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Sara Bernstein, Editor, Research Now
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INSIDE:
60 The deep science of cannabinoids
62 Creating a global network to stop MS

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How are you? Why quality of life matters in MS research and care

by Sara Bernstein

Clinicians have several ways of assessing the impact of MS, and of determining whether new treatments are working. The Expanded Disability Status Scale—or EDSS—looks at neurologic signs and symptoms. The Timed 25-foot Walk computes walking speed. The Paced Auditory Serial Addition Test measures how fast and how accurately a person is processing information. All these are important, but increasingly researchers are seeking to incorporate “quality of life” in tracking the success of MS treatments.

How are you?
It’s a simple question, but not that easy to measure, given the variety of symptoms that occur in people with MS.

“Including quality of life assessment in clinical care is one way to achieve personalized medicine,” said Deborah Miller, PhD (Cleveland Clinic Foundation), a noted expert in MS quality of...
life research and a 2005 Inductee into the National MS Society’s Volunteer Hall of Fame. “We can identify what areas of quality of life are deficient for people with MS and target interventions to help them manage those areas.”

How MS affects quality of life
People with MS may think, “Of course MS affects the quality of my life,” but key studies have been conducted to determine exactly how, and how much. The answers are not always obvious.

Dr. Miller’s team compared quality of life in people with MS, inflammatory bowel disease and rheumatoid arthritis, all potentially disabling immune system disorders. Scores were significantly lower in the MS group than the other two, and did not correlate with medical assessment as determined by the EDSS, or with the length of time that the person had had MS. Archives of Neurology 1992;49(12):1237–42

Sarah Minden, MD, and colleagues looked at quality of life in more than 2,000 people enrolled in the Sonya Slifka Longitudinal MS Study, funded through the Society’s Promise: 2010 campaign. The authors made note of the symptoms that stood out in this population: problems with walking, pain, spasticity, bowel, vision, mood, fatigue and cognition. They concluded that “symptom management is crucial for improving the quality of the lives of people with MS.” Journal of Health and Human Services Administration 2007;30(3)233–67

Such results present a sobering look at how MS affects individual lives, but Dr. Miller emphasizes that research is crucial to developing the most effective interventions to improve the lives of people with MS. “It’s good to delve into what is negatively influenced so that we can find interventions to address it,” she says. “For example, a person might be isolating themselves socially because of bladder dysfunction. If we knew that, we could treat it and improve the quality of their life. Likewise, if we know what is working well in a person’s life, we can help build on that strength.”

Patient-centered outcomes
“The whole idea of quality of life is that it’s from the patient’s perspective,” said Dr. Miller. Scales such as the 138-question MS Quality of Life Inventory reflect the variety of symptoms that can affect people with the disease. Here are some sample questions:

- Does your health limit you in moderate activities, such as moving a table, pushing a vacuum cleaner or bowling?
- How much time during the past four weeks have you felt so down in the dumps that nothing could cheer you up?
- During the past four weeks, how satisfied have you been with the amount of affection expressed physically in your relationship?

Answering a 138-item questionnaire, however, can be daunting. Dr. Miller has joined a team of researchers from around the U.S. who are currently developing and testing “Neuro-QOL.” Funded by the National Institute of Neurologic Disorders and Stroke, Neuro-QOL features computer-adaptive testing, which maximizes background information and tailors questions to the individual.
Quality of Life webcast
Join us from 2:00–3:00 p.m. ET, Tuesday, May 24, 2011, when we host Working Toward Your Best Life: Advances in Quality of Life Research, a live webcast featuring Drs. Allen Bowling, Nicholas LaRocca and Robert Motl.
Topics will include:
• Research that is improving quality of life
• Treating the whole person, including complementary therapies
• Fatigue management
• Taming stress
• Combating emotional and cognitive challenges
To register, visit nationalMSSociety.org/may24webcast.

“The benefit of this testing is that it can ask just five questions and give us complete and accurate responses,” said Dr. Miller. Neuro-QOL comprises a core set of questions universal to those with chronic neurological disease, along with specific concerns of people with a particular disease, or at a certain age.

One population that may benefit in particular from this testing is children with MS. “For example, we know that cognitive problems happen in kids with MS, but we don’t know how this affects their self-esteem,” Dr. Miller pointed out. “We need pediatric- and adolescent-specific measures to show how they feel about themselves in certain situations.”

The United Kingdom’s MS Clinical Trials Network is developing a new outcome measure specific to people with progressive MS. The U.K. MS Society established this network to plan and conduct clinical trials of neuroprotective agents. They are interviewing people with progressive MS to identify what aspects of quality of life are relevant to them. The network is beginning a study of an experimental drug this year, and hopes to put this new measure in place to determine whether any benefit of the drug extends beyond the physical aspects of the disease.

What improves poor quality of life?
Improving the quality of life of people with MS is a top goal in the Society’s strategic response for 2011–15. The Society is committed to pursuing new rehabilitation techniques and symptomatic treatments that will restore function and enhance quality of life.

Researchers funded through the Society’s Health Care Delivery and Policy Research Program investigate such issues and acquire data that help to develop practical ways for improving MS care and quality of life. Barbara G. Vickrey, MD, MPH (University of California, Los Angeles), was awarded a contract to define what constitutes quality MS health care. She consulted both the scientific literature and a group of stakeholders in MS care, including people with MS. They related what symptoms they considered to be most important to address, including bladder dysfunction, cognition dysfunction, depression, fatigue and spasticity. These findings will be further explored in studies to test whether
addressing them improves the quality of life of people with MS. (Multiple Sclerosis, published online 18 June 2010.)

**Self-management and other strategies**

With a Society Mentor-Based Fellowship in Rehabilitation Research Marcia Finlayson, MSc, OTR, PhD (University of Illinois at Chicago) is currently training researchers to conduct “self-management” training. This will help people with MS to develop the skills to manage their disease, its symptoms, and its consequences on their daily life, with the aim of improving quality of life.

Other Society-funded efforts include clinical trials of interventions to improve the symptoms most likely to interfere with a good quality of life:

- Barbara Giesser, MD, and her colleagues (University of California, Los Angeles) are comparing the effects on cognitive performance of an aerobic exercise program lasting six months to the effects of non-aerobic stretching exercises.
- Dean M. Wingerchuk, MD (Mayo Clinic Scottsdale) is conducting a clinical trial of aspirin to improve MS-related fatigue in 135 people at three sites in the U.S.
- Robert Motl, PhD (University of Illinois at Urbana-Champaign) is testing an exercise regimen that incorporates balanced amounts of aerobic, resistance, and balance modes of training, to help manage mobility problems.
- A new grant to Jacob J. Sosnoff, PhD (University of Illinois at Urbana-Champaign) is funding a clinical trial investigating the effects of different durations and intensities of leg cycling exercise on MS spasticity.

**Looking at long-term quality of life**

MS is a lifelong experience, and quality of life may change over time. Dr. Miller’s team is looking at these changes in people who are seen at the Mellen MS Center at the Cleveland Clinic. More than 80% of patients are completing questionnaires in advance of every clinic appointment, via computer, either at home or at the clinic.

“We plan to compare people who report that their quality of life is good and those who report that it’s not as good,” said Dr. Miller. “What are the differences in their lives and their MS experience? If we can see that, we can get an idea of what interventions can improve quality of life.” The team has been collecting data in this ongoing effort since 2007, and has now begun analyzing them.

Dr. Miller wants to see quality of life measures used in practice, not just clinical trials. As less time-consuming and less cumbersome measures are developed, this may become a reality. “It’s simply essential. We need to understand fully how this disease affects the lives of the people who have it,” Dr. Miller concluded.

**The deep science of cannabinoids for MS**

There’s a lot of talk about marijuana: Does it relieve MS symptoms? The jury is still out (see “Marijuana and MS—An Unfinished Story,” Momentum, Fall 2010). But another side of cannabis is gaining in interest. Is there a role for it in battling MS itself?

**The neuroprotective prospects of cannabis**

Cannabis works by interacting with “cannabinoid receptors” (think of cannabis as a key and receptors as the lock) that exist on certain cells in the body, including brain cells. Gareth Pryce, PhD, David Baker, PhD (University College London) and colleagues regulated the receptor CB₁ in mice with a progressive form of EAE, an MS-like disease, to determine what the effects would be.

Mice that were genetically engineered to lack CB₁ experienced considerably increased nerve degeneration. Compounds that activated CB₁ reduced damage to nerve cells. Brain 2003;126:2191–202 These results, along with research in other diseases such as stroke, suggest that cannabis might be capable of protecting the brain from damage.

A clinical trial is already ongoing to test this idea in MS. John
Zajicek, FRCP, PhD (Peninsula Medical School, Plymouth, UK) and colleagues expect to report results this year from a study exploring whether a cannabis derivative taken orally can slow disease progression in 500 people with primary-progressive and secondary-progressive MS (the “CUPID” trial).

Cannabis versus the immune system
Multiple sclerosis involves immune system attacks and inflammation in the brain and spinal cord. Dr. Pryce’s team, this time joined by Katarzyna Maresz, PhD, and Bonnie Dittel, PhD (Blood Research Institute, Milwaukee, Wis.) looked at the possibility that CB$_1$ and CB$_2$ may have immune-regulating capabilities as well.

The team induced EAE in mice using immune T cells that lacked CB$_2$ molecules, and found that the disease was significantly more severe in these models. These results indicate that CB$_2$ controls the extent of inflammation in the CNS during EAE specifically through its activity on these immune cells.

In other experiments, the team administered the cannabis derivative tetrahydrocannabinol (THC) to mice lacking CB$_1$. When CB$_1$ was deficient on nerve cells, THC did not suppress EAE. When CB$_1$ was deficient on T cells, however, THC did suppress EAE. These results indicate that CB$_2$ works through T cells and CB$_1$ works through nerve cells. *Nature Medicine* 2007;13(4):492–7

Now Dr. Dittel has been funded with a research grant from the National MS Society to study cannabis derivatives that bind to CB$_2$ to determine which ones suppress EAE most strongly, with an eye toward refining them for use in MS.

The highs and lows
Unfortunately, it has proven difficult to do carefully controlled clinical trials because marijuana is psychoactive and makes people feel “high.” People taking the active drug usually become aware of it—thus “unblinding” the study and possibly biasing results. Study participants have often reported uncomfortable side effects and smoked marijuana poses health risks known to be similar to tobacco. The fact that marijuana is an illegal drug in many states and by federal statute further complicates the issue.

The Society’s National Clinical Advisory Board continues to examine the use of cannabis in MS, and finds that there are currently insufficient data to recommend marijuana or its derivatives as a treatment for MS symptoms. The Society is also currently funding a carefully controlled trial of cannabis to treat MS spasticity. It is recommended that people wait for evidence from clinical trials and the possible development of less dangerous ways to take cannabis products before using them medicinally.
Creating a global network to stop MS
by Dr. Timothy Coetzee

It’s who you know. One of the greatest resources of the National MS Society is that, as a driving force of MS research, we are connected to scientists throughout the world who share our vision of a world free of MS. When we engage the best and brightest of these researchers and their colleagues, the resulting collaboration moves MS research forward dramatically.

One of my first assignments as the Society’s chief research officer was to welcome the four international research teams that we created through the Nerve Repair and Protection Initiative funded through the Promise: 2010 campaign. Armed with the largest grants ever awarded by the Society, this talented group of men and women spent five years focused on key aspects of nerve repair and protection in MS:

- Developing new disease models to understand the biology of repair
- Advancing non-invasive tools to monitor disease and repair
- Designing clinical trials that pave the way to restoring function in people with MS.

I was amazed by the progress these teams reported, and by the web of other scientists and trainees they have pulled into our cause.

- They have used cutting-edge technology—for example, screening all human genes using genomics—to find several promising targets for MS therapies.
- They have discovered or refined animal models that specifically mimic progressive forms of MS.
- They have provided new evidence that cell-based strategies can turn off immune forces and induce widespread repair in MS animal models.

Thanks to the repair teams, we have new, clearer windows into the tissue damage caused by MS. OCT, a quick eye test, can show us damage over time in people with MS even if they do not have inflammation of the optic nerve. Simple tests, like evaluating vibration sensation, may link well with damage as seen on the latest MRI technology. These findings will help us to determine more quickly whether treatments are protecting nerves and their myelin coatings, or not.

Surely the greatest thrill was hearing about the clinical trials underway, or being planned, by team members’ colleagues:

- A Phase II study of phenytoin (a drug previously used to treat epilepsy) to determine its neuroprotective effects in people with optic neuritis (funded by the U.S. and the U.K. MS societies).
- A Phase I study of neural stem cell transplantation in children born with a lack of myelin (this is a “proof of principle” study for MS).
- A large multicenter study of whether cannabis can slow disease progression in 500 people with primary-progressive and secondary-progressive MS.

I was motivated by the group’s suggestions for how to keep this momentum going. Many recommended more “meetings of the minds.” These researchers recognize that their individual accomplishments were enhanced through this international collab-
oration, and especially through face-to-face meetings—like this one—which we’ve been holding every two years.

We also brought great minds together for a think tank in Boston in December 2010, focusing on the challenges associated with progressive MS. This groundbreaking meeting—hosted by the Society and its drug development subsidiary, Fast Forward—engaged researchers from universities and pharmaceutical/biotech companies and MS society leadership from the U.S., Canada, Italy and the United Kingdom.

The discussion made it clear that the Society’s new Strategic Response focusing on progressive MS is right on target. Advances in pathology and imaging are finally yielding new information about progressive MS. We now know that progressive MS features “diffuse” or “smoldering” inflammation, rather than the acute immune attacks that are seen in relapsing MS. This inflammation appears to be driven by cells called microglia, immune cells that reside in the brain. More work is needed to understand their role, but they are already being targeted by therapies in the MS pipeline.

Also, novel brain imaging techniques are offering new ways to see the nervous system injury that occurs during the course of MS. These techniques, such as DTI (diffusion tensor imaging), may be helpful for detecting whether the nervous system is being repaired or protected by experimental therapies.

Dr. Timothy Coetzee is the Society’s chief research officer.

Think tank participants noted recent findings suggesting that a proportion of individuals with progressive MS who show signs of active inflammation on MRI scans are likely to respond to the disease-modifying therapies currently available for treating relapsing forms of MS. This makes it clear to me that we need to re-evaluate the clinical definitions of progressive types of MS and identify biological underpinnings that can improve treatment today, and also help determine whom to enroll in clinical trials.

To further a more collaborative approach to stopping MS progression, we are now holding talks with MS societies internationally to lay the groundwork for a global consortium on progressive MS research. The think tank steering committee is identifying key areas needing research, and will form study groups to make recommendations for moving the field forward in these areas.

Our collaborative efforts have continued. This May the Society and the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) convene an international workshop aimed at developing more sensitive measurements for MS progression. We need the quickest, most efficient ways to determine if therapies are stopping MS symptoms from getting progressively worse. I am excited to see how this meeting will move us closer to our goals.

We will not stop there. We will pursue all promising avenues; connect people, resources and ideas; speed development of treatments; and identify and fill gaps — until we have stopped MS progression in its tracks and restored lost function to people with MS.