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**A Representative Survey of M.S. Patients on
Attitudes toward the Benefits and Risks of Drug Therapy**

John E. Calfee*

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Executive Summary

Background: Although M.S. patients face significant trade-offs between risks and benefits of drug therapy, little is known of their attitudes toward these risks and benefits.

Methods: A representative telephone survey of 200 patients with relapsing remitting M.S.

Results: Respondents suffered substantial disability, most of them requiring a wheel chair or support for walking any significant distance, and over half suffering relapses in the past year. All were on drug therapy; half had switched drugs; 1/3 had switched at least twice. Most patients had seen their neurologist at least 4 times in the previous two years and said they and their physician were equally involved in drug decisions. About 55% said they would definitely or probably use a drug that significantly reduces frequency of relapse or progression in disability even if the drug involves a 1-in-1,000 chance of a fatal side-effect. Willingness to tolerate risk bore little relationship with disability levels. A substantial majority agreed that the FDA should tightly control drugs with safety concerns, but a larger majority agreed that once the FDA has provided a warning, patients should be free to decide with their physician whether to use such drugs. Virtually all said they were willing to visit their neurologist more often in order to use risky drugs.

Conclusions: M.S. patients are accustomed to playing a large role in their own drug therapy but do so in close collaboration with their physicians. After the FDA has reviewed drug safety and provided reasonable warnings, many M.S. patients wish to be free to choose to incur a 1-in-1,000 (or even greater) risk of a fatal side-effect in return for significantly more effective drugs, and are willing to work with the physicians in doing so.

A Representative Survey of M.S. Patients on Attitudes toward the Benefits and Risks of Drug Therapy

John E. Calfee

1. Background

Patients and their physicians almost always face trade-offs between risks and benefits in drug therapy. Often, the trade-offs involve treatments that provide exceptional benefits even as they pose significant risks of serious adverse events. Little is known, however, of how often patients confer with their physicians to discuss these trade-offs, the extent to which they work with their doctors to monitor side-effects and therapeutic progress, and perhaps most important of all, what choices they would make when faced with a specific set of odds.

Multiple Sclerosis (M.S.) is a degenerative disease of the central nervous system that usually strikes in late youth or in mid-life and typically progresses to severe disability and sometimes death, but does so at highly varied and unpredictable rates. Although several disease-modifying drugs have been approved by the Food and Drug Administration (FDA) for M.S., most have strong and sometimes dangerous side-effects, and none have been confirmed to halt progression of the disease. Newer drugs could, at least in principle, offer the prospect of retarding progression but at the risk of rare but severe side-effects.

Natalizumab (Tysabri; Biogen-Idec and Elan) is a humanized monoclonal antibody that offers such a trade-off. Natalizumab was approved in November 2004 for treatment of relapsing M.S. after clinical trials demonstrated dramatic reductions in relapses and the number of new brain lesions.² In February 2005, however, the drug was voluntarily removed by its manufacturer after the discovery of two cases, one fatal, of progressive multifocal leukoencephalopathy (PML). PML usually results from reactivation of the JC virus, which is frequently present in humans but is sufficiently suppressed by the immune system to prevent inflammation of the brain (Berger and Koralnik 2005). In this instance, the two cases of PML occurred in clinical trials of M.S. patients in which natalizumab was administered as co-therapy with interferon beta-1a (Avonex; Biogen-Idec) (Kleinschmidt-DeMasters and Tyler 2005).

² Results from the AFFIRM and SENTINEL trials are summarized in the FDA approved drug label available at <http://www.fda.gov/cder/foi/label/2004/125104lbl.pdf>. Natalizumab reduced the rate of relapse by 66% relative to placebo in the AFFIRM monotherapy trial, and by 54% relative to placebo plus Avonex in the SENTINEL add-on trial.

Another PML fatality (originally thought to be astrocytoma, a brain tumor) was later discovered during a safety review of patients in a clinical trial on Crohn's disease (Van Assche, et al. 2005). Although the PML had clearly occurred after re-initiation of natalizumab monotherapy, the patient had previously been treated with immuno-suppressive drugs. On Sept. 26, 2005, after a thorough exploration of data from clinical trials and commercial usage of natalizumab revealed no additional cases of PML, Biogen-Idec and Elan applied to the FDA for permission to resume marketing of the drug. On Nov. 17, the FDA granted priority review of this application, and on Feb. 15, 2006, the FDA lifted its hold on clinical trials for patients with M.S.

On March 7-8, 2006, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee met to consider Biogen-Idec and Elan's request to resume marketing. Shortly before the advisory committee meeting, the *New England Journal of Medicine* released four articles on natalizumab. Two articles reported two-year results from the two pivotal trials underpinning FDA's original approval of natalizumab. In a placebo-controlled trial, natalizumab reduced disability progression by 42% (17% vs 29%) and the one-year relapse rate by 68% (confirming results from the first year of the trial), and led to 83% fewer enlarging brain lesions (Polman, et al. 2006). A combination therapy trial comparing natalizumab plus interferon beta to interferon beta plus a placebo generated roughly comparable results (Rudick, et al. 2006). Yousry, et al. (2006) reported on a post facto surveillance examination of possible PML cases in 3,116 patients in 11 trials, finding no new cases of PML beyond the 3 cases discovered at the time of natalizumab's withdrawal. An accompanying editorial by Ropper (2006) pointed out that the 68% and 83% decreases in relapses and enlarging brain lesions, respectively, compared very favorably to the 1/3 reductions typical of approved disease-modifying drugs. Ropper also noted that rates of relapse and clinical progression in the placebo and interferon groups were quite similar, "emphasizing again the unimposing effects of the current generation of treatments." Finally, Ropper concluded "It seems that less than two years of treatment with natalizumab alone is relatively safe, but the possibility remains that PML will develop in 1 in 1000 patients."

The FDA Advisory Committee voted unanimously in favor of returning Tysabri to the market, and narrowly recommended (by a 7-to-5 vote) Tysabri as a first-line therapy. Considerable discussion centered on risk management without any votes on specific measures. As of this writing, the FDA has not published a decision on any of these questions, but will almost certainly do so very soon.

These circumstances reinforce the importance of assessing how M.S. patients view the effects of M.S. and the various trade-offs involved in drug therapy. To investigate these issues, the author designed a telephone survey of relapsing remitting M.S. patients. The survey was funded by Biogen-Idec, co-marketer of natalizumab. The survey was constructed in collaboration with two survey researchers at Roper Public Affairs, part of GfK NOP, an international market research firm.³ These researchers and their colleagues possess considerable experience in surveys of patients and physicians. They wrote most of the survey instrument, constructed a sampling frame, recruited subjects, supervised the interviews, and collected the results. The author also consulted Biogen-Idec personnel with a knowledge of M.S. patients and the medical literature on M.S. treatments.⁴

2. Methods

Sample

To avoid potential biases in convenient lists of M.S. patients (e.g., of patient group members or of patients who had participated in other surveys), physicians on the American Medical Association's list of practicing neurologists were asked to recruit patients from their practice to participate in the survey.⁵ The list includes both members and nonmembers and is apparently comprehensive. Physicians who responded but did not treat adult M.S. patients were screened out during the initial telephone contact. Physician recruitment involved multiple telephone contacts and, where fax numbers were available, faxes that explained the purpose of the study and asked neurologists to call a toll-free number. Those who agreed to participate received follow-up faxes containing information for initiating patient interviews. Additional reminder faxes and telephone calls were used to increase participation. To protect patient confidentiality, neurologists were not asked for names or any other identifying information about the patients being recruited. Rather, patients were asked by their physicians to call a toll-free number to complete the interview.

³ The researchers were Sally Daniels and Staats Abrams.

⁴ The main contribution from Biogen-Idec personnel was a suggestion that we construct questions to generate data to facilitate rough comparisons with the EDSS scale, discussed in a later footnote. The survey also contains two questions about Tysabri at the end, after all but demographic questions had been answered.

⁵ The sample was supplemented with a few patients who treated by neurologists but were recruited through other health care workers. As indicated in the appendix, 4 of the 200 respondents fell into this category.

A total of 207 neurologists agreed to participate by recruiting four patients, two male and two female. Because experience has shown that female respondents are more likely than males to actually participate, the final achieved sample was expected to be (and in fact turned out to be) close to the 2/3 female and 1/3 male distribution of M.S. patients in the United States. Patients were eligible if they were 18 years of age or older, suffered from relapsing remitting multiple sclerosis, and were currently or had previously been on drug therapy for M.S. As incentives, neurologists were promised that each qualified patient who participated would receive a check for \$50 on completion of the study and the neurologist would also receive \$50 for each of these patients, which the neurologist could choose to be sent to him or her directly or donated to the National Multiple Sclerosis Foundation (which was not involved in this survey). Interviews began approximately Jan. 1, 2006.

Questionnaire

The study sponsor was not identified. Pretest interviews were used to ensure that questions were clear and easy to answer and that the interview length was within the maximum 20 minutes that had been determined as appropriate for this group of respondents. The survey instrument is contained in the appendix as a posted questionnaire.

3. Results

This paper presents the results for 200 interviews. The appendix contains the posted questionnaire, which shows percentage responses for all questions.

The average age of respondents was 43 years. Seventy percent were female. Educational attainment was generally high: 75% had completed at least some college work, 36% were college graduates, and 17% had completed at least some graduate work (Questions D-1 through D-3).

All patients had relapsing M.S. Ninety-seven percent were currently on drug therapy, and the others had been on drug therapy in the past (Questions S3-S4). Almost half (45%) had received a M.S. diagnosis in the past 5 years (11% in the previous year), and 32% were diagnosed more than 10 years ago (Question 2).

Impact of M.S.

Two-thirds rated their health as excellent (17%) or good (51%) (Question 1). Nonetheless, 29% said that M.S. has a “great deal” of effect on their quality of life and 34% said it had a moderate effect. Responses were similar when patients were asked to what extent M.S. limits their activities: 23% said a great deal; 34% said a moderate amount (Questions 3-4). One question asked about the extent to which specific symptoms are a problem. The responses are summarized in Table 1. It can be seen that all six symptoms were either major or minor problems for the great majority of respondents. Fatigue was especially prevalent (a major problem for 59%).

Table 1
Symptoms as Problems

Symptom (randomized order)*	Major problem	Minor problem	Not a problem at all	Don't know
Becoming very tired	58%	35	7	1
Difficulties walking, or the inability to walk	34%	43	23	1
Numbness -- in your arms, legs, hands or feet	35%	46	19	--
Problems with your vision	19%	46	35	1
Problems thinking or concentrating	26%	53	22	--
Feeling depressed or sad	26%	44	30	1

Source: Survey Question 5 (see appendix).

* The order in which the statements were read to interviewees was random.

A series of questions asked about impaired mobility (Questions 6-9B).⁶ Nine percent said they use a wheel chair half or more of the time, while 53% said they never use one.

⁶ This series of questions was designed to track, insofar as seemed practical, the Expanded Disability Status Scale (EDDS) designed by Kurtzke (1983).

Twenty-one percent said they use a cane, crutch, or other support always or nearly always, and 62% said they do so at least occasionally. Twenty-five percent said they can never walk a distance of 3 blocks without a cane or other support, and another 15% said they can only occasionally walk 3 blocks. When asked whether they can walk a distance of 25 feet without a cane or other support, 17% said never or only occasionally and another 5%, about half the time. (All percentages are of the total sample, not the sample that remained after earlier questions. For example, 25% of the entire sample could not walk unsupported for 3 blocks and 17% said they never or only occasionally are able to walk a distance of 25 feet.)

Relapses (“flare-ups or attacks”) were fairly common. Only 24% of respondents had not suffered any in the past year. About half (49%) had suffered 1 or 2 relapses, 14% had suffered 3 or 4, and 11% had suffered 5 or more (Question 10).

Patients’ relationship with their neurologist

Several questions explored the patients’ relationship with their neurologists. Asked how often they had seen their neurologist in the previous two years, 39% said they had done so 4 to 6 times and another 35% said they had seen their neurologist more than 6 times. Only 3% said they had seen their neurologist but once, and only 1% said they had not done so at all in the past two years.⁷ Approximately two-thirds (62%) said they talk to their neurologist about drug side-effects in half or more of their visits (34% said they did so almost every time), and 38% said less than half the time or almost never (26%). (We did not ask interviewees which drug they were taking or whether their treatment involved multi-drug therapy.) Additional questions, described below, focused on how patients work with their physicians when deciding about drug therapy.

Current drug therapies

Four questions asked patients about their experience with drug therapy. Practically everyone (99%) had used an injectable drug (Question 11), hardly a surprise because the dominant M.S. drugs are injectable (although noninjectables are sometimes prescribed to reduce inflammation during attacks). Asked to apply a worst-to-best 1-to-10 scale to “how well the drugs currently available for treating M.S. meet your needs,” 61% assigned ratings of 8 to 10,

⁷ Because neurologists essentially drew a convenience sample of their patients, subject to an even gender split, we would expect our sample to be biased toward patients who visit their physician more frequently than the average patient.

and only 6% gave ratings of 1 to 3; the average was 7.7. (This question did not specifically ask about the drug or drugs that respondents were taking at the time.) Fifty-five percent had never switched drugs. Others had switched once (18%), twice (12%), three times (10%), or more than three times (6%). Thus more than one-fourth had switched therapies at least twice (Question 15). Those who had switched were asked about several possible reasons, with the responses tabulated in Table 2.

Table 2
Reasons for Switching Drug Therapy

Reasons for switching drug therapy (order randomized)	Major reason	Minor reason	Not a reason at all	Don't know
The effectiveness of the drug in controlling your M.S.	60%	21	18	1
Concern about, or experience with side-effects	53%	12	33	2
The frequency with which you were required to have injections	20%	17	62	1
The way in which the drugs were administered -- that is, by pill, injections, etc.	20%	13	66	1
Cost or insurance factors	15%	5	79	--
Other factors	43%	12	43	2

Source: Survey Question 16 (see appendix).

The main reasons for switching, unsurprisingly, were effectiveness (a major reason for 60% of respondents) and side-effects (53%). Only 18% said effectiveness was not a reason at all, while 33% said side-effects were not a reason. Only 20% said administration (injections versus pills) was a major reason, but again, all the dominant drug therapies are administered by injection. A substantial proportion (43%) cited “other factors” as a major reason for switching. We did not explore this choice in the interviews (which were already rather long). We suspect that “other factors” includes such basic influences as physicians’ recommendations to make a

change. The very low numbers who responded “don’t know” to all choices are remarkable. They suggest that virtually all patients were consciously involved in decisions about drug therapy. This implication is also consistent with responses to later questions in the survey.

Importance of improved drug therapies

Question 17 asked about five ways in which drug therapies could be improved, with respondents applying a 10-point scale from least to most important. The results are presented in Table 3.

Table 3
Relative Importance of Possible Improvements in Drug Therapy

Possible improvements (order randomized)	Not important (bottom 3: 1, 2, & 3)	Important (top 3: 8, 9, & 10)	Mean	Don't know
More effective in reducing frequency of relapse	1%	95%	9.6	1%
more effective in slowing down progression of disability	1%	98%	9.8	1%
more effective in reducing the number of brain lesions	1%	95%	9.7	1%
more effective in reducing effects of M.S. on mental abilities or thinking	1%	88%	9.3	1%
more effective in slowing the development of physical disabilities	1%	97%	9.8	1%

Source: Survey Question 17 (see appendix).

The results speak for themselves. Almost all respondents rated all five improvements as very important, although preventing cognitive decline was somewhat less important than the others (an average rating of 9.3 vs 9.6 to 9.8).

Safety of current drugs

The interviewers asked patients how satisfied they were with the *safety* of currently available drugs (not the specific drug or drugs they were taking). Forty-nine percent said they were very satisfied and 40% said they were moderately satisfied (Question 18).

Tolerating risks in more effective drugs

Two questions asked patients about whether they would use a more effective drug if it had rare but fatal side-effects. Question 19 began: “If there were a drug treatment for M.S. that was significantly more effective than currently available drugs at slowing down the progression of disability, how likely would you be to use the drug if . . .” The alternatives were “1-in-1000 M.S. patients who took the drug died as a result?,” followed by a 1-in-500 chance, a 1-in-100 chance, and a 1-10 chance. Table 4 tabulates the responses.

Table 4
Risk-Benefit Tolerance for Progression of Disability

Side-effect fatality rate	Definitely would	Probably would	Probably would not	Definitely would not	Not asked: would not use even with better odds	Don't know
1-in-1,000 M.S. patients who took the drug died as a result?	14%	41%	28%	17%	--	1%
1-in-500 died as a result	8%	24%	34%	19%	17%	--
1-in-100 died as a result	3%	15%	21%	26%	35%	1%
1-in-10 died as a result	4%	10%	13%	13%	61%	1%

Source: Survey Question 19 (see appendix).

Before considering these data, we should see the results of Question 20, which was identical except that it referred to a drug treatment that was significantly more effective “at preventing relapses.” Table 5 tabulates the results for Question 20.

Table 5
Risk-Benefit Tolerance for Prevention of Relapse

Side-effect fatality rate	Definitely would	Probably would	Probably would not	Definitely would not	Not asked: would not use even with better odds	Don't know
1-in-1,000 M.S. patients who took the drug died as a result?	19%	38%	25%	19%	--	--
1-in-500 died as a result	8%	26%	29%	19%	19%	--
1-in-100 died as a result	4%	15%	17%	27%	38%	--
1-in-10 died as a result	5%	8%	12%	12%	65%	--

Source: Survey Question 20 (see appendix).

Because the results for Questions 19 and 20 are quite similar, I focus on Question 19, which asked about a drug that would significantly retard the progression of disability. First, note that the “not asked” column is the cumulative percentage of respondents who had already said they would definitely not use the drug when it involved better odds, i.e., a smaller likelihood of a fatal side-effect. Thus in Table 4, the first four cells in the 1-in-500 row break down the responses of those who were not among the 19% (cell 5) that had already said they would not consider using the drug if it involved a 1-in-1000 risk. Also, the 17% figure representing those who definitely would not try the drug with a 1-in-1000 risk is not directly comparable to the 13% “definitely-would-not” figure for the 1-in-10 risk; the latter number represents a proportion of respondents who have already said they would at least consider using a drug with higher risk levels and thus is a proportion of a different group.

Perhaps the most striking result is simply that 55% of the sample definitely or probably would use a drug that involves a 1-in-1000 risk of a fatal side-effect if the drug were

significantly more effective than current ones at retarding the progression of disability, and that 32%, 19%, and 14%, respectively, definitely or probably would use such a drug if it posed a 1-in-500, 1-in-100, or 1-in-10 risk, respectively. Also notable is the steady reduction in willingness to use the drug as risk increased, and the fact that virtually no one responded “don’t know” when asked about these trade-offs. The numbers are roughly the same for question 20, about a drug that is significantly more effective at preventing relapses.

These results raise at least two questions. One is whether the willingness to tolerate risk is closely related to the disability level of the respondents. Somewhat to my surprise, there was little evidence of this. Analysis of cross-tabulations for the question about a drug that reduced progression in disability revealed that levels of risk acceptance were relatively consistent among patients of differing circumstances. For example, 50% of patients with no difficulties in walking said they definitely or probably would use the drug with a 1-in-1,000 risk, as did 52% of those who always use a cane or other support and two-thirds of respondents who occasionally use support. Breaking down responses according to frequency of relapse, the percentages that probably or definitely would use the drug were 50%, 54%, 64%, and 62% for those who had incurred 0, 1-2, 3-4, or 5 or more relapses, respectively. These data suggest that the prospect of retarding progression and preventing relapses can be appealing to patients of essentially any stage in M.S. progression.

A second issue is whether patients are inclined to choose a drug with a significant mortality risk more or less on their own, as opposed to doing so only after close consultation with their physician. We posed a series of questions to address that topic.

The role of patients, physicians and the FDA

Two questions addressed the roles of physicians, the FDA and patients themselves in making decisions about M.S. drug therapy. Question 21 provided a series of statements and for each, asked how true the statement was for the respondent. The results are presented in Table 6.

Table 6
How Drug Therapy Decisions Are Made

	Completely true	Partly true	Not true at all	Don't know
Your doctor makes the decisions for you	12%	32%	56%	--
Your doctor and you discuss the options and are equally involved in the decision	80%	16%	4%	1%
Your doctor makes recommendations and then you make the decision	73%	25%	3%	--
You request a drug therapy and your doctor prescribes it	37%	32%	30%	1%

Source: Survey Question 21 (see appendix).

Clearly, patients rarely leave everything to their neurologist. Instead, they typically discuss options with their physician and make a decision only after obtaining a recommendation. The fact that a substantial proportion (37%) requests a therapy that the doctor then prescribes is not readily interpretable. The interpretation that seems most consistent with the very high agreement levels with the two previous responses (96% and 98% for the combined “completely” and “partly” true categories) is that in many situations the physician is comfortable with prescribing what the patient requests, perhaps after explaining that the patient must ultimately make the decision.

Question 22 asked about the roles of the patient, her or his physician, and the FDA: “Patients have different feelings about how much they, their doctors, or government agencies such as the Food and Drug Administration (the FDA), should be involved in the decision about the drugs they will use to treat M.S. As I read to you some statements that people might make, please tell me how much you agree or disagree with each of these.” The results are presented in Table 7.

Table 7
Patient, Physician, and FDA Involvement
in Drug Therapy Decisions

Statement (order randomized)	Agree completely	Agree somewhat	Disagree somewhat	Disagree completely	Don't know
I am capable of making my own treatment choices, based on the information and advice I get from my doctor.	71%	24%	3%	3%	--
I would like to be able to choose a drug, in consultation with my doctor, that is more effective, even if it is also riskier.	49%	28%	13%	10%	1%
The FDA should tightly control the use of drugs that might have safety concerns.	54%	32%	10%	5%	--
If a drug has safety concerns, the FDA should warn people, but I should be free to decide with my doctor whether to use those drugs or not.	71%	19%	5%	6%	--
I would be willing to visit my doctor more often than usual if that was required to be able to use a drug that was more effective	81%	17%	2%	1%	--

Source: Survey Question 22 (see appendix).

The responses suggest a subtle mix of patient autonomy and patient reliance upon physicians and the FDA. (In assessing the results, we should bear in mind that the alternatives were offered in random order.) Virtually everyone agreed (71% completely and 24% somewhat) that they were capable of making their own decisions about drug therapy based on “information

and advice” from their physician. Eighty-six percent completely or partly agreed that the FDA should “tightly control” drugs with safety concerns, but 90% (71% completely, 19% partly) thought that after being warned by the FDA, they should be free to decide with their doctor whether to use such drugs. About half (49%) agreed completely (and 28% agreed partly) that they should be free to choose with their physician a drug that is both more effective and riskier. Finally, overwhelming majorities agreed (81% completely) that they would be willing to visit their physician more often, if necessary, to use a more effective drug.⁸

A recently withdrawn M.S. drug

The last two substantive questions (23 and 24, placed immediately before demographic questions) asked the patients whether they had heard or read about an M.S. drug that was introduced in 2005 but then taken off the market because of serious side-effects. Overall awareness was substantial. Twenty-six percent said this was something they read or heard about a great deal, and another 29% said, a moderate amount, and 23%, only a little. Respondents in those categories were asked if they could tell the interviewer the name of the drug; 34% (of the entire sample) correctly identified the drug as Tysabri.

4. Discussion

The results reported here came from interviews with a representative sample of 200 relapsing remitting M.S. patients recruited from a census of neurologists. Most of them thought M.S. symptoms were a major or minor problem in their lives. Disability levels were substantial, as 9% used a wheel chair half or more of the time, 21% used a cane or other support most of the time, 62% required support for walking at least some of the time, and 25% could not walk a distance of three blocks without support. Over half had suffered relapses in the past year.

Screening ensured that all patients were experienced with drug therapy. About half had switched drugs, and about one-third had switched at least twice. The usual reasons were effectiveness and side-effects. The patients were very interested in improved drug therapy, especially in terms of preventing relapse, disease progression, physical disability, and the number of brain lesions.

⁸ An anonymous reviewer pointed out that because respondents were recruited by neurologists, they might have closer relationships with their neurologist than the typical patient. I cannot rule out this possibility.

Many of the patients were prepared to incur a risk of fatal side-effects in return for more effective drugs. Nineteen percent said they definitely would take a drug that significantly reduces relapse frequency even it involves a 1-in-1,000 chance of a fatal side-effect, and 14% said they would take a drug with the same risk in order to significantly reduce disability progression. An additional 40% of so said they would probably take such drugs. Willingness to tolerate risk bore little relationship with disability levels.

The patients also had strong feelings about the environment in which they would exercise such choices. A substantial majority agreed that the FDA should tightly control drugs with safety concerns, but an even larger majority agreed that once the FDA has provided a warning, they should be free to decide with their physician whether to use such drugs. Virtually all said they would be willing to visit their neurologist more often if that was required. As it was, nearly three-fourths had seen their neurologist 4 or more times in the previous 2 years, usually talking about drug side-effects in those visits. The bulk of the patients also reported that they and their neurologists were equally involved in making drug treatment decisions.

These results strongly suggest, first, that M.S. patients are accustomed to playing a large role in their own drug therapy but do so in close collaboration with their physicians; and second, that after the FDA has reviewed drug safety and provided reasonable warnings, many M.S. patients are prepared in a reasoned manner to incur a 1-in-1,000 (or even greater) risk of a fatal side-effect in return for significantly more effective drugs, and are willing to work with the physicians in doing so.

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Appendix:

**Survey of MS Patients
PRELIMINARY Posted Questionnaire, March 3, 2006
Base: 200 respondents**

All percentages based on full sample of 200 respondents unless otherwise indicated. This includes 196 patients of neurologists from the AMA list and 4 patients of other health care providers.

*** represents less than 0.5%
-- represents zero**

Introduction and Screener (Respondents calling in to an 800 number)

Thank you very much for calling us. We are conducting a survey among people who are being treated for MS – Multiple Sclerosis. We are interested in learning about your experiences and your opinions about different options for treating MS.

We are not selling anything. Your responses will be held in the strictest of confidence and reported out only in combination with the responses from all other survey participants.

S1. Are you 18 years or older?

Yes100% (CONTINUE)
No.....-- (THANK & TERMINATE)

S2. As you probably know, there are two main types of MS -- “Relapsing MS,” and “Progressive MS.” Which of these two types of MS do you have?

IF NEEDED:

“Relapsing MS” includes relapses – times when the symptoms become worse – followed by times of remission, when you recover from most of the symptoms you had during the relapse.
“Progressive MS” is a more steady increasing of symptoms over time, without those relapses and recoveries.

Relapsing MS.....100% (CONTINUE)
Progressive MS-- (THANK & TERMINATE)
(VOL.) Both.....-- (THANK & TERMINATE)
(VOL.) Don’t know-- (THANK & TERMINATE)

S3. Are you currently being treated by drugs for your MS?

Yes97% (SKIP TO Q1)

No.....4 (ASK S4)
 (VOL.) Don't know-- (ASK S4))

S4. (IF NO OR DON'T KNOW IN S3) Have you been treated by drugs for your MS in the past?

Yes4% (ASK Q1)
 No.....-- (THANK AND TERMINATE)
 (VOL.) Don't know-- (THANK AND TERMINATE)
 (NOT ASKED-CURRENTLY ONDRUG THERAPY)97

Main Questionnaire:

First we'd like to know a little about your own experience with MS.

1. In general, would you say your health is (READ LIST)

Excellent,17%
 Good,.....51
 Only fair, or.....26
 Poor?6
 (VOL.) Don't know--

2. How long ago were you first diagnosed with MS? Were you diagnosed (READ LIST)

Within past year,11%
 1-5 years ago,34
 6-10 years ago, or.....24
 More than 10 years ago?32
 (VOL.) Don't know--

3. Overall, how much of an affect, if any, do you feel MS has on your quality of life? Would you say it as has lowered the quality of your life (READ LIST)

A great deal,30%
 A moderate amount,.....34
 Only a little, or30
 Not at all.....7
 (VOL.) Don't know--

4. As a result of your MS, are you limited a great deal, a moderate amount, only a little, or not at all, in the activities you are able to do during a typical day?

- A great deal,23%
- A moderate amount,34
- Only a little, or26
- Not at all?18
- (VOL.) Don't know1

5. Symptoms and problems caused by MS are, of course, very different from one person to the next. I'll read to you some problems that some people with MS have. Please tell me, how much of a problem, if at all, each of these is for you, personally, as a result of your MS.

The first/next is (ITEM). (REPEAT AS NECESSARY) Is that a major problem, a minor problem, or not a problem at all for you, as a result of your MS?

(Order randomized)

	Major problem	Minor problem	Not a problem at all	Don't know
a. Becoming very tired	58%	35	7	1
b. Difficulties walking, or the inability to walk	34%	43	23	1
c. Numbness -- in your arms, legs, hands or feet	35%	46	19	--
d. Problems with your vision	19%	46	35	1
e. Problems thinking or concentrating	26%	53	22	--
f. Feeling depressed or sad	26%	44	30	1

6. Do you, yourself, ever need to use a wheel chair?

7. (IF YES) How often do you need to use one? Would you say always, nearly always, about half of the time, only occasionally, or only when you're having an attack, or relapse?

- Yes, (Total)24%
- Always3
- Nearly always.....2
- About half of the time4
- Only occasionally.....11

Only when having attack/relapse5
 Don't know how often--
 No, never need to use a wheel chair53%
 NOT ASKED (Difficulties walking
 not a problem at all)23%
 Don't know if ever need to use one--

8. (IF NOT "ALWAYS" IN Q7) Do you ever need to use a cane or crutch or some other support – such as touching a wall or leaning on someone's arm, for walking?
9. (IF YES IN Q8) How often do you need to use that cane or other support? Would you say always, nearly always, about half of the time, only occasionally, or only when you're having an attack, or relapse?

NOT ASKED (Always use a wheel chair)3%
 Yes (Total)62
 Always14
 Nearly always.....7
 About half of the time10
 Only occasionally.....18
 Only when having an attack/relapse13
 Yes, don't know how often--
 No, never use a cane or other support.....13
 NOT ASKED (Difficulties walking not a
 problem at all)19

- 9A (IF Q5b NOT "Not a problem at all" AND Q7 IS NOT "Always" USE A WHEELCHAIR) How often, if at all, are you able to walk a distance of 3 blocks without a cane or other support?

NOT ASKED (Walking is not a problem at all).....23%
 Always13 (SKIP TO Q10)
 Most of the time,15
 Yes, about half of the time,8
 Only occasionally,15
 Never25
 Don't know how often--
 NOT ASKED (Always use a wheel chair)3

- 9B How often, if at all, are you able to walk a distance of 25 feet – that is, about as far as walking across two average sized rooms – without a cane or other support?

NOT ASKED (Walking is not a problem at all).....23%
 NOT ASKED (Always able to walk 3 blocks)13
 Always25 (SKIP TO Q10)
 Most of the time,16

Yes, about half of the time,.....5
 Only occasionally,.....7
 Never.....10
 Don't know how often --
 NOT ASKED (Always use a wheel chair)3

10. Many people with MS experience occasional relapses (also called flare-ups or attacks) when their MS symptoms suddenly worsen. How many relapses, if any, have you had during the last 12 months?

None.....23%
 1 or 249
 3 or 414
 5 or more11
 (VOL.) Don't know3

11. Have any of the drugs that you have used for your MS required you to get injections of the drug?

Yes99%
 No.....1
 (VOL.) Don't know --

12. How many times, if at all, have you seen your neurologist about your MS in the past two years?

None.....1%
 Once3
 2 or 3 times.....22
 4 to 6 times.....39
 More than 6 times35
 (VOL.) Don't know1

13. (IF CURRENTLY ON DRUG THERAPY – S3=YES) How often, if at all, do you talk to your neurologist about potential side effects from the drugs you use to treat your MS? Would you say (READ LIST)
 (IF NOT CURRENTLY ON DRUG THERAPY – S4=YES) When you were using drugs to treat your MS, how often, if at all, did you talk to your neurologist about potential side effects from the drugs you were using to treat your MS? Would you say (READ LIST)

Almost every time you see/saw him or her,.....34%
 More than half of the time,8

About half of the time,20
 Less than half of the time, or11
 Almost never?27
 (VOL.) Don't know1

14. We're interested in your feelings about how well the drugs currently available for treating MS meet your needs. On a scale from 1 to 10, where 1 means they do a very poor job of meeting your needs and 10 means they do an extremely good job, how would you rate the drugs that are currently available for treating your MS?

Good -- Top-3 box (8, 9, or 10)61%
 Poor -- Bottom-3 box (1, 2, or 3).....6
 (VOL.) Don't know2

Mean rating7.7

15. Since you first started drug therapy for your MS, how many times have you switched drug therapies – that is, changed the drugs you were using for your MS?

Never.....55%
 1.....18
 2.....12
 3.....10
 More than 3 times6
 (VOL.) Don't know--

16. (IF 1 OR MORE TIMES, IN Q15) I will read to you some things that may or may not have affected your decisions to change your drug therapies. Please tell me how much of a reason, if at all, each of these was in your decisions to change your drug therapies. The first/next is (ITEM). Was that a major reason, a minor reason, or not a reason at all for changing your drug therapy?

BASE: Those who have switched drugs, in Q15 n=78

(Order randomized)	Major reason	Minor reason	Not a reason at all	Not asked (Doesn't get injections)	Don't know
a. The effectiveness of the drug in controlling your MS	60%	21	18	--	1
b. Concern about, or experience with side effects	53%	12	33	--	2
c. (IF Q11= "YES") The frequency with which you were required to	20%	17	62	--	1

have injections

d. The way in which the drugs were administered – that is, by pill, injections, etc.	20%	13	66	--	1
e. Cost or insurance issues	15%	5	79	--	--
f. Other factors	43%	12	43	--	2

17. There are many ways that the drugs used to treat MS might be improved. As I read a few of these possible improvements to you, please tell me how important, if at all, each of these would be to you personally. Please rate the importance of each of these on a 10-point scale, where 1 means not at all important and 10 means extremely important. You may use any number from 1 to 10. The first/next is (ITEM). How important would that be to you, on a scale from 1 to 10?

Top/Bottom 3 Box

<i>(Order randomized)</i>	Not important (Bottom-3) 1, 2, & 3	Important (Top-3) 8, 9, & 10	Mean	Don't know
a. A new drug that is more effective in reducing the frequency of relapses	1%	95%	9.6	1%
b. A new drug that is more effective in slowing progression of disability	1%	98%	9.8	1%
c. A new drug that is more effective in reducing the number of new lesions in the brain	1%	95%	9.7	1%
d. A new drug that is more effective in reducing the effect of the disease on mental abilities or thinking	1%	88	9.3	1%
e. A new drug that is more effective in slowing down the development of physical disabilities	1%	97%	9.8	1%

18. How satisfied are you with the safety of drugs that are currently available for treating your MS? Would you say you are (READ LIST)

Very satisfied,50%
 Moderately satisfied,.....40
 Only a little satisfied, or.....7
 Not satisfied at all?.....3
 (VOL.) Don't know1

19. If there were a drug treatment for MS that was significantly more effective than currently available drugs at slowing down the progression of disability, how likely would you be to use the drug if (ITEM).

SKIP TO Q20 WHEN RESPONDENT ANSWERS (“DEFINITELY WOULD NOT USE” TO ANY ITEM

	Definitely would	Probably would	Probably would not	Definitely would not	Not Asked/ Would not use even with better odds)	Don't know
a. 1-in-1,000 MS patients who took the drug died as a result?	14%	41	28	17	--	1
b. 1-in-500 MS patients who took the drug died as a result?	8%	24	34	19	17	--
c. 1-in-100 MS patients who took the drug died as a result?	4%	15	21	26	35	1
d. 1-in-10 MS patients who took the drug died as a result?	4%	10	13	13	61	1

20. If there were a drug treatment for MS that was significantly more effective than currently available drugs at preventing relapses, how likely would you be to use the drug if (ITEM).

SKIP TO Q21 WHEN RESPONDENT ANSWERS (“DEFINITELY WOULD NOT USE” TO ANY ITEM

	Definitely would	Probably would	Probably would not	Definitely would not	Not Asked/ Would not use even with better odds)	Don't know
a. 1-in-1,000 MS patients who took the drug died as a result?	19%	38	25	19	--	--
b. 1-in-500 MS patients who took the drug died as a result?	8%	26	29	19	19	--
c. 1-in-100 MS patients who took the drug died as a result?	4%	15	17	27	38	--
d. 1-in-10 MS patients who took the drug died as a result?	5%	8	12	12	65	--

21.I will read to you some ways that some MS patients say decisions are made about the drug therapies they use in treating their MS. Please tell me how true or untrue each of these is for you personally, when deciding on what drugs you will use in treating your MS. The first/next is (ITEM). Is that completely true for you, partly true, or not at all true?

	Completely true	Partly true	Not at all true	Don't know
a. Your doctor makes the decisions for you.	12%	32	56	--
b. Your doctor and you discuss the options and are equally involved in the decision.	80%	16	4	1
c. Your doctor makes recommendations and then you make the decision.	73%	25	3	--
d. You request a drug therapy and your doctor prescribes it	37%	32	30	1

22. Patients have different feelings about how much they, their doctors, or government agencies such as the Food and Drug Administration (the FDA), should be involved in the decision about the drugs they will use to treat their MS. As I read to you some statements that some people might make, please tell me how much you agree or disagree with each of these. The first/next is (ITEM). Do you (READ LIST)

(Order randomized)

	Agree completely	Agree somewhat	Agree completely	Agree somewhat	Don't know
a. I am capable of making my own treatment choices, based on the information and advice I get from my doctor.	71%	24	3	3	--
b. I would like to be able to choose a drug, in consultation with my doctor, that is more effective, even if it is also riskier.	49%	28	13	10	1
c. The FDA should tightly control the use of drugs that might have safety concerns.	54%	32	10	5	--
d. If a drug has safety concerns, the FDA should warn people, but I should be free to decide with my doctor whether to use those drugs or not.	71%	19	5	6	--
e. I would be willing to visit my doctor more often than usual if that was required to be able to use a drug that was more effective.	81%	17	2	1	--

23. How much, if any, have you heard or read about a new MS drug that was introduced in 2005, but was taken off the market because of serious side effects? Is that something you heard or read a great deal, a moderate amount, only a little, or nothing at all about?

Great deal	26%
Moderate amount	29
Only a little	23
Nothing at all.....	22 (SKIP TO D1)
(VOL. (Don't know	2 (SKIP TO D1)

24. (IF “Great deal,” “Moderate amount,” or “Only a little” in Q27.) Can you tell me the name of that drug?

(DO NOT READ LIST)

Tysabri	34%
Antegren.....	1
Natalizumab	1
Avonex	--
Other	4
NOT ASKED/HEARD OR READ NOTHING AT ALL	23
Don't know	39

Demographic Questions

I have just a few more questions to make sure our survey accurately reflects the views and experiences of all MS patients.

D-1. Please tell me, how old are you?

Mean age: 43 years

REFUSED.....--

D-2. What is the highest level of education, or grade in school, that you completed? (*DO NOT READ LIST*)

Less Than High School Graduate (0-11 th Grade)	3%
High School Graduate (12 th Grade)	24
Some College (1-3 Years).....	33
Trade/Technical/Vocational Training.....	6
College Graduate (4 Years)	19
Postgraduate Work/Postgraduate Degree (5+ Years)	17
(VOL.) Don't know	--
(VOL.) Refused.....	--

D-3. (INTERVIEWER RECORD RESPONDENT SEX)

MALE	30%
FEMALE.....	70

D-4. That's all the questions I have for you. Thank you for helping with our survey! I just need to get your name and mailing address, now, so we can send you the \$50 that we promised as our thanks for your help with our research. Would you give that to me now, please?

NAME: _____

MAILING ADDRESS: _____

Again, thank you for your help!