CME ARTICLE

Total drug treatment and comorbidity in myasthenia gravis: a population-based cohort study

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Background and purpose: Comorbidity in myasthenia gravis (MG) is important for diagnosis, treatment and prognosis. Disease complexity was assessed by examining total drug treatment, immune therapy and comorbidity in a complete national MG cohort.

Methods: All recipients of the MG-specific drug pyridostigmine 2004–2010 registered in the compulsory Norwegian Prescription Database who met the inclusion criteria were included. The pyridostigmine group was compared with the general Norwegian population.

Results: Myasthenia gravis patients received co-medication more often than the controls for nearly all groups of medication, including insulins (95% confidence interval 2.0–3.7), thyroid therapy (1.7–2.5), antidepressants (1.3–1.7), anti-infectives (1.2–1.4), lipid-modifying agents (1.1–1.4) and immunomodulating agents (6.8–8.8).

Conclusions: Myasthenia gravis patients are more often treated with non-MG prescription drugs than controls, reflecting frequent co-medication and comorbidity.

Introduction

Autoimmune myasthenia gravis (MG) is mainly caused by the destruction of acetylcholine receptors by autoantibodies at the neuromuscular junction. MG is a heterogeneous disease with several subtypes and autoantibodies against skeletal muscles [1]. Life expectancy for MG patients is now near normal [2], but management of a fluctuating disease remains challenging. New therapeutic options are emerging, and MG subtype classification has implications for treatment strategies [3].

The task of controlling symptoms whilst minimizing adverse effects of long-term immunosuppressive treatment is intricate. Furthermore, the clinical implications of heart muscle antibodies, involvement of respiratory function in MG and use of drugs that may worsen neuromuscular blockade have not been widely studied, nor have autoimmune comorbidity and psy-

chiatric disorders been described in unselected MG cohorts. Our study provides a national cohort for evaluating the total drug management of symptomatic MG, offering a new insight into the total disease burden for this group.

The aims of the study were to evaluate drug treatment and thereby also comorbidity in patients with MG. First, an overview is given of the overall national drug consumption amongst MG patients. Secondly, MG autoimmune comorbidity is assessed through co-medication. Thirdly, psychiatric disorders in MG are explored through specific drug treatment. Fourthly, prescription practice is investigated with regard to selected drugs considered as relatively contraindicated in MG. Finally, first- and second-line drug treatment of MG is investigated.

Methods

Registration of all prescription drugs dispensed from Norwegian pharmacies in the Norwegian Prescription Database (NorPD) has been mandatory since 2004, covering the entire Norwegian population (5 096 300). A unique personal identifier enables consecutive monitoring of individuals in the health system over their entire life span. The specific diagnosis or indication

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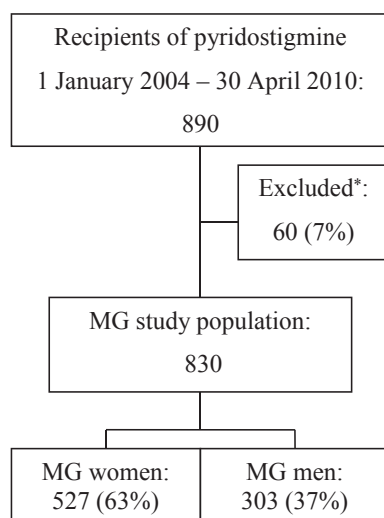
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for the prescription is not registered in NorPD, but the International Classification of Diseases, 10th revision (ICD-10), and/or the International Classification of Primary Care, 2nd edition (ICPC-2), have been recorded since 2008. Medication for chronic diseases such as MG is reimbursed. The reimbursement codes together with the ICD-10 and ICPC-2 codes function as a proxy of diagnosis. The following variables were studied: the patient's year of birth and sex, the prescriber's medical speciality, reimbursement codes, ICD-10/ICPC-2 codes, name of the drug, Anatomical Therapeutic Chemical (ATC) code, date of expedition at the pharmacy, and the defined daily dose (DDD) of the drugs dispensed. In NorPD, the DDD corresponds to the assumed mean maintenance dose of the drug used per day for its main indication in adults [4].

About 890 individuals with at least one prescription of pyridostigmine from 1 January 2004 to 30 April 2010 were identified. Amongst these, 830 (93%) met one or more of the criteria preset by us to confirm a diagnosis of MG and were regarded as having MG: (i) ≥2 prescriptions of pyridostigmine during the study period; (ii) pyridostigmine prescription made by a neurologist; (iii) pyridostigmine prescription with reimbursement code (§13) or ICD-10 code (G70.0)/ICPC-2 code (N99) specific for MG (Fig. 1). Final inclusion for this study was done from the date when one or more of the criteria were fulfilled. Sensitivity analyses with more stringent inclusion criteria to test the robustness of our study population were performed (Table S1).

For each subgroup of patients categorized by age and sex, drug statistics for the corresponding age and

Table 1 Demographic characteristics of the study population and population controls, year 2004

	MG patients ($n = 830$)	Population controls ($n = 4\,577\,457$)
Age (mean)[a]	57	39
Sex (n, %)		
Female	527 (64)	2 269 049 (50)
Male	303 (37)	2 308 408 (50)
Age group (n, %)		
0–9	3 (0.4)	598 503 (13)
10–19	29 (4)	591 853 (13)
20–29	36 (4)	570 889 (13)
30–39	105 (13)	698 413 (15)
40–49	97 (12)	639 053 (14)
50–59	148 (18)	595 423 (13)
60–69	159 (19)	374 975 (8)
70–79	175 (21)	299 162 (7)
80–89	67 (8)	180 640 (4)
> 90	11 (1)	28 546 (0.6)

[a]Patient age was calculated from year of birth and defined as age at 1 July 2004.

sex groups in the Norwegian population registered in NorPD from the same period functioned as controls (Table 1). Total drug treatment of MG patients was assessed by investigating every prescription dispensed in all main ATC groups during the study period. Comparisons of age- and sex-specific drug use amongst MG patients and controls were done by calculating the standardized incidence ratio (SIR), i.e. the observed number of prescriptions for all main ATC groups divided by the estimated number of prescriptions for the same drug groups dispensed to a similar group, with regard to age and sex, in the general population. Patient age was defined as age at 1 July 2004. The SIR was computed, with 95% confidence interval (CI), assuming a Poisson distribution. The ATC group 'Various' was considered non-specific and was excluded from the analyses.

When exploring comorbidities and contraindicated medications, the following groups of drugs were included: drugs used in diabetes, insulins and analogues, thyroid hormones, antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants, antiepileptics, beta-blocking agents, calcium-channel blockers, lipid-modifying agents and aminoglycoside antibacterials. The following groups of immunomodulating agents were assessed: prednisolone, selective immunosuppressants, tumor necrosis factor alpha inhibitors, interleukin inhibitors, calcineurin inhibitors, and other immunosuppressants.

To detect any differences in prescription of ATC groups related to age and sex, linear regressions were performed, estimating the mean difference and 95% CIs. Two-sided P values ≤ 0.05 were considered

Figure 1 Selection of the MG study cohort. *Recipients of pyridostigmine who did not meet the inclusion criteria during the study period.

statistically significant. The median DDD prescribed each year was compared for pyridostigmine and for each of the following immunomodulating agents: prednisolone, azathioprine, mycophenolic acid, cyclosporine and methotrexate, as recommended by the European Federation of Neurological Societies guidelines for MG treatment [5]. Non-parametric tests were performed for comparisons regarding amount dispensed between age and sex groups. IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA), and Microsoft Excel were used in all statistical analyses. Ethics committee approval is not required for studies using anonymous data retrieved from central health registers.

Results

In total, 87 556 prescription medications were dispensed to the 830 MG patients during the registration period (Table 2). The mean number of new ATC groups per year is shown in Table S2. Only 19 individuals (2.3%) received no other medication than pyridostigmine. MG patients more often received nearly all types of medication compared with the control group, most pronounced for the following treatment groups: alimentary tract and metabolism (A); systemic hormonal preparations, excluding sex hormones and insulins (H); antineoplastic and immunomodulating agents (L). Patients <50 years received fewer ATC groups than patients ≥50 years and women received fewer than men, but neither of the differences was significant.

Insulins were almost three times more frequently prescribed to MG patients (95% CI 2.0–3.7, Table 3) compared with controls. This was observed for MG patients ≥50 years (1.9–3.7), for men (1.7–4.3) and for women (1.7–4.0). MG patients <50 years also had increased prescriptions of insulins (SIR = 2.8), but there were too few users to provide sufficient statistical power (N = 5). A hundred and ten MG patients (13%) received a prescription of thyroid hormones. Thyroid hormones were prescribed about four times more frequently to MG patients <50 years (2.4–5.5) and male MG patients (2.3–5.0). Patients ≥50 years and female MG patients received thyroid hormones about twice as often compared with controls (1.5–2.2 and 1.4–2.2, respectively).

In all, 29% of MG patients received treatment with hypnotics and sedatives, and such drugs were twice as often given to MG patients than to controls for the age group <50 years (1.2–2.3). 21% received antidepressants, twice as often given to male MG patients than to male controls (1.3–2.2). For the remaining age and sex groups, slightly more MG patients than controls were treated with hypnotics, sedatives and an-

tidepressants. 20% received anxiolytics, whilst 7% received antipsychotics (Table 3). Anxiolytics and antipsychotics were prescribed to MG patients and controls with the same frequency.

Myasthenia gravis patients were twice as often treated with antiepileptic drugs (1.7–2.5). They were also more frequently treated with calcium-channel blockers (1.2–1.7) and lipid-modifying agents (1.1–1.4), but with the same frequency as in the controls with beta-blocking agents (0.9–1.2). All four drug groups were given more frequently to MG patients <50 years compared with controls at the same age (Table 3). However, the number of users of calcium-channel blockers, lipid-modifying agents and beta-blocking agents was too low to provide enough statistical power (N = 6, 11, 11 respectively).

The DDDs of pyridostigmine were significantly lower for MG patients <50 years compared with those ≥50 years (P < 0.001). There was no difference between men and women (P = 0.8). Immunomodulating agents were prescribed less to patients <50 years (P < 0.001) and women (P = 0.001) compared with patients ≥50 years and men (Table 4); 406 MG patients (49%) had no immunomodulating agents expedited during the study period. The mean number of new groups of immunomodulating agents used per year was not significantly different between the two age and sex groups (P = 0.2 and P = 0.9, respectively; Fig. 2a and b). Regression analyses with mutual adjustment for age and sex did not alter the differences regarding age and sex.

Significantly fewer DDDs of prednisolone was prescribed to patients <50 years compared with patients ≥50 years (P < 0.001). No age difference was seen for azathioprine (P = 0.1). Women were prescribed significantly fewer DDDs of prednisolone (P < 0.001) and azathioprine (P = 0.002) than men. For mycophenolic acid, cyclosporine and methotrexate, the number of users and DDDs prescribed were too small to be included in the calculations.

Discussion

This is the first study to assess the total drug management and comorbidity of MG in a complete national cohort. Our findings show that co-medication in MG is widespread, requiring more frequent drug treatment for several major disease groups than in the general population. Treatment for diabetes, thyroid disease and psychiatric disorders in MG is common, as well as co-medication relatively contraindicated in MG. These findings demonstrate the extensive disease burden of MG and the complexity of the disease.

Table 2 Number of the 830 MG patients receiving prescription medications in the main ATC groups compared with the number in a similar group, with regard to age and sex, in the general national population

ATC group	Total (n = 830)			Women (n = 527)			Men (n = 303)			<50 years old (n = 270)			≥50 years old (n = 560)		
	n (%)	SIR[a] (95% CI)	P value[b]	n (%)	SIR[a] (95% CI)	P value[b]	n (%)	SIR[a] (95% CI)	P value[b]	n (%)	SIR[a] (95% CI)	P value[b]	n (%)	SIR[a] (95% CI)	P value[b]
A – Alimentary tract and metabolism	512 (62)	1.9 (1.7–2.0)	<0.001	318 (60)	1.7 (1.6–1.9)	<0.001	194 (64)	2.1 (1.8–2.4)	<0.001	101 (37)	2.3 (1.9–2.8)	<0.001	411 (73)	1.8 (1.6–2.0)	<0.001
B – Blood and blood forming organs	364 (44)	1.5 (1.3–1.6)	<0.001	206 (39)	1.5 (1.3–1.7)	<0.001	158 (52)	1.5 (1.3–1.8)	<0.001	41 (15)	2.2 (1.6–2.9)	NA	323 (58)	1.4 (1.3–1.6)	<0.001
C – Cardiovascular system	460 (55)	1.4 (1.2–1.5)	<0.001	258 (49)	1.3 (1.1–1.4)	<0.001	202 (67)	1.5 (1.3–1.7)	<0.001	49 (18)	1.7 (1.3–2.3)	NA	411 (73)	1.3 (1.2–1.5)	<0.001
D – Dermatologicals	360 (43)	1.3 (1.2–1.5)	<0.001	237 (45)	1.3 (1.2–1.5)	<0.001	123 (41)	1.4 (1.2–1.6)	<0.001	99 (37)	1.5 (1.2–1.9)	NA	261 (47)	1.3 (1.1–1.4)	<0.001
G – Genito urinary system and sex hormones	308 (37)	1.3 (1.2–1.5)	<0.001	225 (43)	1.2 (1.1–1.4)	0.002	83 (27)	1.5 (1.2–1.9)	<0.001	101 (37)	1.3 (1.0–1.5)	0.02	207 (37)	1.3 (1.2–1.5)	<0.001
H – Systemic hormonal preparations, excluding sex hormones and insulins	456 (55)	3.0 (2.7–3.3)	<0.001	272 (52)	2.5 (2.2–2.8)	<0.001	184 (61)	4.2 (3.7–4.9)	<0.001	105 (39)	3.9 (3.2–4.7)	<0.001	351 (63)	2.8 (2.5–3.1)	<0.001
J – Anti-infectives for systemic use	604 (73)	1.3 (1.2–1.4)	<0.001	391 (74)	1.2 (1.1–1.4)	<0.001	213 (70)	1.4 (1.2–1.6)	<0.001	146 (54)	1.2 (1.0–1.4)	0.02	458 (82)	1.3 (1.2–1.5)	<0.001
L – Antineoplastic and immunomodulating agents	249 (30)	7.7 (6.8–8.8)	<0.001	146 (28)	8.0 (6.8–9.4)	<0.001	103 (34)	7.4 (6.1–9.0)	<0.001	63 (23)	16.4 (12.6–21.0)	NA	186 (33)	6.6 (5.7–7.6)	<0.001
M – Musculoskeletal system	464 (56)	1.2 (1.1–1.3)	<0.001	308 (58)	1.1 (1.0–1.3)	0.01	156 (51)	1.3 (1.1–1.5)	0.005	120 (44)	1.3 (1.0–1.5)	0.01	344 (61)	1.2 (1.0–1.3)	0.006
N – Nervous system	582 (70)	1.4 (1.2–1.5)	<0.001	393 (75)	1.4 (1.2–1.5)	<0.001	189 (62)	1.3 (1.2–1.5)	<0.001	134 (50)	1.5 (1.3–1.8)	<0.001	448 (80)	1.3 (1.2–1.4)	<0.001
P – Antiparasitic products, insecticides and repellents	78 (9)	1.2 (1.0–1.5)	NA	55 (10)	1.2 (0.9–1.5)	NA	23 (8)	1.3 (0.8–2.0)	NA	24 (9)	1.2 (0.8–1.8)	NA	54 (10)	1.2 (0.9–1.6)	NA
R – Respiratory system	488 (59)	1.4 (1.3–1.5)	<0.001	314 (60)	1.3 (1.2–1.4)	<0.001	174 (57)	1.6 (1.3–1.8)	<0.001	127 (47)	1.4 (1.2–1.7)	<0.001	361 (64)	1.4 (1.2–1.5)	<0.001
S – Sensory organs	354 (43)	1.4 (1.2–1.5)	<0.001	241 (46)	1.4 (1.2–1.5)	<0.001	113 (37)	1.4 (1.1–1.7)	0.001	76 (28)	1.4 (1.1–1.7)	NA	278 (50)	1.4 (1.2–1.5)	<0.001

NA, not available or insufficient data available for analysis. [a]SIR, standardized incidence ratio calculated by comparing age- and sex-specific drug use amongst MG patients with the general population (i.e. the control group); [b]the difference between MG patients and the control group.

Table 3 Number of the 830 MG patients receiving various prescription medications compared with the number in a similar group, with regard to age and sex, in the general national population

ATC code – Drug	Total (n = 830)			Women (n = 527)			Men (n = 303)			<50 years old (n = 270)			≥50 years old (n = 560)		
	n (%)	SIR[a] (95% CI)	P value[b]	n (%)	SIR[a] (95% CI)	P value[b]	n (%)	SIR[a] (95% CI)	P value[b]	n (%)	SIR[a] (95% CI)	P value[b]	n (%)	SIR[a] (95% CI)	P value[b]
Autoimmune co-medication															
A10 – Drugs used in diabetes	83 (10)	1.8 (1.4–2.2)	NA	45 (9)	1.8 (1.3–2.4)	NA	38 (13)	1.8 (1.3–2.5)	NA	8 (3)	2.0 (0.8–3.9)	NA	75 (13)	1.8 (1.4–2.2)	NA
A10A – Insulins and analogues	42 (5)	2.7 (2.0–3.7)	NA	22 (4)	2.6 (1.7–4.0)	NA	20 (7)	2.8 (1.7–4.3)	NA	5 (2)	2.8 (0.9–6.6)	NA	37 (7)	2.7 (1.9–3.7)	NA
H03AA – Thyroid hormones	110 (13)	2.1 (1.7–2.5)	<0.001	81 (15)	1.8 (1.4–2.2)	NA	29 (10)	3.5 (2.3–5.0)	NA	25 (9)	3.7 (2.4–5.5)	NA	85 (15)	1.8 (1.5–2.2)	NA
Psychiatric co-medication															
N05A – Antipsychotics	60 (7)	1.1 (0.8–1.4)	NA	47 (9)	1.2 (0.9–1.6)	NA	13 (4)	0.7 (0.4–1.3)	NA	13 (5)	1.3 (0.7–2.2)	NA	47 (8)	1.0 (0.7–1.3)	NA
N05B – Anxiolytics	170 (20)	1.2 (1.0–1.4)	0.03	120 (23)	1.1 (1.0–1.4)	0.13	50 (17)	1.3 (0.9–1.7)	NA	26 (10)	1.2 (0.8–1.8)	NA	144 (26)	1.2 (1.0–1.4)	0.05
N05C – Hypnotics and sedatives	244 (29)	1.3 (1.2–1.5)	<0.001	168 (32)	1.3 (1.1–1.5)	0.001	76 (25)	1.4 (1.1–1.8)	NA	39 (14)	1.7 (1.2–2.3)	NA	205 (37)	1.3 (1.1–1.5)	<0.001
N06A – Antidepressants	175 (21)	1.5 (1.3–1.7)	<0.001	123 (23)	1.4 (1.2–1.7)	<0.001	52 (17)	1.7 (1.3–2.2)	NA	39 (14)	1.5 (1.1–2.1)	NA	136 (24)	1.4 (1.2–1.7)	<0.001
Contraindicated co-medication															
N03 – Antiepileptics	80 (10)	2.1 (1.7–2.6)	NA	57 (11)	2.3 (1.7–2.9)	NA	23 (8)	1.8 (1.2–2.7)	NA	16 (6)	2.2 (1.3–3.6)	NA	64 (11)	2.1 (1.6–2.7)	NA
C07 – Beta-blocking agents	157 (19)	1.0 (0.9–1.2)	0.7	79 (15)	0.9 (0.7–1.1)	0.7	78 (26)	1.2 (0.9–1.5)	NA	11 (4)	1.5 (0.8–2.7)	NA	146 (26)	1.0 (0.9–1.2)	0.9
C08 – Calcium-channel blockers	137 (17)	1.4 (1.2–1.7)	<0.001	75 (14)	1.4 (1.1–1.7)	NA	62 (21)	1.5 (1.1–1.9)	NA	6 (2)	2.0 (0.7–4.3)	NA	131 (23)	1.4 (1.2–1.7)	<0.001
C10 – Lipid-modifying agents	194 (23)	1.3 (1.1–1.4)	0.002	99 (19)	1.1 (0.9–1.4)	NA	95 (31)	1.4 (1.1–1.7)	NA	11 (4)	1.8 (0.9–3.2)	NA	183 (33)	1.2 (1.1–1.4)	0.01
J01G – Aminoglycoside antibacterials	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-

NA, not available or insufficient data available for analysis. [a]SIR, standardized incidence ratio calculated by comparing age- and sex-specific drug use amongst MG patients with the general population (i.e. the control group); [b]the difference between MG patients and the control group.

Table 4 Number of MG patients using selected immunomodulating drugs with comparisons of DDDs prescribed, 2004–2010

ATC group − Drug	Women (n = 527)	Men (n = 303)		<50 years (n = 270)	≥50 years (n = 560)	
	n (%)	n (%)	P value[a]	n (%)	n (%)	P value[a]
H02AB06 − Prednisolone	220 (42)	167 (55)	<0.001	102 (38)	285 (51)	0.001
L04AX01 − Azathioprine	109 (21)	92 (30)	0.002	56 (21)	145 (26)	0.12
L04AA06 − Mycophenolic acid	16 (3)	7 (2)	NA	8 (3)	15 (3)	NA
L04AD01 − Cyclosporine	11 (2)	4 (1)	NA	7 (3)	8 (0.1)	NA
L04AX03 − Methotrexate	9 (2)	1 (0.3)	NA	3 (0.1)	7 (0.1)	NA
All immunosuppressants	246 (47)	178 (59)	0.001	113 (42)	311 (56)	<0.001

NA, not available or insufficient data available for analysis. [a]Non-parametric tests were used to calculate the difference in median defined daily dose between sex and age groups in the period 2004–2010.

Increased treatment frequency with drugs for the cardiovascular system in MG patients younger than 50 years was found. Arguably, there is a risk of ascertainment bias as MG patients more regularly visit a physician. However, physical inactivity due to muscle weakness, side effects of steroid treatment such as weight gain and elevated blood glucose levels are factors that may contribute to the increased risk of cardiovascular disease, even in younger individuals. The possibility for cardiac involvement in MG is also well recognized [6], although death caused by cardiac diseases is not increased [2]. The clinical implications remain unclear [7], but our data strongly indicate that there is a clinically relevant association between MG and cardiovascular disease. Early treatment of airway infections in MG patients is recommended [3], and may account for the increased use of anti-infectives. Immunosuppressed patients are also in general more prone to infections [5].

In this study, thyroid hormones were most frequently prescribed to MG patients <50 years and to men compared with controls. A recent systematic review estimated concomitant autoimmune diseases in MG at 13%, with thyroid disease as the most frequent [8]. In prospectively identified MG patients, type 1 and 2 diabetes was found in 10% and 8%, respectively [9]. All antidiabetics in our study were most frequently prescribed to patients ≥50 years. In addition to the general autoimmune disease overlap, reduced physical activity, corticosteroid treatment as well as other comorbid conditions may serve as catalysts for acquired metabolic syndrome and type 2 diabetes.

Use of antidepressants was more frequent amongst MG patients than controls. The frequency of patients receiving antidepressants in our study is in good agreement with previous reports of affective disorders in MG [10]. Drug treatment of anxiety and sleep disturbances was lower in our study compared with previous reports [11,12]. Psychiatric symptoms can mimic MG symptoms, but may also be under-recognized due to overlapping symptoms [13].

Age ≥50 years and male sex were predictors for immunosuppressive treatment in our study. Immunosuppressive drugs and thymectomy represent the main principles in treating moderate to severe MG [3], often lifelong in late-onset and thymoma cases (15% of MG patients). Complete stable remission can be induced in early-onset cases after thymectomy. The benefit of thymectomy for MG symptom relief is questionable for late-onset MG and thymoma MG patients [14]. Only 56% of the patients in our study over 50 years were treated with immunoactive drugs. Some muscle weakness is probably under-recognized in older patients due to the aging process or concomitant illness. One recent hospital-based study reported immunosuppressive therapy in 65% of late-onset cases [15]. In our study early- and late-onset cases were combined in the group above 50 years. A biological explanation implicating differences in disease severity is possible, but inadequate immunosuppression in our patients is also highly probable. Teratogenic and other adverse effects influence immunosuppressive treatment in young females. Such drugs are rarely used in pregnancy [16].

Only 6% of all MG patients in our study had such a severe disease that second-line immunomodulating drugs were required, indicating that prednisolone and azathioprine alone or in combination are sufficient for symptom control in nearly all MG patients. NorPD does not provide information on other treatment modalities, such as thymectomy, plasma exchange and intravenous administration of immunoglobulins. Patients identified with severe MG were predominantly ≥50 years old and females. MuSK-MG is more often seen in females and is associated with more severe disease, but this MG subtype is very rare in Norway [17]. Information on MG subtypes is not available in the NorPD.

The main strength of our study is case ascertainment from one single, unbiased, comprehensive
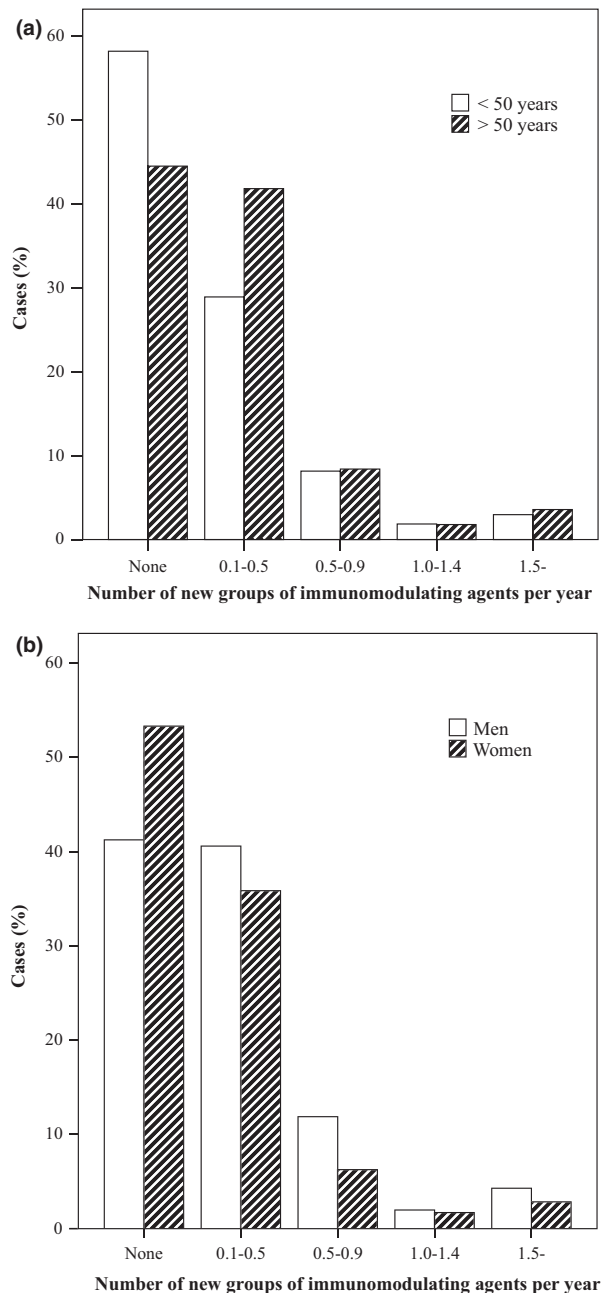
Figure 2 (a) Mean number of new groups of immunomodulating agents used in MG patients (%) below and above 50 years of age after MG diagnosis per year, 2004–2010. Open bars, patients <50 years; hatched bars, patients ≥50 years. (b) Mean number of new groups of immunomodulating agents used in MG men and women (%) after MG diagnosis per year, 2004–2010. Open bars, men; hatched bars, women.

database with a full, national population as controls. 96% of the entire Norwegian population has been included in NorPD since its establishment in 2004 with at least one prescription drug dispensed from a pharmacy. The 1 year prevalence of 68%–69% of the

population in NorPD has proven stable [18]. Identifying MG patients by prescriptions of pyridostigmine is considered sensitive with a high positive predictive value for the diagnosis [19–21], and with good agreement of calculated prevalence rates using pyridostigmine prescriptions registered in the NorPD compared with rates calculated from a nationwide acetylcholine receptor antibody database [22]. Amongst 67 patients treated at our department for the past 30 years, only three did not receive pyridostigmine (unpublished data). NorPD did not include indication for prescription until 2008. This represents a potential source of overestimation. The inclusion criteria used in this study secured high sensitivity, although specificity may be lower. However, sensitivity analyses with more stringent criteria did not alter the basic characteristics of the MG cohort. Moreover, nearly 90% of our study population had confirmed at least one MG-reimbursed prescription of pyridostigmine or from a neurologist. Only MG patients with a confirmed diagnosis are given reimbursement. The reimbursement code is therefore highly specific for MG. Pyridostigmine is not prescribed on a regular basis to any other disease groups. The rare disease Lambert–Eaton myasthenic syndrome, with a prevalence of 2–3 per million [23], is treated with pyridostigmine and reimbursement would be given as for MG. Six patients with pyridostigmine were identified with an additional prescription of fludrocortisone, the standard drug for treating orthostatic hypotension, and may marginally bias our findings.

This study reveals the true complexity of MG and contributes to an understanding of the impact of MG on health. Awareness of comorbidities and knowledge of treatment practice should help physicians in choosing the best treatment strategy.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Characteristics of the study population with different inclusion criteria.

Table S2. Mean (SD) number of new ATC groups for 830 MG patients per year, 2004–2010.

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