

## RESEARCH BULLETIN 28: November 2003



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

Brain	October 2003
British Medical Journal	October 2003
Disability and Rehabilitation	October 2003
Rehabilitation Nursing	September/October 2003
Brain Research	November 2003
Neurology	October 2003

The articles are organised according to topic as follows:

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# **CANNABIS**

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## **Can cannabis protect nerves?**

Title: Cannabinoids inhibit neurodegeneration in models of multiple sclerosis.

Authors: G Pryce, Z Ahmed, D Hankley, S Jackson, JL Croxford, J Pocock, C Ledent, A Petzold, A Thompson, G Giovannoni, ML Cuzner & D Baker.

Place of Report: London, UK.

Journal Reference: Brain, 2003. Vol. 126, pages 2191-2202.

### **Research Summary**

Disease modifying drugs licensed for the treatment of relapsing forms of MS are effective in reducing relapse rate. However, reducing the number of relapses appears to have no effect on progression of disability. Consequently, there is an urgent need for therapies that can inhibit the progression of MS, both in relapsing and progressive forms of the disease. Studies have shown a beneficial effect of cannabinoids (the “active” part of the cannabis plant) on some MS symptoms such as spasticity and tremor in animal models, and there is some subjective evidence of benefit from clinical trials involving people with MS. Cannabinoids are thought to cause these effects by acting on certain types of receptor present in the body, which cannabinoids recognise and bind to, causing therapeutic effect.

Recent laboratory-based studies have shown that various cannabinoids (there are 66 types) can also reduce substances which have been shown to cause nerve cell loss in diseases like MS. This study aimed to definitively investigate whether the cannabinoid receptor system can protect nerves, by using mice genetically manipulated to be bred without cannabinoid receptors i.e. in which cannabinoids don't cause an effect. Results were compared to normal (control) mice i.e. with cannabinoid receptors, after an MS-like disease was induced in both types of mice.

Results showed that mice bred without cannabinoid receptors developed “aggressive” relapsing remitting MS. This was characterised by periods of paralysis and sharply increasing disability, leading to permanent paralysis of the legs. This was a much more severe disease course than that observed in control mice. Mice bred without cannabinoid receptors also exhibited significantly more

nerve fibre loss than in control mice and were found to have increased levels of substances which are toxic to nerve cells and cause nerve fibre loss.

These results suggest that in addition to the possibility of symptom management, cannabinoids might offer the potential to slow the progression of MS. It is acknowledged that there are likely to be many events that cause nerve fibre loss and that these may change during the disease course. The level of disability experienced will be determined by the rate that nerve fibre loss accumulates, and the genetic background of the individual. Nerve fibre loss in MS correlates with disability levels and the authors suggest that any long-term trials of cannabis should include monitoring of nerve fibre loss and disease progression. Slowing the degeneration process early in the disease, before significant damage has accumulated, may help improve and extend a good quality of life.

**This work received support from the Multiple Sclerosis Society of Great Britain and Northern Ireland.**

### **Key Messages**

- There is an urgent need for agents that can inhibit the progression of MS, both in relapsing and progressive forms of the disease.
- Recent laboratory-based studies have shown that cannabis-based medicines can act on certain sites in the body, to reduce substances harmful to nerve cells.
- This study aimed to investigate whether the cannabinoid receptor system can protect nerves in an animal model of MS.
- Mice without cannabis receptors developed a much more severe disease course, with significantly more nerve fibre loss, than normal mice.
- These results suggest that cannabinoids might offer the potential to slow the progression of MS and further research is warranted.

## **NICE**

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### **NICE links to drug manufacturers**

Title: NICE is told to break its close links with drug industry.

Author: Z Kmietowicz.

Journal: British Medical Journal, 2003. Vol. 327, page 637.

#### **Research Summary**

The role of the National Institute for Clinical Excellence (NICE) is to provide the NHS with consistent guidance on health technologies and drug treatments. However, a recent, independent review of how NICE is run, carried out by the World Health Organisation (WHO) was critical of its close links with the pharmaceutical industry. One of the key findings of the report was that to avoid any possible bias, doctors linked with pharmaceutical companies should not be members of the committees that make decisions on which particular drugs or devices to recommend.

The WHO report recognised that while pharmaceutical doctors could offer useful input into how and why trials are run, they could not be expected to be completely unbiased when appraising another company's products. It was recommended that manufacturers views should be gathered through the consultation process instead, before the final version of the guidance is issued.

Another key point raised by the WHO report was whether the NICE guidelines should take into account confidential information, which is typically submitted by pharmaceutical companies. The report recognises that NICE has set very high standards in considering inputs and making documents available through its website. However, in order to make the recommendation process as open and transparent as possible NICE should consider this apparent contradiction.

The WHO report made 28 recommendations on all aspects of how NICE is run which the NICE chairman, Michael Rawlins, said would be fed into a review of current methods and appraisals. The Board is also considering making documents covering the overview of the product appraised, comments received on draft overviews and the contents of the appeals, available to the public.

A full copy of the WHO report “Technology Appraisal Programme of the National Institute for Clinical Excellence” is available at [www.nice.org.uk](http://www.nice.org.uk).

### **Key messages**

- The role of the National Institute for Clinical Excellence (NICE) is to provide the NHS with consistent guidance on health technologies and drug treatments.
- A review of procedures by the World Health Organisation was critical of its close links with the pharmaceutical industry.
- The rules on NICE accepting confidential information from pharmaceutical companies need to be clarified to make the process transparent.
- It was recommended that manufacturers views should be gathered through a consultation process before the final versions of the guidelines are issued.
- Recommendations from the report will be used in a review of current methods and appraisals.
- NICE is considering making overviews of appraised products, comments on draft overviews and product appeals available to the public.

# **STRESS**

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## **Does stress trigger relapses?**

Title: Self-reported stressful life events and exacerbations in multiple sclerosis: a prospective study.

Authors: D Buljevac, W Hop, W Reedeker, A Janssens, F van der Meche, P van Doorn & R Hintzen.

Place of Report: Rotterdam, The Netherlands.

Journal Reference: British Medical Journal, 2003. Vol. 327, pages 646-649.

### **Research Summary**

Relapsing remitting MS (RRMS) is unpredictable and the factors which trigger a relapse are not known. However, relapses have been linked to a number of factors including stress, but there is very little scientific evidence for this – much of the evidence is anecdotal. This study aimed to assess whether life events, perceived as stressful by participants in this study, were associated with a higher chance of having a relapse. Stressful events included illness or death in the family, financial problems, job stress, marriage problems and events related to house and car (e.g. theft).

Participants filled out a weekly diary reporting any stressful events, and these were collected every 8 weeks. Anyone reporting a suspected relapse was assessed by a neurologist. A 4-week period after the report of a stressful event was defined as a high-risk period. The relapse rate of participants during a high-risk period was compared against those not with high risk (i.e. no stressful event).

Of the 73 people who took part, all with RRMS, 70 reported at least one stressful event. During the average monitoring time of 1.4 years, overall 134 relapses occurred in 56 of the 73 participants, which worked out as an average of 1.3 relapses a year. The risk of a relapse was double in the four-week period after a stressful event than after four weeks with no stress.

The authors highlight that the mechanism between increased stress and an increased risk of relapse is not fully understood. They suggest this could be mediated through stress triggering the release of hormones, and that in future

studies, it would be beneficial to measure hormone levels related to stress. This would also provide a measurable marker of the “amount” of stress experienced. Knowledge that these events may be associated with relapses can add important information about the unpredictable nature of the disease to people affected by MS.

### **Key messages**

- Relapses experienced by people with relapsing remitting MS have been anecdotally linked to stress.
- This study aimed to assess whether stressful life events such as family illness, financial and job worries increased the risk of a relapse.
- The risk of a relapse was found to be double in the 4-week period following a stressful event than in four weeks with no stress.
- The mechanism by which increased stress might cause an increase risk of relapse is not fully understood.
- Measurement of hormone levels related to stress is suggested in future studies, to objectively measure the “amount” of stress.
- The knowledge that stressful events can cause an increased risk of relapse can add important information about the unpredictable nature of MS.

## **CLINICAL TRIALS**

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### **A reduction in clinical trials**

Title: Resuscitating clinical research in the United Kingdom.

Author: John Bell (report on behalf of the working group of Academy of Medical Sciences).

Journal Reference: British Medical Journal, 2003. Vol. 327, pages 1041-1043.

Title: Descriptive survey of non-commercialised randomised controlled trials in the United Kingdom, 1980-2002.

Authors: I Chalmers, C Rounding & K Lock.

Journal Reference: British Medical Journal, 2003. Vol. 327, pages 1017-1021.

### **Research Summary**

Knowledge of a wide range of diseases, including MS, has increased substantially over the past 20 years. However, an increase in the number and accuracy of methods to investigate genetic and molecular aspects of disease has shifted the focus of research away from clinical research. Similarly, financial pressures on NHS facilities in teaching hospitals is also pushing out important clinical trial based research, which is the main method of translating discoveries in the laboratory into mainstream therapies for patients.

An important benefit of good clinical research is allowing patients relatively early access to novel therapeutic interventions. Despite this, funding is falling in the UK, and a lot of this type of research is associated with long start-up times, poor participant recruitment, high costs and regulatory constraints. These two articles highlight the importance of thorough clinical research and suggest some possible ways of overcoming the problems described.

This report recommends that "networks" for specific types of disease (e.g. neurodegenerative disease) are established within the NHS to enable co-ordination of large-scale clinical trials between centres. The report also suggests that the NHS should set aside a proportion of its budget specifically for clinical research and should set up research facilities for this within hospitals and clinics. Educating people affected by disease is also identified as key in encouraging people to recognise the value of clinical trials and encourage participation.

The main limitation on an expansion of clinical research is funding, and this report suggests that the Medical Research Council (a national organisation which funds medical and health-related research) should ringfence a greater percentage of money specifically for clinical research and training clinical scientists. While there have been positive developments with the Wellcome Trust (an independent research-funding charity) funding five purpose-built clinical trial units across the UK, there are limitations in the number of clinical scientists available, and long-term support is needed to encourage scientists into this area of research. Major charities are identified as needing to commit to funding clinical research relevant to them, and pharmaceutical companies should increase their spend in this area. Encouraging collaboration between potential funders would also result in larger and more comprehensive trials.

Clinical research is declining in the UK and in other countries, and failure to support this type of research is identified as having a serious impact on patients in the long-term. Joining together some of the major potential funding bodies, including the NHS, major charities and pharmaceutical companies should have an important beneficial outcome on patients who need new therapies, and biotechnology and pharmaceutical industries who are developing potential new treatments.

### **Key messages**

- Although knowledge of many diseases, including MS, has increased substantially over the past 20 years, focus has shifted away from clinical research.
- Clinical research is associated with problems such as long start-up times, poor participant recruitment and high costs.
- This report recommends that links are established within the NHS to enable effective co-ordination of large-scale clinical trials between centres.
- The main limitation on an expansion of clinical research is funding.
- Encouraging collaboration between potential funders (NHS, charities and industry) will result in larger and more comprehensive trials and should have important beneficial outcomes for patients who need new, effective therapies.

## MOBILITY

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### Experiencing mobility loss in MS

Title: Experiencing the loss of mobility: perspectives of older adults with MS.

Authors: M Finlayson & T Van Denend.

Place of Report: Chicago, USA.

Journal Reference: Disability and Rehabilitation, 2003. Vol. 25, no. 20, pages 1168-1180.

### Research Summary

Many people with MS experience problems with their mobility, during relapses or as a result of disease progression. Loss of mobility is associated with a reduction in social activities and decreased abilities to perform self-care and leisure activities. This is particularly true for older people with MS who may have had the disease for some years. These changes require the affected person to adapt psychologically, emotionally and physically to this reduced mobility.

This study analysed interviews that had taken place with 27 people who were over 55 years old and had had MS for more than 15 years, to explore their perceptions and thoughts on having MS, their own mobility needs and concerns. Participants were also asked to report their experiences of limited mobility, the consequences and how they dealt with these.

Three main factors were found to contribute to the participant's mobility experience, as a person with MS:

- **Reality of having MS;** including dealing with physical sensations (e.g. loss of balance, and limb heaviness) and the unpredictability of symptoms, which were found to influence the nature and extent of mobility.
- **Mobility needs;** including the need to maintain control over mobility, particularly in everyday tasks related to self-care. Participants reported that initial negative feelings about needing to use mobility equipment were often replaced with a sense of freedom and control, once they had made the decision to start using it.

- **Practical factors;** including the physical environment (both within the home and wider community), transportation needs, personal attitudes towards mobility aids and the level of social support available.

A main consequence was that all participants reported “mourning the loss of their mobility”, in doing a wide range of activities from shopping to leisure, to a greater or lesser extent. People were required to shift their expectations and prioritise activities. Planning in advance also allowed people to develop skills to moderate their future mobility experiences. The other consequence was contemplation on the future. All participants reported that they were very aware that their lack of mobility and other symptoms were likely to progress. Many expressed fears and uncertainties about the future and were particularly concerned about becoming a burden to family, friends and carers.

The authors suggest that mobility issues are of high importance to older people with reduced mobility, due to MS, and highlight the need for healthcare providers to talk to people with MS about the reasons behind their symptoms, and their feelings about mobility aids. They also identified the potential positive aspects of people being able to talk and share their experiences and feelings with people in similar situations, who were also affected by progressive MS. The complexity of living with and adapting to a progressive loss of mobility is highlighted and the importance of empowering the individual to feel they are in control of their situation is emphasised.

### **Key messages**

- Many people with MS, particularly those who have been affected for a long time, experience problems with their mobility.
- Reduced mobility is associated with reduced social activities and decreased ability to perform self-care and leisure activities.
- This study used interviews to explore how older people with MS adapted psychologically, emotionally and physically to reduced mobility.
- Dealing with the reality of having MS, mobility needs and practical concerns were found to contribute to the participant’s mobility experience.
- People reported mourning the loss of their mobility and expressed concerns about the future.
- The complexity of living with and adapting to a progressive loss of mobility is highlighted and the importance of empowering the individual to feel they are in control of their situation is emphasised.

## **COMPLEMENTARY THERAPIES**

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### **Use and effectiveness of complementary therapies in MS**

Title: Complementary and Alternative Therapy Use in Persons with Multiple Sclerosis.

Authors: M A Stuijbergen & T Harrison.

Place of Report: Austin, USA.

Journal Reference: Rehabilitation Nursing, 2003. Vol. 28, no. 5, pages 141-147.

### **Research Summary**

MS is a long-term condition and although there are disease modifying drugs which have a beneficial effect on relapse rate, treatments to relieve specific symptoms are limited. Consequently, many people with MS choose to use a range of complementary or alternative therapies (CAT) in an attempt to improve symptoms and enhance quality of life. This study describes the use of CAT and the perceived effectiveness of various therapies from a questionnaire survey sent to 621 people with MS.

Results showed a third of people reported that they were currently using some form of CAT, with almost half reporting they had tried one or more form of CAT at some point. Nutritional supplements, massage, special diets, chiropractic and herbal treatments were the most frequently used. Over half of people who tried these specific therapies (and yoga) reported experiencing benefit. More than a third of people who tried bee venom, acupuncture and chiropractic treatment reported they were ineffective or harmful, although no distinction is made between these.

CAT use was more frequent among people who undertook regular exercise and ate a healthy diet. On the basis of this, the authors suggest that people who use CAT may feel more in control and responsible for their health. The authors also suggest that future studies should investigate why people who have reported benefit from various therapies then discontinue their use. It would also be useful to find out whether therapies which were discontinued were either harmful or ineffective, rather than grouping these together.

The study indicated that people with MS use CAT at the same rate as the general population. It highlights that providers of CAT need to be familiar with a number of therapies and know of the potential harmful or beneficial effects and that this information must be conveyed to patients to enable informed joint decisions about the potentially harmful or beneficial CATs.

### **Key messages**

- MS is a long-term condition and treatments to relieve specific symptoms are limited.
- Many people with MS use a range of complementary or alternative therapies to attempt to improve symptoms and enhance quality of life.
- Almost half of people with MS surveyed reported they had tried one or more complementary or alternative therapies at some point.
- Nutritional supplements, massage, special diets, chiropractic and herbal treatments were the most frequently used.
- Complementary or alternative therapy use was associated with people who had increased "health promoting" behaviours
- The authors suggest that people who use CAT may feel they have a higher level of control and responsibility for their health.
- It is important that providers and recipients of these therapies are aware of their potentially harmful or beneficial effects, enabling an informed decision on use.

# **NEUROPROTECTION**

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## **A neuroprotective drug for people with MS?**

Title: Riluzole suppresses experimental autoimmune encephalomyelitis: implications for the treatment of multiple sclerosis.

Authors: Y Gilgun-Sherki, H Panet, E Melamed & D Offen.

Place of Report: Tel Aviv, Israel.

Journal Reference: Brain Research, 2003. Vol. 989, pages 196-204.

### **Research Summary**

MS is characterised by a number of processes, including inflammation, damage to myelin (the protective sheath surrounding nerve fibres) and nerve fibre loss in the brain and spinal cord (central nervous system: CNS). Recently glutamate, a substance that normally enables brain cells to pass messages to each other, has been identified as a potential cause of these processes. This is based on the knowledge that a build-up of glutamate in the CNS is toxic to a variety of cells, and in large amounts can lead to nerve cell loss.

Increased glutamate levels have been reported in people with MS and appear to correlate with severity of MS symptoms. Agents which reduce the levels of glutamate might, therefore, protect nerves from this type of damage, reducing nerve fibre loss and thereby reducing the progression of disability. This study used an animal (mouse) model of MS to assess the effects of a drug called riluzole, currently used as treatment for a form of motor neurone disease. This drug is thought to reduce dangerously high levels of glutamate.

The study showed that mice treated with riluzole were highly resistant to developing MS, when researchers attempted to induce the disease. In addition, the severity of the disease and level of disability was much less in mice receiving riluzole than in "control" mice, who didn't receive the drug. This was true when riluzole was administered, by injection, at the disease onset and also when administered after the development of full MS symptoms. Long-term administration, rather than a short course of riluzole, was shown to be most effective in reducing symptoms.

Examination of the spinal cords of the mice showed that riluzole-treated mice had less inflammation and damage to myelin, when compared with controls (mice which received no treatment). Similarly, there was less nerve fibre loss in riluzole treated mice and the loss that did occur was mainly limited to the areas immediately around areas of inflammation.

These results suggest that riluzole may be effective against nerve fibre loss, probably acting by reducing high, potentially harmful level of glutamate in nerve fibres. Riluzole has also been shown to protect nerve fibres in animal models of stroke and Parkinson's disease. The authors refer to a small study in people with primary progressive MS treated with riluzole, which showed a reduction in nerve fibre loss (seen using MRI scanning) in the CNS (this research is summarised in Research Bulletin 20). They suggest that this study provides further evidence that riluzole may be useful in the future treatment of MS, both during relapses and in limiting disease progression.

### **Key messages**

- MS is characterised by inflammation, damage to myelin (the protective sheath surrounding nerve fibres) and nerve fibre loss in the brain and spinal cord.
- Build up of a substance called glutamate, which normally enables brain cells to pass messages to each other, has been identified as a potential cause of nerve cell loss.
- A drug called riluzole is thought to reduce dangerously high levels of glutamate, and therefore protect nerve fibres.
- Mice treated with riluzole were shown to be highly resistant to developing MS, when researchers attempted to induce the disease.
- The severity of MS disease and level of disability was much less in mice receiving riluzole than in mice, who didn't receive the drug.
- Riluzole has been trialled in people with primary progressive MS and initial results show reduced damage, as seen by MRI scans.
- Riluzole may be useful in the future treatment of MS, both during relapses and in limiting disease progression.

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