

# Drug exposure and Multiple Sclerosis: results from a systematic literature review.

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**Background.** Multiple sclerosis (MS) is an autoimmune disease characterized by inflammatory degeneration of the nervous system, affecting more frequently women aged 20-40 years with inhomogeneous distribution worldwide. Different risk factors have been associated with MS: low blood vitamin D level [1], smoking [2], viral infection [3] and genetic factors [4], whereas the possible role of drug exposure on MS onset and progression is unclear.

**Aim.** To investigate published evidence on drug exposure and risk of multiple sclerosis, in terms of both class of drugs and strength of evidence.

**Methods.** The following search strategy was performed in pubmed in March 2016, with 'English language' and 'Human species' filters: "Multiple Sclerosis/epidemiology"[MAJR] AND (drug\* or Medication\* or medicine\*) OR "Multiple Sclerosis/chemically induced".

All references were screened for the coherence with the aim of the study, by reading the abstracts; reviews were also snowballed to include relevant articles not found by the general search strategy. Molecular, animal, vaccines exposure, cross-sectional studies and letters to the editor were excluded, as well as studies lacking information on drug exposure or on MS onset/worsening.

The included articles were classified into the following categories: review, case report, RCT, case control study or cohort study. Then, strength of evidence hierarchy was applied.

Case reports and case series were assessed for causality by applying Naranjo algorithm, whereas for case control study and cohort study the most appropriate indicator of association was identified (e.g., OR).

Studies were also classified to distinguish positive (documented risk), negative (documented protective role) or irrelevant effect of drug exposure and onset or worsening of disease.

**Results.** Overall, 669 articles were found and 47 full articles were selected. Snowballing of reviews provided additional 13 studies. A half of selected articles were case report/case series (n=29) reporting possible or probable association between drug exposure and MS risk (4-7 points score with Naranjo algorithm). Observational studies represented 40% (24) of records, clinical studies 6% (4) and 5% (3) were reviews. The 50% of articles showed association between immunomodulatory drugs and MS risk (major suspected drugs were adalimumab, infliximab and etanercept). Increased risk to develop MS was also found for anaesthetics (3 studies), fluoxetine (1), carbamazepine (1), assisted reproduction treatment (3), sulfasalazine (1), ethambutol (1), rimonabant (1) and drug abuse (1). Beneficial effects in delaying MS onset or progression were observed for contraceptives, whereas studies on antibiotics showed conflicting results.

**Conclusion.** Different classes of drugs were associated with increased risk to develop MS or worsening its progression, especially monoclonal antibodies. The general low strength of evidence (intrinsic limitations of case reports/case series) together with conflicting results observed in population studies (e.g., antibiotics) highlighted difficulties in addressing this topic and call for dedicated studies, taking into account the multifactorial and complex pathogenesis of MS (e.g., appropriate follow-up and adjustments for multimorbidity).

[1] A. Ascherio, et al. JAMA Neurol., 71 (2014) 306-314.

[2] R. Ramanujam, et al. JAMA Neurol., 72 (2015) 1117-1123.

[3] C. Pfuhl, et al. J. Neuroimmunol., 285 (2015) 156-160.

[4] N. Mohammadi, et al. J. Neuroimmunol., 290 (2016) 115-118.