References

1. Aarsland D, Perry R, Brown A, Larsen JP, Ballard C. Neuropathology of dementia in Parkinson's disease: a prospective, community-based study. Ann Neurol 2005;58:773–776.
2. Compta Y, Parkkinen L, O'Sullivan SS, et al. Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? Brain 2011;134:1493–1505.
3. Kempster PA, O'Sullivan SS, Holton JL, Revesz T, Lees AJ. Relationships between age and late progression of Parkinson's disease: a clinico-pathological study. Brain 2010;133:1755–1762.
4. Bohnen NI, Kaufer DI, Ivanco LS, et al. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. Arch Neurol 2003;60:1745–1748.
5. Tiraboschi P, Hansen LA, Alford M, et al. Cholinergic dysfunction in diseases with Lewy bodies. Neurology 2000;54:407–411.
6. Meyer PM, Strecker K, Kendziorra K, et al. Reduced alpha 4 beta 2*-nicotinic acetylcholine receptor binding and its relationship to mild cognitive and depressive symptoms in Parkinson disease. Arch Gen Psychiatry 2009;66:866–877.
7. Litvan I, Goldman JG, Troster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 2012;27:349–356.
8. Di Lazzaro V, Oliviero A, Tonali PA, et al. Noninvasive in vivo assessment of cholinergic cortical circuits in AD using transcranial magnetic stimulation. Neurology 2002;59:392–397.
9. Nardone R, Bergmann J, Kronbichler M, et al. Abnormal short latency afferent inhibition in early Alzheimer's disease: a transcranial magnetic demonstration. J Neural Transm 2008;115:1557–1562.
10. Di Lazzaro V, Pilato F, Dileone M, et al. Functional evaluation of cerebral cortex in dementia with Lewy bodies. Neuroimage 2007; 37:422–429.
11. Di Lazzaro V, Oliviero A, Profice P, et al. Muscarinic receptor blockade has differential effects on the excitability of intracortical circuits in the human motor cortex. Exp Brain Res 2000;135:455–461.
12. Celebi O, Temucin CM, Elibol B, Saka E. Short latency afferent inhibition in Parkinson's disease patients with dementia. Mov Disord 2012;27:1052–1055.
13. Tokimura H, Di Lazzaro V, Tokimura Y, et al. Short latency inhibition of human hand motor cortex by somatosensory input from the hand. J Physiol (Lond) 2000;523(pt 2):503–513.
14. Sakuma K, Murakami T, Nakashima K. Short latency afferent inhibition is not impaired in mild cognitive impairment. Clin Neurophysiol 2007;118:1460–1463.
15. Tsutsumi R, Hanajima R, Hamada M, et al. Reduced interhemispheric inhibition in mild cognitive impairment. Exp Brain Res 2012;218:21–26.
16. Francis PT. Biochemical and pathological correlates of cognitive and behavioural change in DLB/PDD. J Neurol 2009;256(suppl 3): 280–285.
17. Di Lazzaro V, Pilato F, Dileone M, et al. Segregating two inhibitory circuits in human motor cortex at the level of GABAA receptor subtypes: a TMS study. Clin Neurophysiol 2007;118:2207–2214.
18. Di Lazzaro V, Pilato F, Dileone M, Tonali PA, Ziemann U. Dissociated effects of diazepam and lorazepam on short-latency afferent inhibition. J Physiol 2005;569:315–323.
19. Alle H, Heidegger T, Krivanekova L, Ziemann U. Interactions between short-interval intracortical inhibition and short-latency afferent inhibition in human motor cortex. J Physiol 2009;587: 5163–5176.
20. Udupa K, Ni Z, Gunraj C, Chen R. Interactions between short latency afferent inhibition and long interval intracortical inhibition. Exp Brain Res 2009;199:177–183.
21. Kish SJ, Rajput A, Gilbert J, Rozdilskv B, Chang LJ, Shannak K, Hornykiewicz O. Elevated gamma-aminobutyric acid level in striatal but not extrastriatal brain regions in Parkinson's disease: correlation with striatal dopamine loss. Ann Neurol 1986;20:26–31.
22. Emir UE, Tuite PJ, Oz G. Elevated pontine and putamenal GABA levels in mild-moderate Parkinson disease detected by 7 tesla proton MRS [serial online]. PLoS ONE 2012;7:e30918.
23. Halliday GM, Macdonald V, Henderson JM. A comparison of degeneration in motor thalamus and cortex between progressive supranuclear palsy and Parkinson's disease. Brain 2005;128:2272–2280.
24. Helmich RC, Baumer T, Siebner HR, Bloem BR, Munchau A. Hemispheric asymmetry and somatotopy of afferent inhibition in healthy humans. Exp Brain Res 2005;167:211–219.
25. Sailer A, Cunic DI, Paradiso GO, et al. Subthalamic nucleus stimulation modulates afferent inhibition in Parkinson disease. Neurology 2007;68:356–363.
26. Sailer A, Molnar GF, Paradiso G, Gunraj CA, Lang AE, Chen R. Short and long latency afferent inhibition in Parkinson's disease. Brain 2003;126:1883–1894.

Impact of Placebo Assignment in Clinical Trials of Tic Disorders

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ABSTRACT

Background: Understanding the impact of placebo treatment is pivotal to the correct interpretation of clinical trials. The aim of present study was to examine the placebo effect in tic disorders.

Methods: Raw data were obtained for 6 placebo-controlled parallel and cross-over trials that involved medical interventions for tic disorders. Tic severity was measured using the Yale Global Tic Severity Scale. Placebo effect was defined as an improvement of at least 30% over baseline scores in the total tic score and was considered clinically relevant when at least 10% of patients in the placebo-arm met that benchmark.

Results: In total, 91 placebo-treated patients (80% males; mean age, 16.5 years; standard deviation, 10.5 years) were included. Although there was a trend toward improvement in the total tic scores after placebo administration (P=0.057), the magnitude of the placebo effect was small (Cohen's d=0.16) but relevant (19% of the sample). Females were more likely than males to have a placebo effect.

Conclusions: The magnitude of the placebo effect in tic disorders appeared to be small. Further longitudinal studies using objective assessments for tic disorders are warranted to confirm the current results. © 2013 *Movement* Disorder Society

Key Words: placebo, tics, Tourette syndrome, movement disorders, clinical trials

Little is known about the placebo effect in tic disorders. Recent evidence suggests that a positive placebo effect is related to the activation of reward circuitry by the modulation of dopamine outflow in the nigrostriatal mesolimbic, mesocortical, and motivation circuits.[1–4] Consequently, especially in disorders involving dopamine neuroanatomy, the placebo effect may have important implications for the design of clinical trials and outcome measures and for the duration of clinical benefit. Identifying the placebo effect in tic disorders can be especially challenging considering the fluctuating course of the disease. To address issues of placebo-related clinical changes in tic disorders, we analyzed the magnitude of the placebo effect in data sets from randomized placebo-controlled trials for tic disorders.[5–10] We also investigated whether differences in trial design and baseline clinical and demographic characteristics could influence the likelihood of showing a positive response to placebo.

Patients and Methods

Study Selection

The following criteria were used to select relevant clinical trials: double-blind, placebo-controlled, longitudinal studies of patients who had chronic tic disorders or Tourette syndrome (TS) according to either the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition* or the Tourette Syndrome Classification Study Group[11,12] that used the Yale Global Tic Severity Scale (YGTSS)[13] as an outcome measure. In all included trials, the participants (children and adults) and the raters were blind to whether they were in a placebo group or an active treatment group.

TABLE 1. Clinical trials characteristics

Tic clinical trials	Age: Mean ± SD/median (range), y	Follow-up, weeks	Sex, % males
Total sample, N=91	16.5 ±10.5/13 (7–56)	2–10	80
Muller-Vahl et al.,[5] N=12 [1 parallel study]	32.8±9.4/31.5 (18–48)	10	75
Singer et al.,[9] N=32 [2 cross-over studies]	12.4±2.1/12.7 (12–17)	2	88
Cummings et al.,[10] N=12 [1 parallel study]	11.3±2.3/11 (8–16)	4	67
Scahill et al.,[6] N=18 [1 parallel study]	14.4±1.9/15 (12–18)	8	78
Scahill et al.,[7] N=17 [1 parallel study]	8.5±16.5/11 (6–55)	8	94

Abbreviations: SD, standard deviation.

The literature search covered January 1990 through June 2008 using the MEDLINE electronic database. The lead author (E.C.) contacted colleagues who had directed clinical trials with placebo arms that met the inclusion criteria. Five principal investigators consented to participate, and 6 studies could be included (4 parallel studies, including 3 American studies and 1 German study, and 2 cross-over American studies) (Table 1).[5–10] In all studies, placebo treatment was provided using a look-alike pill/capsule preparation similar in appearance to the "active" treatment. For parallel studies, the likelihood of being on placebo was 50%. For cross-over trials, only the first arm of the trial was included. All included studies were approved by the respective institutional review board, and all participants gave informed consent.

Endpoints

We used the YGTSS[13] as the clinical rating scale to assess disease severity. The YGTSS consists of separate severity ratings for motor and vocal tics scored from 0 to 50 points, producing the total tic score (TTS). The YGTSS also includes a subscale with an impairment scale (IS) scored from 0 to 50 points. Thus, the YGTSS score is the sum of the TTS and IS scores, ranging from 0 to 100.

Placebo Effect Definition

There are no established definitions of placebo effect in tic disorders. Based on prior studies of placebo effect in Parkinson's disease (PD) and Huntington's disease (HD),[14,15] and because, in many studies, a 30% tic reduction is regarded as an improvement, which calls for an intra-person and significant effect, a

30% improvement over baseline on the TTS was used as the benchmark. A clinically relevant population placebo effect was considered when at least 10% of the population in the placebo arm met the threshold for an intra-person placebo effect.

Data Analysis

Patients were classified as children, defined as age<18 years, or as adults (age≥18 years). For the run-in period, only 1 YGTSS measurement at baseline was available. Because we could not obtain consistent information on the presence of co-occurring disorders (attention deficit disorder, obsessive compulsive disorder, etc), this information was not included in our analysis. Baseline YGTSS scores were compared with the scores after placebo treatment using Wilcoxon signed-rank tests; for group differences (e.g., gender and age), we used Mann-Whitney tests. Analysis of covariance was used to establish homogeneity among the 6 trials with different designs. We used effect size (Cohen's d) to determine the magnitude of the placebo effect, which was calculated by dividing the mean change YGTSS scores by the standard deviation of the baseline score.

Primary outcome measures included overall placebo effect on the TTS and IS. To be eligible for analysis, patients had to have a score of at least 1 on items from the TTS and IS at baseline. Secondary outcome measures included the impact of demographic variables on the placebo effect (meeting the 30% improvement threshold on the TTS or IS) using a stepwise logistic regression analysis. In that regression analysis, the presence of a significant placebo effect was the response variable (yes vs. no), and the explanatory variables were demographics (age and gender). The analysis was performed using the IBM-SPSS Statistics 19 software package (SPSS, Inc., Chicago, IL). Statistical significance was set at $P \leq 0.05$ (2-tailed).

Results

A sample of 91 patients (80% males, 20% females) with tic disorders with a mean (±standard deviation) age of 16.5 7 years (±10.5 years; range, 6–55 years) were included (Table 1). In all studies there was at least 1 follow-up visit within 1 to 10 weeks after the baseline evaluation. The TTS was available in 85 patients (93%), and the IS in was available 51 (56%). Five patients (9%) were excluded for IS analysis, because they had a score of 0 at baseline. When the mean baseline YGTSS scores were compared, there were no significant differences between the parallel and cross-over studies using covariance analysis ($P=0.51$); therefore, the parallel and cross-over studies were combined for statistical analysis. Likewise, average baseline TTS and IS values also were similar when they were compared in terms of age and gender (Mann-Whitney test; $P>0.10$), except for lower scores in the baseline IS for adults compared with that for children (Mann-Whitney test; $P=0.05$). The mean scores at baseline and after placebo treatment for the TTS and the IS are shown in Table 2. There was a statistical trend toward improvement when the baseline and follow-up TTS and IS values were compared, especially for children. However, the magnitude of the placebo treatment was small (d=0.16), except for the female group (Table 2), but it was relevant (at least 30% improvement was observed in 17 of 85 patients [19%] for the TSS and in 20 of 51 patients [39%] for the IS).

Impact of Demographic and Clinical Variables on Placebo Effect

During the first follow-up visit, females were more likely to have a significant placebo effect in terms of the total TTS score (odds ratio [OR], 9.10; 95% confidence interval [CI], 1.88–44.03; Nagelkerke coefficient of determination [R^2]=0.21), and IS score (OR, 5.76; 95% CI, 1.19–27.81; $P=0.02$; $R^2=0.14$). Children also had a trend toward improvement in their TTS scores (OR, 10.50; 95% CI, 0.93–118.58; $P=0.057$). These models classified 50%, 36%, and 35% of the sample as having a significant placebo effect, respectively.

Discussion

To our knowledge, this is the first study analyzing the placebo effect in tic disorders. Our data were obtained from several data sets to avoid biases like sample selection, drug and measurement errors, small sample size, and small age range from a single study. We found that the magnitude of the placebo-induced improvements in motor and vocal tic severity and related impairment was small but clinically relevant. Females seemed to have a greater likelihood of showing a positive response to placebo compared with men, in contrast to PD or HD's studies, in which no gender differences were found in placebo responses.[14,15] It is noteworthy that children had a trend toward improvement after placebo treatment, perhaps reflecting the positive expectation of parents, who often serve as raters. A significant placebo effect also has been observed in adults who evaluate children with ADHD.[16] Therefore, both placebo effect and observer bias have the potential to inflate estimates of clinical response. Adults also have been considered inaccurate in their self-assessment of tic severity (up to 50% of adult patients who considered themselves tic-free still had objective evidence of tics).[17] In a recent study that used pramipexole in children with TS,[18] a high placebo response similar to that with the active drug was observed, resulting in an absence of significant differences between the 2 groups. Those authors reported that either a high placebo response in their participants or study-related factors, such as a larger number of enrolling sites and heterogeneity of investigator assessments, may have obscured true drug effects.

TABLE 2. Baseline versus follow-up Yale Global Tic Severity scores

Group	Mean scores ± SD		*P* value for baseline vs. follow-up scores: Comparison per group	Cohen's d for effect size
	Baseline score	First follow-up score		
Total tic scores				
Total sample	21.8±8.1	20.0±9.1	0.05	0.16
Children	21.0±7.7	19.6±9.1	0.08	0.18
Adults	23.8±8.3	23.1±8.7	0.30	0.08
Males	23.5±8.3	22.3±8.2	0.38	0.09
Females	20.7±6.6	18.2±11.1	0.18	0.37
Impairment scale				
Total sample	22.5±10.6	19.9±10.7	0.07	0.09
Children	22.0±12.0	18.0±12.2	0.08	0.19
Adults	12.2±10.9	11.1±11.6	0.34	0.00
Males	23.0±10.7	20.1±9.7	0.52	0.18
Females	20.4±10.3	18.6±16.8	0.68	0.19
Total YGTSS				
Total sample	42.0±18.5	37.3±19.2	0.11	0.21
Children	42.3±16.3	38.0±19.1	0.15	0.26
Adults	36.3±18.2	34.1±20.3	0.22	0.12
Males	48.2±17.2	39.6±16.6	0.67	0.13
Females	38.3±13.4	27.6±26.3	0.15	0.79

Abbreviations: SD, standard deviation; YGTSS = Yale Global Tic Severity score.

Limitations of our study include the relatively short-term period of observation and the small number of female participants. However, longer duration placebo-controlled trials could be a barrier for enrollment. Furthermore, this study does not allow us to examine the biochemical basis of the placebo effect in tic disorders. We recognize that several unexplored factors may explain our results without invoking a placebo effect, including the regression to the mean effect (a statistical phenomenon that occurs whenever a nonrandom population is selected), study design or scale-related bias, or nonspecific factors (e.g., Hawthorne effect, in which "patients can be polite and prone to pleasing the investigators by reporting improvements, even when there are none felt").[19] Likewise, it has been well established now that, in PD trials, the placebo effect is highly influenced and associated with physician expectation or bias regarding the putative effect of the therapy under scrutiny.[20] Perhaps we have included studies in which the expectation was low, conditioning, at least partially, the outcome.

In conclusion, the magnitude of the placebo effect in tic disorders seems to be small. Further longitudinal studies using objective assessments for tic disorders are warranted to confirm our results. ■

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References

1. De la Fuente-Fernandez R, Ruth TJ, Sossi V, et al. Expectation and dopamine release in Parkinson's disease: mechanisms of the placebo effect in Parkinson's disease. Science 2001;293:1164–1166.
2. Fricchione G, Stefano GB. Placebo neural systems: nitric oxide, morphine and the dopamine brain reward and motivation circuitries. Med Sci Monit 2005;11:54–65.
3. De la Fuente-Fernandez R, Schulzer M, Stoessl AJ. Placebo mechanism and reward circuitry: clues from Parkinson's disease. Biol Psychiatry 2004;56:67–71.
4. De la Fuente-Fernandez R, Schulzer M, Stoessl AJ. The placebo effect in neurological disorders. Lancet Neurol 2002;1:85–90.
5. Muller-Vahl KR, Schneider U, Koblenz A, Jobges M, Kolbe H, Daldrup T, Emrich HM. Treatment of Tourette's syndrome with Delta tetrahydrocannabinol (THC): a randomized crossover trial. Pharmacopsychiatry. 2002;35:57–61.
6. Scahill L, Chappell PB, Kim YS, et al. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. Am J Psychiatry 2001;158:1067–1074.
7. Scahill L, Leckman JF, Schultz RT, Katsovich L, Peterson BS. A placebo-controlled trial of risperidone in Tourette syndrome. Neurology 2003;60:1130–1135.
8. Smith-Hicks CL, Bridges DD, Paynter NP, Singer HS. A double blind randomized placebo control trial of levetiracetam in Tourette syndrome. Mov Disord 2007;22:1764–1770.
9. Singer HS, Wendlandt J, Krieger M, Giuliano J. Baclofen treatment in Tourette syndrome: a double-blind, placebo-controlled, crossover trial. Neurology 2001;56:599–604.
10. Cummings DD, Singer HS, Krieger M, Miller TL Mahone EM. Neuropsychiatric effects of guanfacine in children with mild Tourette syndrome: a pilot study. Clin Neuropharmacol 2002;25:325–332.
11. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Health Disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
12. The Tourette Syndrome Classification Study Group. Definitions and classification of Tic Disorders. Arch Neurol 1993;50:1013–1016.
13. Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, Cohen DJ. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry 1989;28:566–573.
14. Cubo E, Gonzalez M, del Puerto I, de Yebenes JG, Arconada OF, Gabriel y Galan JM; European Huntington's Disease Initiative Study Group. Placebo effect characteristics observed in a single, international, longitudinal study in Huntington's disease. Mov Disord. 2012;27:439–442.
15. Goetz CG, Leurgans S, Raman R, Stebbins GT. Objective changes in motor function during placebo treatment in Parkinson's disease. Neurology 2000;54:710–714.
16. Waschbusch DA, Pelham WE, Waxmonsky J, Johnston C. Are there placebo effects in the medication treatment of children with attention-deficit hyperactivity disorder? J Dev Behav Pediatr 2009;30:158–168.
17. Pappert EJ, Goetz CG, Louis ED, Blasucci L, Leurgans S. Objective assessments of longitudinal outcome in Gilles de la Tourette's syndrome. Neurology 2003;61:936–940.
18. Kurlan R, Crespi G, Coffey B, Mueller-Vahl K, Koval S, Wunderlich G; Pramipexole for TS Trial Investigators. A multicenter randomized placebo-controlled clinical trial of pramipexole for Tourette's syndrome. Mov Disord 2012;27:775–778.
19. Kohli E, Ptak J, Smith R, Taylor E, Talbot EA, Kirkland KB. Variability in the Hawthorne effect with regard to hand hygiene performance in high- and low-performing inpatient care units. Infect Control Hosp Epidemiol 2009;30:222–225.
20. Alterman RL, Tagliati M, Olanow CW. Open-label surgical trials for Parkinson disease: time for reconsideration. Ann Neurol 2011;70:5–8.