations include the observational study design and non-blinded assessments.

In the survey study (Calaprice et al., 2017), 154 out of 698 patients received short steroid tapers (< 14 days) with 49% considering this treatment to be “very effective” and 7% discontinuing due to lack of efficacy. Out of 72 patients who received treatment with long steroid tapers (> 14 days), 54% considered their treatment as “very effective” and 3% discontinued due to lack of efficacy.

A total of 15 patients who were treated with corticosteroids were identified in the case reports (Allen et al., 1995; Chmelik et al., 2004; Frankovich et al., 2015; Kovacevic et al., 2015; Kuluva et al., 2008). All patients received corticosteroids in combination with several other treatments. Ten of these individuals were included in a case series in which successful treatments were observed with combined IVIG and corticosteroids (Kovacevic et al., 2015). In another case report, OCD developed as a possible side effect of prednisolone treatment (Chmelik et al., 2004). An initial beneficial effect of prednisolone treatment was reported in 1 patient; however, this treatment was ineffective when symptoms later recurred (Allen et al., 1995).

Treatment with corticosteroids has been described in multiple case reports and case series. Half of the treated patients in the survey study reported corticosteroids as “very effective”. One observational study indicated that PANS flares may be shortened by corticosteroids, but the treatment has not been studied in a controlled setting. Notably, several studies report escalation of psychiatric symptoms as side effects. To conclude, the evidence for corticosteroids as treatment of PANS is inconclusive.

4.2.8. Selective serotonin reuptake inhibitors

In the self-reported survey study 265 patients had been treated with SSRIs (Calaprice et al., 2017). 17% reported SSRIs to be “very effective”, 20% discontinued due to lack of efficacy and another 25% discontinued due lack of tolerability.

SSRIs have not been studied systematically in PANS, PANDAS, CANS, or PITAND. However, treatments with SSRIs were reported in case reports of 29 patients with PANDAS (Alexander et al., 2011; Baytunca et al., 2016; Becker et al., 2004; Bodner et al., 2001; Calkin and Carandang, 2007; Celik et al., 2016; Chmelik et al., 2004; Coffey and Wieland, 2007; Das and Radhakrishnan, 2012; Doshi et al., 2015; Fonseca et al., 2010; Gabbay and Coffey, 2003; Giedd et al., 1996;

Hachiya et al., 2013; Heubi and Shott, 2003; Kovacevic et al., 2015; Kerbeshian et al., 2007; Kuluva et al., 2008; Lawrence and Baggott, 2017; Maini et al., 2012; Murphy et al., 2006; Navkhare and Kalra, 2014; Ray et al., 2013; Sadhasivam and Litman, 2006; Sankaranarayanan and John, 2003; Sharma et al., 2012; Sokol, 2000; Srivastava et al., 2012), 2 patients with PANS (Greenberg, 2014; Ayaydin and Abali, 2010), and 1 patient with PITAND (Allen et al., 1995). For 7 patients, the disorder was unimproved with SSRIs but improved with antibiotics or immunomodulatory treatments (Celik et al., 2016; Das and Radhakrishnan, 2012; Greenberg, 2014; Heubi and Shott, 2003; Lawrence and Baggott, 2017; Navkhare and Kalra, 2014; Sadhasivam and Litman, 2006). Three of the 29 patients experienced paradoxical reactions from SSRIs (Calkin and Carandang, 2007; Maini et al., 2012; Murphy et al., 2006). For 1 of these patients, a therapeutic effect was achieved when the dosage of SSRIs was considerably lowered (Murphy et al., 2006). A total of 9 patients were treated successfully with SSRIs (Baytunca et al., 2016; Chmelik et al., 2004; Doshi et al., 2015; Fonseca et al., 2010; Giedd et al., 1996; Ray et al., 2013; Sharma et al., 2012; Srivastava et al., 2012). In all of these case reports, patients received SSRIs in combination with other psychotropic or immunomodulatory medications. SSRIs have not been tested for PANS or PANDAS in a controlled setting. Therefore, conclusions cannot be drawn regarding the efficacy of SSRIs alone in these patients. However, SSRIs are evidence based treatments for OCD, therefore positive outcomes on OCD are expected and thus unlikely to be published as case reports. It is also possible that treatment response from SSRIs can be generalized to PANDAS and PANS presenting with OCD.

4.2.9. Other treatments

In the self-reported survey study on PANS (Calaprice et al., 2017), psychotropic medication such as non-SSRI-antidepressants ($n = 60$), ADHD medication ($n = 114$), antipsychotics ($n = 95$), anxiolytics ($n = 84$) and mood-stabilizers ($n = 63$) were reported. Furthermore, 352 patients reported improvement from complementary and alternative medicine treatments, including probiotics, Omega 3, vitamin D, homeopathy and gluten free diet.

In a series of 5 complex cases treated at a PANS clinic at Stanford University, 1 patient with severe PANS was successfully treated with monoclonal CD-20 antibody (rituximab) in combination with TPE (Frankovich et al., 2015).

Many treatments of patients with PANDAS and related conditions were given based on specific indications of the patient (e.g., treatment for vitamin D deficiency) (Celik et al., 2016). In 1 case series in which the treatment strategy was to cure sinusitis and thereby alleviate PANDAS, all patients received antibiotics, and 3 patients also were treated with sinus surgery. Upon remission of sinusitis, 8 of 10 patients had improvement in psychiatric symptoms (Mahony et al., 2017). In another case report, authors observed spontaneous remission of PANDAS symptoms in absence of treatment (Cengel-Kultur et al., 2009). In total, 26 case reports reported treatment with non-SSRI psychotropic medications, including benzodiazepines, haloperidol, and atomoxetine. All patients received additional treatments and/or surgical procedures (e.g., SSRIs, antibiotics, steroids, CBT and tonsillectomy) in combination with these psychotropic therapies. A full summary of all case reports is presented in Supplementary Table S1.

5. Discussion

In this systematic review of articles published during a 17-year period that addressed treatments for PANS, PANDAS, CANS, and PITAND we identified only 4 RCTs, 1 cross-over study, 2 open trials, 4 observational studies and one survey study. We also identified 65 case reports and case series that encompassed a total of 240 patients. No authors used the diagnostic entity CANS, and only 7 case reports (Allen et al., 1995; Ercan et al., 2008; Sokol and Gray, 1997) used the diagnostic criteria for PITAND to diagnose patients.

Therapies that have been systematically studied for PANDAS and PANS are antibiotics, IVIG, TPE, tonsillectomy, CBT, NSAID and corticosteroids. The studies are few and in general have moderate or high risk of bias. The bulk of the published evidence is case reports and case series. Using traditional methods of determining the evidence, there is currently insufficient evidence to clearly propose any treatment for PANDAS and related disorders. Nevertheless, there are 3 recent papers proposing guidelines for how to treat PANDAS and PANS using psychiatric and behavioral interventions (Thienemann et al., 2017), immunomodulatory therapies (Frankovich et al., 2017) and antibiotics (Cooperstock et al., 2017). These guidelines are proposed by a consortium of clinicians and researchers, and propose use of these 3 therapeutic approaches for children who fulfill criteria for PANDAS or PANS. We believe that our results are in line with the proposed guidelines, and that the lack of evidence for treatment is based not on the inefficacy of the treatments, but on lack of systematic research. This being said, there is clearly need for more high quality research to determine if and which treatment approaches are beneficial for patients fulfilling criteria for PANDAS and PANS.

5.1. Methodological issues in the included articles

Several of the studies included patients receiving off-protocol study medication, which makes it difficult to conclude an effect of the investigated treatment. In 2 of the studies on antibiotics, adjustments of the drug dosage were permitted (Garvey et al., 1999; Snider et al., 2005), and in 1 of these (Snider et al., 2005), off-study antibiotics were prescribed for treatment of GABHS infection. In 1 of the tonsillectomy studies (Pavone et al., 2014), IVIG was given to 8 patients, and antibiotics were given to several patients – apart from tonsillectomy. Moreover, open-label IVIG was provided in 2 studies after the blinded phase (Perlmutter et al., 1999; Williams et al., 2016). In the survey study, a majority of the patients received multiple treatments, yet the outcomes are reported on a treatment-by-treatment basis (Calaprice et al., 2017). Because patients with PANDAS and related conditions present with severe and acute psychiatric symptoms and infections, the use of off-study medications was deemed necessary. Symptomatic streptococcal infections are painful and can cause sequelae; these infections should be treated if detected. The same is true with severe psychiatric symptoms, which may require high doses of psychotropic medication and result in long-term psychosocial impairment.

The episodic course of PANDAS and related disorders also complicates these studies (Swedo et al., 1998). Treatment effects are difficult to interpret in the context of a relapsing-remitting course and absence of a control or placebo group. If the disorder enters a remitting phase coinciding with the beginning of treatment, the treatment effect could be overestimated.

Relevance of the outcome measures also should be considered. The main criterion for PANDAS, PANS, CANS, and PITAND is the abrupt nature of onset of OCD, tics, or an eating disorder. Treatment outcomes for OCD typically are measured as change in score on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; CY-BOCS for children) (Goodman et al., 1989; Scahill et al., 1997). The Y-BOCS ranges from 0 to 40 points, with a higher score indicating more severe symptoms. The cutoff for clinically important OCD is 16 points. A significant effect of treatment for OCD is defined as a 35% reduction in Y-BOCS score combined with a Clinical Global Impression Improvement (CGI-I) score of 1 or 2 (i.e., very much improved or much improved) (Mataix-Cols et al., 2016). These outcome measures were used in several studies included in this review (Garvey et al., 1999; Murphy et al., 2013; Murphy et al., 2017; Nadeau et al., 2015; Pavone et al., 2014; Perlmutter et al., 1999; Storch et al., 2006; Williams et al., 2016).

In addition to OCD and tics, the proposed diagnostic criteria for PANDAS and related disorders also include a level of disease severity and the presence of multiple other symptoms, such as violent behavior, anxiety, hyperactivity, psychotic symptoms, motor problems, cognitive

decline, separation anxiety, and impaired overall function. The combination of severe symptoms and sudden onset is thought to differentiate these disorders from non-PANDAS OCD and Tourette syndrome. However, in the studies and case reports analyzed herein, the outcome measure typically is limited to obsessive-compulsive symptoms measured on the CY-BOCS. By this rubric, if a treatment results in remission of compulsions – but aggravation of anxiety or psychotic symptoms – the patient would be defined as a treatment responder. Thus, the interpretation of treatment response in multiple-dimension disorders can be confounded when a single-dimension outcome measure is applied. In 2 of the reviewed studies involving penicillin prophylaxis, psychiatric exacerbations were the main outcome measure (Snider et al., 2005; Garvey et al., 1999). In the two studies by Brown et al. (2017a,b) the primary outcome measure was duration of symptom flares, which is also in line with PANS and PANDAS diagnostic criteria. The flares evaluated in the studies by Brown et al. include not only OCD, but all psychiatric symptoms, and therefore this is a suitable outcome measure when evaluating treatments for PANS and PANDAS. A combined outcome measure that includes exacerbation onset and duration, target symptoms, and global function may be needed to assess treatment response adequately. The development of credible outcome measures is a current challenge in the field of sudden-onset neuropsychiatric disorders with proposed autoimmune etiology.

5.2. Non-PANDAS OCD

In the review process, we identified 2 treatment studies of antibiotics and TPE for non-PANDAS OCD (Murphy et al., 2015; Nicolson et al., 2000). These studies did not meet inclusion criteria, but they are relevant to this discussion. In a study by Murphy et al. (2015), treatment with antibiotics (cefdinir) was compared to placebo for recent onset OCD (not fulfilling PANS or PANDAS criteria) in 19 patients. No significant between-group difference in treatment effect was found, possibly owing to the small sample size. Nevertheless, there were indications in this study that cefdinir may ameliorate non-PANDAS OCD and tics, and further research involving larger sample sizes is needed to determine this effect.

In a second study, TPE was given to 5 treatment-refractory patients with non-PANDAS OCD (Nicolson et al., 2000). These patients had no history of exacerbations related to streptococcal infections. No patient experienced an improvement after 4 weeks. The lack of an effect was interpreted as an indication of non-immune-related OCD. However, this has not been studied further.

5.3. Adverse events

Most of the adverse events reported in the articles reviewed herein were mild to moderate (e.g., nausea, vomiting, headache, and stomachache). Thus, potential benefits of the treatments usually exceeded the occasional negative effects. Treatments with antibiotics, corticosteroids, IVIG, or TPE may be less harmful than antipsychotic drug treatments, which often are prescribed in severe cases of OCD and psychosis and for children who present aggressive behaviors – symptoms that are common in PANDAS and PANS. Notably, 3 case reports and 10 patients in the survey study reported paradoxical effects of SSRIs (Calaprice et al., 2017; Calkin and Carandang, 2007; Maini et al., 2012; Murphy et al., 2006), which is in line with previous reports (Murphy et al., 2006; Swedo et al., 2012).

5.4. Limitations and methodological discussion

We attempted to collect all available literature describing treatment outcomes of patients with PANDAS, PANS, CANS, and PITAND. The initial screening of 1087 abstracts was made by 2 investigators (E.H. and S.S.), but all abstracts were not read by both individuals. In the Scopus search, we used the filter “document type: article,” and this may

have led to some case reports being missed. The full-text review of 162 articles and extraction of data from 77 articles that met inclusion criteria were carried out by both investigators, reading all articles. Our goal was to obtain a complete data set; therefore, we included all articles that had been identified by at least 1 of the authors as containing data from a case report. However, we excluded articles that were not in English, which eliminated articles in Swedish (Bejerot et al., 2013), German (Schubert et al., 2006), Spanish (Fernández Ibieta et al., 2005; Morer and Massana, 2000), Italian (Ferrafiat et al., 2017), and Polish (Brynska and Wolanczyk, 2004). Hence, the data described in this review are not comprehensive.

To minimize the risk of missing relevant articles, we were liberal in our evaluation, and all articles in which we thought a case report may be involved were included in the full-text review, even if the study was not defined in the abstract or title as a case report. We also included all cases in which the authors stated that the diagnosis “may be” PANDAS, PANS, CANS, or PITAND as well as studies with unclear use of diagnostic criteria (Bodner et al., 2001; Boseley et al., 2007; Ceylan et al., 2011; Coffey and Wieland, 2007; Gabbay and Coffey, 2003; Giedd et al., 1996; Kuluva et al., 2008; Maguire et al., 2010; Martinelli et al., 2002; Navkhare and Kalra, 2014; Sankaranarayanan and John, 2003; Sharma et al., 2012; Vitaliti et al., 2014). We have also chosen to include a large survey study of self-reported treatment outcome in a self-selected sample as one of the systematic evaluations of treatments in this review (Calaprice et al., 2017). Despite the inherent limitations of using a survey to study treatment outcome, this study is the largest study of treatment outcome in PANS. Our liberal inclusion strategy enabled us to conduct a more complete review, but the permissive application of inclusion criteria should be considered when interpreting our results.

5.5. Conclusions

Successful treatment of any medical disorder depends on careful diagnostic workup, identification of pathogeneses, appropriate treatment, and valid evaluation of response. In the field of PANDAS, PANS, CANS, and PITAND, all of these steps are problematic. Our findings indicate that there is no strong evidence to recommend treatment of PANDAS, PANS, CANS, and PITAND with antibiotics, tonsillectomy, immunomodulation, CBT, SSRIs, or neuroleptics. Nevertheless, in many case reports, authors note remarkable improvement after treatment with IVIG, antibiotics, and TPE and it is possible that flare duration may be shortened by NSAID or corticosteroids.

In the era of personalized medicine, symptoms of PANDAS, PANS, and PITAND and related disorders should be treated on a case-by-case basis. Careful collection of etiological clues and treatment outcomes can be beneficial to patients and the research field alike. While awaiting valid and well-designed RCTs, treatment of PANDAS and PANS with antibiotics, IVIG, TPE, and/or corticosteroids – in addition to SSRIs and CBT – can be defended in clinical practice if treatment response can be expected. For instance, the use of antibiotics and tonsillectomy may prevent recurring strep infections (Burton et al., 2014), and treatments with IVIG, TPE, NSAIDs, and corticosteroids should be considered in cases with clinical evidence of neuroinflammation. Our findings should encourage further evaluations of potential treatments for these disabling disorders.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.neubiorev.2018.01.001>.

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