# A Pilot Study of Penicillin Prophylaxis for Neuropsychiatric Exacerbations Triggered by Streptococcal Infections

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**Background:** *Some children with obsessive-compulsive disorder (OCD) and tic disorders appear to have symptom exacerbations triggered by group A beta-hemolytic streptococcal infections in a manner that is similar to rheumatic fever and its neurologic variant, Sydenham's chorea. Because penicillin prophylaxis has proven to be effective in preventing recurrences of rheumatic fever, it was postulated that it might also prevent streptococcal-triggered neuropsychiatric symptom exacerbations in children with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS). These children are identified by five clinical characteristics: presence of OCD or tic disorder, prepubertal onset, episodic symptom course, neurologic abnormalities (i.e., choreiform movements) and streptococcal-triggered symptom exacerbations.*

**Methods:** *Thirty-seven children with PANDAS were enrolled in an 8 month, double-blind, balanced cross-over study. Patients were randomized to receive either 4 months of the active compound (twice daily oral 250 mg penicillin V) followed by 4 months of placebo, or placebo followed by penicillin V. Tic, OCD, and other psychiatric symptoms were monitored monthly. Throat cultures and streptococcal antibody titers were also obtained.*

**Results:** *There were an equal number of infections in both the active and placebo phases of the study. There was no significant change seen in either the obsessive-compulsive or tic symptom severity between the two phases.*

**Conclusions:** *Because of the failure to achieve an acceptable level of streptococcal prophylaxis, no conclusions can be drawn from this study regarding the efficacy of penicillin prophylaxis in preventing tic or OCD symptom exacerbations. Future studies should employ a more effective prophylactic agent, and include a larger sample size.* Biol Psychiatry 1999;45:1564–1571 © *1999 Society of Biological Psychiatry*

**Key Words:** Penicillin prophylaxis, streptococcal, obsessive compulsive disorder, tic disorders, clinical trials

## Introduction

Recent reports have provided evidence for a possible connection between group A beta-hemolytic streptococcal infections and neuropsychiatric disorders (Swedo et al 1994; Swedo et al 1998; Kerbeshian et al 1990; Tucker et al 1996). In a subgroup of children with tic and/or obsessive-compulsive disorders, symptom exacerbations appear to be temporally linked to streptococcal infections (Allen et al 1995; Swedo et al 1991; Kiessling 1989). This subgroup has been identified by the acronym PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections), the key features of which have been outlined in a recently published study (Swedo et al 1998). As in Sydenham's chorea (SC) (Garvey et al 1998; Swedo 1994), the pathogenesis of PANDAS is thought to be autoimmune. Though other major manifestations of rheumatic fever such as carditis and polyarthritis are not found in children with PANDAS (Swedo et al 1998), they do manifest some of the neuropsychiatric features that are hallmarks of SC. The most characteristic of these are abnormal movements similar to chorea (Touwen 1979), attentional difficulties, and emotional lability, all of which fluctuate with exacerbations of their OCD or tics. In both conditions, there is a strong positive correlation between antistreptococcal titers and the reappearance or exacerbation of symptoms (Allen et al 1995; Stollerman 1961; Stollerman 1975; Swedo 1994; Swedo et al 1998).

Penicillin is routinely used to prevent recurrences in rheumatic fever and Sydenham's chorea. Early reports studying the prevention of rheumatic fever (RF) using sulfanilamide or related compounds (Coburn and Moore

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Received July 16, 1998; revised December 22, 1998; accepted January 19, 1999.



0006-3223/99/$20.00
PII S0006-3223(99)00020-7

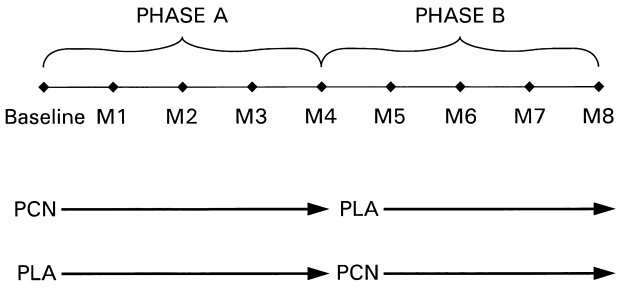


Figure 1. Randomization procedure. Children started on the phase A study compound after the baseline assessment. Each phase was divided into four months; M1, M2, M3, etc., mark the end of months. At the end of M4, each child was commenced on the phase B compound and continued on this for a further four months. PCN, penicillin; PLA, placebo.

1939; Thomas and France 1939; Stowell et al 1941; Thomas et al 1941; Kuttner and Reyersbach 1943; Hansen et al 1942) and penicillin (Maliner and Amsterdam 1947; Brick et al 1950; Evans 1950) were inconclusive but led the way towards larger studies. These established the efficacy of oral prophylactic penicillin in reducing the frequency of RF recurrences (Dajani et al 1988; Miller et al 1958a; Stollerman 1954; Wood et al 1964a). Because of the postulated pathophysiologic similarities between SC and PANDAS, we hypothesized that penicillin prophylaxis would reduce neuropsychiatric exacerbations in children with PANDAS by preventing streptococcal infections. To test this hypothesis, we conducted a placebo-controlled double-blind crossover trial of oral penicillin V prophylaxis in children with a history of streptococcal related exacerbations of tics and OCD. We expected that the prophylactic penicillin dose would be effective in preventing streptococcal infections, while the placebo would not, and therefore, we anticipated fewer symptom exacerbations during the active phase.

## Methods and Materials

### *Subjects*

Children with a history of a sudden onset or abrupt exacerbations of tic or OCD symptoms were recruited locally for this study over a period of 3 years. Advertisements were placed in the newsletter of the local chapter of the Tourette Syndrome Association and also sent to pediatricians and psychiatrists in the Washington, DC metropolitan area. Potential subjects were screened by telephone and in person using a semi-structured interview. Children were eligible for the study if they met the following inclusionary criteria.

1. A tic disorder and/or obsessive compulsive disorder meeting criteria established in the Diagnostic and Statistical Manual of Mental Disorders–III revised or IV edition (DSM-III-R or DSM-IV diagnostic criteria).
2. A history of a sudden onset of symptoms or an episodic course with abrupt symptom exacerbations interspersed with periods of partial or complete remission (a sawtooth, rather than a waxing and waning course).
3. Age between 4 and 15 years.
4. Onset of neuropsychiatric symptoms prior to puberty.
5. Evidence of an association between streptococcal infections and the onset or exacerbations of symptoms.

A streptococcal infection-associated exacerbation of neuropsychiatric symptoms was defined as a sudden dramatic worsening of tic or OCD symptoms within 3 months of a documented streptococcal infection. The methods used to establish this association are outlined in a prior report (Swedo et al 1998). At least two streptococcal associated exacerbations of neuropsychiatric symptoms were required to be eligible for entry into this study.

Children considered not suitable for study entry were those who had tics or OCD of such a severity that hospitalization was considered. In addition, children requiring treatment for severe, active comorbid major psychiatric disorders were also excluded, as were those with autism, pervasive developmental delay, or mental retardation. Also excluded were children with neurologic diagnoses other than tics and Tourette syndrome, serious concurrent or chronic medical disorders, and a personal history of penicillin allergy. The study was approved by the National Institutes of Health Institutional Review Board committee, Bethesda, MD, and each child and his or her parents gave assent/consent, respectively, for the investigation.

### *Methods*

**BASELINE ASSESSMENT.** Children who met criteria for study entry underwent a baseline evaluation consisting of history, physical examination, psychological testing, and laboratory studies. A semi-structured clinical interview and the Diagnostic Interview for Children and Adolescents (Welner et al 1987) were used to assign psychiatric diagnoses. Each child also had a complete medical examination and a standardized neurologic examination.

**STUDY DESIGN.** Following the baseline assessment, children were randomized in a double-blind, counterbalanced fashion to receive either penicillin or placebo for 4 months, and then the alternate compound for the other 4 months (Figure 1). The cross-over trial was conducted on an outpatient basis and subjects were evaluated monthly for eight consecutive visits. Since streptococcal infections peak during the winter months and exposure is greatest in the classroom setting, children were entered into the study as early in the school year as possible in order to standardize exposure to streptococcal infections throughout the two phases (Kaplan et al 1998b).

Following recommendations of the American Heart Association (Dajani et al 1988), a standard prophylactic dose of 250 mg twice daily penicillin V was used for this study. The placebo compound was administered in an identical formulation. To ensure that the blind was maintained, at the first monthly visit following crossover, parents and children were asked if there was any difference between the taste of the two compounds or if they had any new symptoms (for example, diarrhea or rash). Compli-

ance was checked monthly by asking if the child had missed any doses during the preceding month.

Treatments received prior to study entry were continued throughout the study and adjustments were permitted as needed during the course of treatment. At each monthly visit, any medication changes were noted. Also recorded were any illnesses in the preceding month (including the results of throat cultures taken during the illness), and possible contacts with family members, friends, or classmates who had streptococcal infections.

**MONTHLY ASSESSMENTS.** Subjects and their families were seen monthly for behavioral ratings of tics, obsessive compulsive symptomatology, anxiety, and depression. Rating scales included the Yale Global Tic Severity Scale (YGTSS), a 50-point scale that indicates severity of tic disorders (Leckman et al 1989; Walkup et al 1992); the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), a 40-point scale that measures severity of obsessions and compulsions (Goodman et al 1989a; Goodman et al 1989b); and the National Institutes of Mental Health (NIMH) rating scales for rating global functioning, anxiety, depression, and OCD symptom severity (Murphy et al 1982). In addition, the Children's Global Assessment Scale (GAS), a 100-point scale giving a measure of the overall functioning of the patient (Shaffer et al 1983), and Clinical Global Impression (CGI) Change Scale, a 7-point scale that monitors changes in symptom severity (Kurlan and McDermott 1993; Leckman et al 1988) were used. Rating scales validated for measures of change in choreiform movements are not available and for this reason, did not form part of the monthly assessment.

Monthly laboratory evaluation included serum titers of anti-streptolysin-O, anti-deoxyribonuclease B (anti-DN-ase B), and throat culture. During the first 2 years of the study, children received open label antibiotics at adequate treatment doses for 10 to 14 days for positive cultures whether or not they had symptoms of pharyngitis. As the study progressed, it was noted that a number of children received antibiotic treatment multiple times while receiving the placebo compound. Therefore, for the third year of the study, physicians and parents were blind to the results of the routine culture. In this way, asymptomatic positive throat cultures were not treated, similar to the situation in clinical practice (Kaplan 1980). At all times during the study, if the child had a symptomatic pharyngitis, a throat culture was obtained (at NIH or by the local physician) and, if positive, the child was taken off study medications and treated with the appropriate antibiotic.

Once phase B had been completed, a global rating was obtained from the parents. Parents were asked whether they could discern a difference in their child's behavior between the two phases. If so, they were asked to state during which of the two phases the behavior had been better. This was designated the active phase, since the hypothesis of the study was that an improvement would be detected while the child was taking penicillin. The blind was then broken.

**ANALYSIS.** This study was carried out to determine whether prevention of streptococcal infections with prophylactic penicillin would reduce the number of exacerbations of neuropsychiatric symptoms and thereby improve overall neuropsychiatric symptom severity. Therefore, the outcome variables sought were the difference in the number of streptococcal infections during the active and placebo phases, the number of exacerbations of neuropsychiatric symptoms, and the change in overall neuropsychiatric symptoms across the two phases.

Streptococcal infections were defined as either a positive throat culture, a two-dilution rise in antistreptococcal antibodies, or a combination of these two. The presence of a sore throat was not included in the definition. Changes in neuropsychiatric symptoms were sought in both the number of exacerbations (defined as a 20% or greater increase of one or more of the psychiatric rating scales) and in the overall scores of the psychiatric rating scales. Streptococcal infections and neuropsychiatric exacerbations were compared across phases using chi square. An analysis of variance (ANOVA) was performed on the clinical measures from the rating scales from phase A comparing data from children who had received the penicillin with those who had received the placebo compound in that phase. A repeated measures ANOVA for the entire group was also performed with phase (A or B) and month (1, 2, 3, 4) as the variables. The SAS version 6.07 of the repeated measure ANOVA with the Greenhouse–Geyser correction for multiple comparisons was used for this analysis. Identification of the active phase by the global rating of parents was analyzed using a kappa measure of reliability to determine if the answers were significantly different from those expected by chance.

Patients who received off-study antibiotics during the study were not dropped from the study and their entire dataset is included in the analysis. Data from children who dropped out of the study within the first 2 months of phase A were not included in any part of the analysis. However, children who completed phase A before dropping out were included in the phase A analysis. The last data point from children who dropped out of the study during phase B of the study was carried forward to the end of the study and included in the analysis in this format.

## Results

### *Study Subjects*

Over a 3-year period, 150 telephone screenings were conducted and 60 children were seen in the outpatient clinic for an in-person assessment. Fifty of these met criteria for study entry. Ten children either chose not to take part in the study ($n = 3$) or were excluded from study entry after the baseline evaluation ($n = 7$). Of the latter group, one child had an atrial septal defect requiring antibiotic prophylaxis prior to all dental procedures, five children had a primary psychiatric diagnosis other than tics or OCD [schizophrenia ($n = 1$) and trichotillomania ($n = 3$), pervasive developmental delay ($n = 1$)], and one child had a penicillin allergy.

Two children dropped out within 1 month of starting the study ($n = 2$; both on placebo at the time) and a third child was excluded from the analysis because she received

BIOL PSYCHIATRY 1999;45:1564–1571



Table 1. Streptococcal Infections and Neuropsychiatric Symptom Exacerbations Throughout the Study Period

A Distribution of Streptococcal Infections According to Randomization Order

| | Months after baseline | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Randomization order | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| PCN/PLA | 1 | 0 | 3 | 1 | 6 | 2 | 1 | 1 |
| PLA/PCN | 3 | 2 | 2 | 4 | 3 | 3 | 2 | 1 |

Total penicillin = 14
Total placebo = 21

B Distribution of Exacerbations According to Randomization Order

| | Months after baseline | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Randomization order | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| PCN/PLA | 3 | 7 | 7 | 5 | 10 | 6 | 5 | 3 |
| PLA/PCN | 2 | 6 | 0 | 6 | 5 | 3 | 3 | 2 |

Total penicillin = 35
Total placebo = 38

C Number of Exacerbations Per Child Through the Study Period

| | Number of exacerbations | Number of children |
|---|---|---|
| | 0 | 2 |
| | 1 | 12 |
| | 2 | 12 |
| | 3 | 7 |
| | 4 | 4 |
| Total | 73 | 37 |

PCN, penicillin; PLA, placebo; PCN/PLA, children received penicillin followed by placebo; PLA/PCN, children received placebo followed by penicillin.

placebo during the first month of her active phase due to a pharmacy dispensing error. Data from these children are excluded from the analysis.

Data from 37 children form the basis of this study. Nineteen children were randomized to receive penicillin followed by placebo (PCN/PLA) and 18 to receive placebo followed by penicillin (PLA/PCN). ANOVA analysis showed no differences in any of the baseline variables when comparing the two randomization groups. Two children dropped out of the study at the end of phase A; both had been randomized to PLA/PCN. Difficulty in traveling to the monthly visits was the reason given by both families. The data from these children are included in the phase A analysis. Three children (all randomized to PCN/PLA) dropped out in the third month of phase B. Each reported that an exacerbation of symptoms was the reason for not continuing in the study.

Of the 37 children who entered the study, 27 were boys and 10 were girls. Twenty-eight (77%) of the children were enrolled at the beginning of the school year and thus were in school for the entire duration of the study. The remaining 9 children were in school for at least 6 of the 8 months of the study. Mean age (± standard deviation) for the group was 9.61 (± 2.59) years (range 5.2 to 15.9 years). Thirteen children (35%) had both a primary diagnosis of OCD and tics, 13 (35%) had tics and subclinical obsessive-compulsive symptoms, 10 (27%) had tics only, and 1 (3%) had OCD only. At baseline, for the group as a whole, OCD symptoms were in the subclinical range with a mean NIMH OCD score of 3.95 (± 2.16). Tics were more prominent with a mean YGTSS score of 15.36 (± 9.03). Comorbidity was common: 19 of the 37 children (51%) had attention deficit hyperactivity disorder (ADHD) (16 boys and 3 girls); 15 children (40%) had anxiety symptoms, and four (11%) had depressive symptoms. Although two children met criteria for an anxiety disorder and one child had clinical depression, these were mild and were considered secondary to their OCD.

Table 2. Off-Study Antibiotics In The Different Phases According To Randomization Order

| Randomization order | Off-study antibiotic days | | |
|---|---|---|---|
| | PCN phase | PLA phase | Total |
| PCN/PLA | 80 | 200 | 280 |
| PLA/PCN | 40 | 170 | 210 |
| Total | 120 | 376 | 496 |

## *Presence of Streptococcal Infections*

A total of 35 streptococcal infections occurred during the study. Fifteen were manifest with a positive throat culture, and 20 as a two dilution rise in antibody titer in the absence of a positive throat culture. Although fewer infections occurred in the active ($n = 14$) than in the placebo phase ($n = 21$) the difference was not statistically significant. Table 1A shows the number of infections per child through the study and the distribution of the infections according to the randomization order.

Off-study antibiotics were prescribed for a total of 496 days in 18 children during the investigation (Table 2); 376 of these days were during the PLA phase, 120 during the active phase. There was no significant difference between the number of off-study antibiotics days between the phases, even when randomization order was considered. Ten children received antibiotics for asymptomatic positive throat cultures during the first 2 years of the study; 16 children received antibiotics for 21 episodes of pharyngitis; one of these also received 26 days of antibiotics for chronic sinusitis.

## *Blinding and Compliance*

One parent reported discoloration of her child's teeth upon commencing the new compound (penicillin); she had

noted this side effect when her child took penicillin on a previous occasion. This lead the parent to conclude that her child was taking the active compound. The remaining 36 children were unable to detect a difference between the two compounds.

Lack of compliance was reported by 26 of the children in the study but was limited to one or two missed doses per month or less. However, one child had a lapse of 10 days of the study compound (placebo) while away on vacation and another child received only one dose of the study compound (penicillin) each day for the first month of phase A, due to a misunderstanding on his mother's part. The parents of 9 children reported no missed doses at any stage of the study.

### *Neuropsychiatric Symptoms*

Analysis of phase A group data for overall symptom severity (NIMH global), global impairment (GAS), and of OCD and tic symptoms (Y-BOCS and YGTSS, respectively) comparing children who had received penicillin ($n = 19$) with those who had received placebo ($n = 18$) found no statistical significance between the two groups.

Twelve children were on psychotropic medications for tic and OCD symptoms at the start of the study; 7 of these were randomized to PCN/PLA and 5 were randomized to PLA/PCN. During the study, 5 of these 12 children had an increase in medication doses and an additional 4 medication-naive children commenced therapy. Medications were started or increased in 3 children during the active phase, and in 6 during the placebo phase. One child decreased his level of medication during the placebo phase.

There were 73 symptom exacerbations during the study (Table 1B and C). There were no differences in the distribution across the two phases (placebo = 38; penicillin = 35). Although repeated measures ANOVA (Table 3) showed significant improvement in the NIMH depression and anxiety scales during the active as compared to the placebo phase (df = 3,96, $F = 3.23$, $p = .03$; df = 3,99, $F = 4.63$, $p = .01$; respectively), this was not clinically significant as overall symptom severity was in the subclinical range. There were no significant between-phase differences in ratings of tic or OCD severity. Similarly, the GAS and CGI ratings were not significantly improved during the penicillin phase.

The parent global rating was obtained from 27 sets of parents and 22 (81%) were able to determine an improvement in behavior during one of the phases. Eighteen (82%) of these 22 parents correctly identified the active phase based on an improvement in behavior. In five subjects, there was no discernible difference between the two phases of the study and the parents guessed at the randomization order: two guessed correctly, the other three did not. Of the 22 parents who could discern a difference between the phases, the overall percentage of agreement was .82 between parent rating and correct phase, and a kappa of .61 indicated that these ratings were not merely chance occurrences.

## Discussion

We hypothesized that an improvement of neuropsychiatric symptoms would occur as a result of the prophylactic effect of penicillin. The presence of an equal number of streptococcal infections in both the active and placebo phases of the study indicates a failure to achieve the first aim of the study and therefore substantially decreased the chances of accomplishing the secondary aim. The number of exacerbations was similar in both phases and there were no significant changes observed in the tic and OCD ratings between the two phases. A statistically significant difference was observed in the scores of the depression and anxiety scales but since the scores were in the subclinical range, these were not considered clinically significant.

Failure to achieve adequate levels of prophylaxis could be due to a number of factors. Recommendations regarding the prevention of rheumatic fever state that prophylactic penicillin V may be given as an oral dose of 250 mg twice per day as an alternative to the use of intramuscular penicillin G (Dajani et al 1988). However, one recent study found that penicillin V blood levels drawn immediately before the fifth dose were undetectable (Thamlikitkul et al 1992), suggesting that the pharmacokinetics of oral penicillin V may be inadequate to maintain continued streptococcal prophylaxis. Identifying a more effective form of prophylaxis will be an important preparatory step when planning future studies. It should be noted that no method of prophylaxis will completely stop streptococcal infections since breakthrough infections occur even with intramuscular depot injections (Stollerman 1954; Wood et al 1964b; Newman et al 1984).

The incidence of infections in the group receiving active prophylaxis will decrease the effect size of a comparative study and increase the chance of producing a type II error. It is worthy of note that even in the rheumatic fever literature, the effect size was small and studies which firmly established the efficacy of streptococcal prophylaxis in the prevention of rheumatic fever enrolled from 100 to 500 patients in each treatment group (Rubbo et al 1949; Miller et al 1958b; Wood et al 1964a; Wood et al 1957; Massell et al 1957). It is likely that similar numbers will be required to definitively establish whether streptococcal prophylaxis will prevent exacerbations of tic or obsessive-compulsive symptoms in children with PANDAS. Based on the effect size in this pilot study, the lack of significant results could be due to a type II error,

Table 3. Neuropsychiatric Symptoms by Month of Study comparing Active with Placebo Phases ($n = 37$)

| | PCN | | | | | PLA | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Phase Month | Baseline | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | df | $F$ | $p$ |
| Rating Scales | | | | | | | | | | | | |
| GAS | 74.27 (10.83) | 74.07 (12.81) | 74.43 (11.13) | 74.43 (11.02) | 76.36 (10.31) | 74.00 (10.23) | 74.14 (10.21) | 76.93 (9.93) | 78.86 (11.67) | 3,39 | 0.91 | 0.41 |
| NIMH Scales | | | | | | | | | | | | |
| Depression | 2.18 (1.65) | 2.47 (1.26) | 2.23 (1.18) | 2.62 (1.46) | 3.00 (1.52) | 2.79 (1.72) | 2.79 (1.70) | 2.47 (1.37) | 2.70 (1.38) | 3,99 | 4.63 | .01 |
| OCD | 3.95 (2.16) | 3.85 (2.28) | 3.59 (2.06) | 3.68 (2.14) | 3.56 (2.27) | 3.76 (2.23) | 3.79 (2.57) | 3.47 (2.34) | 3.79 (2.42) | 3,99 | .86 | 0.45 |
| Global | 4.21 (1.41) | 4.45 (1.48) | 4.48 (1.62) | 4.54 (1.68) | 4.48 (1.82) | 4.54 (1.68) | 4.39 (1.98) | 4.21 (1.90) | 4.33 (1.76) | 3,96 | 1.00 | 0.39 |
| Anxiety | 2.95 (1.85) | 3.00 (1.56) | 2.91 (1.42) | 3.12 (1.71) | 3.33 (1.57) | 3.45 (1.79) | 3.45 (1.86) | 3.27 (1.77) | 3.27 (1.84) | 3,96 | 3.23 | .03 |
| CGI | | | | | | | | | | | | |
| Tic change | — | 3.77 (1.05) | 3.71 (1.35) | 3.32 (1.37) | 3.37 (1.59) | 3.84 (1.48) | 3.64 (1.62) | 3.26 (1.24) | 3.29 (1.35) | 3,90 | .05 | .97 |
| Global change | — | 3.89 (1.03) | 3.71 (1.21) | 3.61 (1.23) | 3.64 (1.57) | 4.39 (1.13) | 3.96 (1.48) | 3.78 (1.52) | 3.93 (1.51) | 3,81 | .32 | .76 |
| YGTSS | | | | | | | | | | | | |
| Combined | 15.36 (9.03) | 14.06 (8.08) | 13.55 (10.85) | 13.10 (10.66) | 13.39 (10.65) | 16.61 (10.82) | 14.34 (12.07) | 14.24 (10.08) | 12.97 (9.49) | 3,90 | 1.28 | .28 |
| Motor Tics | 9.36 (4.92) | 8.87 (5.21) | 8.61 (6.42) | 8.22 (6.51) | 8.35 (6.85) | 9.97 (6.32) | 8.87 (7.02) | 8.81 (6.13) | 8.00 (5.92) | 3,90 | .71 | .54 |
| Vocal Tics | 7.07 (4.82) | 5.19 (4.08) | 4.93 (5.45) | 4.87 (4.98) | 5.03 (4.60) | 6.64 (5.49) | 5.47 (5.71) | 5.43 (5.05) | 4.97 (4.81) | 3,90 | 1.13 | .34 |
| CY-BOCS | | | | | | | | | | | | |
| Obsessions | 4.40 (3.93) | 3.69 (4.28) | 3.65 (4.29) | 3.93 (4.41) | 3.27 (4.11) | 3.48 (4.24) | 3.55 (4.67) | 3.07 (3.98) | 3.96 (5.08) | 3,84 | 1.83 | .16 |
| Compulsions | 3.91 (4.46) | 3.59 (4.75) | 2.92 (4.47) | 3.30 (4.16) | 2.52 (3.90) | 2.56 (4.24) | 2.11 (3.58) | 1.96 (3.20) | 2.96 (4.93) | 3,78 | 2.44 | .08 |
| ASOT | 2.03 (1.39) | 2.06 (1.50) | 1.81 (1.20) | 1.97 (1.33) | 1.56 (0.98) | 2.09 (1.40) | 2.09 (1.55) | 1.97 (1.49) | 1.91 (1.40) | 3,93 | 2.10 | .13 |

Numbers, mean (standard deviation); GAS, Global Assessment Scale; NIMH, National Institute of Mental Health; CGI, Clinical Global Impression; YGTSS, Yale Global Tic Severity Scale; CY-BOCS, Child Yale-Brown Obsessions and Compulsions Scale; ASOT, Anti-streptolysin-O (numbers are coded according to dilution; 1 = <120; 2 = 240; 3 = 360; etc.).
Repeated measures ANOVA was used for all comparisons.

since at least 300 patients would have been required in each group to detect a significant difference between the two phases (using a power of 80%).

The cross-over design used in this study increased statistical power, but it may have introduced some possible confounds such as carryover and order effects. The pharmocokinetics of penicillin V would suggest that it ceases to protect that individual 24 to 48 hours after it is stopped (Thamlikitkul et al 1992). However, prevention of streptococcal infections depends not only on blood levels, but also on exposure to the offending pathogen. Theoretically, penicillin given during phase A would not only prevent streptococcal-triggered exacerbations during that phase, but this "protection" would continue until the next exposure to the streptococcal pathogen. In practice, 8 (61%) of the 13 infections in the children randomized to PCN/PLA occurred soon after the child had switched to the placebo compound. Cross-over effect attributable to the drug would not have been an issue for those children who were randomized to receive PLA/PCN. However, if an infection had occurred in the last month of the first phase, the antibody rise may not have been detected until the first visit of phase B; if the associated symptom exacerbation then occurred at that time or in the following month, both would have been counted against the active phase. To avoid these confounds, future studies should use a parallel design of sufficient duration to ensure that ratings will be obtained for several months after exposure to the streptococcus organism. In addition, the analysis should consider and control for factors such as seasonal variability of streptococcal infections. Information from the larger RF prophylactic studies cited above and more recent experience with streptococcal infections in the community (Kaplan et al 1998; Kaplan and Gerber 1998) suggest that in order to adequately address the hypothesis of this report, future studies should be at least 12 to 24 months in duration (personal communication, Kaplan E).

A number of other factors relating to the design and nature of the present study may have contributed to its failure to detect a difference between the active and placebo phases. Compliance is one such factor. Although parents and patients who took part in this trial were encouraged to take their medications as prescribed, other precautions to ensure compliance were not

employed. The majority of parents reported that their children had missed no more than one or two pills per month, but it is possible that lack of compliance may have been underreported and therefore, underestimated.

Violation of the blinding process in many clinical drug trials is brought about by medication side effects; the factor most likely to break the blind in the present study was the presence of a positive streptococcal throat culture. Although infections as a whole were evenly distributed across the two phases, 12 of the 15 positive throat cultures identified in this study occurred in the placebo phase. The presence of these identifiable infections may have biased the global ratings, since the parents would presume that the child got an infection because he or she was taking placebo. However, the parent global ratings were correct just as often in the children who did not have a positive throat culture (9 of 16, or 68%), as they were in those who had a positive throat culture (6 of 9, or 67%) suggesting that this potential bias was unlikely to have played a role in the ratings.

Although this study failed to provide support for the use of penicillin prophylaxis in children with streptococcal triggered OCD and tic disorders, there are a number of points that support the need for further research in this area. The unsatisfactory prophylactic efficacy of oral penicillin suggests that a better method of prophylaxis may increase the ability of a study to detect a difference between active and placebo groups. The results from the parent's ratings indicate that penicillin may have had an ameliorative effect on the baseline level of neuropsychiatric symptoms, even when exacerbations continue to occur. Indeed, the decline in depression and anxiety symptoms in the active phase may be a reflection of this overall improvement. However, the lack of effect on the primary symptoms of OCD and tics means that it is premature to recommend penicillin prophylaxis for children with OCD or tic disorders, even if it appears that their symptoms are triggered by streptococcal infections. Future studies are required, first to develop an effective method of streptococcal prophylaxis, and then to determine whether the potential risks of prolonged antibiotic administration are offset by the benefits of decreased neuropsychiatric symptomatology.

We are indebted to the many people who participated with us during this project, especially Dan Richter, Jason Zamkoff, Sara Dow, and the Pharmacy Department of the Clinical Center.

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