FONDATION CHARCOT STICHTING

56

Fighting multiple sclerosis

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A FOCUS ON TWO NEW MS-RELATED AREAS

This 56th issue of the Foundation's newsletter describes two aspects that are of increasing importance in pharmacological research and neurological practice: the repositioning/repurposing of existing medications for the treatment of MS (Prof. Muccioli), and the use of telemedicine to monitor and measure the progression of clinical symptoms (Prof. Nagels and his team).

In his paper, Prof. Muccioli emphasises the huge cost of developing new drugs and analysing not only their positive effects but also their potential toxicity. The process is a lengthy one and takes at least ten years. There are therefore considerable advantages to repositioning or repurposing a pharmaceutical agent that is already in use, since as a rule its dosage and toxicity are well-known and the risks involved, both medical and financial, are considerably lower. He also supplies several instances of commonly used drugs that have recently been tested on MS due to their anti-inflammatory or remyelinating properties.

During neurology appointments, it is often difficult to measure the ultimately irreversible progress of MS symptoms. The development of remote measuring devices will improve the detection of this slow progression, which may even have escaped the patient's notice. Often, they are applications that are downloaded onto mobile phones. They can measure distances walked, balance and hand function, and can also serve during remote neurology appointments and for home rehabilitation exercises. They can also store large amounts of quantitative data that can be used in AI research and efficiency measurements.

I would therefore like to thank the authors of these papers, whose work has also been financially supported in the past by the Foundation, which, of course, would not have been possible without your faithful support.

Prof. Dr **Christian Sindic**
PRESIDENT

The references for all studies mentioned in this newsletter are available upon request from the Charcot Foundation.

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DRUG REPURPOSING IN MS

MAKING SOMETHING NEW OUT OF THE OLD.

Drug repositioning or repurposing is a drug development approach that is gaining traction in the pharma industry and in academia, also in the context of diseases of the central nervous system (CNS).

Indeed, the approach is generally considered to be less risky and faster (and therefore less expensive) than more traditional approaches.

Drug repositioning and drug repurposing are often used interchangeably. They can be broadly defined as the use of a therapeutic agent in an indication other than the one for which it was initially developed. While both terms can be found in the literature, several authors make a distinction between both concepts.

Indeed, drug repositioning can be considered as “the development of an agent for an indication other than the one it was originally intended for” while drug repurposing can be defined as “the application of established drug compounds to new therapeutic indications”.

To understand the potential benefit of drug repurposing / repositioning, it is important to keep in mind that drug discovery and development are a lengthy (12-15 years, or more) and costly (several billions of €) process.

Part of the time and cost is due to the need to thoroughly assess the pharmacokinetic (PK) and safety profiles of the developed drug, first in preclinical and then in clinical studies.

Thus, one clear advantage of drug repurposing / repositioning is that the safety profile of the candidate has already been established. This means that there is no need for additional preclinical assessment of the safety profiles of the molecule being developed. As a consequence, the cost of development is drastically reduced.

Besides, repurposing / repositioning also “de-risks” the development of the molecule as the risk of failure due to toxicity is largely reduced.

In this context, previously marketed drugs (see two examples below) are even more advantageous compared to drugs that have been developed until the clinical trials but never reached the market as the developer has access to post-marketing (i.e. “real life”) data.

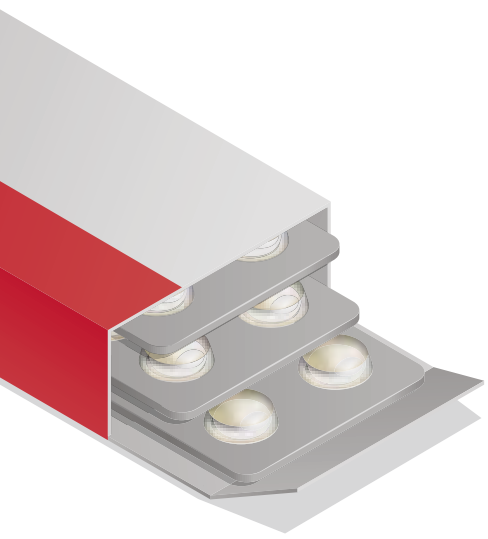
Drug repositioning / repurposing can be very valuable, especially in areas where the attrition rate during drug development is very high (typically for CNS diseases) or for neglected / orphan diseases.

In the context of CNS diseases, drug repositioning / repurposing can be illustrated with two examples.

Fenfluramine, originally developed for weight loss and later withdrawn from the market, received a new marketing authorisation from the EMA in 2020 as a treatment for several forms of epilepsy. Amantadine was originally marketed as a prophylactic anti-influenza virus drug but was later approved (in 2017) by the FDA for the treatment of dyskinesia in patients with Parkinson’s disease receiving levodopa.

> Thus, the question is: “are there any research efforts in “repurposing” drugs in the context of MS?”

Thus, the question is: “are there any research efforts in “repurposing” drugs in the context of MS?” Before delving into the current efforts, we can mention that dimethylfumarate was already on the market as an anti-psoriasis drug before being approved by the FDA in 2013 as treatment for MS.



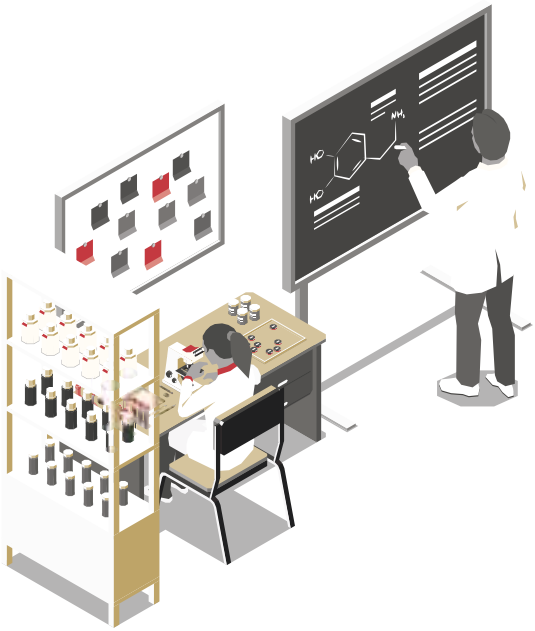
Current repurposing / repositioning efforts include:

A Statins (e.g. atorvastatin), originally developed to lower cholesterol levels, were potentially helpful for treating MS, in part due to their anti-inflammatory and immunomodulatory properties. However, the data obtained from controlled clinical trials are less supportive. Indeed, while they might have beneficial effects on the inflammatory component of the disease, reducing cholesterol levels may negatively affect the remyelinating processes.

B Clemastine is a well-known antihistaminergic drug used to manage allergies. It was shown to induce remyelination in vitro and in several animal models of MS. In the ReBUILD Phase II clinical trial, clemastine improved myelination-related parameters supporting the positive preclinical data. However, in the more recent TRAP-MS trial, the clemastine-treated arm of the study had to be halted due to increased disability accumulation in patients with non-lesional MS activity.

C Metformin is the main first-line treatment for type II diabetes. Several in vitro and in vivo preclinical studies have shown that metformin can have a positive effect on oligodendrocyte progenitor cell (OPC) differentiation and remyelination processes. A clinical trial involving patients with obesity and MS found that metformin use was associated with a significant decrease in the number of T2 lesions and gadolinium-enhancing lesions. Several ongoing clinical trials are further investigating the safety and efficacy of metformin as treatment for MS. Of note, in Belgium the ongoing MACSiMiSE-BRAIN clinical trial will assess if metformin can prevent clinical disability in patients with progressive MS by enhancing remyelination.

Several Bruton tyrosine kinase inhibitors (e.g. HERCULES; EVOLUTION RMS) and the phosphodiesterase 4 inhibitor Ibudilast (e.g. NN102/SPRINT-MS) are other examples of current repurposing / repositioning efforts.



Prof. **Giulio G. Muccioli**
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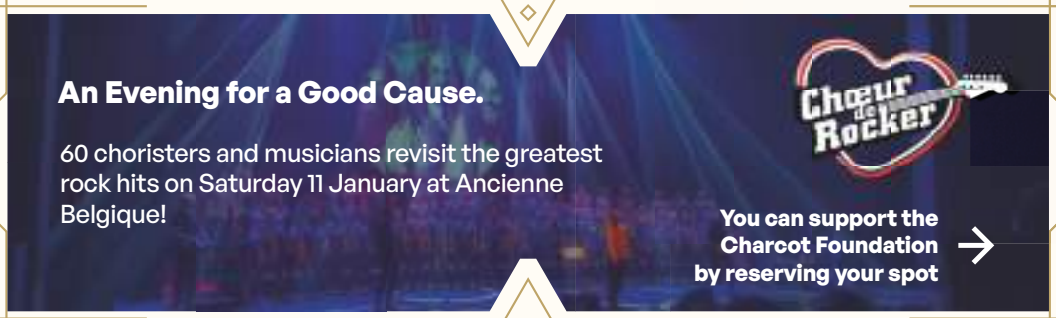

TELEMEDICINE IN MS

Telemedicine, the use of technology to provide clinical care at a distance, has become increasingly popular in recent years.

In MS, it is found to be effective, relatively low-cost and both patients and care providers are satisfied with the level of care. While face-to-face visits remain essential, technology can facilitate several aspects of MS care.

First, it can be used to improve clinical follow-up. This can be done using audiovisual teleconsultations, which allow for easier patient access and reduced transport costs. Studies show that these teleconsultations are just as feasible and no more expensive as traditional physical consultations and that patients were very satisfied with the quality of care.

Furthermore, there are digital care platforms available to patients and care providers that provide a holistic view of the status of an MS patient.

This includes mapping symptoms and treatment (medication and rehabilitation), as well as storing patient information such as clinical test results, MRI images and pre-visit checklists.

> The goal of such platforms is to improve the early detection of disease activity and support MS care.

Second, smartphones are broadly accessible and are used by the majority of patients with MS. They therefore offer an alternative to traditional on-site testing with paper-pencil tests; symptom screening can be performed by smartphone or tablet applications.

A large number of such tests already exist, such as for the detection of cognitive impairment (information processing speed & memory), motor impairment (walking, balance & hand function) and visual impairment.

Testing can be done at the patient's home, at a time of their choosing, without the need for trained personnel. Moreover, by carrying out tests independently, the patient can take a more active role in their own clinical follow-up.

Third, telerehabilitation can be used to improve some of the above-mentioned impairments. This can be done using teleconsultations, internet-based exercise platforms or training software to be installed on the patient's computer.

The content of these training programs differ and can be holistic or targeted at a specific function such as memory or finger dexterity.

Treatments have already been investigated, and have been shown to improve cognitive performance, balance and walking performance, physical activity, fatigue and mental health. These telerehabilitation programs can be carried out at home at any time, making it easier to combine with other duties such as (home)work.

Furthermore, telerehabilitation has a favourable environmental impact, as it reduces the need for the frequent clinic visits required for traditional in-clinic rehabilitation. The evidence for the effectiveness of these treatments remains limited but is increasing fast.

Lastly, telemedicine facilitates research and advanced data analysis by directly storing data digitally, allowing easy integration in clinical and research databases. This, for example, drives artificial intelligence research, that typically requires large data sets to train models.

> To summarise, studies clearly highlight the effectiveness of telemedicine as a tool to improve patient care, underlining its potential to facilitate future clinical workflows

However, further research is needed to bring these new technologies into daily practice.

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