SUPPLEMENT TO

NEUROLOGY REVIEWS®

JULY 2015

Highlights From the 2015 CMSC ANNUAL MEETING

Revised Standardized MRI Protocol for the Diagnosis and Follow-Up of MS

A CMSC Task Force has updated its recommendations for a standardized MRI protocol and clinical guidelines for diagnosis and follow-up of patients with MS.

INDIANAPOLIS—A standardized MRI is important for the diagnosis and follow-up of patients with multiple sclerosis (MS). However, acquisition and interpretation of MRI scans may be complicated due to differences in pulse sequence (eg, FLAIR vs PD/T2), the use of contiguous and thinner (eg, 3 mm vs 5 mm) slices, as well as differences in patient positioning. Therefore, the Consortium of Multiple Sclerosis Centers (CMSC) convened a task force to develop and periodically revise indications and guidelines for a standardized MRI protocol in the diagnosis and follow-up of patients with MS. The panel's most recent recommendations were presented at the 2015 CMSC Annual Meeting and will be published in an upcoming issue of *American Journal of Neuroradiology*.

Lead author Anthony Traboulsee, MD, Associate Professor at the University of British Columbia in Vancouver, and colleagues reported that a standardized brain MRI protocol with gadolinium is recommended for the diagnosis of MS. A spinal cord MRI is additionally recommended if the brain MRI is nondiagnostic or if the presenting symptoms are at the level of the spinal cord. A follow-up brain MRI with gadolinium is recommended to demonstrate dissemination in time and ongoing clinically silent disease activity while on treatment, to evaluate unexpected clinical worsening, to reassess the original diagnosis, and as a new baseline prior to starting or modifying therapy. A routine brain MRI should be considered every six months to two years for all patients with relapsing MS. The standardized brain MRI protocol includes 3-D T1-weighted, 3-D T2-FLAIR (fluid-attenuated inversion recovery), 3-D T2-weighted, post single-dose gadolinium-enhanced T1-weighted, and diffusion-weighted sequences.

According to the 2015 Revised CMSC MRI Protocol, a simplified progressive multifocal leukoencephalopathy (PML) surveillance protocol includes FLAIR and diffusion-weighted imaging sequences only.

The spinal cord MRI protocol includes sagittal T1-weighted and proton density, short-time inversion recovery (STIR) or phase-sensitive inversion recovery (PSIR), axial T2- or T2*-weighted through suspicious lesions, and, in some cases, post-contrast gadolinium-enhanced T1-weighted imaging.

The task force's revised guideline specifies that the clinical question being addressed should be provided in the requisition for the MRI. The radiology report should be descriptive with results referenced to previous studies. MRI studies should be permanently retained and available.

Key 2015 Changes

Key changes to the MRI protocol since the last revision in 2006 include an emphasis on 3-D sequences for brain MRI, a PML-specific monitoring protocol, and an optional orbit MRI protocol for severe optic neuritis.

Key changes to the clinical guidelines since the 2006 revision include more specific guidance on timing of brain MRI for patients on disease-modifying therapy, timing of brain MRI for PML surveillance, updated evidence on the value of MRI changes in determining treatment effectiveness, and inclusion of radiologically isolated syndrome. ■

For your patients with relapsing multiple sclerosis

START AT THE TECFIDERA LEVEL

(dimethyl fumarate)

Where **EFFICACY**, **SAFETY**, and **ORAL DOSING** all come together

>135K
PATIENTS
TREATED GLOBALLY[1]

TECFIDERA has been prescribed in the US more than any other oral therapy for RMS*

5+ YEARS
OF CLINICAL AND REAL-WORLD EXPERIENCE[1,2]

TECFIDERA is contraindicated in patients with known allergy to dimethyl fumarate or to any of the excipients of TECFIDERA[2]

Indication

Tecfidera® (dimethyl fumarate) is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

Important Safety Information

TECFIDERA is contraindicated in patients with known hypersensitivity to dimethyl fumarate or any of the excipients of TECFIDERA. TECFIDERA can cause anaphylaxis and angioedema after the first dose or at any time during treatment. Patients experiencing signs and symptoms of anaphylaxis and angioedema (which have included difficulty breathing, urticaria, and swelling of the throat and tongue) should discontinue TECFIDERA and seek immediate medical care.

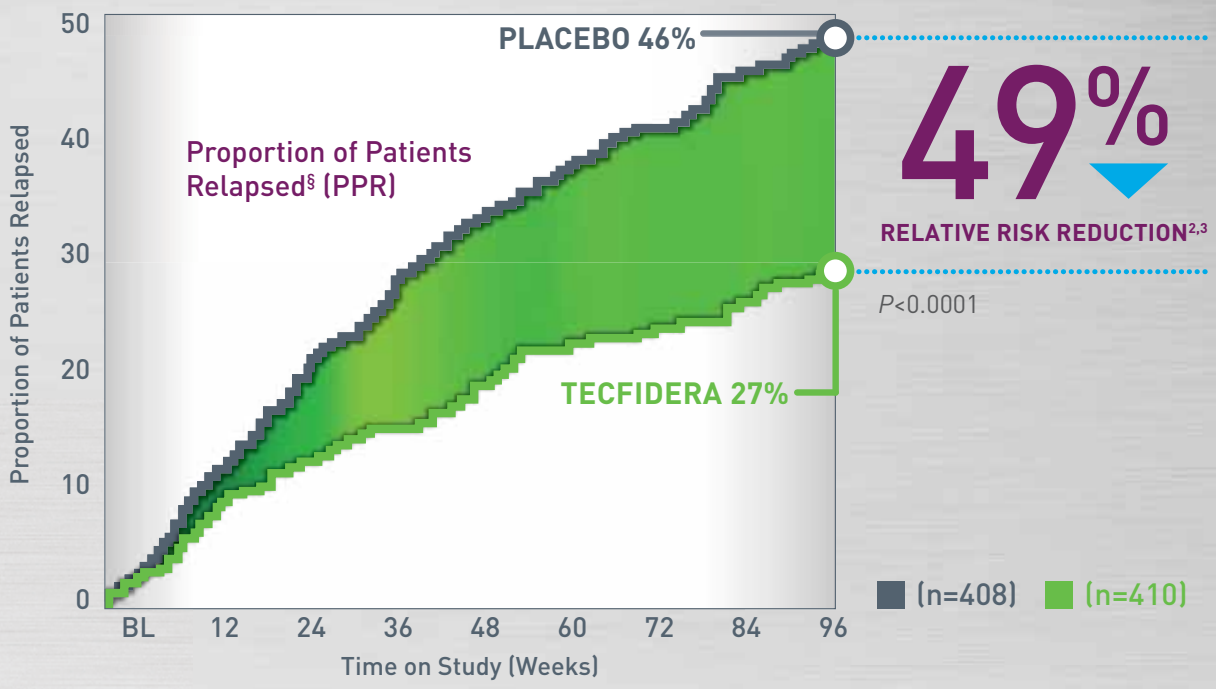
A fatal case of progressive multifocal leukoencephalopathy (PML) occurred in a patient who received TECFIDERA. PML is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. The symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. At the first sign or symptom suggestive of PML, withhold TECFIDERA and perform an appropriate diagnostic evaluation.

TECFIDERA may decrease lymphocyte counts; in clinical trials there was a mean decrease of ~30% in lymphocyte counts during the first year which then remained stable. Four weeks after stopping TECFIDERA, mean lymphocyte counts increased but not to baseline. Six percent of TECFIDERA patients and <1% of placebo patients had lymphocyte counts <0.5x10^9/L. TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts.

There was no increased incidence of serious infections observed in patients with lymphocyte counts <0.8x10^9/L or 0.5x10^9/L in controlled trials, although one patient in an extension study developed PML in the setting of prolonged lymphopenia (lymphocyte counts predominantly <0.5x10^9/L for 3.5 years). In controlled and uncontrolled clinical trials, 2% of patients experienced lymphocyte counts <0.5x10^9/L for at least six months. In these patients, the majority of lymphocyte counts remained <0.5x10^9/L with continued therapy. A complete blood count including lymphocyte count should be obtained before initiating treatment, after 6 months, every 6 to 12 months thereafter and as clinically indicated. Consider treatment interruption if lymphocyte counts <0.5x10^9/L persist for more than six months and follow lymphocyte counts until lymphopenia is resolved. Consider withholding treatment in patients with serious infections until resolved. Decisions about whether or not to restart TECFIDERA should be based on clinical circumstances.

TECFIDERA may cause flushing (e.g. warmth, redness,

TECFIDERA cut risk and frequency of relapse in half in the 2-year DEFINE† Trial‡



Annualized relapse rate§ (ARR): 53% relative reduction (TECFIDERA 0.172 [n=410] vs placebo 0.364 [n=408]; *P*<0.0001)[2]

itching, and/or burning sensation). 40% of patients taking TECFIDERA reported flushing which was mostly mild to moderate in severity. Three percent of patients discontinued TECFIDERA for flushing and <1% had serious flushing events that led to hospitalization. Taking TECFIDERA with food may reduce flushing. Alternatively, administration of non-enteric coated aspirin prior to dosing may reduce the incidence or severity of flushing.

TECFIDERA may cause gastrointestinal (GI) events (e.g., nausea, vomiting, diarrhea, abdominal pain, and dyspepsia). Four percent of TECFIDERA patients and <1% placebo patients discontinued due to GI events. The incidence of serious GI events was 1%. The most common adverse reactions associated with TECFIDERA versus placebo are flushing (40% vs 6%) and GI events: abdominal pain (18% vs 10%), diarrhea (14% vs 11%), nausea (12% vs 9%).

Elevations in hepatic transaminases have been reported. A transient increase in mean eosinophil counts was seen during the first two months. TECFIDERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Encourage patients who become pregnant while taking TECFIDERA to enroll in the TECFIDERA pregnancy registry by calling 1-866-810-1462 or visiting www.TECFIDERApregnancyregistry.com.

For additional important safety information, please see adjacent Brief Summary of full Prescribing Information.

*Based on number of prescriptions from IMS NPA™ Weekly Data (September 27, 2013 to March 20, 2015).
†Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS, a 2-year, randomized, double-blind, placebo-controlled study in 1234 patients with relapsing-remitting multiple sclerosis (RRMS).[2,3]
‡Included patients who had experienced at least 1 relapse over the year preceding the trial or had a brain magnetic resonance imaging (MRI) scan demonstrating at least 1 gadolinium-enhancing (Gd+) lesion within 6 weeks of randomization and had an Expanded Disability Status Scale (EDSS) score ranging from 0 to 5.[2]
§Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection that lasted for at least 24 hours and were accompanied by new objective neurologic findings.[3]

References: 1. Biogen, Data on file. **2.** TECFIDERA Prescribing Information, Biogen, Cambridge, MA. **3.** Gold R, Kappos L, Arnold DL, et al. *N Engl J Med*. 2012;367:1098-1107. Erratum in: *N Engl J Med*. 2012;367:2362.

Biogen

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

MAKE IT YOUR FIRST CHOICE FOR FIRST LINE™

Tecfidera® (dimethyl fumarate) delayed-release capsules, for oral use

Brief Summary of Full Prescribing Information

1 INDICATIONS AND USAGE

TECFIDERA is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The starting dose for TECFIDERA is 120 mg twice a day orally. After 7 days, the dose should be increased to the maintenance dose of 240 mg twice a day orally. TECFIDERA should be swallowed whole and intact. TECFIDERA should not be crushed or chewed and the capsule contents should not be sprinkled on food. TECFIDERA can be taken with or without food.

Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose. Within 4 weeks, the recommended dose of 240 mg twice a day should be resumed. Discontinuation of TECFIDERA should be considered for patients unable to tolerate return to the maintenance dose. The incidence of flushing may be reduced by administration of TECFIDERA with food. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to TECFIDERA dosing may reduce the incidence or severity of flushing *[see Clinical Pharmacology (12.3)]*.

2.2 Blood Test Prior to Initiation of Therapy

Obtain a complete blood cell count (CBC) including lymphocyte count before initiation of therapy *[see Warnings and Precautions (5.3)]*.

3 DOSAGE FORMS AND STRENGTHS

TECFIDERA is available as hard gelatin delayed-release capsules containing 120 mg or 240 mg of dimethyl fumarate. The 120 mg capsules have a green cap and white body, printed with “BG-12 120 mg” in black ink on the body. The 240 mg capsules have a green cap and a green body, printed with “BG-12 240 mg” in black ink on the body.

4 CONTRAINDICATIONS

TECFIDERA is contraindicated in patients with known hypersensitivity to dimethyl fumarate or to any of the excipients of TECFIDERA. Reactions have included anaphylaxis and angioedema *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Angioedema

TECFIDERA can cause anaphylaxis and angioedema after the first dose or at any time during treatment. Signs and symptoms have included difficulty breathing, urticaria, and swelling of the throat and tongue. Patients should be instructed to discontinue TECFIDERA and seek immediate medical care should they experience signs and symptoms of anaphylaxis or angioedema.

5.2 Progressive Multifocal Leukoencephalopathy

A fatal case of progressive multifocal leukoencephalopathy (PML) occurred in a patient with MS who received TECFIDERA for 4 years while enrolled in a clinical trial. PML is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. During the clinical trial, the patient experienced prolonged lymphopenia (lymphocyte counts predominantly $<0.5 \times 10^9$/L for 3.5 years) while taking TECFIDERA *[see Warnings and Precautions (5.3)]*. The role of lymphopenia in this case is unknown. The patient had no other identified systemic medical conditions resulting in compromised immune system function and had not previously been treated with natalizumab, which has a known association with PML. The patient was also not taking any immunosuppressive or immunomodulatory medications concomitantly.

At the first sign or symptom suggestive of PML, withhold TECFIDERA and perform an appropriate diagnostic evaluation. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

5.3 Lymphopenia

TECFIDERA may decrease lymphocyte counts. In the MS placebo controlled trials, mean lymphocyte counts decreased by approximately 30% during the first year of treatment with TECFIDERA and then remained stable. Four weeks after stopping TECFIDERA, mean lymphocyte counts increased but did not return to baseline. Six percent (6%) of TECFIDERA patients and <1% of placebo patients experienced lymphocyte counts $<0.5 \times 10^9$/L (lower limit of normal 0.91×10^9/L). The incidence of infections (60% vs 58%) and serious infections (2% vs 2%) was similar in patients treated with TECFIDERA or placebo, respectively. There was no increased incidence of serious infections observed in patients with lymphocyte counts $<0.8 \times 10^9$/L or 0.5×10^9/L in controlled trials, although one patient in an extension study developed PML in the setting of prolonged lymphopenia (lymphocyte counts predominantly $<0.5 \times 10^9$/L for 3.5 years) *[see Warnings and Precautions (5.2)]*. In controlled and uncontrolled clinical trials, 2% of patients experienced lymphocyte counts $<0.5 \times 10^9$/L for at least six months. In these patients, the majority of lymphocyte counts remained $<0.5 \times 10^9$/L with continued therapy. TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts.

Before initiating treatment with TECFIDERA, a CBC including lymphocyte count should be obtained. A CBC including lymphocyte count should also be obtained after 6 months of treatment, every 6 to 12 months thereafter, and as clinically indicated. Consider interruption of TECFIDERA in patients with lymphocyte counts $<0.5 \times 10^9$/L persisting for more than six months. Given the potential for delay in lymphocyte recovery after discontinuation of TECFIDERA, consider following lymphocyte counts until lymphopenia is resolved. Withholding treatment should be considered in patients with serious infections until the infection(s) is resolved. Decisions about whether or not to restart TECFIDERA should be individualized based on clinical circumstances.

5.4 Flushing

TECFIDERA may cause flushing (e.g., warmth, redness, itching, and/or burning sensation). In clinical trials, 40% of TECFIDERA treated patients experienced flushing. Flushing symptoms generally began soon after initiating TECFIDERA and usually improved or resolved over time. In the majority of patients who experienced flushing, it was mild or moderate in severity. Three percent (3%) of patients discontinued TECFIDERA for flushing and <1% had serious flushing symptoms that were not life-threatening but led to hospitalization. Administration of TECFIDERA with food may reduce the incidence of flushing. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to TECFIDERA dosing may reduce the incidence or severity of flushing *[see Dosing and Administration (2.1) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following important adverse reactions are described elsewhere in labeling: Anaphylaxis and Angioedema *(5.1)*, Progressive multifocal leukoencephalopathy *(5.2)*, Lymphopenia *(5.3)*, Flushing *(5.4) [see Warnings and Precautions]*.

6.1 Clinical Trials Experience

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

The most common adverse reactions (incidence ≥10% and ≥2% more than placebo) for TECFIDERA were flushing, abdominal pain, diarrhea, and nausea.

Adverse Reactions in Placebo-Controlled Trials

In the two well-controlled studies demonstrating effectiveness, 1529 patients received TECFIDERA with an overall exposure of 2244 person-years *[see Clinical Studies (14)]*.

The adverse reactions presented in the table below are based on safety information from 769 patients treated with TECFIDERA 240 mg twice a day and 771 placebo-treated patients.

Table 1: Adverse Reactions in Study 1 and 2 reported for TECFIDERA 240 mg BID at ≥2% higher incidence than placebo

	TECFIDERA N=769 %	Placebo N=771 %
Flushing	**40**	**6**
Abdominal pain	**18**	**10**
Diarrhea	**14**	**11**
Nausea	**12**	**9**
Vomiting	**9**	**5**
Pruritus	**8**	**4**
Rash	**8**	**3**
Albumin urine present	**6**	**4**
Erythema	**5**	**1**
Dyspepsia	**5**	**3**
Aspartate aminotransferase increased	**4**	**2**
Lymphopenia	**2**	**<1**

Gastrointestinal

TECFIDERA caused GI events (e.g., nausea, vomiting, diarrhea, abdominal pain, and dyspepsia). The incidence of GI events was higher early in the course of treatment (primarily in month 1) and usually decreased over time in patients treated with TECFIDERA compared with placebo. Four percent (4%) of patients treated with TECFIDERA and less than 1% of placebo patients discontinued due to gastrointestinal events. The incidence of serious GI events was 1% in patients treated with TECFIDERA.

Hepatic Transaminases

An increased incidence of elevations of hepatic transaminases in patients treated with TECFIDERA was seen primarily during the first six months of treatment, and most patients with elevations had levels <3 times the upper limit of normal (ULN). Elevations of alanine aminotransferase and aspartate aminotransferase to ≥3 times the ULN occurred in a small number of patients treated with both TECFIDERA and placebo and were balanced between groups. There were no elevations in transaminases ≥3 times the ULN with concomitant elevations in total bilirubin >2 times the ULN. Discontinuations due to elevated hepatic transaminases were <1% and were similar in patients treated with TECFIDERA or placebo.

Eosinophilia

A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.

Adverse Reactions in Placebo-Controlled and Uncontrolled Studies

In placebo-controlled and uncontrolled clinical studies, a total of 2513 patients have received TECFIDERA and been followed for periods up to 4 years with an overall exposure of 4603 person-years. Approximately 1162 patients have received more than 2 years of treatment with TECFIDERA. The adverse reaction profile of TECFIDERA in the uncontrolled clinical studies was consistent with the experience in the placebo-controlled clinical trials.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. In animals, adverse effects on offspring survival, growth, sexual maturation, and neurobehavioral function were observed when dimethyl fumarate (DMF) was administered during pregnancy and lactation at clinically relevant doses. TECFIDERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In rats administered DMF orally (25, 100, 250 mg/kg/day) throughout organogenesis, embryofetal toxicity (reduced fetal body weight and delayed ossification) were observed at the highest dose tested. This dose also produced evidence of maternal toxicity (reduced body weight). Plasma exposure (AUC) for monomethyl fumarate (MMF), the major circulating metabolite, at the no-effect dose is approximately three times that in humans at the recommended human dose (RHD) of 480 mg/day. In rabbits administered DMF orally (25, 75, and 150 mg/kg/day) throughout organogenesis, embryolethality and decreased maternal body weight were observed at the highest dose tested. The plasma AUC for MMF at the no-effect dose is approximately 5 times that in humans at the RHD.

Oral administration of DMF (25, 100, and 250 mg/kg/day) to rats throughout organogenesis and lactation resulted in increased lethality, persistent reductions in body weight, delayed sexual maturation (male and female pups), and reduced testicular weight at the highest dose tested. Neurobehavioral impairment was observed at all doses. A no-effect dose for developmental toxicity was not identified. The lowest dose tested was associated with plasma AUC for MMF lower than that in humans at the RHD.

Pregnancy Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to TECFIDERA during pregnancy. Encourage patients to enroll by calling 1-866-810-1462 or visiting www.TECFIDERApregnancyregistry.com.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TECFIDERA is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of TECFIDERA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information)

Dosage

Inform patients that they will be provided two strengths of TECFIDERA when starting treatment: 120 mg capsules for the 7 day starter dose and 240 mg capsules for the maintenance dose, both to be taken twice daily. Inform patients to swallow TECFIDERA capsules whole and intact. Inform patients to not crush, chew, or sprinkle capsule contents on food. Inform patients that TECFIDERA can be taken with or without food *[see Dosage and Administration (2.1)]*.

Anaphylaxis and Angioedema

Advise patients to discontinue TECFIDERA and seek medical care if they develop signs and symptoms of anaphylaxis or angioedema *[see Warnings and Precautions (5.1)]*.

Progressive Multifocal Leukoencephalopathy

Inform patients that progressive multifocal leukoencephalopathy (PML) has occurred in a patient who received TECFIDERA. Inform the patient that PML is characterized by a progression of deficits and usually leads to death or severe disability over weeks or months. Instruct the patient of the importance of contacting their doctor if they develop any symptoms suggestive of PML. Inform the patient that typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. *[see Warnings and Precautions (5.2)]*.

Lymphocyte Counts

Inform patients that TECFIDERA may decrease lymphocyte counts. A blood test should be obtained before they start therapy. Blood tests are also recommended after 6 months of treatment, every 6 to 12 months thereafter, and as clinically indicated *[see Warnings and Precautions (5.3), Adverse Reactions (6.1)]*.

Flushing and Gastrointestinal (GI) Reactions

Flushing and GI reactions (abdominal pain, diarrhea, and nausea) are the most common reactions, especially at the initiation of therapy, and may decrease over time. Advise patients to contact their healthcare provider if they experience persistent and/or severe flushing or GI reactions. Advise patients experiencing flushing that taking TECFIDERA with food or taking a non-enteric coated aspirin prior to taking TECFIDERA may help. *[see Adverse Reactions (6.1)]*.

Pregnancy and Pregnancy Registry

Instruct patients that if they are pregnant or plan to become pregnant while taking TECFIDERA they should inform their physician.

Encourage patients to enroll in the TECFIDERA Pregnancy Registry if they become pregnant while taking TECFIDERA. Advise patients to call 1-866-810-1462 or visit www.TECFIDERApregnancyregistry.com for more information *[see Use in Specific Populations (8.1)]*.

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04/2015

Smoked Cannabis May Impair Cognition in Patients With MS

Neurologists should weigh the drug's potential adverse effects against its possible benefits for pain and spasticity.

INDIANAPOLIS—Smoked cannabis may compromise cognitive function in patients with multiple sclerosis (MS), according to an overview presented at the 2015 CMSC Annual Meeting. Evidence does not support the hypothesis that cannabis affects mood or causes anxiety or psychosis, however. Clinicians should weigh the potentially harmful effects of cannabis on cognition against the drug's possible benefits for pain, spasticity, and urinary problems.

Between 40% and 70% of people with MS have cognitive dysfunction, which may include deficits in information processing speed, working memory, visuospatial memory, or executive function, said Anthony Feinstein, MD, PhD, Professor of Psychiatry at the University of Toronto. Approximately 40% of patients with MS have used cannabis, and Dr. Feinstein studies the drug's effects on cognition among patients with MS.

Evidence suggests that smoked cannabis may compromise cognitive function in patients with MS, but no current evidence indicates that it affects mood or causes anxiety or psychosis.

In 2008, he and his colleagues interviewed 140 consecutive patients with MS with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) Axis I disorders. The researchers assessed cognition using the Neuropsychological Battery for MS, supplemented with the Symbol Digit Modalities Test (SDMT). When the investigators compared 10 current cannabis users with 40 matched controls with MS, they found that cannabis users had a slower mean performance time on the SDMT and a different pattern of response, compared with the matched controls.

In 2011, Dr. Feinstein and colleagues compared 25 patients with MS who smoked cannabis with 25 patients with MS who did not smoke cannabis. Participants underwent the Minimal Assessment of Cognitive Function in MS battery of neuropsychologic tests, the Hospital Anxiety and Depression Scale (HADS), and the Structured Clinical Interview for the DSM-IV Axis I Disorders. The two patient groups were matched for demographic and disease variables. Cannabis users were more likely to be unemployed than nonusers and also had more cognitive deficits, including in visuospatial perception, executive function, and information processing speed, compared with nonusers. The researchers found no differences between groups in depression or anxiety, however.

Finally, in 2014, Dr. Feinstein and colleagues performed a cross-sectional study of 20 patients with MS who smoked cannabis and 19 patients with MS who did not. Participants underwent fMRI while completing the N-Back test of working memory. Spatial memory and Paced Auditory Serial Addition Test scores were lower among patients who smoked cannabis. These patients also had slowed responses and more errors on the N-Back test, compared with cannabis nonusers. During this test, cannabis users also had increased activation in parietal and anterior cingulate regions implicated in working memory, compared with nonusers. ■

—Erik Greb

Is There a Better Screening Tool for Cognitive Function and Employment Status in Patients With MS?

A computerized cognitive testing tool outperformed the Symbol Digit Modalities Test as a screening tool for cognitive impairment and employment status.

INDIANAPOLIS—NeuroTrax computerized cognitive testing (NT-CCT) provides an easy, independent, objective screening tool highly predictive of employment status in patients with multiple sclerosis (MS), according to research presented at the 2015 CMSC Annual Meeting. Lead author Mark Gudesblatt, MD, and colleagues said that objective assessment of cognitive function, such as NT-CCT provides, is an important adjunct to the Expanded Disability Status Scale (EDSS) in routine MS care. Dr. Gudesblatt is a neurologist at South Shore Neurologic Associates in Patchogue, New York.

Cognitive impairment is common in patients with MS. Routine cognitive screening in MS care, however, is not common. Employment status may be affected by cognitive impairment, but the latter may not be apparent on routine EDSS assessment. "MS affects cognitive domains differently in people with MS," said Dr. Gudesblatt. "Easily available and utilized objective cognitive screens are needed to evaluate cognition in MS independent of EDSS or MRI."

The Symbol Digit Modalities Test (SDMT) is not commonly used in routine MS care. As a single-score cognitive measure, the SDMT does not provide information about individual cognitive domains or the presence or degree of impairment in multiple domains. Computerized cognitive screening tools, in comparison, provide scores for individual cognitive domains.

To explore the predictability and effect size between the SDMT and the NT-CCT domains in patients with MS who self-reported their employment status, Dr. Gudesblatt and colleagues conducted a retrospective review of patients with MS referred for screening cognitive testing in the course of routine clinical care. Patients were evaluated with the oral version of the SDMT and the NT-CCT on the same day.

The study included 113 MS patients, mean age 48.9, and 85% were female. The standardized SDMT score significantly correlated with NT-CCT Global Cognitive Score (GCS) and executive function. The SDMT and NT-CCT GCS both predicted employment status. The effect size of the NT-CCT GCS was 0.83, and that of SDMT was 0.70. For the NT-CCT Executive Function index, the effect size was 0.87.

Both SDMT and NT-CCT screening significantly differentiate patients with MS who are employed and those who are not. However, the NT-CCT provided a greater effect size for this differentiation.

In the NeuroTrax Catch Game, with scores standardized for age and education, overall score predicted employment. Unemployed patients with MS had NT-CCT cognitive domain index scores less than one standard deviation below average for cognitively healthy age and education norms.

"Unemployed patients with MS demonstrated reduced cognitive function relative to employed patients," Dr. Gudesblatt and colleagues reported. Both SDMT and NT-CCT screening significantly differentiate patients with MS who are employed and those who are not. However, NT-CCT predictability of employment provided a greater effect size for this differentiation. ■

How Does Insurance Coverage Influence Patient Perspectives on MS Treatment Decisions?

Some patients with MS may be making treatment decisions for financial rather than clinical reasons.

INDIANAPOLIS—For patients with multiple sclerosis (MS), making treatment decisions is a complex undertaking. The decisions involve clinical factors such as symptom severity, level of disability, and disease duration. Physician recommendations play a major role, but insurance coverage and financial situation also may be factors. Important changes to insurance coverage in the last few years may have required some patients to change their disease-modifying therapies (DMTs) for financial rather than clinical reasons.

To examine this issue, Stacey S. Cofield, PhD, a biostatistician at the University of Alabama at Birmingham, and her colleagues used patient-reported data from the NARCOMS registry to describe the insurance status of patient participants and how insurance and financial situation affect their DMT choices. Their findings were reported at the 2015 CMSC Annual Meeting.

Many patients in the NARCOMS patient registry rely on assistance for DMT coverage or are not able to take a DMT as directed or at all because of their current insurance or financial situation.

The NARCOMS Fall 2014 Update survey included the following questions about health insurance and DMT choices related to insurance: current health insurance (Yes/No), health insurance for the prior six months (Yes/No), comparison of current health insurance to 12 months prior (better, worse, unchanged), and how insurance or financial situation has influenced treatment of MS. Dr. Cofield and colleagues reported on only registry participants who completed the survey online. Data entry for paper forms collected during the Fall 2014 Update is ongoing.

Of the 5,106 participants who completed the survey online, 4,507 (96.9%) completed the health insurance questions, 78.8% were female (mean age 56.7), and 62.1% had relapsing-remitting MS. Nearly all (99.5%) participants had health insurance. Likewise, nearly all (98.6%) had insurance for the prior six months, with 68.6% reporting insurance coverage had not changed in the prior year, while 23.0% reported worse coverage compared to 12 months ago. Coverage did not differ by gender or MS type, but more females than males reported their insurance coverage to be worse compared with 12 months ago (23.9% vs 19.7%). More respondents with progressive MS reported no change in insurance coverage compared with those with relapsing-remitting MS (73.3% vs 66.8%).

When asked about influence of insurance or financial situation on DMT choice, 30.0% reported not taking DMT by choice or physician recommendation, 15.9% took their DMT of choice with full coverage, 46.6% with a co-pay, 19.1% with a free or discounted drug program, 3.6% were able to switch DMTs with insurance approval, 1.3% would like to switch but could not due to lack of insurance approval or coverage, while 2.4% had to stop, change, or skip DMTs due to higher co-pays, and 1.6% did not take DMTs because they did not have insurance or insurance denied the DMT.

Dr. Cofield reported that most participants in the NARCOMS MS patient registry did not perceive major impacts from their insurance or financial situation with regard to DMT choice. Many patients, however, rely on assistance for DMT coverage or are not able to take a DMT as directed or at all because of their current insurance or financial situation. ■

How Should Neurologists Treat Menopausal Women With MS?

Disease management decisions need to take into account the effects of menopause among women with MS.

INDIANAPOLIS—Although many women with multiple sclerosis (MS) are perimenopausal, the literature contains few data about effective ways to manage these women's symptoms, according to research presented at the 2015 CMSC Annual Meeting. The topic could be considered to inhabit an "evidence-free zone," but general recommendations are possible, according to Riley Bove, MD, Instructor at Harvard Medical School in Boston.

During menopause, women may have vasomotor symptoms such as hot flashes, vascular instability, and rapid heartbeat. For patients with MS, these symptoms may disturb sleep, contribute to fatigue, and affect mood. Vasomotor symptoms also may cause exacerbations.

The literature contains few data about effective strategies to manage the symptoms of menopausal women with MS, but general recommendations are possible.

Hormone replacement therapy is the most effective treatment for vasomotor symptoms. In the Women's Health Initiative Memory Study, however, hormone replacement therapy initiated in women age 65 or older was associated with an increased risk of dementia and cognitive decline. This association should be examined in longitudinal placebo-controlled trials, said Dr. Bove.

Bladder symptoms and sleep apnea are more common during menopause and can cause frequent awakenings, which lead to mood disturbances (eg, depression or anxiety) and relational problems in patients with MS. To improve sleep, neurologists should advise their patients about good sleep hygiene. Patients should stay in bed for only a certain amount of time, use their bed for sleep or intimacy only, schedule regular wake times, and moderate caffeine intake, among other behaviors.

Fatigue is common in MS, and its severity and frequency tend to increase during menopause. Neurologists should rule out additional contributors to fatigue, such as thyroid disease. Patients should be advised to arrange their daily schedule so that work routines are spaced out. They should take intermittent rest breaks and try to concentrate their activity in the morning when it is cooler. Relaxation and meditation practices can reduce stress and decrease fatigue. Drugs such as modafinil and amantadine can promote wakefulness, and methylphenidate can be used as a stimulant.

Pain tolerance may decrease during menopause, and patients with MS often have cervical and lumbar spondylosis, joint immobility, spasticity, and deconditioning. Baclofen, diazepam, dantrolene, and tizanidine may be effective for pain resulting from spasticity. Phenytoin, carbamazepine, and tricyclic antidepressants can alleviate neuropathic pain and paresthesias. Neurologists also might recommend weight loss or exercise or refer a patient to a pain center for an integrated approach to the condition.

Mood disorders are common among patients with MS, and mood fluctuations may accompany menopause. In response to this problem, a neurologist may recommend psychotherapy to help optimize the patient's coping abilities. Spousal and interpersonal support also are important for the patient. Antidepressants such as fluoxetine, sertraline, escitalopram, and citalopram can be effective if drug therapy is warranted. Support groups also may help stabilize the patient's mood. ■

—Erik Greb

Promoting MS Medication Adherence Through Telehealth

An automated telehealth program can improve medication adherence among patients with MS and lessen healthcare provider workload.

INDIANAPOLIS—Self-reported monitoring through an automated telehealth mechanism can provide a valid assessment of disease-modifying therapy (DMT) adherence among patients with multiple sclerosis (MS), according to study findings reported at the 2015 CMSC Annual Meeting. Furthermore, using an automated electronic system reduces the time spent by healthcare providers making phone calls and researching pharmacy refill records, according to Jill R. Settle and her research colleagues. Ms. Settle is affiliated with the MS Center of Excellence at the Veterans Affairs Medical Center in Washington, DC.

DMTs for MS have been available for more than 20 years; however, adherence to DMT regimens is often poor. The most common reason cited by patients is forgetting to take their medications on the specific day they are to be administered. To address the issue of nonadherence, Ms. Settle and colleagues sought to establish the feasibility of implementing a home telehealth program to support and monitor MS medication adherence without increasing healthcare provider burden.

The researchers addressed the assessment of poor adherence using a comprehensive Home Automated Telemanagement system for MS (MS HAT). MS HAT is a home-based Internet module that supports patient self-management, patient–provider communication, and patient education.

For approximately six months, 30 study participants were randomized to either MS HAT or treatment as usual. All participants stored their interferon β-1a syringes in a clear syringe container and maintained a paper calendar of medication adherence. Pharmacy refill rates were also collected from medical records. Participants in the MS HAT study arm received text or e-mail reminders to administer their medication.

There were no significant differences in demographic variables between the two groups. Likewise, overall adherence did not differ between the two groups. MS HAT alert rates were negatively correlated with syringe counts. As alerts decreased, the number of syringes collected increased.

The strong correlation between self-report and objective measures of adherence suggests that the MS HAT system is effective and cost-efficient.

Syringe count was positively related to change in Morisky score for interferon β-1a. As self-reported adherence improved, the number of syringes collected also increased. Pharmacy refills were directly related to calendar reports of taking the medication and syringe counts. As pharmacy refills increased, so did calendar reports and the number of syringes collected.

The strong correlation between self-report and objective measures of adherence suggests that the MS HAT system is effective and cost-efficient. ■

Is CBT Effective for Mood Disorders in Patients With MS?

Cognitive behavioral therapy can address some of the psychiatric and social symptoms experienced by patients with MS.

INDIANAPOLIS—Cognitive behavioral therapy (CBT) can be an effective treatment for psychiatric and interpersonal problems in patients with multiple sclerosis (MS), according to research presented at the 2015 CMSC Annual Meeting. Data indicate that CBT can reduce anxiety and depression and improve marital satisfaction and marital communication.

CBT is a form of psychotherapy that identifies patterns of thought and behavior that change with depression or other mood disorders, said Frederick W. Foley, PhD, Professor of Psychology at Yeshiva University in Bronx, New York. The treatment helps people change these patterns of thinking and behavior to lessen the symptoms of the mood disorder or achieve remission.

Dr. Foley and colleagues examined 40 patients with MS in a study published in *Journal of Consulting and Clinical Psychology*. The investigators randomized the participants to current available care or stress inoculation training (SIT), which included CBT and progressive deep-muscle relaxation training adapted for patients with MS. At the end of the trial, Dr. Foley and colleagues found that participants randomized to SIT had significantly less depression, anxiety, and distress, compared with participants who received current available care. In addition, individuals randomized to SIT used more problem-focused coping strategies than those randomized to current available care.

In a pilot study published in *Multiple Sclerosis* in 2001, Dr. Foley and colleagues tested the efficacy of a counseling intervention that included CBT in nine couples with MS and sexual dysfunction. The intervention included 12 counseling sessions, communication with the MS medical treatment team, education, and tailoring of symptomatic treatments so that they would interfere less with sexual function. Repeated measures analysis of variance indicated that the couples had significant improvements in affective and problem-solving communication, marital satisfaction, and sexual satisfaction during the treatment, compared with a phase of the study during which they were on a waiting list. Patients with MS and their spouses reported similar levels of improvement.

Data indicate that CBT can reduce anxiety and depression and improve marital satisfaction and marital communication.

CBT also may improve marital communication for patients with MS and cognitive disorders. In a study published in *Journal of Neurologic Rehabilitation*, Dr. Foley and colleagues developed templates to enable patients and their spouses to communicate. The investigators taught participants listening skills, how to empathize with their spouses using templates, and how to make positive (ie, noncritical) requests. In addition, the researchers instructed participants in how to provide feedback when their spouse's behavior is not acceptable, as well as how to make positive requests for changes in behavior. This intervention has not been studied in a randomized controlled trial, however. ■

—Erik Greb

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