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An agent-based simulation model for informed shared decision making in multiple sclerosis

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Abstract
Shared decision making (SDM) is concerned with patient involvement into medical decisions and chronic conditions such as Multiple sclerosis (MS), with only partially effective treatments leading to potential severe side effects, conflicting evidence, and uncertain evidence on outcomes, constitute a typical condition for SDM. As treatment options increase and patients participate more intensively in decisions, the need for evidence-based information (EBI) becomes clear.
Natural history (NH) studies of MS represent the basic sources for required EBI and are especially useful to contribute to the practical exercise of prognosis formulation and to enable the evaluation of effectiveness in the context of treatment. Several of these identify early clinical factors predictive of the course of MS but there is no consensus method for determining the long term progression of disability and evolution of individual patients on the basis of observations on the early stages of the disease, which constitutes a major challenge for the practicing neurologist.
Aiming at delivering more reliable prognosis estimation, this study combines the distribution of patients reaching specific levels of disability within defined time periods as determined in NH studies, with disability curves and severity scores as a function of time, in terms of percentiles and deciles respectively, derived from longitudinal data analysis studies. A computer agent-based simulation model was implemented as a comprehensive and easy to utilize tool able to predict and monitor progression of disability in MS patients, and to support the neurologist discussing prognosis scenarios with the individual patient for effective SDM.

1. Introduction

The goal of both diagnosis and therapeutic decisions is to improve the prognosis for the patient, since prognosis refers to all medical outcomes that may occur during the patient's disease process. This also implies that patient management should be driven by two major prognosis related topics: the natural history (NH), which is the prognosis of the disease without medical interventions, and the prognosis changes as

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resulting from medical interventions. Additionally, prognosis is a major concern to the patient who wants to be informed about his prospects and prognosis related information is a mandatory requirement for an informed and active participation of the patient on self-clinical decision-making.

A major challenge in multiple sclerosis (MS) for the practicing neurologist is to make a prediction of the long term evolution of individual patients on the basis of observations on the early stages of the disease. An immediate effect of such difficulty is to inhibit the communication to the patient of a realistic estimation of his/her evolution, particularly in a long term basis.

Prognosis' estimates or prediction can be made in several ways. As opposed to an informal way (e.g. intuitively or using expert opinions), modern patient management requires that appropriateness of medical interventions is supported by scientific evidence, integrating clinical expertise, patient values, and the best research evidence into the decision making process for patient care, the basis for evidence-based medicine (Sackett et al., 1996). Including patient values and preferences in the clinical decision-making is an ethical issue (Hughes and Larson, 1991) and can contribute to improve patient care (O′Connor et al., 2007; Sepucha et al., 2004). Shared decision-making (SDM) is a major component of such patient-centered care, and has been defined as a process that "allows both physicians and patients to honor the values and preferences of the patient, while also permitting the physician to provide medical expertise to promote the patient′s health" (O′Connor et al., 2007). Hence, SDM takes informed consent a step further in the process of communication between a patient and a physician. It is much more than obtaining the patient′s authorization or agreement to undergo a specific medical intervention; SDM means to involve the patient actively on the medical decisions and such patient empowerment also means giving the patient more responsibility.

Chronic conditions such as MS, with only partially effective treatments with potential severe side effects, conflicting evidence, and uncertain evidence on outcomes, where the benefit–harm ratio is short and/or doubtful, or when available options have different benefit–harm profiles that patients value differently, constitute a typical condition for this SDM and enforces its need (Heesen et al., 2011; Wennberg et al., 2002).

As treatment options increase and patients participate more intensively in decisions, the need for evidence-based information becomes clear. There is an evidence that patients may, in exchange for therapeutic benefits, be willing to accept greater levels of risk than are actually posed by some therapies (Calfee, 2006; Johnson et al., 2007a, 2007b). Drug therapies for MS offer a range of potential benefits, but they may also involve life-threatening risks, including liver failure, leukemia, and progressive multifocal leukoencephalopathy (Brassat et al., 2002; Francis et al., 2003; Yousry et al., 2006). Yet patients may be misinformed particularly by means of internet information, misinterpret the results of scientific research (Jadad et al., 2000; Kaplan and Brennan, 2001), have unrealistic expectations of treatment benefits and harms, and clinicians may be poor judges of a patient′s values (O′Connor et al., 2007).

There also is evidence that patient decision aids are better than usual care in improving patients' knowledge and expectations about interventions, as well as improving agreement between values and choice (Elwyn et al., 2006).

A diversity of methods has emerged for decision support from different scientific fields such as Statistics, Decision Analysis and Artificial Intelligence. Cox models, recursive partitioning analysis, Weibull models, decision trees, Markov models, Partially Observable Markov Decision Process, Bayesian networks and influence diagrams. No matter the approach, the first step is to build up a prognostic model able to predict the probability of some outcome as optimally as possible.

Several studies have been performed to identify early clinical factors predictive of the MS course (Levic et al., 1999; Runmarker and Andersen, 1993; Weinshenker et al., 1989, 1991; Kremenchutzky et al., 2006; Confavreux and Vukusic, 2006; Ebers, 2005; Vukusic and Confavreux, 2007; Scalfari et al., 2012), such as: gender, disease course, age at onset of disease, initial symptoms, number of functional systems involved, first interval attack, attack frequency, and incomplete remission after the first episode. However, the majority of work in this area is not focused on the individual prognosis to the patient; neither does address treatment effects on the NH of the disease.

Daumer et al. (2007), describe an online analytical processing tool that matches the characteristics of a given patient with the most similar patients of the Sylvia Lawry Centre for Multiple Sclerosis Research database. An "individual risk profile" in terms of the disease course of all similar patients in the database is displayed, hence enabling to project a hypothesized outcome for that patient (Daumer et al., 2007). The main limitations of this tool are related to the characteristics of the patients included in the database. The clinical data are derived only from the placebo groups of randomized clinical trials, and the respective observation period is limited to a maximum of three years (Daumer et al., 2007).

In the study of Wolfson and Confavreux (1985, 1987), a Markov model is proposed to represent the disease course by means of transitions between disease states, as to evaluate the effect of prognostic factors on those transitions. Because Markov processes are memory less, once a state is known, the future evolution of the disease is independent of the past evolution. This limitation is handled in the work of Bergamaschi et al. (2007, 2001), by proposing a Bayesian model specifying the full joint probability distribution for a set of random variables that characterize the entire course of the disease. The risk of reaching secondary progression was significantly related to specific clinical factors presented during the first year of the disease, all of them associated with a specific statistical weight, the Bayesian local relative risk, used to calculate the Bayesian Risk Estimate for MS (BREMS) score for any given patient (Bergamaschi et al., 2007, 2001). However, no other prognostic outcomes are provided.

Achiron et al. (2003) use NH information from a large database to generate longitudinal disability curves for prediction of disease progression based on the mean Expanded Disability Status Scale (EDSS) scores from the first year of disease onset represented as a major percentile group. These curves represent cohort percentiles and enable to foresee the relative risk of disease progression, as well as to identify deviations in the curves (Achiron