

**RESEARCH BULLETIN 37:
August 2004**



This bulletin provides a short summary of the research relating to MS and other neurological diseases in the following major scientific journals:

The International MS Journal	June 2004
Multiple Sclerosis	August 2004
Journal of the Neurological Sciences	August 2004
Neurology	July 2004 August 2004
Journal of Neurology, Neurosurgery and Psychiatry	July 2004

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DIAGNOSIS

Supporting people with a diagnosis of MS

Title: Paraclinical Support of the Person Diagnosed with Multiple Sclerosis.

Author: S Vitali.

Place of Report: Oxford, UK.

Journal Reference: The International MS Journal, 2004. Vol. 11, pages 3-9.

Research Summary

Receiving a diagnosis of MS often has a severe emotional impact on the patient. Traditionally, diagnosis has centred on the neurologist giving the diagnosis, and then answering questions from the patient. However, with limited time this is often unsatisfactory for both parties. A large Canadian MS clinic has used a new model of providing psychosocial support at the time of diagnosis – where a mental health practitioner works in tandem with the diagnosing neurologist in order to increase the level of patient care.

The report highlights the need for the diagnosing neurologist to consider the patients' personality type and emotional make-up, to determine how best to deliver the diagnosis. Finding out what the patient wants and why (e.g. to wait for a firm diagnosis, or receive written information), and providing follow up support afterwards can give the patient time to come to terms with the diagnosis.

The authors suggest that wherever possible the patient should bring a family member or friend with them to the meeting and the neurologists should deliver the diagnosis clearly and concisely in a private area. It is recognised that patients may well not "hear" much of what is being said to them and they should be reassured that they will have the opportunity to speak to the neurologist again. After diagnosis, it is suggested that patients are transferred to a mental health practitioner - called a Clinic Co-ordinator in the Canadian clinic, in addition to an MS specialist nurse.

This report recommends that all newly diagnosed people should be given printed practical information on MS, to suit their needs at that specific time, a

contact number for the Clinic Co-ordinator or MS-specialist nurse, information about the MS Society and reassurance regarding access to care and follow-up contact. The report stresses the importance of a follow-up telephone call a week after diagnosis.

This model is a multi-disciplinary approach to managing the diagnosis of MS, in order to optimise the process for the patient. The goal of the diagnostic process should not be patient acceptance of the diagnosis, but reassurance that good quality of life is attainable. Similarly, provision of the necessary support is applicable at all stages of MS and is part of the process in helping the person with MS to live with the diagnosis.

Key messages

- A diagnosis of MS is a life-changing event, and limited time with the neurologist means the diagnostic process is often unsatisfactory.
- This study utilised a mental health practitioner, in combination with a neurologist, at diagnosis to improve patient care.
- Considering the patients' personality type, and finding out what the patient wants can give people time to come to terms with the diagnosis.
- Taking a friend or family member is recommended.
- Printed information, contact details for an MS professional and the MS Society should be provided along with information on follow up contact.
- The goal of the diagnostic process should be to reassure the patient that good quality of life is attainable.

IMMUNE SYSTEM SUPPRESSANTS

1. Mitoxantrone - who benefits?

Title: Predictive parameters of mitoxantrone effectiveness in the treatment of multiple sclerosis.

Authors: M Debouverie, N Vandenberghe, S Morrissey, R Anxionnat, S Pittion-Vouyovitch, H Vespignani & G Edan.

Place of Report: France.

Journal Reference: Multiple Sclerosis. 2004. Vol. 10, pages 407-412.

Research Summary

Mitoxantrone is a potent immune system suppressant used in the treatment of certain forms of cancer. Clinical trials have shown that mitoxantrone has a beneficial effect on disability progression in MS and it is now licensed in the US for the treatment of secondary progressive MS (SPMS), SPMS with relapses and worsening relapsing remitting MS. It is not licensed for MS in the UK, but is available on a "named patient" basis. This study reports on the use and effectiveness of mitoxantrone in clinical practice, to identify the clinical characteristics of people with MS most likely to benefit from treatment.

94 people who received mitoxantrone for their MS were studied retrospectively. Type of MS, amount of new and old damage in the brain and spinal cord (as visualised by MRI), relapse rate and average level of disability were assessed before and after treatment. Each participant received mitoxantrone intravenously once a month for six months.

Participants were divided into two groups depending on the outcome of mitoxantrone treatment, after the six month treatment. Group A (44% of participants) consisted of people with a measurable improvement in disability one year after the end of treatment. Group B participants remained the same (39% of participants) or worsened (17%). However, disability levels were lower in Group A (both before and after treatment), more people had relapsing remitting MS and a greater amount of new damage in the brain and spinal cord, prior to treatment, than those in group B. Results showed that there were no serious side effects and mitoxantrone was generally well tolerated.

Nausea, mild hair loss and urinary tract infections were the most common side effects. 50% of women experienced a disruption of periods.

The people who responded best to mitoxantrone treatment were identified as those with:

- RRMS
- People who had at least 3 relapses affecting different areas of the body within the two years prior to treatment
- Those with at least one active area of damage (inflammation) visualised on MRI

The authors acknowledge that this is an observational study with a relatively small number of participants and no comparison group. However, their findings are consistent with previous findings from clinical trials reporting an improvement or stabilisation in disability levels after mitoxantrone treatment. This study has found that a combination of MRI and clinical criteria can help to identify those people most likely to benefit from mitoxantrone treatment. Further research is needed to replicate this finding in larger groups of people with MS.

Key messages

- Mitoxantrone is a potent immune system suppressant, which is licensed for secondary progressive MS (SPMS), and worsening relapsing remitting MS in the US.
- This study aimed to identify the clinical characteristics of people most likely to benefit.
- 94 people who received mitoxantrone over six months were analysed.
- 44% of people showed a measurable improvement in disability after one year after the end of treatment. 39% stabilised and 17% worsened.
- There were no serious side effects but nausea, mild hair loss, urinary tract infections and period problems were all reported.
- The best responders were those with RRMS who had at least 3 relapses and one active area of inflammation prior to starting treatment.
- This is an observational study, with a small number of participants and no control group, although results are consistent with previous findings.
- A combination of MRI and clinical criteria can help to identify those people most likely to benefit from mitoxantrone treatment.
- Further research is needed to replicate this finding in larger groups of people with MS.

2. Pixantrone - a new therapy for MS?

Title: Pixantrone (BBR2778): a new immunosuppressant in multiple sclerosis with a low cardiotoxicity.

Author: R Gonsette.

Place of Report: Belgium.

Journal Reference: Journal of the Neurological Sciences, 2004. Vol. 223, pages 81-86.

Research Summary

Mitoxantrone is a potent immune system suppressant used in the treatment of certain forms of cancer. It reduces the amount of damaging immune cells in the brain and spinal cord (central nervous system – CNS) that occurs in MS and has been shown in clinical trials to reduce relapse rates and improve disability. It is now licensed in the US to treat worsening relapsing remitting MS and secondary progressive MS, both with and without relapses. Its most serious potential side effect is damage to the heart, which limits treatment to two years. Previous research suggests this serious side effect is rare, but a therapy with a similar effectiveness and low cardiac toxicity, enabling longer treatment, would be an advantage.

Pixantrone is a drug with a similar chemical structure to mitoxantrone. It has a similar anti-cancer effect and in animal testing does not appear to have a significant toxic effect on the heart, even after multiple doses. Experiments using pixantrone in animal models of MS showed that, compared to no treatment, it reduced the number of damaging immune cells in the CNS and decreased the relapse rate. Preliminary trials of pixantrone in people with cancer have confirmed that there is minimal cardiac toxicity.

This evidence suggests that pixantrone is as effective as mitoxantrone in animal models of MS, both biologically and clinically. This supports the idea that pixantrone might be as effective as mitoxantrone in people with MS, with lower cardiac toxicity. This would allow earlier and longer treatment of people with progressive MS. The authors suggest that on these grounds a preliminary trial of pixantrone in people with rapidly worsening MS appears warranted.

Key messages

- Mitoxantrone is a potent immune system suppressant which reduces relapse rates and improves disability in MS.
- A serious potential side effect is cardiac toxicity. This is rare but limits treatment to two years.
- Pixantrone has a similar anti-cancer effect to mitoxantrone but without substantial cardiac toxicity.
- In animal models of MS pixantrone reduces the number of damaging immune cells in the CNS and decreases the relapse rate.
- In clinical trials of pixantrone for cancer there was a minimal toxic effect on the heart.
- This supports the idea that pixantrone might be as effective as mitoxantrone in people with MS, with lower cardiac toxicity.
- The authors suggest that on these grounds a preliminary trial of pixantrone in people with rapidly worsening MS appears warranted.

CANNABIS

1. Use amongst people with MS

Title: Patterns of cannabis use among patients with multiple sclerosis.

Authors: A Clark, M Ware, E Yazer, T Murray & M Lynch.

Place of Report: Nova Scotia, Canada.

Journal Reference: Neurology, 2004. Vol. 62, pages 2098-2100.

Research Summary

Anecdotal reports suggest that cannabis can have a beneficial effect on a number of MS symptoms, although research-based evidence to support this is limited. However, reports suggest that as many as 16% of people with MS use cannabis for MS-related symptoms, privately. This study evaluated the patterns and prevalence of cannabis use by people with MS in Halifax, Canada.

Questionnaires were returned from 205 people with MS. Information was collected on participant characteristics, frequency and type of cannabis use and any side effects.

14% of respondents reported private use of cannabis for their MS symptoms. The most common method of cannabis use was smoking, although a third of users took cannabis orally. The frequency and quantity of cannabis use varied widely - half of participants reported cannabis use in the previous 24 hours, although just under half reported "rare" use.

More than half of users reported that cannabis was very effective, for individual symptoms. Self-reported effectiveness was greatest for stress, sleep problems, stiffness and spasms and mood. The most common side effect was euphoria (a "high") reported by 75% of users. Drowsiness and a dry mouth were also common.

This survey reports on a relatively high usage of cannabis amongst people with MS and describes anecdotal reports of a benefit. Controlled clinical trials, including the large-scale trial of a cannabis-based tablet in the UK (the CAMS

study) have not reported objective symptom improvements, although there was subjective evidence of benefit. This report highlights that cannabis may be beneficial for stress, sleep and muscle problems and mood. There also appears to be strong variability between the doses needed to produce an effect. This study suggests that further exploration of cannabis as a potential therapy is warranted.

Key messages

- Anecdotal reports suggest cannabis is effective for a range of MS symptoms and is often used privately.
- Patterns and prevalence of cannabis use by people with MS were analysed by completion of a questionnaire.
- 14% of the 205 respondents reported private use – half reported use in the last 24 hours and just under half reported “rare” use.
- Self reported effectiveness was greatest for stress, sleep problems, stiffness, spasms and mood.
- The main side effect was euphoria (a “high”) reported by 75% of users. Drowsiness and dry mouth were also common.
- Cannabis may be beneficial for stress, sleep and muscle problems and mood, although the doses needed to produce an effect vary widely.

2. Oral cannabis for spasticity

Title: Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomised, double-blind, placebo-controlled, crossover study.

Authors: C Vaney, M Heinzel-Gutenbrunner, P Jobin, F Tschopp, B Gattlen, U Hagen, M Schnelle & M Reif.

Place of Report: Montana, Switzerland.

Journal Reference: Multiple Sclerosis, 2004. Vol. 10, pages 417-424.

Research Summary

Muscle spasms and spasticity are common symptoms of MS. Currently available therapies are often not fully effective and can have intolerable side effects. Anecdotal reports suggest cannabis is beneficial for these symptoms although the research-based evidence to support this is limited. The aim of this research was to determine the tolerability, safety and effectiveness of an oral (capsule) form of cannabis extract on reducing spasm frequency. This was studied in people with MS who had spasticity which was not effectively controlled by standard spasticity medications.

37 people with MS and spasticity completed the study. All received cannabis extract (in addition to their usual medication) for 14 days, or a control substance known to cause no effect (a placebo). Participants then swapped treatments after this period. A trained physiotherapist used a specialised assessment scale to measure the degree of spasticity and mobility. Each participant kept a daily diary detailing symptoms, including spasm frequency, tremor, bladder problems and sleep quality.

Generally there were no significant improvements seen in the majority of measures with the cannabis extract, compared to placebo. However, there was a slight improvement in spasm frequency and a tendency to report better sleep. Further analysis of those participants able to walk showed a significant improvement in mobility. In general, the cannabis extract was well tolerated with no serious side effects.

These results indicate that the cannabis extract is relatively safe to use, with a small effect on spasm frequency. However, the small number of participants and the short duration of treatment are limitations of the study, as is the inability of the assessment scale to measure small improvements. The authors note that disability in people with MS may be more related to weakness than spasticity but suggest that future research should concentrate on monitoring participants over a longer period of time, with, if possible, more sensitive measurement scales.

Key messages

- Muscle spasms and spasticity are common in MS, although current treatments may not be fully effective.
- This study investigated whether an oral cannabis extract could reduce spasm frequency and impact on other common MS symptoms.
- 37 people with MS-related spasticity took part.
- A significant improvement in mobility and slight improvement in spasm frequency was measured.
- Side effects were minimal.
- The small number of participants and short study period are study limitations - further studies should be longer with more sensitive measurement scales.

3. Cannabis for bladder problems?

Title: An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis.

Authors: C Brady, R DasGupta, C Dalton, O Wiseman, K Berkley & C Fowler.

Place of Report: London, UK.

Journal Reference: Multiple Sclerosis. 2004. Vol. 10, pages 425-433.

Research Summary

It is estimated that up to 90% of people experience bladder problems 10 years after the onset of MS. This typically causes a frequent, urgent need to urinate and can cause incontinence as a result. Drug treatments and/or self-catheterisation (inserting a thin plastic tube – the catheter – into the urinary opening to drain the bladder) are often very effective initially, but with increasing disability an indwelling catheter (one which is left in place) is sometimes needed. There are anecdotal reports that cannabis is effective in helping relieve bladder problems but research-based evidence is limited.

This study evaluated the effectiveness of two cannabis preparations - a combination of two compounds called tetrahydrocannabinol (THC) and cannabidiol (CBD), and THC alone, on bladder problems and other symptoms in people with advanced MS. These cannabis extracts are the two “active” components of cannabis and produce its psychoactive effects.

15 people with advanced MS with bladder problems (not effectively treated with conventional treatment) completed the study. All participants continued on their prescribed medications and continued to self-catheterise as necessary. Participants were asked to self-rate their bladder symptoms and complete a diary detailing problems. The cannabis preparations were given as an additional medication, in the form of a daily spray under the tongue.

All participants took the maximum dose of the two cannabis extracts without unacceptable side effects. Each took THC/CBD for the first eight weeks, followed by THC alone for the next eight weeks. 14 of the 15 participants chose to continue taking the THC extract after the end of the monitoring period – all chose THC only.

The number and volume of daily incontinence episodes and number of times people needed to urinate (both during the day and night) all significantly decreased after eight weeks of treatment. This effect was present with both treatments, although participants appeared to be drinking less over the study period. Participants also reported significant improvements in spasticity, pain and sleep with THC. Side effects were minimal, although the authors acknowledge that only a small number of people took part and no comparison was made against no treatment.

This trial showed a sustained improvement in bladder symptoms with the cannabis extracts. Additionally, participants reported improvements in pain, spasticity and sleep quality. The authors suggest that these results support the use of cannabis-based medicines for bladder problems in people with advanced MS.

Key messages

- Bladder problems are very common in MS and in advanced cases, conventional treatment is sometimes not effective.
- This study evaluated the effects of two cannabis extracts on bladder problems and symptoms in people with advanced MS.
- 15 people took the cannabis extracts in the form of a spray under the tongue, in addition to their usual medication.
- Results showed that the number and volume of daily incontinence episodes and number of times people needed to urinate significantly decreased.
- Participants also reported significant improvements in spasticity, pain and sleep.
- Side effects were minimal.
- These results support the use of cannabis-based medicines for bladder problems in people with advanced MS.

BETA INTERFERON

What's best for flu-like side effects?

Title: Corticosteroids, ibuprofen and acetaminophen for IFN beta 1a flu symptoms in MS.

Authors: J Rio, C Nos, I Bonataventura, *et al.*

Place of Report: Spain.

Journal Reference: Neurology, 2004. Vol. 63, pages 525-528.

Research Summary

Beta interferon, licensed in the UK for the treatment of relapsing forms of MS has been shown to reduce the relapse rate in people with relapsing remitting MS by around a third. There are two types, beta interferon 1a (drug names Rebif and Avonex) and beta interferon 1b (drug name Betaferon). The most common side effects, which usually appear at the start of treatment are fever, muscle aches, and chills that can last for up to 24 hours after injection. These can contribute to people stopping treatment and need to be managed. This study compared the effectiveness of paracetamol, ibuprofen (another type of painkiller) and steroids (very occasionally used to manage fever) in the management of flu-like symptoms in MS.

Three groups of 27 participants took either paracetamol or ibuprofen before, six and 12 hours after injection, or daily steroids for a one week period, after their weekly injection of Avonex. If symptoms were severe than participants could also take additional paracetamol tablets every four hours as needed. This study focused on effects during the first four weeks of treatment. Neither the participants nor the investigators knew who received which treatment.

Results showed that during the first four weeks of treatment with Avonex, the incidence and severity of the flu-like symptoms were similar regardless of which additional treatment was taken. However, the appearance of flu-like symptoms on the day of the Avonex injection were less severe in those people who received ibuprofen. People receiving ibuprofen also needed less additional paracetamol to control their symptoms. No differences were found between the severity and frequency of adverse side effects between the three

drugs. An advantage of ibuprofen (and paracetamol) treatment over steroids is that people can self-medicate at home.

This report highlights the significant impact that flu-like symptoms can have on quality of life when people start taking beta interferon. Minimising these symptoms is important in minimising the number of people who stop treatment in the early stages. These results indicate that ibuprofen could be the “drug of choice” in minimising injection day flu-like symptoms.

Key messages

- Flu-like symptoms are a common, early side effect of beta interferon treatment.
- This study compared the effectiveness of paracetamol, ibuprofen and steroids in their management.
- Three groups of 27 participants took either one of the drugs after their weekly beta interferon injection.
- The incidence and severity of the flu-like symptoms were similar regardless of which additional treatment was taken.
- Flu-like symptoms were less severe and required less additional medication in those people taking ibuprofen.
- Side effects were comparable with all the additional medications, but people can self-medicate with paracetamol and ibuprofen at home.
- Flu-like symptoms can be severe enough to stop people continuing with beta interferon and need to be managed.
- These results indicate that ibuprofen could be the “drug of choice” in minimising injection day flu-like symptoms.

COGNITIVE PROBLEMS

Cognitive problems – are they linked to type of MS?

Title: Differences in cognitive impairment of relapsing remitting, secondary and primary progressive MS.

Authors: S Huijbregts, N Kalkers, L de Sonneville, V de Groot, I Reuling & C Polman.

Place of Report: Amsterdam, The Netherlands.

Journal Reference: Neurology, 2004. Vol. 63, pages 335-339.

Research Summary

Cognitive problems are common in people with MS, with an estimated 40-60% of people affected at some stage. The type of cognitive problems people experience has been linked to their type of MS. This study aimed to evaluate the differences in the type of cognitive difficulties experienced by people with relapsing remitting MS (RRMS), secondary progressive (SPMS) and primary progressive MS (PPMS).

234 people with MS took part in the study. Of those, 108 had RRMS, 71 had SPMS and 55 had PPMS. Age, duration of MS, levels of physical disability and education were all recorded. All participants completed a comprehensive series of cognitive tests designed to test various aspects of learning, cognition and memory.

Results showed that all types of MS were associated with some degree of cognitive problem. People with RRMS generally performed better than those with progressive MS, with people with SPMS most severely affected - particularly in tasks requiring extensive working memory. However, people with SPMS did perform better on tasks where speed of information processing was important. People with RRMS showed relatively poor "verbal fluency" (ability to generate word lists). In general, being older, with higher levels of disability and a longer duration of MS were all associated with significantly lower cognitive performance.

The authors suggest that differences in the biology which causes the various types of MS may help explain the cognitive differences between the three types. However, the lack of a comparison with the general population is a limitation of the study. They suggest that future studies in this area should employ very sensitive measurement scales which focus on assessing working memory and information processing speed, in order to further explore the findings of this study.

Key messages

- Cognitive problems are common in people with MS and may vary depending on type of MS.
- In this study people with different types of MS underwent a comprehensive series of tests to evaluate learning, cognition and memory.
- All types of MS were associated with some degree of cognitive problem.
- People with relapsing remitting MS generally performed better than those with progressive MS.
- Greater age, disability level and duration of MS were all associated with a significantly lower performance on the tasks.
- The authors suggest that differences in the biology which causes the different types of MS may help explain the cognitive differences.
- Further research using more sensitive assessment measures is suggested, to further explore these findings.

FATIGUE

Disease modifying drugs – effects on fatigue

Title: The effect of immunomodulatory treatment on multiple sclerosis fatigue.

Authors: L Metz, S Patten, C Archibald, J Bakker, C Harris, D Patry, R Bell, M Yeung, W Murphy, C Stoian, K Billesberger, L Tillotson, S Peters & D McGown.

Place of Report: Alberta, Canada.

Journal Reference: Journal of Neurology, Neurosurgery and Psychiatry, 2004. Vol. 75, pages 1045-1047.

Research Summary

Fatigue is a common symptom of MS with up to 85% of all people with MS estimated to experience it at some point. Its precise cause is unknown and current treatments are only partly effective. Fatigue has been reported to worsen during a relapse and the authors suggest that this symptom may be a marker of disease activity. They suggest that reducing disease activity in MS may therefore improve fatigue. The aim of this study was to determine the effect of disease modifying therapy with beta interferon or Copaxone (licensed for the treatment of relapsing remitting MS) on MS fatigue.

218 people who were due to start disease modifying therapy completed the study. All had relapsing remitting or secondary progressive MS. All participants decided on which therapy to receive themselves, after discussion with an MS nurse. Participants were asked to self-rate the severity of their fatigue and the impact it had on physical, social and cognitive activities. Ratings were completed before and six months after the start of treatment.

61% of participants chose to receive Copaxone. The remaining 39% chose one of the three different forms of beta interferon – results were amalgamated to form a single beta interferon group. The beta interferon group contained people with secondary progressive MS and with, on average, greater disability than the Copaxone group initially. Self-rated fatigue was similar in the two groups prior to treatment. A quarter of people receiving Copaxone reported improved fatigue after six months, compared to just 13% of those receiving

beta interferon. There were also improvements in social, cognitive and physical activities. However, the treatment benefits were similar with both therapies when people with secondary progressive MS were excluded from the analysis.

These results indicate that when fatigue levels of people taking Copaxone were compared against those taking beta interferon, Copaxone appeared to lead to a greater reduction in fatigue. However, the authors highlight that this result may possibly be due to a feature of the group which chose Copaxone (for example, less severe MS), rather than the drug itself. Further research is necessary to determine the amount of change on self-rated fatigue scales that represents a clinically meaningful improvement. It is unclear why Copaxone is more likely to improve fatigue than beta interferon but improvements in fatigue can provide important benefits for people with MS. Finally the report concludes that additional, longer term studies are needed to confirm these findings.

Key messages

- Fatigue is a common symptom of MS, although the cause is unknown and available treatments are limited.
- Disease activity may correlate with fatigue so this study aimed to determine the effect of beta interferon and Copaxone on MS fatigue.
- 218 participants due to start on either beta interferon or Copaxone were asked to self-rate their fatigue and the impact on daily activities.
- 61% of people chose Copaxone compared to 39% who chose beta interferon.
- A quarter of people taking Copaxone reported improvements in fatigue compared to 13% taking beta interferon. However, effects were similar when people with secondary progressive MS were not included.
- It is unclear why Copaxone appears more likely to reduce MS fatigue than beta interferon.
- Additional long-term studies are needed to confirm these findings.

Research Bulletins are produced by:

**Alison Handford BSc
Research Officer**

&

**Marianne Miles PhD
Research Manager**