

Validation of an algorithm identifying relapses in multiple sclerosis using the French nationwide claims database

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Background

- **Multiple sclerosis (MS)**
 - Incapacitating, progressive, chronic neurological disorder that involves a selective, chronic inflammation and demyelination of the central nervous system
 - Relapsing-remitting MS forms (RRMS) are the most common, and are characterized by the presence of relapses without disability progression between relapses
 - In France :
 - Prevalence in 2012 : 151 per 100 000 inhabitants
 - 87 000 cases in 2017
- **Relapses**
 - Clinically defined as the occurrence of new neurologic symptoms or the recurrence of old neurological symptoms that last at least 24 hours
 - SNDS (national healthcare system database): No direct indicator available, complex algorithm based on :
 - hospitalization(s) related to relapse or related to MS,
 - or outpatient dispensation(s) of IV or oral high dose corticosteroid therapy,
 - or combination of hospitalization(s) related to relapse or related to MS and outpatient dispensation(s) of IV or oral high dose corticosteroid therapy.

- **Validation of the algorithm**
 - Was conducted by clinician using all information of the database (as a patient's medical file, see below) for a random sample of patients

Objectives

- **To assess the validity of an algorithm identifying relapses in MS patients in SNDS database**

Declaration of Interest Statement

This study was supported by an unconditional grant from Biogen. It was designed, conducted, and analysed independently by the Bordeaux PharmacEpi of the Bordeaux University. It was overseen by independent experts.

Methods

- **Data source:** extraction of SNDS data from 2011 to 2016 (EVIDEMS cohort)
- **General approach**
 - ① Execution of the algorithm for relapses identification
 - ② Assessment of randomly selected cases by a committee of experts
 - ③ Calculation of positive (PPV) and negative (NPV) predictive values of the algorithm
 - ④ Adjustment of algorithm
 - ⑤ Calculation of positive (PPV) and negative (NPV) predictive values of the algorithm
- **Validation Committee organization (Figure 1)**
 - Random selection of 200 patients among 37 986 MS patients of the cohort:
 - 100 MS patients with at least one relapse during follow-up period
 - 100 MS patients without relapse
 - Constitution of 2 expert pairs (each pair with 1 neurologist member of the Scientific Committee + 1 independent neurologist)
 - Double blind review of 100 patients (50 with at least one relapse and 50 without relapse) per experts pair
 - Assessment by each expert of the presence or absence of relapses and the number of relapses, when available
 - In case of disagreement within a pair of experts: the case was discussed by the 4 experts to reach consensus
 - Algorithm performance was estimated using the positive and negative predictive values (PPV, NPV).

Patient N°4 (Woman - [40 - 50] years old)						
Flag	Medical act	History (in days)	Duration (in days)	Prescription (in days)	Retails healthcare	Retails healthcare : GHM and associated diagnosis
	Pharmacy	-28		-67	LYRICA 50MG capsule 84 (PREGABALINE) / 1 box / Physician : Unknown specialty	
	Pharmacy	-28		-83	GILENYA 0.5 MG capsule 28 (FINGOLIMOD) / 1 box / Physician : Unknown specialty	
	Pharmacy	-28		-92	KEPPRA 500MG CPR 60 (LEVETIRACETAM) / 2 boxes / Physician : Unknown specialty	
	Pharmacy	-28		-92	CERIS 20MG CPR 30 (TROSPiUM) / 2 boxes / Physician : Unknown specialty	
	Pharmacy	-28		-92	UVEDOSE 2.5MG/2ML (COLECALCIFEROL) / 1 box / Physician : Unknown specialty	
	CCAM	0			Eye tomography by optical coherence scan	
	CCAM	0			Fundus by biomicroscopy with contact lens	
	Pharmacy	0		0	GILENYA 0.5 MG capsule 28 (FINGOLIMOD) / 1 box / Physician : Unknown specialty	
	Pharmacy	1		-92	KEPPRA 500MG CPR 60 (LEVETIRACETAM) / 2 boxes / Physician : Unknown specialty	
	Pharmacy	1		-92	CERIS 20MG CPR 30 (TROSPiUM) / 2 boxes / Physician : Unknown specialty	
	Pharmacy	167		167	GILENYA 0.5 MG capsule 28 (FINGOLIMOD) / 1 box / Physician : Hospital physician (undetermined specialty)	
	Pharmacy	168		115	LYRICA 75MG capsule 56 (PREGABALINE) / 1 box / Physician : Hospital physician (undetermined specialty)	
	Pharmacy	168		76	KEPPRA 500MG CPR 60 (LEVETIRACETAM) / 1 box / Physician : Hospital physician (undetermined specialty)	
	Pharmacy	168		76	CHOLECALCIFEROL MYLAN 100000 UI (COLECALCIFEROL) / 1 box / Physician : Hospital physician (undetermined specialty)	
	Pharmacy	168		76	TROSPiPHARM G6 20 MG CPR 30 (TROSPiUM) / 1 box / Physician : Hospital physician (undetermined specialty)	
➡	1 Hospit	176	2		DP : G35 - Multiple Sclerosis	GHM : Multiple sclerosis and cerebellar ataxia, level 1
	Medical device	178			Wheelchair with 1 accessory, weekly rental, < ou = 52 weeks	
➡	1 Pharmacy	178		178	SOLUMEDROL 1 G (METHYLPREDNISOLONE) / 1 box / Physician : Unknown specialty	
	Pharmacy	178		178	SODIUM CHLORURE MACO PHARMA 0.9 P, 100 BAG 1/250 ML (ELECTROLYTES) / 1 box / physician : Unknown specialty	
	Pharmacy	178		178	BISEPTINE SOL FL 250ML 1/250 ML (CHLORHEXIDINE IN ASSOCIATION) / 1 box / physician : Unknown specialty	
	Medical device	181			Infusion, non-refillable filling accessories	

Figure 2. Reconstructed medical chart of patient using SNDS data

Results

- **Inter-expert and algorithm discrepancy**
 - Inter-expert discrepancy: among the 200 MS patients selected, the summary sheets of 35 patients were reviewed in a collegiate manner, in order to reach a consensus.
 - Algorithm discrepancy: finally 11 discordant cases (9 patients) : a patient may have many relapses) have been identified by the experts: 7 related to the criteria "relapse presence" and 4 to the criteria "relapse absence".
- **PPV and NPV calculation (Table 1)**
 - Confirmation of 95 out of 100 MS patients with at least one relapse and 96 out of 100 patients without relapse
 - PPV = 0.95 and NPV = 0.96

		Experts		Total
		Relapse	Without relapse	
Algorithm	Relapse	95	5	100
	Without relapse	4	96	100
Total		99	101	200

Table 1. PPV and NPV calculation

- **PPV and NPV calculation after algorithm adjustment (Table 2)**
 - Discordant cases have been discussed by the experts in order to adjust the algorithm
 - Finally, the algorithm was revised to include all changes proposed by the experts.
 - The proposed changes increased algorithm performance: the PPV and NPV of the revised version of the algorithm became 95.2% and 100% respectively.

		Experts		Total
		Relapse	Without relapse	
Algorithm	Relapse	99	5	104
	Without relapse	0	96	96
Total		99	101	200

Table 2. PPV and NPV calculation after algorithm adjustment

Conclusion

- **The wealth of data available in the SNDS enables**
 - The implementation of algorithms to detect complex event
 - The validation of these algorithms *via* the reconstitution of pseudonymized medical charts based on SNDS data
- **This claim-bases algorithm**
 - Appeared to successfully detect MS relapse
 - Could thus be applied to future observational MS studies in SNDS database and also to compare effectiveness of MS treatment on relapses

