

religious orientation and income. But the users of CAM were older ($p < 0.05$), had a longer duration of illness ($p < 0.05$) and a higher EDSS ($p < 0.001$) than non-users. CAM users reported more active coping behavior ($p < 0.01$) than non-users. In their personality users and non-users did not differ on the scale neuroticism ($p = 0.54$), but users scored higher on the scale openness to experience ($p < 0.01$). Regarding their locus of control users of CAM reported higher values on the scale internality than non-users ($p < 0.05$). **Conclusion:** Patients with MS are using CAM more often (81.1%) during their disease than former research has suggested. Besides age and aspects of illness (EDSS and duration of illness) the utilization of CAM is influenced by psychological factors like coping, locus of control and personality. Users report to a greater extent active coping and internal locus of control and they are more open to new experiences.

101

Use of cannabinoids in MS: is it evidence based?

*C. Vaney, Berner Klinik (Crans-Montana, CH)
Invited Speaker*

Recent years have witnessed the rise of evidence-based medicine (EBM) as an approach towards rationalizing clinical practice in the face of a growing body of knowledge. While the goal of EBM is laudable, it is entirely based on the proposition that truth can be exclusively gleaned from statistical studies and that our clinical practice should essentially rely on clear, evidence based judgements. But how should we decide when we are faced - as often in science - with grey, rather than black and white results? Our dilemma is well illustrated by the results of a large recently published RCT study (CAMS) using an orally taken cannabis extract containing Delta⁹-THC and Cannabidiol (CBD), which failed to show a significant effect on the primary outcome measure, an objective reduction in muscle tone, as measured by the Ashworth score. Although these, and previous studies, have not been able to produce a convincing tone reduction, patient continue, despite its illegality, to obtain cannabis on the black market for self-medication, claiming that cannabis is the only substance that alleviates their muscle spasms. Do we have to accept that, in this case, a current practice is highly effective without being evidence - based? Or, phrased in other words, is the absence of evidence of effect not the same as the evidence of absence of effect? Critical voices suspect that MS patients just want to be put into high spirits to forget that they are severely disabled. Although the recreational qualities of THC cannot be denied, the large majority of patients dislike being stoned and prefer to take THC at night time just to have fewer spasms while falling a sleep. On the other hand, some authors, convinced of the efficacy of cannabis, have argued that the Ashworth scale was not sensitive enough to pick up clinically relevant changes in muscle tone. Since several - though not all - RCT testing conventional drugs (tizanidine, baclofen) showed a significant tone reduction and because in one of the THC extract study the combined effect of physiotherapy and THC reduced muscle tone clearly, it would be unfair just to blame the insensitivity of the measure to explain why the aforementioned studies did not show any measurable tone reduction. But maybe our studies are too narrow sighted and we have to take the focus from pure muscle tone reduction away, and ask ourselves if Cannabis hasn't any other, more relevant properties, our patients have already intuitively discovered, namely that the substance might influence favourably on the course of the disease, since there is increasing experimental evidence of a neuroprotective effect of cannabinoids? Here again clinical evidence is still lacking and further research is urgently needed using eventually other delivery methods for THC such as sublingual sprays or skin patches. Maybe the use of endocannabinoids that stimulate the receptors without inducing psychoactive effects will be future options for cannabinoid therapy.

102

The Cannabinoids in MS study - final results form 12 months follow-up
*J. Zajicek, P. Fox, H. Sanders, D. Wright, J. Vickery, A. Nunn, A. Thompson
on behalf of the UK MS Research Group*

Background: The Cannabinoids in Multiple Sclerosis (CAMS) study was a multicentre randomised placebo-controlled study, which tested the

notion that cannabinoids may be effective in treating the symptoms of multiple sclerosis (MS). We now report results from up to 12 months follow-up. **Methods:** 657 patients with stable MS and muscle spasticity were randomised across 33 UK centres to receive oral cannabis extract, Δ⁹ tetrahydrocannabinol (Δ⁹-THC) or placebo. The study was based on the Ashworth scale of muscle spasticity, but data on other measures of symptoms and disability were also collected. After the main 15-week study period, patients were given the option of resuming their medication, in a double blind fashion, for up to 12 months. We sought to monitor all patients over this period using a range of measures, whether or not they continued medication. **Findings:** There was evidence of a treatment effect on muscle spasticity as measured by change in Ashworth score from baseline to 12-months follow-up in an intention to treat analysis, $p = 0.04$ unadjusted for ambulatory status and centre, $p = 0.01$ adjusted. In the group taking Δ⁹-THC, the Ashworth score was reduced by an average of 1.82 ($n = 154$, 95%CI = 0.53,3.12) compared to either cannabis extract ($n = 172$, mean 0.1, 95% CI = -0.99,1.19) or placebo ($n = 176$, mean -0.23, 95% CI = -1.41,0.94). Additionally, in the follow-up period there was suggestive evidence for treatment effects on disability of Δ⁹-THC compared to placebo, particularly in the Rivermead Mobility Index. There were no major safety concerns. Overall, patients felt that these drugs were helpful in the treatment of their disease. **Interpretation:** These results require cautious interpretation since the study was designed as a short-term study of MS-related symptoms. However, they provide preliminary evidence for a role for cannabinoids in long-term disease management, which supports the hypothesis that cannabinoids may have a neuroprotective action. Further studies are urgently needed.

Plenary Session 2

112

Pathophysiology of spasticity

G. Sheean, University of California (San Diego, USA)

Damage to the upper motor neurons (UMN) and pathways, from whatever cause, may result in several types of motor overactivity, including spasticity. Some of these motor overactivities arise from disinhibition of spinal reflexes, which are normally controlled by a balance of inhibitory and excitatory upper motor neuron inputs. Spasticity is a form of hypertonia arising from hyperexcitability of the spinal tonic (sustained) stretch reflex. This reflex is both length and velocity dependent. It is arguable whether the tonic stretch reflex is a native reflex that is disinhibited by damage to the UMN tracts or a completely new one, because it does not exist in normal people. If due to release of a suppressed reflex it is also not entirely clear whether it emerges through lowered threshold or increased gain. Hyperexcitable phasic (brief) stretch reflexes cause deep tendon hyperreflexia and clonus. Both phasic and tonic stretch reflexes are mediated by Ia muscle spindle afferents. Overactive flexor withdrawal reflexes produce flexor spasms and are mediated by flexor reflex afferents. In some cases, extensor reflexes are increased, causing extensor spasms in the lower limbs. Another contribution to increased muscle tone is spastic dystonia, in which there is continuous muscle contraction in the absence of voluntary effort (at rest) or reflex activity. Like spasticity, spastic dystonia is sensitive to stretch. Biomechanical changes in muscles and associated tissues also lead to increased tone (reduced compliance or increased stiffness) and reduced range movement from contractures (reduced length). Voluntary movement requires coordinated action of agonist and antagonist muscles and depends upon reciprocal inhibition in the spinal cord. In the UMN syndrome, reciprocal inhibition fails, leading to pathological co-contraction and impaired movement. In some cases, this causes movement opposite to that intended, for example, finger flexion when attempting finger extension. In other cases, action-induced dystonic posturing interferes with movement. For example, muscle tone may be normal at rest but attempting to stand or walk induces strong extension of the leg and ankle plantarflexion. The basic mechanisms underlying these motor overactivities are unknown. The delay in their emergence after UMN damage suggests that it is not a