

# My prog-MS ezine

## For people with progressive MS and other interested people

Issue number 24, March/April 2019

**Hello and welcome to the latest edition of my ezine about progressive MS and MS progression in general. My name is Ian Cook. I'm a secondary progressive MSer who lives in Birmingham, UK.**

In this issue are eight pages of important prog-MS news stories plus two features about issues that matter to prog-MSers. In the first feature (page 5) I look at the problems of trying to find disability accessible accommodation.

The second feature looks at the results of the MS-SMART trial to find drugs for secondary progressive MS which makes me wonder whether the trial was really so smart after all . See page 10.

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# Rituximab significantly delays progression in secondary progressive MS, study shows

**A team of investigators has compared rituximab in secondary progressive MS (SPMS) patients to patients not taking the drug in an effort to evaluate the drug's potential for SPMS .**

Among the results, the team observed a significantly lower EDSS score for up to 10 years of follow-up and a significantly delayed confirmed progression in patients with SPMS who were given rituximab compared with matched controls, suggesting rituximab may be beneficial for patients with SPMS.

In the study  a team of investigators analysed data from patients with SPMS from 2004-2017 at 3 multiple sclerosis centres in Basel, Lugano, Switzerland, and Amsterdam, Netherlands. The research team compared disability progression in patients with SPMS who were given rituximab versus those who weren't.

The study authors noted that: "Time to confirmed disability progression was significantly delayed in the rituximab-treated group (hazard ratio, .49; 95% CI, .26-0.93; P = .03)."

Overall, a significantly lower EDSS score for up to 10 years of follow-up and a significantly delayed confirmed progression compared with matched controls was experienced by patients SPMS who were taking rituximab, implying that B-cell depletion by rituximab may be therapeutically beneficial in these patients.

The study, titled, "Association of Rituximab Treatment With Disability Progression Among Patients With Secondary Progressive Multiple Sclerosis," was published in the Journal of the American Medical Association (JAMA).

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# Another Phase II Stem Cell Trial to take place in Progressive MS

**A Phase II stem cell trial of mesenchymal stem cells in secondary progressive MS is being organised by US bio-pharma company BrainStorm Cell Therapeutics.**

BrainStorm's stem cell-based technology called NurOwn uses autologous stem cells, (these are cells taken from the individual) that are then reinserted into the same person. The stem cells are mesenchymal stem cells which are cells taken usually from bone marrow which can differentiate into a variety of cell types.

The mesenchymal stem cells are grown and manipulated under patented conditions to make them generate high levels of immunomodulatory cytokines (signals that affect the immune system) and neurotrophic factors (those related to the growth of nerve cells). These therapeutic signals are communicated to the site of damage to bring about a desired biological effect, and ultimately slow or stabilize disease progression.

The whole process is being evaluated as a treatment For MS and other neurodegenerative diseases including motor neurone disease. NurOwn has been tested in several animal models for various diseases, and has shown a good safety profile and is already showing promising signs of efficacy in clinical trials in motor neurone disease.

In December 2018, the U.S. Food and Drug Administration approved BrainStorm's Investigational New Drug application for NurOwn, which allowed the company to open this Phase 2 trial of mesenchymal stem cells in progressive MS patients.

Mesenchymal stem cell therapy does not aim to replace the person's own immune system, and so does not require pre-treatment with cancer chemotherapy drugs, so is less aggressive than the better known HSCT. (Hematopoietic stem cell transplantation).

A UK phase II trial into mesenchymal stem cells and progressive MS is expected to report its results in the Autumn. The ACTiMuS trial which is taking place in Bristol is a two year study of 80 people with primary or secondary progressive MS.

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# Study Shows Benefits of Low Temperature Exercise for MS Patients

**Reducing body temperature during physical exercise can help rewire the brain and improve motor control in patients with MS even when the disease reaches its progressive phase, a new research study at Canada's Memorial University shows.**

Michelle Ploughman, PhD, who is Memorial's Canada Research Chair in neuroplasticity, neurorehabilitation and brain recovery, and her collaborators wanted to investigate if cooling a patient's body could help them exercise, and how much cooling would be needed.

The researchers designed a study which enrolled nine patients with MS who were asked to walk on a treadmill with a supportive harness for 30 minutes in a room that was kept at 16°C (approximately 60.8°F). Patients exercised three times a week, for a total of 12 weeks.

The research team then evaluated the participants' brains to assess how the brain cells were working. They also measured walking speed, oxygen use, lesions in the brain, and markers of recovery in the blood. According to the research team, patients were able to tolerate the treatment with significant improvements in their walking ability during the study period. "It's remarkable," Ploughman said. "This is not supposed to happen, according to the textbooks. It hasn't been recorded before."

One of the participants was Jennifer Archer. "Psychologically, this has helped me so much. My depression is non-existent since I started this," Archer said. "That means MS has not beaten me down. MS does not have control over my life. I have control over my life. I'm a person who has MS, but I've pulled MS away from who I am." Since the study, Archer continues to exercise at home three times a week for 40 minutes — with no harness and holding on with one hand – on a new treadmill she bought.

"When you have MS, you never think you're going to get better than what you are because it's degenerative. You think, this is the way my life is and I can't get any stronger or do what other people do. But now I feel like I have my life back," Archer said.

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# My own personal housing crisis

**As my MS continues to progress there are several life changes I need to make. One of these is to my housing.**

I live alone and five years ago I moved from an inaccessible flat on the second floor of a rambling Victorian house to a more modern accessible ground floor flat. The new flat has most of the things I needed five years ago, and after buying some aids and adaptations I thought it would be suitable as my home for decades to come.

Of course the problem with progressive MS is that it progresses and while my new flat met my needs five years ago today it only just about meets them and certainly won't in five years' time, when I will be 65. Moreover, with things like steps to the front and the back door, I don't think it will be possible for me to make my current flat totally accessible. I have accepted reluctantly that it's time for another move. The question is: where to?

At one level my choices are straightforward. My first option is to buy a totally accessible flat locally that has all the facilities that I need if I become completely dependent on a wheelchair or walking frame As a 60 year old my second option is retirement accommodation.

Looking first of all at the buying option, I immediately hit a problem, there isn't much of this type of housing on the market. And progress in increasing the amount accessible housing has been slow. According to a report "Housing and Disabled People" compiled by the Equalities and Human Rights Commission (EHRC) in 2015 only 7% of English homes offered minimal accessibility features and there were around 365,000 disabled people with unmet housing needs.

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***Looking for a new place***



***the step at my existing flat***

**Continued from page 5** Not wishing to become one of these 365,000 people I have started to earnestly look at property websites like Rightmove and phoned local estate agents explaining my situation. After two months not a single local estate agent has come up with a property that meets my needs and neither has Rightmove. It is confirmation more or less of everything the EHRC report warned of. So I have started looking in the sheltered accommodation sector.

As a 60 year old I am now eligible for retirement housing which typically means buying or more often renting a one or two bedroom flat in a block where you often share communal areas like a residents' lounge and a laundry. The advantage of this type of accommodation is you get some support if needed. You have added security and help. The disadvantage is that you can lose some privacy and independence. Initially I was reluctant to consider sheltered accommodation but after overcoming my reluctance I registered with four providers of rented sheltered accommodation locally, and am currently waiting for a suitable one bed or two bed flat to become available. (One has just become available to rent)

I suppose what I have learned is that while there are solutions to finding accessible accommodation, the problem of finding the right home is difficult and time consuming and you may not find what you really want. The 2015 EHRC housing report "Housing and Disabled People" was subtitled "Britain's Hidden Crisis" and for the past two months I have been finding out how very accurate that subtitle is. There certainly is a crisis in accessible housing and now my MS has progressed it has become my own personal crisis and one I can't hide from any longer. **For further details go to page 14**

# Thousands sign petition for Ocrevus on the NHS

**More than 21,000 people have signed a petition calling for Ocrevus (ocrelizumab) to be made available on the National Health Service (NHS) in England for people with primary progressive MS (PPMS).**

According to an MS Trust press release, the petition was signed by the MS Society, MS Trust, Shift MS, and leading neurologists, and was given to the National Institute for Health and Care Excellence (NICE), NHS England, and Roche (Ocrevus's manufacturer) urging them to act to make the treatment available. Currently, no approved treatments for PPMS exist.

Clinical trials have shown that Ocrevus has therapeutic promise in PPMS. A Phase 3 trial, called ORATORIO (NCT01194570), in PPMS patients showed Ocrevus reduced the relative risk of disease progression by 25%, compared with placebo, an important achievement given the fact no other therapy so far had been able to slow disability progression in these patients. Ocrevus also reduced the volume of chronic brain lesions and total brain volume loss in PPMS patients.

Yet, in September 2018, NICE announced that it would not be recommending ocrelizumab as an NHS treatment in the U.K. for early PPMS.

In October 2018, NICE announced that it was pausing the publication of final guidelines for Ocrevus for PPMS treatment. Further discussions have taken place among NICE, Roche, and NHS England on the matter; however, they have not come to a deal. According to the MS Society, although Ocrevus can be paid out of pocket, it costs £19,000 (about $24,600) per year, which is not affordable for most patients or their families.

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# Positive results for high-dose anti-retroviral MS drug Temelimab in new clinical trial

**Swiss bio-pharma GeNeuro has reported positive data from a Phase I clinical trial evaluating the safety and tolerability of high doses of its anti-retroviral drug GNbAC1 for the treatment of neurological and autoimmune disorders, including progressive MS.**

The company also announced that the World Health Organization has assigned the international non-proprietary name "temelimab" to GNbAC1.

The development of temelimab is the result of a quarter century of research into human endogenous retroviruses - stretches of foreign, viral DNA inserted into the human genome. Some human endogenous retroviruses are known to be associated with auto-immune diseases. For example, one of these viruses, the MS-associated retrovirus (MSRV), encodes a protein (MSRV-envelope protein, or MSRV-Env) that is found in MS patients, particularly in active lesions. Temelimab works by neutralizing the MSRV-Env protein associated with MS, and subsequently blocks inflammation. Also, the therapy has been shown to restore myelin.

This new trial follows a previous GeNeuro clinical trial CHANGE-MS testing temelimab in the treatment of MS. In October 2018 GeNeuro announced the final results of CHANGE-MS, showing that temelimab could reduce the levels of key markers related to MS progression, lessen brain atrophy and lesion load, and protect the nervous system.

Now, in this new Phase 1 trial, GeNeuro has tested the safety of temelimab at a higher dose range. Results showed no side effects related to safety when taking temelimab at all the higher doses tested, suggesting that the therapy had a robust safety profile even at higher doses.

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# Small molecule can limit autoimmune response in MS, mouse study shows

**A small molecule called Sephin1 may significantly delay harm to neurons in MS by protecting oligodendrocytes— cells that produce myelin — limiting the body's autoimmune response, a mouse study shows.**

The study, "Sephin1, which prolongs the integrated stress response, is a promising therapeutic for multiple sclerosis," was published in the journal "Brain".

MS is thought to be caused by immune-mediated inflammation that damages myelin — an insulating sheath around nerve cells. For this reason, current MS disease-modifying treatments focus on immune-mediated inflammation. Although these treatments moderate disease relapses, their impact on disease progression is unclear.

Previous studies have demonstrated that oligodendrocytes are critical in protecting against neuron demyelination and axon (nerve fibre) damage. As a result, researchers have been keen to develop alternative therapeutic approaches that protect oligodendrocytes, and ultimately limit disease progression.

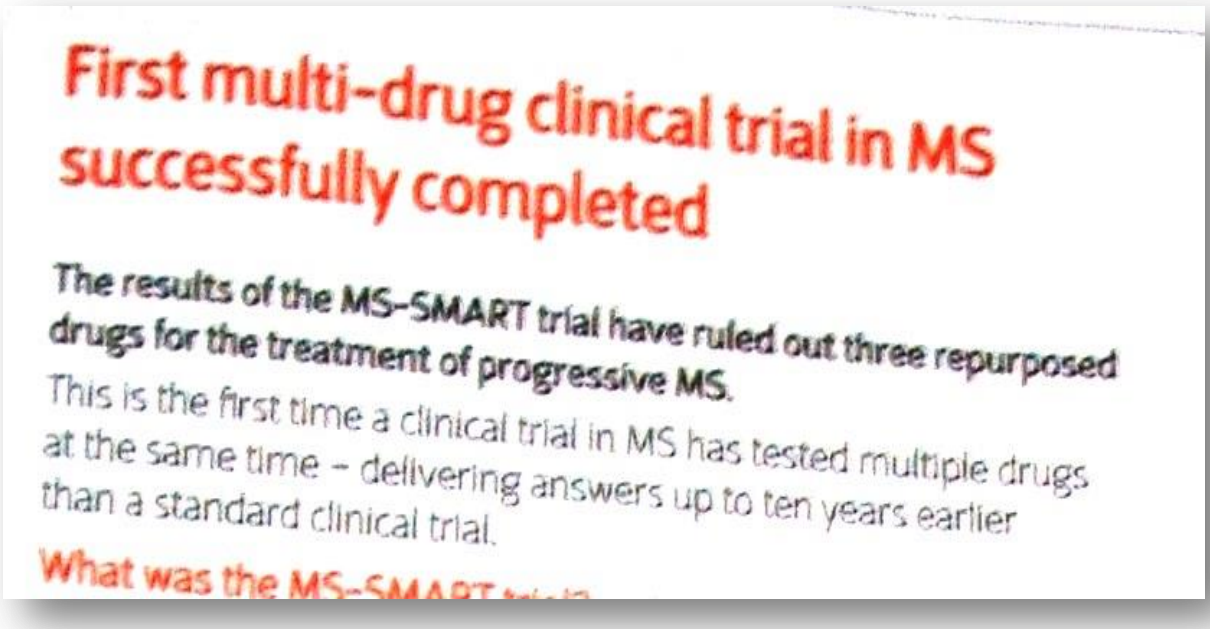
In this study, researchers at the University of Chicago proposed that Sephin1, by producing the synthesis of protective proteins in oligodendrocytes could protect them and slow the progress of the disease. The team tested their hypothesis in a mouse model called experimental autoimmune encephalomyelitis (EAE), which is similar to MS in humans.

Results showed that treatment with Sephin1 did trigger a protective response against inflammation. More importantly, myelin-producing oligodendrocytes were also protected, and disease onset was significantly delayed.

This correlated with diminished oligodendrocyte loss, protected neuronal axons and myelin, and prolonged integrated stress response. In addition, Sephin1 decreased the levels of inflammatory immune T-cells, and the production of inflammatory signals within the central nervous system.

The team concluded that the results "suggest that a neuroprotective treatment based on the enhancement of the integrated stress response would likely have significant therapeutic value for multiple sclerosis patients."

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First multi-drug clinical trial in MS successfully completed

**The results of the MS-SMART trial have ruled out three repurposed drugs for the treatment of progressive MS.**

This is the first time a clinical trial in MS has tested multiple drugs at the same time – delivering answers up to ten years earlier than a standard clinical trial.

What was the MS-SMART

# Why MS-SMART was not so smart

**The news may not have been shouted from the rooftops but the results of the MS-SMART trial have just been publicised. Sadly the trial of all three re-purposed drugs to treat progressive MS failed.**

This bad news was tucked away on page 15 of the latest (February 2019) issue of the MS Society's booklet "Your Advances" under the surprisingly upbeat headline "First multi-drug clinical trial in MS successfully completed"

Yes, the trial may have been successfully completed, and under the up-beat headline about successful completion there are further up-beat statements about us having learned a huge amount, being better placed to identify and rule out treatments which don't work etc. However, the really important news is that the trial failed in not one but three drugs, and this is less high profile in the story.

It may be churlish to talk about burying bad news but I think we should ask some important questions. Just how did the scientists get it so wrong in their choice of not one but three

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**Ctd from p10** drugs? How come fluoxetine, riluzole and amiloride had no effect at all on secondary progressive MS, when we were told there was suggestion they might work?

Take fluoxetine (Prozac) first. Optimism was raised by the Fluoxetine in Progressive Multiple Sclerosis (FLUOX-PMS) study in 2016 which showed the drug lowered progression of disability after 108 weeks when tried out in patients with PPMS and SPMS . It's a sodium and calcium channel blocker and both these two are "over expressed" in MS lesions, so there was a chance it might work in the new trial. The MS-SMART trial was shorter (98 weeks ) than the earlier 108 week trial but the dose was the same so it's puzzling. Perhaps if MS-SMART had been 108 weeks it would have made a difference.

Moving on to Riluzole, which is used to treat motor neurone disease, this drug reduces glutamate release which was thought would also help in SPMS. The reason is that progressive MSers have increased levels of the neurotransmitter glutamate in their brains— a process that likely leads to the loss of brain volume. It has been suggested that glutamate might be a driver of neuronal cell death. In 2005 a single phase IIA clinical trial was performed in progressive MS; a trial involving 16 primary progressive (not secondary progressive) patients observed for 1 year before and during treatment with riluzole tablets 50 mg twice a day. Once again there was hope this drug might work in SPMS. But once again the drug failed. So perhaps PPMS drugs won't work in SPMS.

The third drug amiloride has been noted to have myeloprotective and neuroprotective effects in experimental models of progressive MS. In a 2013 phase IIA clinical trial, 14 patients with primary progressive MS (PPMS) were observed for 1 year before treatment and after treatment with oral amiloride 5 mg twice a day. A significant reduction was observed in the whole brain atrophy rate compared with pre- treatment. But in the MS-SMART trial amiloride like the other two drugs failed in SPMS.

So, what, if anything, does the failure of these three drugs tell us? The first thing I notice is that two drugs - amiloride and riluzole -had been shown to have some effect on primary progressive MS – amiloride even seemed to reduce brain shrinkage. This suggests that s primary progressive MS and secondary progressive MS don't have as much in common as was thought. The second observation I would make is that fluoxetine and amiloride are sodium and calcium channel blockers and these don't seem to work as well as potassium channel blockers like fampridine which is licensed for MS.

But in conclusion there is very little positive to report in this trial although the MS Society's Advances put a different spin on things by saying "We are now better placed to identify and rule out treatments that won't work". I suppose you can't deny that, but all the same patients are more interested in treatments that do work rather than those that don't. Perhaps MS-SMART wasn't so smart after all. Tell me if I am wrong or unfair. Like everyone else with prog-MS I just want to get better.

# FDA asked to fast track cannabis-based therapy for treating progressive MS

**A request for a potential cannabis-based treatment for progressive MS to be given Fast Track designation, speeding its development as it readies to enter clinical testing, is now before the U.S. Food and Drug Administration (FDA), MMJ International Holdings has announced.**

MMJ-001, as the new treatment is known, aims to treat the spasticity (muscle stiffness) associated with progressive multiple sclerosis. MMJ International Holdings is a company specialising in medicinal cannabis and other botanic drugs.

Specifically, MMJ-001 is a liquid therapeutic formulation made from highly purified components of cannabis - cannabidiol (CBD) and tetrahydrocannabinol (THC), the company states on its website. CBD and THC are the most abundant cannabinoids in the cannabis plant; CBD is non-psychoactive component of the cannabis oil and believed to have neuro-protective properties, while THC is the principal psychoactive constituent of cannabis.

MMJ International is exploring the potential of a range of cannabinoid and other botanical molecules targeting neurological diseases, the company said in a news release.

It is also planning to bring MMJ-001 into a first “dose-ranging” study — a clinical trial testing different treatment doses to establish which dose works best and is safest and most tolerable, MMJ said in a separate release. In this study, still in the planning stages, researchers will compare therapeutic formulations of THC and CBD to placebo.

The request to place MMJ-001 on a fast track is related to its development as a therapy for primary progressive multiple sclerosis (PPMS). The FDA’s fast track expedites the review and approval of experimental treatments for serious or life-threatening diseases with the potential to fill patients’ unmet medical needs.

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# Low income and education levels are linked to MS progression, study claims

**Low income and education levels are linked to a higher risk of physical disability and disease progression in MSesrs, according to research by a Canadian academic.**

The study called, “Socioeconomic status and disability progression in multiple sclerosis,” was published in the journal Neurology.

“This study is the first of its kind,” Helen Tremlett, PhD, the study’s senior author, said . “Previous studies have looked at the relationship between socioeconomic status and risk of developing MS. Here, we were able to show a relationship between socioeconomic status and subsequent risk of disability progression,” Tremlett said.

In the study, a team of scientists from UBC, Canada, together with collaborators from Wales, gathered health, economic, and education data from a total of 3,113 MS patients — 2,069 from British Columbia (Canada), and 1,044 from Southeast Wales.

Results showed that high socioeconomic status, as well as education levels, were associated with a low risk of high EDSS scores, and a low risk of developing secondary progressive MS (SPMS). Conversely, low socioeconomic status and/or education levels were linked to a high risk of moderate/severe physical impairment and SPMS.

The team did not analyse which factors might account for this inverse relationship between patients’ socioeconomic status/education level and higher risk of MS disability and progression, but argue that several lifestyle parameters, including diet and exercise, may be involved.

“If that is the case, the risk may be amenable to change,” said Tremlett. “One of the next steps is to understand why this relationship exists.”

In the future, the team hopes that more MS studies will take into account the socioeconomic status and education level of patients, since these parameters seem to play an important role in disease progression and physical disability.

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## *References contact details etc*

**Page 2**

Rituximab story

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**Page 3 Stem cells story**

Sources: https://multiplesclerosisnewstoday.com/2019/01/09/brainstorm-expands-production-autologous-stem-cell-technology-nurown-phase-2-trial/?utm_medium=desktop-push-notification&utm_source=Notifications&utm_campaign=OneSignal

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**Page 4 Cool exercise story**

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**page 7 ocrevus story**

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**Page 9 Sephin 1 story**

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**Page 12 Cannabis story**

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**Page 13 Income, education and progression story**

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