Therapies for Cognitive Impairment and Neurological Protection

Written by Brian Hoyle

Maria P. Amato, MD, University of Florence, Florence, Italy, discussed cognitive impairment, an all-too-common part of multiple sclerosis (MS). Cognitive impairment is seen in >65% of patients in clinical studies of MS [Fischer JS et al. *Ann Neurol.* 2000]. The impairment has been documented in all subtypes and stages of MS [Amato MP et al. *Neurology.* 2010; Amato MP et al. *Neurology.* 2008; Potagas C et al. *J Neurol Sci*. 2008; Amato MP et al. *J Neurol*. 2006; Fischer JS et al. *Ann Neurol.* 2000]. The mental impairment is independent of the disease duration or physical state of the affected person [Benedict RH *J Int Neuropsychol Soc*. 2006].

According to Prof Amato, cognitive impairment can involve information-processing speed, memory, executive functions (eg, reasoning, planning, and problem solving), and visual and spatial abilities. Potential therapies include drugs and rehabilitation [Amato MP et al. *J Neurol.* 2013]. The former can involve disease-modifying therapies that seek to prevent, delay, and slow impairment, and so are more prudently applied early in the course of MS. Another therapeutic approach is to use symptomatic therapies to improve an already impaired function. Examples include drugs for fatigue, psychostimulants, and Alzheimer's drugs. Both approaches suffer from limited clinical trial evidence as well as negative or inconsistent findings.

The concept of cognitive rehabilitation is based on 4 pillars: prevention, restoration, compensation and maintenance, and palliative care. The format of interventions is mainly based on the use of computerized programs to train different cognitive functions or behavior interventions. Behavior interventions that can aid in improving learning include, for example, the modified story memory technique (use of context and images), the self-generation effect (items that are subject generated tend to be remembered better than items that are presented), the spacing effect (presentations of new information throughout time instead of all at once), and the testing effect [DeLuca C. *Educ Res.* 2011; O'Brien AB et al. *Arch Phys Med Rehabil.* 2008].

Application of the modified story memory technique approach has been promising, with greater learning-associated cerebral activity seen with functional magnetic resonance imaging (f-MRI) [Chiaravalloti ND et al. *J Neurol.* 2012] and improved learning and memory after 6 months in cognitively impaired MS patients, documented in a randomized double-blind trial [Chiaravalloti ND et al. *Neurology.* 2013]. Other studies have provided evidence of the benefits of intellectual enrichment, in lessening the effects of brain atrophy in MS [Sumowski JF et al. *Neurology.* 2014; Sumowski JF et al. *Brain.* 2009], and there is also preliminary evidence that physical exercise in MS may have a positive impact on cognition, possibly enhancing neuroprotection, neuroregeneration, and neuroplasticity [Feinstein A. *Mult Scler.* 2011].

Cris S. Constantinescu, MD, PhD, University of Nottingham, Nottingham, United Kingdom, discussed the evidence for the use of cannabinoids for the relief of MS symptoms and as a neuroprotective mechanism.

According to Prof Constantinescu, cannabinoids constitute >60 identified compounds from the *Cannabis sativa* plant. Although the plant has been used as a source of hemp and marijuana for millennia, its potential in MS therapy is in its infancy.

Routes of administration of MS cannabis-related therapy include the familiar—smoking of cannabis, ingestion of cannabis-laden food, and drinking of cannabis-containing tea—as well as consumption of whole plant extract containing tetrahydrocannabinol (THC) or

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cannabidiol (CBD), swallowing capsules containing THC or synthetic cannabinoids (eg, nabilone), or the use of a oromucosal spray containing an equal mixture of THC and CBD.

Patients with MS have related the capability of cannabis to lessen or relieve MS-associated symptoms, including pain and spasticity [Chong MS et al. *Mult Scler.* 2006]. Other symptomatic targets being assessed include overactive bladder, sleep disturbance, anxiety and other mood disturbances, cognitive impairment, and nystagmus and cerebellar symptoms. Other possible routes of relief include neuroprotection [Koppel BS et al. *Neurology*. 2014] and modulation of the immune system. In assessing the effect of cannabis-related therapy on MS symptoms, the use of an 11-point visual analog scale has proven instructive, said Prof Constantinescu. For example, when queried about muscle stiffness during the previous week of therapy as compared with that experienced prior to the start of therapy, subjects can rate their subjective impression according to numerical categories ranging from 1 (very much better) to 11 (very much worse). Subjects also have the option of not answering the question if it is irrelevant.

Studies using similar numerical rating scales have reported better patient outcomes than using the Ashworth Scale, which objectively assesses outcome [Notcutt W et al. *Mult Scler*. 2012; Collin C et al. *Neurol Res*. 2010; Collin C et al. *Eur J Neurol.* 2007]. The Ashworth Scale, which assigns scores based on defined degrees of increased tone, has been questioned concerning its efficacy as an indicator of MS-related symptom change. A comprehensive 88-item Multiple Sclerosis Spasticity Scale was demonstrated as a reliable, valid, patient-based instrument [Hobart JC et al. *Brain.* 2006].

Randomized controlled studies investigating the use of inhaled cannabis (ie, THC) for relief of MS-associated pain and painful spasms have been equivocal, with both positive and borderline negative results reported [Zajicek J et al. *J Neurol Neurosurg Psychiatry.* 2012; Zajicek J et al. *J J Neurol Neurosurg Psychiatry*. 2005; Vaney C et al. *Mult Scler.* 2004; Zajicek J et al. *Lancet.* 2003]. The data concerning the effect of oromucosal-administered cannabis-based spray are also mixed, with both positive and negative effects reported.

Little is known of the neuroprotective effect of cannabinoids. The randomized, placebo-controlled CAMS trial [Zajicek J et al. *Lancet.* 2003] for the treatment of spasticity and other symptoms related to MS that enrolled 667 patients provided limited evidence for a longer-term beneficial effect on spasticity. A follow-up of the CAMS cohort intends to address the effect of therapy on disability.

In addition, the randomized, double-blind, placebo-controlled CUPID trial [Zajicek J et al. *Lancet Neurol.* 2013] involving 498 patients failed to provide evidence for dronabinol-mediated slowing of progressive MS in the overall cohort, with a similar rate of Extended Disability Severity Scale (EDSS) progression as with placebo (HR, 0.92; 95% CI, 0.68 to 1.23). A subgroup of patients, however, who were younger with lower EDSS scores demonstrated a better response to the 36-month dronabinol treatment.

The CUPID results provide insight into the possibility that cannabinoids may be relatively more beneficial at earlier stages of MS. Also, the use of combination therapy, such as THC plus CBD, in a delivery system other than a nasal spray warrants study.