The impact of blinding on the results of a randomized, placebo-controlled multiple sclerosis clinical trial

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Article abstract—In the randomized, placebo-controlled, physician-blinded Canadian cooperative trial of cyclophosphamide and plasma exchange, neither active treatment regimens (group I: IV cyclophosphamide and prednisone; group II: weekly plasma exchange, oral cyclophosphamide, and prednisone) were superior to placebo (group III: sham plasma exchange and placebo medications) using the blinded, evaluating neurologists' assessments of disease course (primary analysis). All patients were examined by both a blinded and an unblinded neurologist at each assessment in this trial. We compared the blinded and unblinded neurologists' judgment of treatment response and analyzed the clinical behavior of patients who correctly guessed their treatment. The unblinded (but not the blinded) neurologists' scores demonstrated an apparent treatment benefit at 6, 12, and 24 months for the group II patients (not group I or placebo; $p < 0.05$, two-tailed). There were no significant differences in the time to treatment failure or in the proportions of patients improved, stable, or worse between the group II and group III patients who correctly guessed their treatment assignments and those who did not. Physician blinding prevented an erroneous conclusion about treatment efficacy (false positive, type 1 error).

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Investigators should take great care in planning treatment trials to ensure that the study design and conduct will adequately test their hypothesis.[1-3] A number of important variables must be considered in planning a trial or evaluating the quality of a completed study (eg, the need for randomization, physician and patient blinding, an assessment of the success of the blinding procedures, an estimate of the degree of compliance with the protocol, the inclusion of a suitable control group, the requirement to define the primary analysis before starting the trial, the adequacy of the sample size, the handling of withdrawals and patients lost to follow-up, and so on). However, few studies have addressed the relative contribution of these variables to the trial outcome.

The randomized, placebo-controlled, evaluating physician-blinded Canadian cooperative cyclophosphamide and plasma exchange trial[4,5] did not confirm earlier reports that either IV cyclophosphamide and ACTH[6] or the combination of oral cyclophosphamide, prednisone, and plasma exchange[7] offered a significant treatment advantage over a convincing placebo treatment in patients with progressive multiple sclerosis (MS). The paired evaluator design used in the Canadian trial[4] and the analysis of the success of the blinding gave us the opportunity to estimate the influence of physician blinding on the assessment of response to treatment in this controlled clinical trial.

Methods. *Treatment protocol.* The trial design and results have been published previously.[4] Briefly, patients with clinically definite or laboratory-supported definite,[8] progressive MS were randomized to one of three treatment programs. Group I received IV cyclophosphamide (1 gram alternate days adjusted to the white blood cell count) and prednisone (40 mg daily, tapered over 16 days); group II received weekly plasma exchange (20 weeks), daily oral cyclophosphamide (1.5 to 2.0 mg/kg for 22 weeks adjusted to reduce the white blood cell count), and alternate day prednisone (20 mg, tapered over 22 weeks); and group III received sham plasma exchange and placebo medications.

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Paired evaluator design. Each clinical assessment was performed consecutively by both a blinded (evaluating) and unblinded (treating) neurologist at 6-month intervals throughout the study (mean follow-up, 30.4 months). The Expanded Disability Status Scale (EDSS)[9] scores at each evaluation were compared with the enrollment score to determine improvement (≥1.0 EDSS fall), worsening (≥1.0 EDSS rise), or apparent stabilization (≤0.5 EDSS change). A treatment failure was defined as a worsening of the blinded evaluating neurologist's score by ≥1.0 EDSS points on two consecutive visits separated by at least 6 months.

Assessment of blindness. The treating neurologists and the patients randomized to group I were unblinded throughout the trial. The evaluating neurologists were blinded to the treatment assignment for all patients in the study. At the final assessment, the evaluating neurologists and the patients in groups II and III were asked to complete a questionnaire to determine the success of the blind. Neither group was told beforehand that they would be asked to complete this questionnaire, nor were they aware that their responses would be used to evaluate the effect of blinding upon assessing efficacy. The evaluating neurologists were asked to indicate whether the patient had been assigned to group I, group II, or group III, or to state that they did not know. Patients were asked whether they felt they had received the "real" plasma exchange treatment, the placebo (sham) treatment, or to state that they did not know. The evaluating neurologists completed this questionnaire on 135 of 165 final assessments (82%). Forty-seven of 57 group II patients (82%) and 39 of 56 group III patients (70%) provided this information. The importance of physician blinding was estimated by comparing the blinded evaluating (published primary analysis[4,5]) and unblinded treating neurologists' assessments of disease course following enrollment. We compared the clinical course of those patients who correctly guessed their treatment with those who guessed incorrectly or were unwilling to offer an opinion to estimate the impact of this degree of patient blinding on the response to these experimental treatments.

Results. *Success of the blind.* The evaluating neurologists felt that they could not identify the allocated treatment for 92% of the trial patients. For the 13 patients (8%) on whom an opinion was expressed, the treatment was correctly identified in eight and incorrectly identified in five. In spite of our attempts to blind the patients randomized to the active and placebo outpatient regimens (eg, double-blinded study for groups II and III) by following identical protocols, using paired dosage adjustments of placebo, and shielding the plasma exchange apparatus, 32 of 40 (80%) group II patients and 21 of 31 (68%) group III patients who offered an opinion correctly guessed their treatment assignments. Seven additional group II patients and eight additional group III patients were unwilling to offer an opinion about their treatment assignment ("did not know"). As such, 68% of group II patients (32 of 47) and 54% of group III patients (21 of 39) correctly identified the treatment they received. If patients were guessing their treatment groups, we would expect a 50% success rate. The number of correct guesses from those patients willing to express an opinion (32 of 40 group II and 21 of 31 group III patients) is significantly higher than 50% for both groups ($p = 0.0001$ for group II and $p = 0.0133$ for group III, one-tailed).

Table 1. p Value* of between-treatment comparison of proportion of subjects improved, stable, or worse

Assessment (no. pts)	IV cyclo versus placebo		PLEX versus placebo	
	Blinded	Unblinded	Blinded	Unblinded
6 Months (165)	0.159	0.069	0.246	0.047
12 Months (144)	0.295	0.084	0.086	0.004
18 Months (108)	0.418	0.255	0.106	0.072
24 Months (91)	0.088†	0.152	0.201	0.031
Final (mean, 30.4 months; 165)	0.290†	0.490	0.990	0.590

* Derived from chi-square test of the 2 (treatment) × 3 (improved, stable, worse) frequency table at each assessment point.
† Trend favoring placebo; all other comparisons favor active therapy.
IV cyclo Intravenous cyclophosphamide group (group I).
PLEX Plasma exchange group (group II).

Impact of physician blinding. The p values for the treatment comparison of the proportion of patients improved, stable, or worse at each assessment point are given in table 1 separately for blinded and unblinded assessors. The unblinded, treating neurologists' scores suggested a beneficial response to oral cyclophosphamide, plasma exchange, and prednisone treatment (group II) at 6, 12, and 24 months compared with the placebo treatment. A favorable trend was seen at 18 months, but not at the final follow-up assessment. The blinded evaluating neurologists' scores did not suggest a significant treatment advantage with this regimen, however (primary analysis[4,5]). Neither the unblinded nor the blinded neurologists' findings suggested a benefit from IV cyclophosphamide and prednisone (group I) compared with the placebo treatment. Indeed, at the 24-month follow-up, the blinded evaluating neurologists' assessment suggested a trend favoring the placebo group ($p = 0.088$, two-tailed). As illustrated in the figure, the unblinded treating neurologists recognized apparent clinical worsening earlier in the placebo patients and later in the group II patients compared with the blinded evaluating neurologists.

Impact of patient blinding. Table 2 illustrates a comparison of the clinical outcomes between the group II and III patients who correctly identified the treatment they received and those who were unaware or uncertain of their treatment assignment. The blinded evaluating neurologists' scores were used to determine clinical status. As shown, the clinical

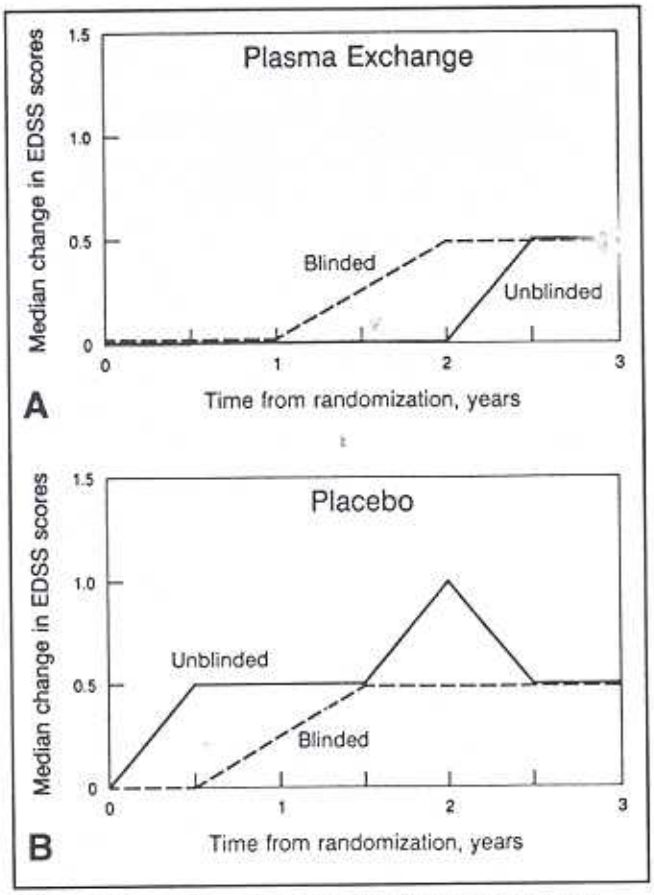

Figure. The median change in EDSS scores after randomization to either an active (A; plasma exchange, group II) or control (B; placebo, group III) treatment limb as recorded by the blinded, evaluating and unblinded, treating neurologists. An increase in EDSS indicates clinical worsening.

behavior of the patients treated with plasma exchange, cyclophosphamide, and prednisone (group II) did not differ significantly from the patients in the placebo group irrespective of the status of the patient blinding in the proportion of patients improved, stable, or worse. Similarly, there was no difference in the time to treatment failure by the techniques of survival analysis for either the patients who correctly guessed ($p = 0.47$, Breslow's test[10]) or did not know their treatment ($p = 0.19$). Within the treatment groups, the clinical course of the patients treated with plasma exchange, cyclophosphamide, and prednisone (group II), as well as the placebo-treated patients (group III), did not vary significantly between those who did and those who did not correctly guess their treatment assignments (data not shown).

Discussion. Physician blinding standardizes the way patients are observed and treated in controlled clinical trials and enhances the objective measurement of treatment responses. Unblinded physicians may inadvertently permit preconceived opinions about the value of various interventions (eg, study and placebo treatments) to influence patient care after randomization and, thereby, dismantle the gains achieved by randomization. Physician blinding is particularly crucial when subjective factors might influence the endpoint used for the primary analysis of a study.[2] In a placebo-controlled trial, patient blinding is essential to provide all participants with the opportunity to enjoy a placebo response. Patient blinding may be particularly important in clinical trials of experimental treatments in MS considering the marked daily variability in patient performance and the many factors that influence neurologic function (eg, intercurrent infection, fever, emotional fac-

Table 2. Impact of patient awareness of treatment assignment on the assessment of clinical outcome

		Patients *not knowing* their treatment			Patients *who correctly identified* their treatment		
Assessment	Status*	Group II *Received* PLEX	Group III *Received* placebo	*p* Value†	Group II *Known* PLEX	Group III *Known* placebo	*p* Value†
6 Months	Improved	3/15 (20.0%)	2/18 (11.1%)		5/32 (15.6%)	1/21 (4.8%)	
	Stable	11/15 (73.3%)	12/18 (66.7%)	0.57	24/32 (75.0%)	16/21 (76.2%)	0.42
	Worse	1/15 (6.7%)	4/18 (22.2%)		3/32 (9.4%)	4/21 (19.0%)	
12 Months	Improved	3/14 (21.4%)	1/13 (7.7%)		1/27 (3.7%)	0/21 (0.0%)	
	Stable	9/14 (64.3%)	9/13 (69.2%)	0.72	24/27 (88.9%)	15/21 (71.4%)	0.11
	Worse	2/14 (14.3%)	3/13 (23.1%)		2/27 (7.4%)	6/21 (28.6%)	
18 Months	Improved	2/10 (20.0%)	0/10 (0.0%)		2/24 (8.3%)	0/14 (0.0%)	
	Stable	6/10 (60.0%)	7/10 (70.0%)	0.63	18/24 (75.0%)	8/14 (57.1%)	0.20
	Worse	2/10 (20.0%)	3/10 (30.0%)		4/24 (16.7%)	6/14 (42.9%)	
Final (mean, 30.4 months)	Improved	1/15 (6.7%)	0/18 (0.0%)		0/32 (0.0%)	1/21 (4.8%)	
	Stable	9/15 (60.0%)	11/18 (61.1%)	0.71	19/32 (59.4%)	12/21 (57.1%)	0.55
	Worse	5/15 (33.3%)	7/18 (38.9%)		13/32 (40.6%)	8/21 (38.1%)	

* Blinded (evaluating) neurologists' scores used to determine clinical status, eg, improved: ≥1.0 EDSS fall; stable: ≤0.5 EDSS change; and worse: ≥1.0 EDSS rise.
† Chi-square derived from 2 × 3 frequency table at each assessment point.
PLEX Plasma exchange.

tors, fatigue, and so on). Although blinding is generally regarded as an essential feature of clinical trial design, few studies report either the success of the blinding procedure[11] or the influence of the integrity of the blind on the results of the trial.

The authors of the double-blinded, placebo-controlled, interferon beta-1b trial state that "the efficiency of evaluating-neurologist blinding ... was excellent."[12] The success of the blinding of the evaluating neurologists and patients and the influence of the blinding on the trial results were not reported, however, as all participants were still blinded at the time the report was published.[12] In a recent report describing the results of the evaluator-blinded, Northeast Cooperative Multiple Sclerosis Treatment study, the authors state that the evaluating neurologist was also the treating neurologist in 20 of the 21 participating centers.[13] In that four different treatment protocols were being tested in this trial, it is clear that the examining neurologists (like the patients) must have been unblinded in these 20 participating centers (171 of 256 study patients). The authors do not report the success of the physician blinding in the single center where two neurologists (one "single-blinded") were involved in the patient assessments.

Our study suggests that there would have been an important systematic bias if we used the unblinded treating neurologists' clinical assessments for the primary analysis. As shown in the figure, the unblinded treating neurologists were more likely to score the placebo-treated patients as being worse (and the plasma exchange-treated patients as being stable) compared with the blinded evaluating neurologists. This observation is significant since the evaluating physician is aware of the treatment received by the patient in clinical practice, case control studies, most pilot trials, and some randomized, clinical trials. This simple but crucial element of clinical trial design prevented a type 1 error (false positive) in the Canadian cooperative MS study.

Patient awareness of treatment assignment might be expected to have an effect on the response to an experimental therapy, irrespective of the biological efficacy of the active treatment. The "positive placebo response" might be magnified in patients enrolled in unblinded clinical trials and in patients who correctly guess that they have been randomized to receive an active treatment in a patient-blinded clinical trial (eg, group II patients in this study).[14,15] Similarly, patients randomized to receive a placebo (blinded trial) who believe that they have received the "active" treatment might be expected to respond more favorably than those who correctly think they have been randomized to the placebo group ("negative placebo response").[16] Although we could determine the impact of physician blinding upon the assessment of efficacy, we did not determine the certainty and duration of the patients' opinions about the treatment they received. Because of these limitations, we are unable to determine the relative impact on the response to these experimental treatments by this degree of patient unblinding compared with the setting in which a patient is completely unblinded from the moment of randomization. The magnitude of this positive (negative) placebo effect on the trial patients who were able to identify their treatment assignment is illustrated in table 2. These data suggest that the degree of patient unblinding in this trial (the ability to guess the assigned treatment at the final evaluation visit) did not alter the apparent response to intervention sufficiently to alter the conclusion of the primary analysis (no treatment effect).

As such, in this study, the bias introduced by physician unblinding would have contributed to an erroneous conclusion about treatment efficacy in what otherwise seems to have been a negative clinical trial. The potentially positive and negative effects of patient unblinding were not sufficiently powerful to influence the primary analysis, however. Attempts to blind clinicians and patients always complicate clinical trial design and sometimes fail. The degree of bias introduced by unblinding presumably varies widely among studies. In this controlled clinical trial, physician blinding was of paramount importance, and we encourage others to consider this observation in designing and reviewing future therapeutic trials.

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Familial vestibulopathy:
A new dominantly inherited syndrome

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Article abstract—Three patients who presented with episodic vertigo followed by gait imbalance and oscillopsia had profound bilateral vestibular loss despite normal hearing. All had a parent with similar findings. The patients, their affected parent, and multiple other family members had a history of migraine headaches, although several of the latter had normal vestibular function. Acetazolamide stopped or markedly decreased the frequency of vertigo attacks in the three patients treated but had little effect on the chronic vestibular loss. This is the first report of a dominantly inherited bilateral vestibulopathy associated with normal hearing.

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Bilateral vestibular loss typically presents with imbalance and head-movement-dependent oscillopsia (Dandy syndrome).[1,2] Ototoxic drugs are the most common cause, although many other inner ear disorders can produce the syndrome (eg, bilateral Meniere's disease, bacterial and syphilitic infections, trauma, etc).[3-5] Some ototoxins, such as streptomycin and gentamicin, are relatively specific for the vestibular system, whereas most other causes of Dandy syndrome also produce severe bilateral hearing loss. In 1989, we described 22 patients with normal hearing and bilateral vestibular loss of unknown cause.[6] All presented with imbalance—particularly prominent at night—but only a minority described head-movement-dependent oscillopsia. About half had prior episodes of vertigo (lasting hours to days), possibly due to viral vestibular neuritis.[7] We speculated that some of the patients may have had an inherited disorder, although we did not obtain a family history of similar problems in any of them.

A large number of inherited disorders result in combined auditory and vestibular loss.[8-11] Typically, such patients describe a slowly progressive imbalance and hearing loss, beginning in adulthood. We know of only one prior report of a familial bilateral vestibulopathy associated with normal hearing. Verhagen et al[12] described two brothers and a sister with bilateral vestibular loss and normal hearing, presumably inherited on an autosomal recessive basis. The mother and father each had large families, and none described any symptoms suggesting vestibular loss. The symptoms in these three patients began in infancy and may even have been present at birth. None of the three complained of vertigo attacks.

We recently saw three patients with Dandy syndrome and normal hearing who had a family history of similar symptoms. The initial symptom in each patient was brief episodes of vertigo, lasting a minute or so, followed years later by progressive bilateral vestibular loss. None was exposed to known ototoxins. In each case, one parent had bilateral vestibular loss, suggesting a dominantly inherited vestibulopathy syndrome.

Case reports. Patient 1. A 34-year-old man had experienced recurrent brief episodes of vertigo followed by progressive imbalance and unsteadiness of gait. His attacks of vertigo typically lasted about a minute and have occurred about three or four times a month for the past 6 years. These attacks came on abruptly without warning

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