Misdiagnosis and Disease-Exacerbating Medication Use in Patients With Neuromyelitis Optica Spectrum Disorder in the United States: A Retrospective Claims Analysis

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BACKGROUND

- Neuromyelitis optica spectrum disorder (NMOSD) is a rare, complement-mediated, autoimmune disease that is characterized by inflammatory relapses (attacks) in the central nervous system that lead to permanent neurological impairment[1]
- Nonspecific presentation of neurological symptoms can lead to misdiagnosis of NMOSD as a condition with similar clinical presentation, most notably multiple sclerosis (MS)[2]
- Preventing misdiagnosis of NMOSD as MS is critical because the use of certain MS medications in patients with NMOSD has been shown to exacerbate symptoms and can potentially lead to catastrophic disease activity[2]

OBJECTIVE

- To evaluate the incidence of NMOSD misdiagnosis and the utilization of medications that could exacerbate disease activity in patients with NMOSD

METHODS

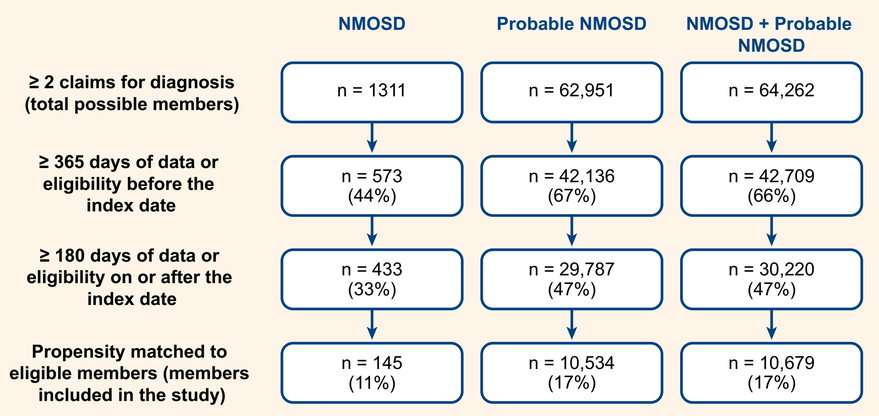
- Data from the Magellan Health (medical/pharmacy) database between January 1, 2016, and December 31, 2021, were analyzed and pooled for patients with NMOSD (≥ 2 claims for NMOSD) and probable NMOSD (≥ 2 claims for NMOSD-related conditions: optic neuritis, encephalitis, myelitis, encephalomyelitis, or disorders of the optic nerve)
- The index date was defined as the first claim for NMOSD or an NMOSD-related diagnosis
- A 1:1 greedy-neighbor propensity-score-matched control group was generated from all other member profiles based on patient demographics and comorbidities using the SAS® procedure PSMATCH
- Members were excluded if they had < 365 days of data or eligibility before the index date, < 180 days of data or eligibility on or after the index date, or failed propensity-matching to eligible members
- Covariates included age, sex, plan type, United States' census region, and comorbidities of infarction, heart failure, kidney disease, chronic respiratory disease, cardiovascular disease, dementia, diabetes, hepatic disease, cancer, rheumatoid diseases, and gastric ulcers as defined by the Charlson Comorbidity Index criteria
- Outcomes included the most common diagnoses and overall medication use in the pre-index period (from January 1, 2016, to the first claim for NMOSD or probable NMOSD)
- Patient demographic and clinical characteristics were described as either total n (%), or mean (median) [standard deviation]
- Statistical significance was described by *P* values and was determined using chi-squared tests for categorical variables n (%) and t tests were performed for continuous variables, mean (median) [standard deviation]
- All calculations and statistical tests were performed using SAS® 9.4

LIMITATIONS

- Only association, not causality, can be determined from this study
- Undetectable data quality issues may exist that are common to all claims-data sources, such as submitting a valid but inaccurate code
- Claims only record dispensing of medication, therefore the claims data cannot ascertain prescriptions that have not been dispensed and patient adherence to medication

RESULTS

Figure 1. Members included in the study as per the selection criteria



NMOSD, neuromyelitis optica spectrum disorder.

Table 1. Demographic characteristics and study durations of the study population

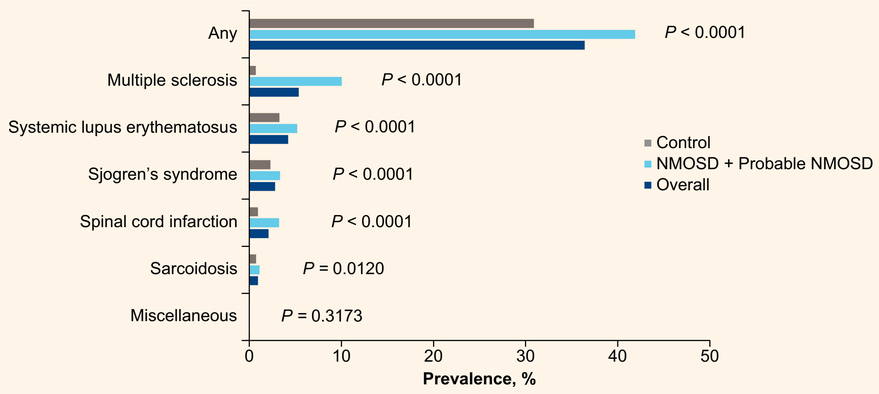
Characteristic	Overall (n = 21,358)	NMOSD + Probable NMOSD (n = 10,679)	Control (n = 10,679)	*P value*
Age, years				
All, mean (median) [SD]	**51.4 (54.0)[12.4]**	**51.2 (54.0) [12.5]**	**51.6 (54.0) [12.2]**	**< 0.0001**
18–30, n (%)	**1623 (7.6)**	**853 (8.0)**	**770 (7.2)**	
31–40, n (%)	**2448 (11.5)**	**1267 (11.9)**	**1181 (11.1)**	
41–50, n (%)	**4493 (21.0)**	**2256 (21.1)**	**2237 (21.0)**	
51–64, n (%)	**10,995 (51.5)**	**5408 (50.6)**	**5587 (52.3)**	
65+, n (%)	**1799 (8.4)**	**895 (8.4)**	**904 (8.5)**	
Sex, n (%)				
Female	12,862 (60.2)	6431 (60.2)	6431 (60.2)	1.0000
Male	8496 (39.8)	4248 (39.8)	4248 (39.8)	1.0000
Charlson Comorbidity Index				
Overall, mean (median) [SD]	**3.6 (3.0) [3.3]**	**3.7 (3.0) [3.2]**	**3.6 (3.0) [3.5]**	**0.0478**
0, n (%)	**1715 (8.0)**	**–**	**–**	**< 0.0001**
1, n (%)	**5182 (24.3)**	**3344 (31.3)**	**1838 (17.2)**	
2, n (%)	**3748 (17.6)**	**1978 (18.5)**	**1770 (16.6)**	
3+, n (%)	**10,713 (50.2)**	**5357 (50.2)**	**5356 (50.2)**	
US census region, n (%)				
East North Central	3878 (18.2)	1958 (18.3)	1920 (18.0)	0.5721
East South Central	1762 (8.3)	884 (8.3)	878 (8.2)	
Middle Atlantic	2913 (13.6)	1412 (13.2)	1501 (14.1)	
Mountain	413 (1.9)	206 (1.9)	207 (1.9)	
New England	1432 (6.7)	718 (6.7)	714 (6.7)	
Pacific	848 (4.0)	417 (3.9)	431 (4.0)	
South Atlantic	5608 (26.3)	2835 (26.6)	2773 (26.0)	
Unknown	744 (3.5)	348 (3.3)	396 (3.7)	
West North Central	1155 (5.4)	582 (5.5)	573 (5.4)	
West South Central	2605 (12.2)	1319 (12.4)	1286 (12.0)	
Plan type, n (%)				
EPO	**1175 (5.5)**	**594 (5.6)**	**581 (5.4)**	**< 0.0001**
HMO	**2875 (13.5)**	**1452 (13.6)**	**1423 (13.3)**	
POS	**992 (4.6)**	**494 (4.6)**	**498 (4.7)**	
PPO	**15,810 (74.0)**	**7999 (74.9)**	**7811 (73.1)**	
Other	**283 (1.3)**	**140 (1.3)**	**143 (1.3)**	
Unknown	**223 (1.0)**	**–**	**223 (2.1)**	
Duration of baseline period, months, mean (median) [SD]	32.3 (32.0) [11.7]	32.3 (32.0) [11.7]	32.3 (32.0) [11.7]	1.0000
Duration of follow-up period, months, mean (median) [SD]	**22.3 (20.0) [11.4]**	**21.7 (20.0) [11.4]**	**22.9 (21.0) [11.3]**	**< 0.0001**

Rows in **bold** show statistically significant differences between the control group vs the NMOSD + probable NMOSD group.

EPO, exclusive provider organization; HMO, health maintenance organization; NMOSD, neuromyelitis optica spectrum disorder; POS, point of service; PPO, preferred provider organization; SD, standard deviation.

- In the pre-index period, patients with NMOSD or probable NMOSD had a significantly higher rate of diagnoses for conditions with similar clinical presentation compared with the matched control group (41.99% vs 31.00%; *P* < 0.001) (**Figure 2**)
  - The largest difference observed was for MS diagnosis (10.13% for NMOSD + probable NMOSD vs 0.79% in the control group; *P* < 0.0001) followed by spinal cord infarction (3.34% vs 1.03%; *P* < 0.0001)

Figure 2. Comparison of the prevalence of conditions with a similar clinical presentation to that of NMOSD in the control group versus the NMOSD + probable NMOSD groups



NMOSD, neuromyelitis optica spectrum disorder.

- Rates of prescription of corticosteroids and NMOSD-related treatments of any type were not different between the patients with NMOSD + probable NMOSD and the control group (**Table 2**)
  - However, modest but statistically significantly lower rates of corticosteroid prescriptions were identified in the NMOSD + probable NMOSD group versus the control group for methylprednisolone (24.63% vs 26.73%; *P* = 0.005), methylprednisolone inpatient (15.67% vs 17.04%; *P* = 0.0065), and prednisone (34.80% vs 36.02%; *P* = 0.0069)
  - Similarly, significantly lower rates of NMOSD-related treatments were identified in the NMOSD + probable NMOSD group versus the control group for hydroxychloroquine (3.78% vs 4.34%; *P* = 0.0408), and tocilizumab treatment (0.07% vs 0.17%; *P* = 0.0497), whereas there were significantly higher rates of intravenous immunoglobulin (1.06% vs 0.25%; *P* < 0.0001) and plasma exchange (0.24% vs 0.09%; *P* = 0.0076), in the NMOSD + probable NMOSD group versus the control group

Table 2. Rate of use of corticosteroids and NMOSD-related treatments in the control group versus the NMOSD + probable NMOSD group

Treatment	Overall (n = 21,358) n (%)	NMOSD + Probable NMOSD (n = 10 ,679) n (%)	Control (n = 10,679) n (%)	*P value*
Corticosteroids				
Any	11,932 (55.87)	5963 (55.84)	5969 (55.89)	0.9341
Dexamethasone	1076 (5.04)	511 (4.79)	565 (5.29)	0.0912
Dexamethasone inpatient	57 (0.27)	22 (0.21)	35 (0.33)	0.0847
Methylprednisolone	**5484 (25.68)**	**2630 (24.63)**	**2854 (26.73)**	**0.0005**
Methylprednisolone inpatient	**3493 (16.35)**	**1673 (15.67)**	**1820 (17.04)**	**0.0065**
Prednisolone inpatient	12 (0.06)	7 (0.07)	5 (0.05)	0.5636
Prednisone	**7563 (35.41)**	**3716 (34.80)**	**3847 (36.02)**	**0.0069**
Prednisone inpatient	0	0	0	–
NMOSD-related treatments				
Cyclophosphamide	11 (0.05)	5 (0.05)	6 (0.06)	0.763
Eculizumab	3 (0.01)	3 (0.03)	0	0.0832
Hydroxychloroquine	**867 (4.06)**	**404 (3.78)**	**463 (4.34)**	**0.0408**
Intravenous immunoglobulin	**140 (0.66)**	**113 (1.06)**	**27 (0.25)**	**< 0.0001**
Mitoxantrone	0	0	0	–
Plasma exchange	**36 (0.17)**	**26 (0.24)**	**10 (0.09)**	**0.0076**
Rituximab	156 (0.73)	89 (0.83)	67 (0.63)	0.0771
Tocilizumab	**26 (0.12)**	**8 (0.07)**	**18 (0.17)**	**0.0497**

Rows in **bold** show statistically significant differences between the control group versus the NMOSD + probable NMOSD group.

NMOSD, neuromyelitis optica spectrum disorder.

- Medications known to exacerbate NMOSD[2] were dispensed at significantly (*P* < 0.001) higher rates in the NMOSD + probable NMOSD group compared with matched controls (0.41% vs 0.05% [fingolimod]; 0.70% vs 0.07% [interferon beta]; 0.53% vs 0.04% [natalizumab]) (**Table 3**)

Table 3. Medications dispensed at higher numbers in the NMOSD + probable NMOSD group versus matched controls, including those medications known to exacerbate NMOSD

Condition Medication	Overall (n = 21,358) n (%)	NMOSD + Probable NMOSD (n = 10,679) n (%)	Control (n = 10,679) n (%)	*P value*
Crohn's disease				
Mesalamine	161 (0.75)	93 (0.87)	68 (0.64)	0.048
Irritable bowel syndrome				
Linaclotide	342 (1.60)	191 (1.79)	151 (1.41)	0.0292
Plecanatide	44 (0.21)	14 (0.13)	30 (0.28)	0.0158
Multiple sclerosis				
Fingolimod[a]	49 (0.23)	44 (0.41)	5 (0.05)	< 0.0001
Interferon beta (any)[a]	88 (0.41	81 (0.70)	7 (0.07)	< 0.0001
Interferon beta1a	25 (0.12)	23 (0.22)	2 (0.02)	< 0.0001
Interferon beta1aalb	37 (0.17)	34 (0.32)	3 (0.03)	< 0.0001
Interferon beta1b	15 (0.07)	14 (0.13)	1 (0.01)	0.0008
Natalizumab[a]	61 (0.29)	57 (0.53)	4 (0.04)	< 0.0001
Peginterferon beta1a	11 (0.05)	10 (0.09)	1 (0.01)	0.0066

[a]Medications known to exacerbate NMOSD.

CONCLUSIONS

- Based on this analysis, NMOSD is misdiagnosed as MS in approximately 10% of patients with NMOSD + probable NMOSD versus 0.8% in matched controls
- In general, misdiagnosis of NMOSD with conditions having similar clinical presentation is more prevalent in patients with NMOSD or probable NMOSD than in matched controls
- Use of NMOSD-exacerbating medications, although a small percentage of the total, is also more prevalent in patients with NMOSD + probable NMOSD and can subsequently cause significant clinical deterioration
- Further research into better diagnostic strategies is needed to promote earlier identification and appropriate disease management for patients with NMOSD

FUNDING

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DISCLOSURES

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REFERENCES

1. Waliszewska-Prosół M, Chojdak- Łukasiewicz J, Budrewicz S, Pokryszko-Dragan A. Neuromyelitis optica spectrum disorder treatment—current and future prospects. *Int J Mol Sci*. 2021;22(6):2801.
2. Traub J, Häusser-Kinzel S, Weber MS. Differential effects of MS therapeutics on B cells—implications for their use and failure in AQP4-positive NMOSD patients. *Int J Mol Sci*. 2020;21(14):5021.

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