Perceived Met and Unmet Health-Care Needs in a Community Population with Multiple Sclerosis

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Community-based studies are required to accurately describe the supportive services needed by people with multiple sclerosis (MS). Characteristics that influence (or result from) care-seeking may introduce bias into other types of studies. The Participation and Activity Limitation Survey (PALS) was a post-census survey conducted by Statistics Canada in association with a 2006 national census. The PALS collected data from a sample of 22,513 respondents having health-related impairments according to their census forms. The survey collected self-reported diagnostic data and obtained ratings for items assessing impairment as well as perceived met and unmet needs for care and support. It identified 245 individuals with MS, leading to an estimated (weighted) population prevalence of 0.2% (200 per 100,000). As expected, those with MS reported more-severe health problems than did those with other types of disability, particularly in the areas of mobility, dexterity, and cognition; they were also more likely to report having multiple caregivers. People with MS also reported more unmet health-care needs than did those with other forms of disability, particularly with respect to meal preparation, housework, shopping, and chores. Despite their more negative health status and greater reliance on caregivers, people with MS reported participation in society comparable to that of people without MS. Thus, people with MS report greater needs than do people with other forms of health-related disability and utilize supportive services more often. However, they also report higher levels of unmet needs. The substantial needs of people with MS are only partially addressed by existing services. Int J MS Care. 2012;14:2–8.

Multiple sclerosis (MS) is the most common disabling neurologic condition among young people,[1,2] but the condition is sufficiently rare that population-based studies are difficult to carry out. Only a few studies have used probability-based general population samples to examine use of health-care services and perceived unmet needs in people with MS. One was a Canadian study based on data from the Canadian Community Health Survey. People with MS were found to use more services, but also to report greater unmet health-care needs.[3] Another was the Stockholm MS Study, which found a high frequency (70%) of reliance on others for activities of daily living.[4] The Stockholm study identified several specific problem areas for people with MS: heavy housework, shopping, and cooking. Transportation outside the home also figured prominently among areas of concern.[5]

An opportunity to examine health status, care needs, and unmet needs in a community sample with MS arises from a Canadian post-census survey called the Participation and Activity Limitation Survey (PALS).[6] This survey is based on a probability sample of respondents reporting health-related impairments during a national census conducted in 2006. Conditions responsible for impairment were recorded in the data set, allowing disease-specific analysis. The survey's linkages to a national census allow some population-based inferences to be

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made. In this analysis, we were interested in examining health status, the use of aids and supports, perceived unmet needs, and participation in society by people with MS in Canada.

Methods

In a Canadian census conducted in 2006, 80% of households received a short-form questionnaire that contained eight basic questions. The remaining, randomly sampled 20% received a more detailed questionnaire containing 61 questions (the census "long form").[7] A copy of the 2006 census long form may be found on the Statistics Canada website.[8] Questions on the long form were usually answered by a single household informant providing data on all residents of the household.

The long form contained two questions concerning health-related impairments: 1) Does this person have any difficulty hearing, seeing, communicating, walking, climbing stairs, bending, learning, or doing any similar activities? 2) Does a physical condition or mental condition or health problem reduce the amount or the kind of activity this person can do: (a) at home? (b) at work or at school? (c) in other activities, for example, transportation or leisure? Affirmative responses to one or more of these items were used by Statistics Canada to develop a sampling frame. The selection of the PALS sample from this frame used stratified random sampling to ensure feasibility of estimation by both province/territory and age group. Severity of disability was also included as a stratification factor during sampling.[8]

Because it is linked to a census, the PALS sampling frame covered people living in private and some collective households in the ten provinces and three territories of Canada. Populations living on First Nations reserves were excluded, as were residents of institutional collectives, military bases, Canadian Armed Forces vessels, merchant vessels, and coast guard vessels, as well as campgrounds and parks. Data were collected primarily by computer-assisted telephone interview. Deterministic imputation for missing data was carried out in specific circumstances by Statistics Canada, but only when sufficient information was available from related questions.[6] Proxy responses were allowed. However, proxies were used only after "every effort" had been made to contact and interview respondents directly. If a respondent was not available when the interviewer called, multiple follow-up attempts were made. The proxy rate among those aged 15 and above in the PALS was 12.1%.[9]

The PALS interview included a questionnaire called the Comprehensive Health Status Measurement System (CHSMS), which was administered to all respondents. This questionnaire was originally designed to classify health status for the Health Utility Index (HUI).[10] The HUI is a health utility measure, but utility weights were not used in this project. The CHSMS items were used to produce impairment ratings in six health status dimensions: vision, speech, mobility, dexterity, emotions, and cognition. Two additional dimensions, hearing and pain, are also covered by the CHSMS but could not be included in this study because of low frequencies of reported impairment. A listing of the CHSMS items can be found in the PALS questionnaire (available at http://www.statcan.gc.ca/imdb-bmdi/indexiP-eng.htm).

The PALS inquired about the use of mobility aids, the extent of instrumental support received, and help with preparing meals. The survey also sought to evaluate aspects of participation in leisure activity using items with the following wording: "Now I will ask you some questions about activities you do. In the past 12 months, did you do any of the following activities within your spare time?" This was followed by a series of specific response choices, such as "exercise, watch TV or videos, listen to radio or CDs." Endorsement of responses indicating participation was followed by items asking about the frequency of participation in each activity.

The PALS incorporated complex design features including stratified sampling (unequal selection probabilities) but as a post-census survey is unique in not requiring clustering in the way that most large population surveys do. Statistics Canada develops sampling weights that account for these design features and support unbiased estimation of statistical parameters and their associated 95% confidence intervals. Adjustments to these weights for nonresponse were also made by Statistics Canada, reducing the risk of bias due to nonresponse. All of the analyses reported here incorporated these sampling weights, helping to ensure unbiased estimation of population parameters despite unequal selection probabilities and nonresponse. Statistical analyses were performed using the survey commands in Stata 11, version 11.0 (Stata Corp, College Station, TX) at the Prairie Regional Research Data Centre on the University of Calgary campus. Certain low-frequency estimates could not be reported in this article (eg, CHSMS ratings for hearing and pain, as mentioned above). The release of low-frequency estimates is prohibited because of data

release rules intended to ensure the confidentiality of census respondents. The project was approved by the University of Calgary Conjoint Ethics Review Board.

Results

The number of sampled respondents aged 15 or older for the PALS was 38,839. The response rate was approximately 74%, with an actual sample of 28,640 respondents. Among these respondents, health-related impairments were confirmed for 22,513 (79%). According to Statistics Canada, the discrepancy between those apparently eligible because of health-related impairments and those confirmed to have health-related impairments arose primarily because some respondents had short-lived health issues that had resolved by the time they were contacted for participation in the PALS. A total of 245 people had MS, representing 1.1% of the PALS sample. Under the unrealistic assumption that no members of the population failing to screen into PALS would have MS, this would translate into a weighted population prevalence estimate of 0.2% (200 per 100,000). In the PALS sample, people with MS were predominantly female (71%) and married (59.8%), percentages comparable to those reported in prior studies.[11-14] They were less likely than the general population to be employed at the time of the survey (26% working as compared with 62% of the general population). The proportion working is lower than the 40% to 70% reported in previous studies.[11-14] This discrepancy may partially reflect a relatively older mean age in PALS respondents with MS (weighted mean of 50.5 years, compared with mean ages of 42 to 51 years in prior studies[11-14] and 45.0 years in the general population). In turn, the older age of people

with MS in PALS may arise partially from the need to have health impairments in order to screen into PALS, because early in the disease there is often no impairment. Thirty-eight percent of the PALS sample reported that they were permanently unable to work. The higher rate of employment in previous studies may also reflect a greater likelihood of working people being identified in the clinical sampling frames used in the previous studies, as they did not screen out those with no impairment.

The percentages of PALS participants reporting various disabling conditions are reported in Table 1. The most common category of conditions was musculoskeletal. A total of 5.3% of the sample reported that their impairments were caused by a neurologic condition; the categories of such neurologic conditions are shown in Table 2. Among respondents with neurologic conditions, MS was among the most common conditions reported.

Health status information from the CHSMS is presented in Tables 3 and 4. The instrument identifies percentages of the sample reporting "none," "some," or "a lot" of impairment in various domains. The sample size supported estimation in six of the CHSMS domains: mobility, cognition, dexterity, vision, emotions, and speech. For mobility, cognition, and dexterity it was possible to estimate the frequencies in people with and without MS, whereas for vision, emotions, and speech the "some" and "a lot" categories had to be collapsed. Those with MS more often reported impairments, particularly severe impairments, in mobility, cognition, and dexterity.

As expected, the use of mobility aids was more common in people with MS (Table 5). The differences were

Table 1. Categories of disabling conditions in the PALS sample

Category	Weighted percentage[a] (95% CI) (N = 22,513)
Endocrine, nutritional, and metabolic conditions	2.9 (2.5-3.4)
Conditions of the nervous system	5.3 (4.7-5.9)
Conditions of the eye and adnexa, ear, and mastoid process	11.0 (10.1-12.0)
Conditions of the circulatory system	7.5 (6.7-8.2)
Conditions of the respiratory system	3.0 (2.5-3.4)
Conditions of the digestive system	1.1 (0.8-1.3)
Conditions of the musculoskeletal system and connective tissue	51.5 (50.1-52.9)
Injury, poisoning, and other consequences of external factors	4.3 (3.8-4.8)

Abbreviations: CI, confidence interval; PALS, Participation and Activity Limitation Survey.
[a]The percentages total less than 100% because some categories contained insufficient numbers to determine estimates.

Table 2. Categories of neurologic conditions in the PALS

ICD-10 code	Diagnosis[a]	Weighted percentage[b] (95% CI)
G20	Parkinson disease	12.6 (8.6-16.6)
G35	*Multiple sclerosis*	*21.9 (17.3-26.6)*
G30.9	Alzheimer disease, unspecified	10.2 (6.7-13.7)
G40.9	Epilepsy, unspecified	7.7 (5.0-10.4)
G43.9	Migraine, unspecified	7.1 (5.1-9.0)
G56.0	Carpal tunnel syndrome	4.0 (2.0-6.0)
G58.9	Mononeuropathy, unspecified	4.6 (2.2-7.1)
G71.0	Muscular dystrophy	2.4 (1.1-3.6)
G80.9	Cerebral palsy, unspecified	6.3 (4.3-8.4)
G81.9	Hemiplegia, unspecified	2.6 (1.1-4.0)

Abbreviations: CI, confidence interval; ICD-10, *International Classification of Diseases, Tenth Revision;* PALS, Participation and Activity Limitation Survey.
[a]Respondents could list up to three contributors; this tabulation is based on the first reported condition.
[b]The percentages do not total 100% because some categories had too few observations to allow data release.

Table 3. Health-related impairments in the PALS sample by MS status: mobility, cognition, and dexterity

	Impairment level					
	None		Some		A lot	
Domain	No MS	MS	No MS	MS	No MS	MS
Mobility	73.7 (72.6-74.8)	35.5 (24.7-46.3)	18.3 (17.3-19.3)	33.6 (20.9-46.4)	8.0 (7.3-8.8)	30.9 (20.1-41.6)
Cognition	61.0 (59.7-62.3)	45.3 (33.4-57.2)	31.4 (30.2-32.6)	37.0 (24.6-49.4)	7.6 (6.9-8.3)	17.7 (8.0-27.4)
Dexterity	95.2 (94.6-95.7)	83.8 (72.2-95.4)	3.7 (3.2-4.1)	7.5 (0.0-18.1)	1.2 (0.8-1.5)	8.7 (2.5-14.8)

Abbreviations: MS, multiple sclerosis; PALS, Participation and Activity Limitation Survey.
Note: Data are given as percentage (95% confidence interval).

Table 4. Health-related impairments in the PALS sample by MS status: vision, emotions, speech

	Impairment level			
	None		Some or A lot	
Domain	No MS	MS	No MS	MS
Vision	26.8 (25.8-27.9)	28.5 (18.7-38.3)	73.2 (72.1-74.2)	71.5 (61.7-81.3)
Emotions	65.7 (64.4-66.9)	67.9 (57.8-78.1)	34.3 (33.1-35.6)	32.1 (21.9-42.2)
Speech	95.6 (95.1-96.0)	95.2 (90.5-99.8)	4.4 (4.0-4.9)	4.8 (0.2-9.5)

Abbreviations: MS, multiple sclerosis; PALS, Participation and Activity Limitation Survey.
Note: Data are given as percentage (95% confidence interval).

most evident in the use of canes, grab bars, wheelchairs, walkers, scooters, and motor-vehicle modifications.

Table 6 presents the types and number of caregivers identified by PALS respondents with and without MS. The people with MS were more likely to have one or more caregivers and to identify multiple caregivers. Sim-ilar proportions of people with and without MS identi-fied family or friend caregivers, but those with MS were far more likely to report having a paid caregiver.

Table 7 presents the percentages of respondents with and without MS reporting that they either received no help or received inadequate help with four activities of

Table 5. Use of mobility aids in the PALS sample by MS status

Type of aid	Overall (N = 22,513)	Without MS (N = 22,268)	With MS (N = 245)
Any	25.9 (24.9-26.9)	25.3 (24.3-26.3)	74.0 (65.2-82.8)
Orthopedic footwear	6.2 (5.6-6.9)	6.1 (5.4-6.7)	16.1 (5.4-26.8)
Cane/walking stick	18.5 (17.6-19.5)	18.1 (17.1-19.0)	55.7 (45.1-66.3)
Crutches	1.3 (1.0-1.5)	—[a]	—[a]
Wheelchair (manual)	4.2 (3.6-4.7)	3.9 (3.3-4.4)	28.0 (18.3-37.7)
Wheelchair (electric)	0.9 (0.6-1.1)	0.8 (0.5-1.0)	9.1 (4.3-13.8)
Walker	8.6 (7.9-9.3)	8.5 (7.8-9.2)	21.9 (11.7-32.2)
Scooter	1.6 (1.2-1.9)	1.4 (1.1-1.7)	14.8 (6.9-22.7)
Braces/supportive devices	3.2 (2.8-3.6)	3.2 (2.8-3.6)	6.2 (2.6-9.9)
Grab bars	15.8 (14.9-16.7)	15.4 (14.5-16.3)	46.0 (34.3-57.8)
Bed/bath lifts	2.0 (1.7-2.3)	1.9 (1.6-2.2)	7.0 (2.7-11.3)
Adapted motor vehicle	0.7 (0.5-0.9)	0.6 (0.5-0.8)	7.9 (2.7-13.1)

Abbreviations: MS, multiple sclerosis; PALS, Participation and Activity Limitation Survey.
Note: Data are given as percentage (95% confidence interval).
[a]These categories were suppressed because of sample size constraints and Statistics Canada data release guidelines.

Table 6. Types and number of identified caregivers by MS status

	Overall (N = 22,513)	Without MS (N = 22,268)	With MS (N = 245)
Type of caregiver			
Partner/family/neighbor/friend/coworker	52.7 (51.4-53.9)	52.6 (51.3-53.9)	61.4 (49.7-73.0)
Nongovernmental/governmental organization/paid employee	13.4 (12.4-14.3)	13.2 (12.3-14.1)	29.2 (18.0-40.3)
Number of caregivers			
0	42.2 (40.9-43.5)	42.4 (41.1-43.7)	25.7 (16.3-35.1)
1	25.0 (23.9-26.1)	25.0 (23.9-26.1)	26.6 (16.9-36.3)
2	16.2 (15.2-17.1)	16.1 (15.1-17.0)	23.9 (12.6-35.3)
3	16.6 (15.7-17.5)	16.5 (15.6-17.4)	23.8 (15.1-32.4)

Abbreviation: MS, multiple sclerosis.
Note: Data are given as percentage (95% confidence interval).

daily living: meal preparation, housework, chores, and shopping. Unfortunately, the sample size did not permit a distinction to be made between those receiving no help and those receiving inadequate help. The differences between people with and without MS are substantial, with people with MS being twice as likely to fall into the "no help/inadequate help" category.

In other domains of functioning, the proportion of people with MS reporting that they either did not need help or received all the help they needed was very high, with no differences discerned from those without MS: caring for self (95.8%), specialized home care (96.3%), and moving around the residence (97.3%).

Leisure activity is an aspect of participation in society. Of those activities evaluated in the PALS, the participation percentages were generally similar between those with MS and the rest of the PALS sample. Exer-

cising at home at least once per week was reported by a higher proportion of those with MS (57.1%; 95% confidence interval [CI], 41.9%-72.2%) than without MS (44.5%; 95% CI, 42.7%-46.2%), but imprecision associated with the MS estimate precludes statistical differentiation from the non-MS component of the sample. Watching television or listening to music was reported as a daily activity by 94.8% (95% CI, 91.3%-98.2%) of those with MS and 91.3% (95% CI, 90.6%-92.0%) of those without MS. Reading was less often a daily activity for people with MS, being reported by 62.9% (95% CI, 51.0%-74.7%), as compared with 76.1% of those without MS (95% CI, 74.9%-77.4%). Participation in activities outside of the home was also comparable between people with MS and those with other types of disability. Of those with MS, 53.7% (95% CI, 41.2%-66.2%) reported visiting with family

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Table 7. Proportions of respondents reporting no support or inadequate support for activities of daily living

Activity	Without MS (N = 22,268)	With MS (N = 245)
Meal preparation	5.0 (4.4-5.6)	10.1 (4.5-15.8)
Housework	11.7 (10.9-12.8)	20.7 (12.4-28.9)
Chores	18.0 (17.0-19.0)	38.3 (26.8-49.9)
Shopping	9.9 (9.1-10.7)	20.4 (11.9-28.9)

Abbreviation: MS, multiple sclerosis.
Note: Data are given as percentage (95% confidence interval).

or friends at least once per week, compared with 48.8% (95% CI, 47.4%-50.1%) of those with other types of disability. Participation in physical activities outside of the home at least once per week was reported by 39.7% (95% CI, 22.6%-56.9%) of those with MS, compared with 45.3% (95% CI, 43.8%-46.9%) of those without MS. In both groups, 40% to 50% reported attending sporting or cultural events or visiting museums, libraries, or parks. Only 4.5% (95% CI, 1.3%-7.7%) reported no participation in society in any of the above-listed domains of participation.

Discussion

A key finding of this study is that people with MS more frequently reported unmet needs in certain activities of daily living than did those with other types of disability. This replicates the finding of Pohar and colleagues[3] of higher levels of unmet need for services in people with MS. The result is also consistent with a report by Ytterberg et al.,[12] although that study did not include a comparison group. Unlike the study of Pohar et al., the current analysis compared people with MS with those with other disabling health conditions rather than with the general population. The Stockholm MS Study found a high frequency (approximately 70%) of reliance on others for activities of daily living, consistent with the results reported here.[4] A detailed analysis of activities of daily living from the Stockholm study identified some of the same problems with activities of daily living found in the present study, including in the areas of heavy housework, shopping, and cooking. Transportation outside the home also figured prominently among problematic areas in that study.[5] In an Italian mail survey, home assistance and home modifications were strongly associated with disease severity.[13] Khan et al.[11] reported irregular access to support and rehabilita-

tive services, another finding broadly consistent with the results reported here. In the current analysis, differences in unmet need between those with and without MS were not evident in self-care, specialized home care, or moving around the house but were dramatic in meal preparation, shopping, chores, and housework. These domains may not receive adequate attention in traditional home-care and community supportive services. These results cannot inform an overall assessment of the quality of home-care services available in Canada, as the comparisons are across MS and non-MS categories. Relatively speaking, however, the results indicate greater unmet need among people with MS than among people with other types of disability.

The PALS is a valuable source of data but has many limitations. One is that it does not use an entirely representative sample. Rather, respondents are screened in because they have impairments of various types. Respondents with MS can be identified because MS is likely to be reported as a cause of impairment by PALS respondents. However, the remainder of the PALS sample is heterogeneous. The most common sources of disability reported in PALS were musculoskeletal conditions. Another weakness of the PALS is a general lack of validated measures, although Statistics Canada did conduct extensive field testing of the items, including obtaining feedback from focus groups, in order to help ensure validity of the responses. The PALS is a general population survey that is not specifically designed for people with MS. The survey did not include standard

PracticePoints

- Although people with MS access more community supportive services than people with other disabling conditions, they also report higher levels of unmet need. This indicates that health-care systems are only partially effective in meeting the needs of people with MS.
- The domains with the greatest unmet needs are meal preparation, housework, shopping, and chores. Innovative strategies are needed to deliver required supportive services in these areas.
- Despite their relatively high level of impairment, people with MS maintain a strong level of participation in society. This can be interpreted as an indication of resiliency in the face of neurologic impairment.

MS measures such as the Expanded Disability Status Scale (EDSS)[15] or any of the fatigue scales commonly used in MS research.[16,17] Nor did it include validated assessment instruments for activities of daily living. Data available from the CHSMS, however, confirm that people with MS often struggle with more-severe health difficulties than do people with other conditions. Another weakness of the PALS is a lack of solid information about health-care utilization. Access to specific types of services has been assessed in previous studies but could not be assessed here because of limitations of the PALS data set.

The PALS provides a snapshot of certain important aspects of health status in the MS population in a way that is not distorted by help-seeking or voluntary subject recruitment. The picture is one of people struggling with a particularly intrusive illness, requiring considerable support, but continuing to have more unmet needs than people with other forms of disability. Despite this challenge, people with MS reported high levels of participation in society. A key finding for policy makers is that the areas of greatest unmet need are those that may be viewed as falling outside of the scope of traditionally defined health-care services and may therefore not receive adequate attention in the current system. □

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The adverse reactions most commonly reported in patients associated with the use of AVONEX® were flu-like and other symptoms occurring within hours to days following an injection. Symptoms can include myalgia, fever, fatigue, headaches, chills, nausea, and vomiting. Some patients have experienced paresthesias, hypertonia and myasthenia.

The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of AVONEX®, or the need for concomitant medication to treat an adverse reaction symptom) were flu-like symptoms and depression.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of AVONEX® cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice.

The data described below reflect exposure to AVONEX® in 351 patients, including 319 patients exposed for 6 months, and 288 patients exposed for greater than one year in placebo-controlled trials. The mean age of patients receiving AVONEX® was 35 years, 74% were women and 89% were Caucasian. Patients received either 30 mcg AVONEX® or placebo.

Table 3 enumerates adverse events and selected laboratory abnormalities that occurred at an incidence of at least 2% higher frequency in AVONEX®-treated subjects than was observed in the placebo group. Reported adverse events have been classified using standard COSTART terms.

Table 3. Adverse Events and Selected Laboratory Abnormalities in the Placebo-Controlled Studies

Adverse Event	Placebo (N = 333)	AVONEX® (N = 351)
Body as a Whole		
Headache	55%	58%
Flu-like symptoms (otherwise unspecified)	29%	49%
Pain	21%	23%
Asthenia	18%	24%
Fever	9%	20%
Chills	5%	19%
Abdominal pain	6%	8%
Injection site pain	6%	8%
Infection	4%	7%
Injection site inflammation	2%	6%
Chest pain	2%	5%
Injection site reaction	1%	3%
Toothache	1%	3%
Nervous System		
Depression	14%	18%
Dizziness	12%	14%
Respiratory System		
Upper respiratory tract infection	12%	14%
Sinusitis	12%	14%
Bronchitis	5%	8%
Digestive System		
Nausea	19%	23%
Musculoskeletal System		
Myalgia	22%	29%
Arthralgia	6%	9%
Urogenital		
Urinary tract infection	15%	17%
Urine constituents abnormal	0%	3%
Skin and Appendages		
Alopecia	2%	4%
Special Senses		
Eye disorder	2%	4%
Hemic and Lymphatic System		
Injection site ecchymosis	4%	6%
Anemia	1%	4%
Cardiovascular System		
Migraine	3%	5%
Vasodilation	0%	2%

No AVONEX®-treated patients attempted suicide in the two placebo-controlled studies. In Study 2, AVONEX®-treated patients were more likely to experience depression than placebo-treated patients (20% in AVONEX® group vs. 13% in placebo group). The incidences of depression in the placebo-treated and AVONEX®-treated patients in Study 1 were similar. In Study 1, suicidal tendency was seen more frequently in AVONEX®-treated patients (4% in AVONEX® group vs. 1% in placebo group) (see WARNINGS).

Seizures

Seizures have been reported in 4 of 351 AVONEX®-treated patients in the placebo-controlled studies, compared to none in the placebo-treated patients (see Precautions: Seizures).

Post-Marketing Experience

The following adverse events have been identified and reported during post-approval use of AVONEX®: New or worsening other psychiatric disorders, and anaphylaxis (see WARNINGS). Autoimmune disorders including autoimmune hepatitis, idiopathic thrombocytopenia, hyper- and hypothyroidism, and seizures in patients without prior history (see Precautions).

Infrequent reports of congestive heart failure, cardiomyopathy, and cardiomyopathy with congestive heart failure with rare cases being temporally related to the administration of AVONEX® (see Precautions: Cardiomyopathy and Congestive Heart Failure).

Decreased peripheral blood counts in all cell lines, including rare pancytopenia and thrombocytopenia (see WARNINGS: Decreased Peripheral Blood Counts). Some cases of thrombocytopenia have had nadirs below 10,000/μL. Some of these cases reoccur upon rechallenge.

Hepatic injury, including hepatic failure and elevated serum hepatic enzyme levels, some of which have been severe, has been reported post-marketing (see WARNINGS: Hepatic Injury).

Meno- and metrorrhagia, rash (including vesicular rash), and rare cases of injection site abscess or cellulitis that may require surgical intervention have also been reported in post-marketing experience.

Because reports of these reactions are voluntary and the population is of an uncertain size, it is not always possible to reliably estimate the frequency of the event or establish a causal relationship to drug exposure.

Adverse Reactions Associated with Subcutaneous Use

AVONEX® has also been evaluated in 290 patients with diseases other than multiple sclerosis, primarily chronic viral hepatitis B and C, in which the doses studied ranged from 15 mcg to 75 mcg, given SC, 3 times a week, for up to 6 months. Inflammation at the site of the subcutaneous injection was observed in 52% of treated patients in these studies. Subcutaneous injections were also associated with the following local reactions: injection site necrosis, injection site atrophy, injection site edema and injection site hemorrhage. None of the above was observed in the multiple sclerosis patients participating in Study 1. Injection site edema and injection site hemorrhage were observed in multiple sclerosis patients participating in Study 2.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. In recent studies assessing immunogenicity in multiple sclerosis patients administered AVONEX® for at least 1 year, 5% (21 of 390 patients) showed the presence of neutralizing antibodies at one or more times. The clinical significance of neutralizing antibodies to AVONEX® is unknown.

These data reflect the percentage of patients whose test results were considered positive for antibodies to AVONEX® using a two-tiered assay (ELISA binding assay followed by an antiviral cytopathic effect assay), and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of neutralizing activity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to AVONEX® with the incidence of antibodies to other products may be misleading.

Anaphylaxis has been reported as a rare complication of AVONEX® use. Other allergic reactions have included dyspnea, orolingual edema, skin rash and urticaria (see WARNINGS: Anaphylaxis).

DRUG ABUSE AND DEPENDENCE

There is no evidence that abuse or dependence occurs with AVONEX® therapy. However, the risk of dependence has not been systematically evaluated.

OVERDOSAGE

Safety of doses higher than 60 mcg once a week have not been adequately evaluated. The maximum amount of AVONEX® that can be safely administered has not been determined.

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