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Remijn-Nelissen, L.; Verschuuren, J.J.G.M.; Tannemaat, M.R.

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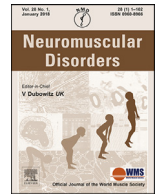
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The effectiveness and side effects of pyridostigmine in the treatment of myasthenia gravis: a cross-sectional study

Linda Remijn-Nelissen, Jan J.G.M. Verschuuren, Martijn R. Tannemaat*

Department of Neurology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands



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ABSTRACT

Pyridostigmine is the most commonly used drug in the symptomatic treatment of myasthenia gravis (MG); however, research into its effectiveness and side effects is scarce. The aim of this study was to assess the effectiveness, prevalence of side effects and net benefit of pyridostigmine. All MG patients participating in the Dutch-Belgian myasthenia patient registry were included. A dynamic online questionnaire was developed to assess the effectiveness, side effects and net benefit of pyridostigmine. Out of 642 invited patients, 410 patients (64%) fully completed the questionnaire; 61% reported that they currently used pyridostigmine, 36% had discontinued pyridostigmine and 2% reported to never have used pyridostigmine. Patients reported a median effectiveness of 60, IQR 28–78 and net benefit of 65, IQR 45–84. Of all patients currently using pyridostigmine, 91% reported side effects (vs. 55% in the control group). Most frequently reported side effects were flatulence, urinary urgency, muscle cramps, blurred vision and hyperhidrosis. In the group of patients who discontinued pyridostigmine, side effects were the reason for discontinuation in 26%. Diarrhea, abdominal cramps and muscle twitching were the most frequently cited reasons to discontinue pyridostigmine. These results can be used to guide shared decision making prior to starting symptomatic treatment for MG.

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1. Introduction

Myasthenia gravis (MG) is the most common neuromuscular junction disorder and is characterized by fluctuating muscle weakness in ocular, bulbar, limb and respiratory muscles. Pyridostigmine, an acetylcholinesterase inhibitor, is recommended as the initial treatment of myasthenia gravis in most patients [1]. The use of acetylcholinesterase inhibitors as a treatment for MG was first described in 1934 by dr. Mary Broadfoot Walker. She identified physostigmine, a partial antagonist of curare, as an effective treatment for MG, based on the observations that clinical symptoms of patients with MG were similar to the symptoms seen in patients with curare poisoning [2]. A year later in 1935, Prostigmin (generic name neostigmine), was shown to have a similar effect [3]. Until 1947, neostigmine was the primary drug for treatment of MG, but due to a short half-life, high daily doses were needed and patients experienced pronounced and difficult to control side effects. Pyridostigmine was first synthesized by Hoffmann-La Roche Laboratories in Switzerland in 1945 [4]. The first published case-studies comparing the effectiveness of

neostigmine to pyridostigmine showed that patients experienced a longer duration of action with pyridostigmine, with fewer fluctuations of symptoms during the day and fewer side effects [5–9]. Since then, pyridostigmine has remained the preferred drug for symptomatic treatment of myasthenia gravis, even though no randomized controlled trials evaluating the efficacy of pyridostigmine have been performed [10]. Importantly, no studies have reported on the perceived effectiveness and net benefit of pyridostigmine from the patient's perspective either. Over the years, very few studies have reported on the frequency of side effects during the use of pyridostigmine [11,12]. One prospective study, with a limited number of patients (n=22), reported that 64% of patients experienced daily muscarinic side effects, most commonly gastro-intestinal symptoms. A total of 36% experienced additional nicotinic side effects, including muscle fasciculations and fatigue [12]. A retrospective study published in 1997 on 100 patients reported side effects in 34% of patients using acetylcholinesterase inhibitors, most commonly gastro-intestinal in nature (30%). Only one patient in this study had to stop taking pyridostigmine because of stomach complaints [11].

The remarkable absence of detailed data may have negative consequences for the treatment of MG patients. Patients do not know the frequency or magnitude of potential side effects and

* Corresponding author.

E-mail address: m.r.tannemaat@lumc.nl (M.R. Tannemaat).

no objective data are available to inform them what to expect after starting pyridostigmine. Additionally, the development of alternative symptomatic treatments requires the establishment of the net effect of the current gold standard (i.e. pyridostigmine), against which future treatment regimens can be compared.

We therefore aimed to provide a comprehensive overview of all relevant aspects of pyridostigmine use in current clinical practice, by formulating the following primary objectives: (1) to quantify the current use of pyridostigmine in a representative cohort of the MG population, (2) to assess patients' perceived effectiveness and its net benefit and (3) to assess the prevalence and characteristics of its side effects. The secondary objective of this study was to identify predictors of pyridostigmine discontinuation.

2. Methods

2.1. Patient selection and selection procedure

All MG patients participating in the Dutch-Belgian myasthenia patient registry were invited to participate in this study. The registry is an initiative of the Dutch patient advocacy organization for neuromuscular diseases, "Spierziekten Nederland" and the Leiden University Medical Center (LUMC) [13]. Only Dutch MG patients were included in the current study, because of the small number of Belgian patients in the registry ($n=10$). Patients received a study invitation by email containing an information letter and a personal link for participation. Upon request, a printed questionnaire was available. Baseline information on sex, age, age at diagnosis and antibody status was obtained from previously completed forms already available from the registry.

The study protocol was reviewed by the Medical Ethics Review Committee of the Leiden University Medical Center; the need for formal approval was waived due to the non-invasive nature of the study. All patients provided (digital) informed consent before study participation.

2.2. Survey design

A study-specific online questionnaire was developed in a conditional format tailored to individual responses to minimize the burden for the patient; responses determined the subsequent questions asked, e.g. if a patient indicated to have never used pyridostigmine, no further questions regarding its effectiveness were asked.

Data was collected on MG (history of medication use, thymectomy, plasmapheresis or intravenous immunoglobulin) and, if applicable, on the use of pyridostigmine (frequency, dose, dose alterations). Patients were subsequently divided into 3 groups by asking the question "Have you ever used pyridostigmine?". Patients were attributed to "the currently using group" when they answered the question with "Yes, I currently use pyridostigmine"; to the "discontinued group" when they answered the question with "Yes, I have used pyridostigmine in the past, but I discontinued it"; and to the "never group" when they answered the question with "No, I have never used pyridostigmine". The currently using group was further divided by asking the question "Have you used a higher dose in the past?"

If applicable, reasons for lowering the dose of pyridostigmine (in the currently using group) or stopping pyridostigmine (in the discontinued group) were identified. Patients in the never group were asked about the reason why they never used pyridostigmine. A schematic overview of the survey structure is shown in Supplementary Fig. 1 in the Appendix.

2.2.1. Effectiveness

The effectiveness of pyridostigmine was established on a VAS-scale with a range from 0 ("no effect") to 100 ("complete resolution of all symptoms") and on individual MG symptoms (ptosis, diplopia, hand weakness, arm weakness, leg weakness, neck weakness, facial weakness, dysarthria, difficulty chewing, dysphagia, dyspnea, fatigue) on a 3-point scale. In addition, patients were asked whether the effectiveness of pyridostigmine changed over the course of time.

2.2.2. Side effects

A list of 30 potential side effects of pyridostigmine was established. The list was adapted from the Dutch Summary of Product Characteristics of pyridostigmine with the accompanying patient information leaflet [14], and included: abdominal cramps, stomach ache, nausea, vomiting, diarrhea, flatulence, heartburn, excessive belching, urinary urgency, headache, increased salivation, increased lacrimation, hyperhidrosis, blurred vision, increased bronchial secretion, irregular heartbeat, slow heartbeat, chest pain, light-headedness, fainting, fatigue, blushing, hot flashes, flu-like symptoms (chills, runny nose, coughing up phlegm), tremor, muscle cramps, muscle weakness, muscle twitching, skin rash and hives. Additionally, patients were given the option to select "other" and specify in a text box.

For each symptom, the presence of the symptom was recorded dichotomously (yes/no); when patients selected "yes", the tolerability of the symptom was subsequently established on a 5-point scale (ranging from "not annoying" to "extremely annoying") and finally patients were asked whether this symptom had been a reason to lower/discontinue pyridostigmine.

All patients, regardless of current pyridostigmine use, were asked to fill out the list of potential side effects with respect to the past 7 days (with the discontinued group and the never group serving as control groups). In addition, the discontinued group were asked to fill out the list over the period they used the highest dose of pyridostigmine. If patients in the current group had used a higher dose in the past, they were asked to fill out the same list over that period as well.

An advisory board consisting of five MG patients assessed the content of the questionnaire and its comprehensibility before it was sent to participating patients. A copy of the questionnaire is available in Dutch upon reasonable request by a qualified researcher.

2.2.3. Net benefit

The net benefit was assessed by asking patients whether the positive effects of pyridostigmine outweigh the negative effects by means of a VAS scale ranging from 0 ("I felt much worse with pyridostigmine") to 100 ("I felt much better with pyridostigmine").

2.3. Statistical analysis

Only patients who fully completed the questionnaire were included in the analysis.

Continuous data are summarized with median (interquartile range) or mean (standard deviation) where appropriate. Comparisons were based on either student's T-test/one-way ANOVA (normal distribution) or Mann-Whitney/Kruskal Wallis (non-normal distribution). Categorical data are presented as proportions (%) and comparisons were assessed by either the Chi-Square test or Fisher's exact test. P values were considered significant when <0.05 . Bonferroni correction was applied to the analysis of the side effects. To determine the correlation between the dose of pyridostigmine and the number of reported side effects, Spearman's rank test was applied. Multivariate logistic regression was performed with currently using/discontinued

Table 1
Baseline characteristics.

| | Currently using (n=252) | Discontinued (n=149) | Never (n=9) | Overall (n=410) | Non-responders (n=232) [§] |
|---|-------------------------|----------------------|---------------|-----------------|-------------------------------------|
| Age at survey (years) | 59.8 (± 13.5) | 62.7 (± 12.6) | 71.0 (± 14.0) | 61.1 (± 13.3) | 63.7 (± 16.8) |
| Age at diagnosis (years)[†] | 48.0 (± 16.3) | 51.0 (± 16.0) | 60.1 (± 16.8) | 49.3 (± 16.3) | 50.7 (± 19.7) |
| Sex | | | | | |
| Male | 99 (39) | 84 (56) | 7 (78) | 190 (46) | 113 (49) |
| Female | 153 (61) | 65 (44) | 2 (22) | 220 (54) | 119 (51) |
| Myasthenia gravis duration (years)[†] | 9 (5–16) | 10 (4–15) | 10 (8–11) | 9 (4–16) | 9 (5–16) |
| Previous thymectomy[‡] | 103 (41) | 51 (34) | 1 (11) | 155 (38) | 70 (35) |
| Autoantibody class | | | | | |
| AChR | 154 (61) | 91 (61) | 5 (56) | 250 (61) | 130 (56) |
| MuSK | 3 (1) | 7 (5) | 0 | 10 (2) | 8 (3) |
| LRP4 | 1 (0) | 0 | 0 | 1 (0) | 1 (0) |
| Seronegative | 36 (14) | 18 (12) | 1 (11) | 55 (13) | 33 (14) |
| Unknown | 58 (23) | 33 (22) | 3 (33) | 94 (23) | 60 (26) |
| Current and previous MG treatments | | | | | |
| Distigmine | 12 (5) | 7 (5) | 0 | 19 (5) | - |
| Corticosteroids | 151 (60) | 110 (74) | 5 (56) | 266 (65) | - |
| Azathioprine | 135 (54) | 93 (62) | 3 (33) | 231 (56) | - |
| Rituximab | 14 (6) | 7 (5) | 0 | 21 (5) | - |
| Intravenous immunoglobulin therapy | 65 (26) | 48 (32) | 2 (22) | 115 (28) | - |
| Plasmapheresis | 44 (17) | 22 (15) | 1 (11) | 67 (16) | - |
| Other | 69 (27) | 27 (18) | 4 (44) | 100 (24) | - |
| No other medication | 55 (22) | 21 (14) | 1 (11) | 77 (19) | - |
| Dose | 300 (180–360) | 220 (90–360) | N.A. | 240 (180–360) | N.A. |
| Clinical symptoms at onset | | | | | |
| Ocular | 27 (11) | 29 (20) | 2 (22) | 58 (14) | 30 (13) |
| Generalized | 208 (83) | 112 (75) | 7 (78) | 327 (80) | 173 (75) |
| Unknown | 17 (7) | 8 (5) | 0 | 25 (6) | 29 (13) |

Categorical data are presented as n (%). Continuous data are presented as mean (± SD) for normal distributed data (age at survey and age at diagnosis) and median (IQR) for non-normal distributed data (myasthenia gravis duration and dose). The “non-responders” group consists of participants of the MG registry who did not complete the questionnaires for the current study. Percentages may not sum to 100 because of rounding.

[§] Data obtained from the Dutch-Belgian myasthenia patient registry.

[†] Missing values: responders (n=16), non-responders (n=13)

[‡] Missing values: non-responders (n=32)

as dependent variable and age at diagnosis, sex, autoantibody class and clinical symptoms at onset as covariates. Missing data of age at diagnosis, autoantibody class and clinical symptoms were imputed using multiple imputation (10 imputations) with the imputation model including all covariates and the outcome variable. Data was assumed to be missing at random. Data were independently analyzed in the multivariate logistic regression analyses, each with missing values imputed. Subsequently, data were pooled to give a single mean estimate and adjusted standard errors. Post-hoc analyses were performed to explore potential explanations for males discontinuing pyridostigmine more often than females. All statistical analyses were performed with IBM SPSS Statistics (version 25.0).

3. Results

3.1. Baseline characteristics

Out of 642 invited patients, 410 (64%) fully completed the survey. Nineteen (3%) patients partially completed the survey and were excluded from further analyses. Baseline data on the 232 non-responders were present in the registry; baseline characteristics did not differ between the responding and non-responding group. At the time of the survey, 61% of patients reported that they currently used pyridostigmine (the currently using group), 37% had discontinued pyridostigmine (the discontinued group) and 2% reported to never have used pyridostigmine (the never group).

Male patients discontinued pyridostigmine more often than female patients (44% vs. 30%, $p=0.001$). Patients with purely ocular MG symptoms at disease onset were more likely to discontinue

pyridostigmine than patients with generalized symptoms (52% vs. 35%, $p=0.024$). Patients in the discontinued group used prednisone ($p=0.005$) and “other medication” ($p=0.040$) more often than patients in the currently using group. In both the currently using group and the discontinued group, five percent of the patients reported the use of distigmine. There was no significant difference between the currently using, discontinued and never groups for age at diagnosis, myasthenia gravis duration, previous thymectomy and autoantibody class (Table 1). The current dose of pyridostigmine was higher in the currently using group (median 300, IQR 180–360) than the highest dose in the discontinued group (median 220, IQR 90–360) ($p=0.011$).

In the currently using group, 165 patients (65%) reported to have used a higher dose in the past. The most frequently reported reason for lowering the dose was that the higher dose of pyridostigmine was no longer required (43%). Twenty-five percent of all patients lowered the dose due to side effects and 17% of patients responded that the higher dose was not effective. The most common reason to discontinue pyridostigmine was that pyridostigmine had no effect (38%) or patients no longer needed it due to the start of other medication (34%). Twenty-six percent of all patients reported side effects as the main reason for ceasing pyridostigmine. Medication to control side effects was used in 20 percent of all patients, of whom 24% used diarrhea inhibitors such as loperamide, 56% used atropine, 18% used “other medication” and 13% responded “I don’t know”. Out of 14 patients that responded to have used “other medication”, proton pump inhibitors were most frequently reported ($n=7$).

The third group of “never used” was too small for detailed and meaningful analysis and therefore the data are only presented in Table 1.

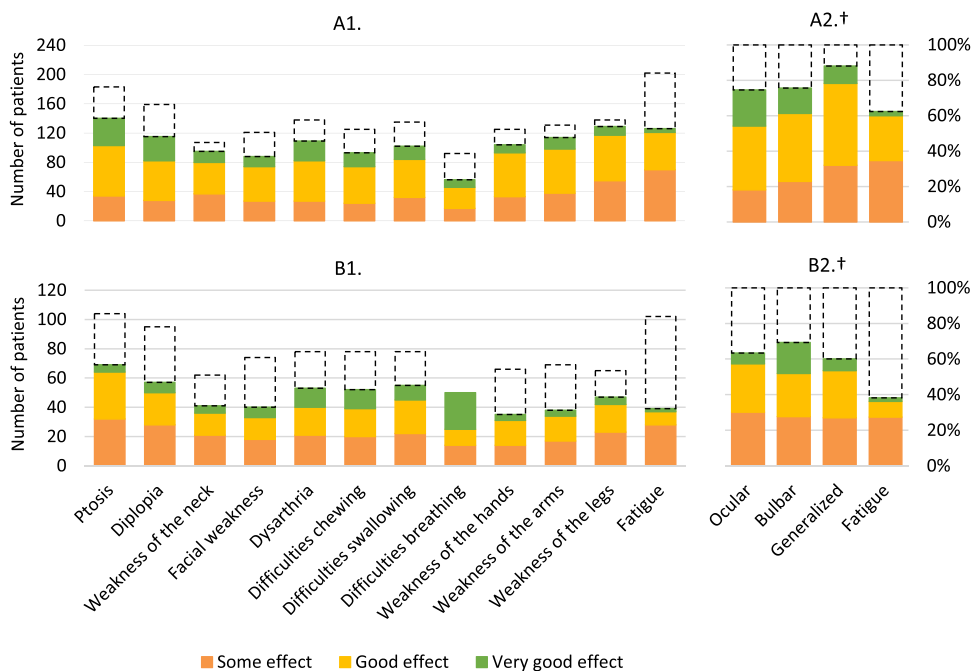


Fig. 1. Perceived effectiveness A1. Number of patients in the currently using group who reported to have effect of pyridostigmine per individual MG symptom A2. Percentage of patients in the currently using group who reported to have effect of pyridostigmine in subgroups: ocular, bulbar, generalized, fatigue. B1. Number of patients in the discontinued group who reported to have effect of pyridostigmine per individual MG symptom. B2. Percentage of patients in the discontinued group who reported to have effect of pyridostigmine in subgroups: ocular, bulbar, generalized, fatigue. The dotted line represents the number of patients who reported in the Dutch-Belgian Myasthenia Patient Registry to have the MG symptom in the first 6 months of the disease. †Ocular (ptosis + diplopia), bulbar (weakness of the neck, dysarthria, difficulties chewing/swallowing/breathing), generalized (weakness of the hands/arms/legs) and fatigue.

3.2. Effectiveness

Overall, patients reported a median effectiveness of 60 (IQR 28–78). Patients in the currently using group perceived a better effect of pyridostigmine (median 69.5, IQR 49–81.75) than patients in the discontinued group (median 35, IQR 4.5–66) ($p < 0.001$).

Fig. 1 shows the number of patients in the currently using and discontinued groups who reported that they experienced a positive effect of pyridostigmine for each individual MG symptom. Fatigue appeared to be less responsive to pyridostigmine than other symptoms, in both the currently using and discontinued groups. Patients in the discontinued group experienced less response on generalized MG symptoms than patients in the currently using group.

Fifty-five percent of patients in the currently using group and 21% of the patients in the discontinued group reported no change of the effect of pyridostigmine over the course of time. In the discontinued group, 23% stated that the initial effect was good, but diminished over time; 12% described that the initial effect was good, but increasing doses were required to accomplish the same effect.

3.3. Side effects

Ninety-one percent of the patients in the currently using group reported one or more side effects in the past seven days, compared with 54% of the patients in the control group (consisting of the discontinued and never groups). Patients in the currently using group reported a higher number of side effects over the past seven days (median 5, IQR 2–8) than patients in the control group (median 1, IQR 0–4) ($p < 0.001$). In the currently using group, the number of side effects was correlated with the pyridostigmine dose (Spearman's $R = 0.196$, $p = 0.002$), but not with disease duration ($p = 0.312$) or age at diagnosis ($p = 0.530$). In the discontinued group,

younger age was correlated with more side effects (Spearman's $R = -0.217$, $p = 0.010$).

Fig. 2 shows the percentage of patients reporting one or more side effects in the currently using group compared to the control group. Flatulence, urinary urgency, muscle cramps, blurred vision, hyperhidrosis, diarrhea, abdominal cramps, increased salivation, light-headedness and flu-like symptoms were reported significantly more frequently than in the control group. "Other" side effects that were reported more than once by patients were a runny nose ($n = 2$), insomnia ($n = 2$) and dyspnea ($n = 2$).

Patients in the discontinued group reported fatigue, flatulence, blurred vision, muscle weakness, urinary urgency, increased lacrimation and excessive belching more frequently than the currently using group (Supplementary Fig. 2 in the Appendix).

Diarrhea was the most frequent cause for discontinuation or lowering of the dose of pyridostigmine ($n = 42$); 32 patients discontinued or lowered the dose due to abdominal cramps; 24 patients discontinued or lowered the dose due to muscle cramps and muscle twitching (Fig. 3). In the group of patients who stopped pyridostigmine because of side effects, diarrhea, abdominal cramps and muscle twitching were most frequently considered a reason to discontinue.

Fig. 4 shows the severity of side effects in the currently using and discontinued group. Abdominal cramps and muscle cramps were considered to be more severe (moderately, very and extremely annoying) in the discontinued group than in the currently using group ($p = 0.008$ and $p = 0.003$ resp.).

3.4. Net benefit

Taken into account the perceived benefit and the burden of the side effects, patients reported a median net benefit of pyridostigmine of 65 on a VAS scale of 0 ("I felt much worse") to 100 ("I felt much better") (IQR 45–84). Patients in the currently

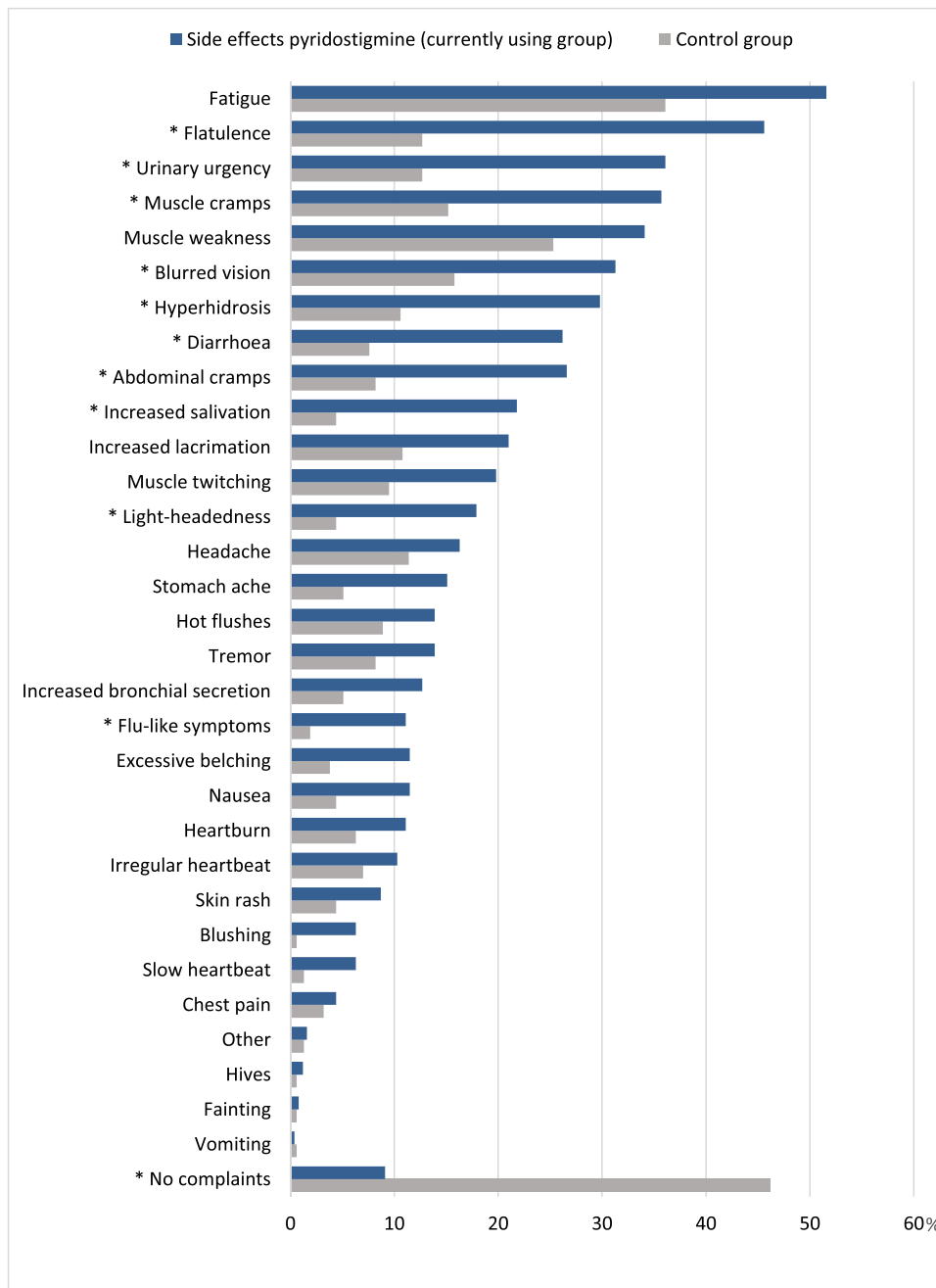


Fig. 2. Percentage side effects in the currently using group vs. controls.

* indicates a significant difference ($p < 0.0017$, Fisher's Exact test) between the currently using group and control group. The control group consists of patients from the discontinued and never group answering the question "Have you experienced one of the following symptoms over the last 7 days?".

using group perceived a better net benefit (median 73, IQR 87-53.25) than patients in the discontinued group (median 49, IQR 72.5-8.5) ($p < 0.001$), as shown in Fig. 5.

3.5. Factors associated with discontinuing pyridostigmine

Table 2 shows the results of the multivariate logistic regression analysis with current use/discontinued as dependent variable. Discontinuation of pyridostigmine was more likely in male patients (OR 1.781, 95% CI 1.125-2.819) and patients with MuSK antibodies (OR 4.127, 95% CI 1.194-14.269).

3.6. Post-hoc analyses of sex differences

After finding that male patients were more likely to stop using pyridostigmine, we performed a post-hoc comparison between men and women.

Female patients were younger than male patients at diagnosis (mean age 43.3 vs. 56.2 years, $p < 0.001$) and at the time of the survey (mean age 57.4 vs. 65.5 years, $p < 0.001$). Furthermore, females had a longer disease duration (median 12 years vs. 7 years, $p < 0.001$), had undergone thymectomy more often (48.6% vs. 25.2%, $p < 0.001$) and presented more frequently with generalized symptoms at disease onset (91.9% vs. 76.4%, $p < 0.001$) than males. There was no significant difference in autoantibody class, other

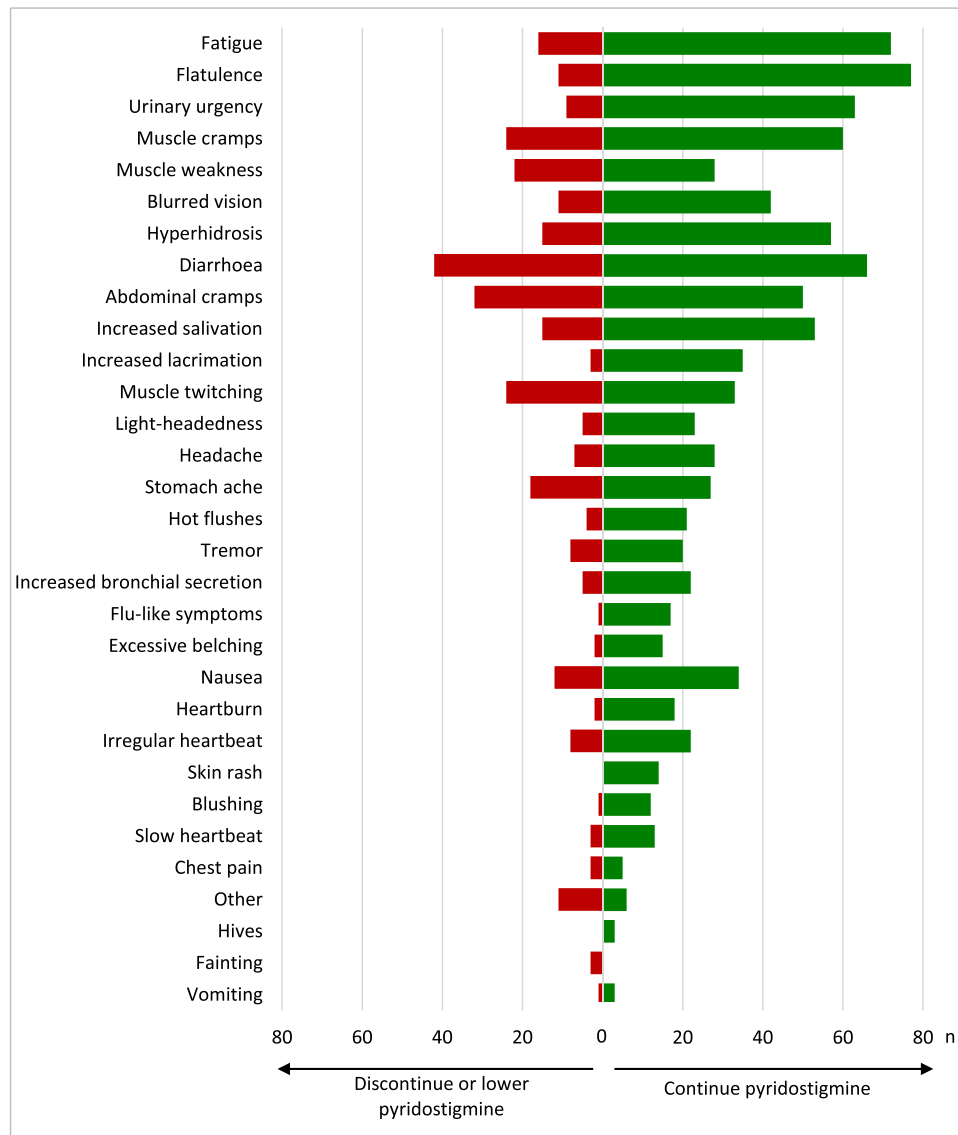


Fig. 3. Number of patients considering the side effect a reason to discontinue or lower the dose of pyridostigmine.

Table 2
Factors potentially associated with discontinuation of pyridostigmine.[†]

| Parameter | B | Std. Error | Sig. | Exp (B) | 95% Confidence interval Exp (B) | |
|-----------------------------------|-------|------------|-------|---------|------------------------------------|--------|
| | | | | | Lower | Upper |
| Age at diagnosis | 0.004 | 0.007 | 0.590 | 1.004 | 0.990 | 1.018 |
| Sex | | | | | | |
| Male | 0.577 | 0.234 | 0.014 | 1.771 | 1.125 | 2.819 |
| Female [‡] | - | - | - | - | - | - |
| Autoantibody class | | | | | | |
| AChR | 0.124 | 0.300 | 0.680 | 1.132 | 0.628 | 2.041 |
| MuSK | 1.417 | 0.630 | 0.025 | 4.127 | 1.194 | 14.269 |
| Seronegative [‡] | - | - | - | - | - | - |
| Clinical symptoms at onset | | | | | | |
| Ocular | 0.461 | 0.321 | 0.151 | 1.586 | 0.845 | 2.976 |
| Generalized [‡] | - | - | - | - | - | - |

[†] Pooled estimates of multivariate logistic regression after multiple imputation

[‡] Reference group for statistical comparison

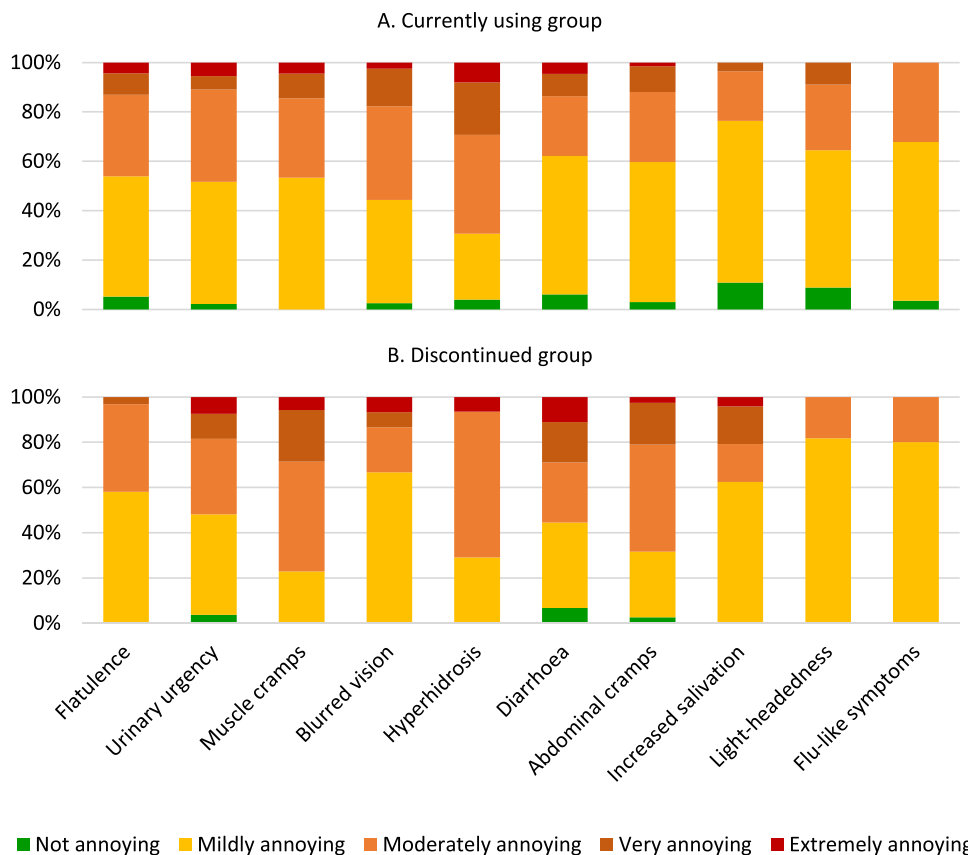


Fig. 4. Severity of side effects in A. the currently using group and B. the discontinued group Only the side effects occurring significantly more often in the currently using group than in the control group as depicted in Fig. 2, are shown.

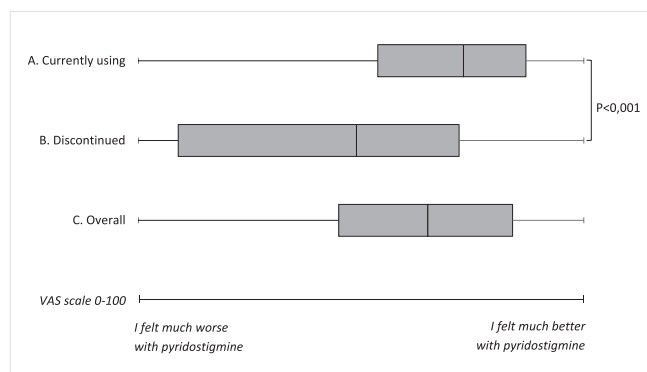


Fig. 5. Perceived net benefit of pyridostigmine on VAS-scale (0-100) for A. currently using, B. discontinued and C. overall group. Box plot indicates 25th and 75th percentile, middle vertical line represents the median response. The perceived net benefit was higher in the currently using group than in the discontinued group ($P < 0.001$, Mann-Whitney U test).

medication use and pyridostigmine dose between male and female patients.

In the entire study population, the experienced net benefit was the same in male (median 63, IQR 46.5-83) and female patients (median 66, IQR 43.25-84.75). Furthermore, there was no significant difference between male and female patients for the perceived effectiveness (males: median 55, IQR 21-80.5, females: 62, IQR 39.25-78).

With regards to side effects, male patients reported more frequently to have “no complaints” compared to female patients

($p < 0.0017$). Fatigue, hyperhidrosis, abdominal cramps, hot flushes and an irregular heartbeat were more frequently reported by females than by males ($p < 0.0017$) (Fig. 6).

No significant differences were found between male and female patients in reasons for discontinuing pyridostigmine. In the discontinued group, 47 (42%) male patients responded that pyridostigmine was no longer needed due to the start of other medication, compared to 26 (32%) female patients ($p = 0.069$). Thirty-two percent of female patients reported side effects as the main reason for discontinuing pyridostigmine, compared to 23% of male patients ($p = 0.224$).

4. Discussion

This study reports a comprehensive assessment of pyridostigmine use, its effect on symptoms, side effects and its net benefit, in a very large, well-defined and representative sample of the Dutch MG population. We show that virtually all MG patients have used pyridostigmine at some point in their disease, and that approximately two thirds (62%) continue to use it. The net benefit and effectiveness are moderate: only a small number of patients reported that pyridostigmine had a very good effect on their symptoms. Side effects are frequent: 91% of all patients currently using pyridostigmine reported at least one side effect (vs. 54% in the control group). Most frequently reported side effects were gastro-intestinal symptoms (flatulence, diarrhea and abdominal cramps), urinary urgency, muscle cramps, blurred vision, hyperhidrosis, increased salivation, light-headedness and flu-like symptoms. The reasons for discontinuing pyridostigmine were varied: 38% stated it was not effective (anymore) and 34%

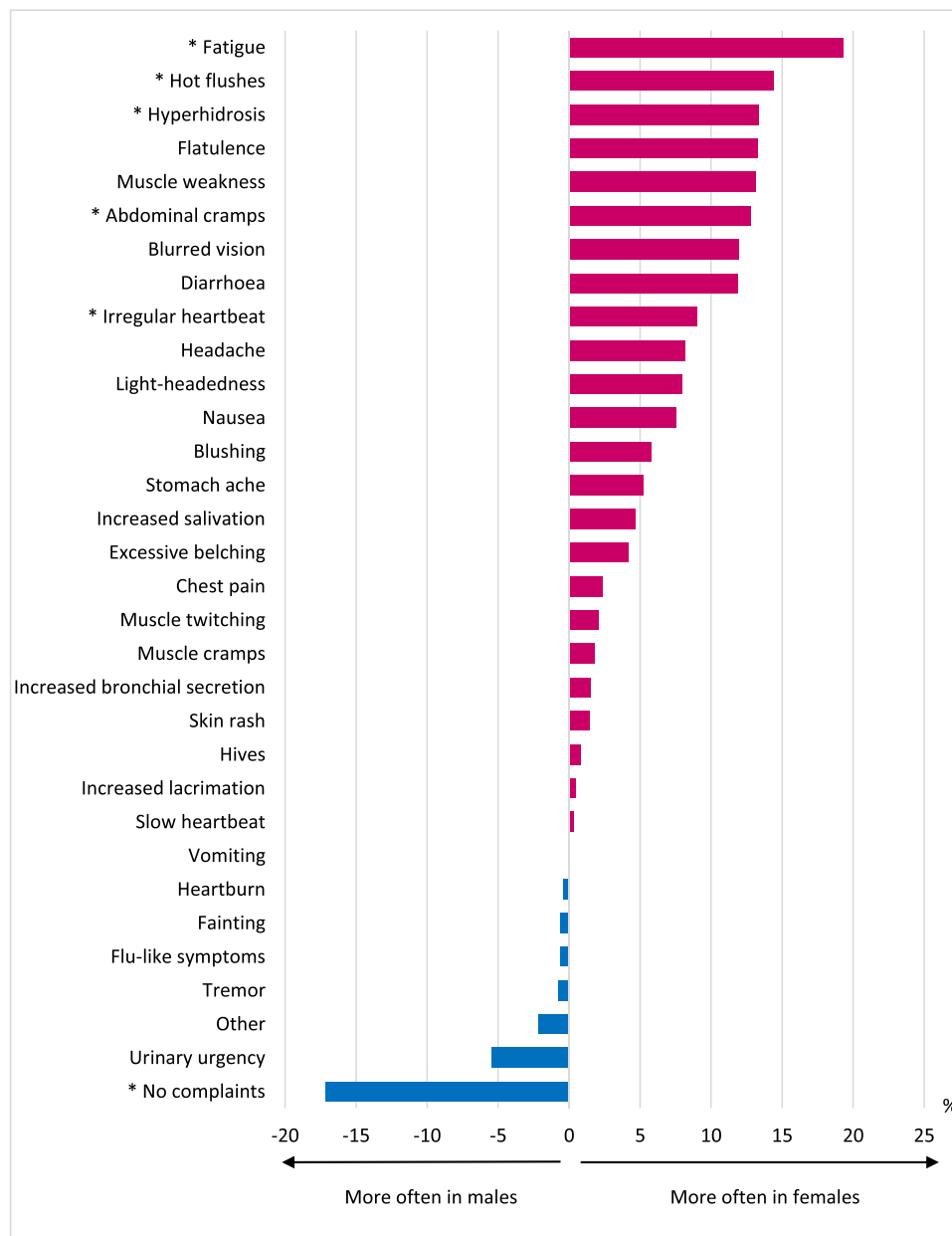


Fig. 6. Difference in occurrence of side effects between male and female patients (%). *indicates a significant difference ($p < 0.0017$, Fisher's exact test) between males and females.

reported that it was no longer needed due to the start of other medication. Twenty-six percent reported side effects as the main reason for discontinuation. Within the latter group, diarrhea, abdominal cramps and muscle twitching were the most frequently cited reasons to discontinue pyridostigmine.

Patients with MuSK antibodies were more likely to discontinue pyridostigmine. This finding is in line with previous studies showing that acetylcholinesterase inhibitors are less effective in patients with MuSK antibodies and that these patients experience more side effects [15–17]. Surprisingly, male patients were also more likely to stop using pyridostigmine, which may be explained by the fact that female patients more frequently have severe or refractory MG [18,19] and male patients appear to respond better to standard care than female patients [20]. This is supported by our post-hoc analysis showing that male patients were more likely than females to report “it was no longer needed due to the start of other medication” as the main reason for discontinuing

pyridostigmine, although this difference did not reach statistical significance (probably due to small numbers). Female patients reported side effects more frequently than males. This is in line with literature reporting that female patients are 50 to 75 percent more likely to experience an adverse drug reaction than males [21], probably due to sex-based differences in pharmacokinetics and pharmacodynamics [22].

One of the main strengths of our study is the large patient sample ($n=642$) with a relatively high response rate of 64%. This response rate demonstrates the importance of this topic to MG patients. The digital format of the questionnaire allowed for standardized data collection, minimizing missing data. The burden of participation was minimized by the dynamic design of the questionnaire, so that patients were only required to fill out questions applicable to their own situation.

A limitation of this study is its observational design. First, the sampling method, consisting of an email invitation to all

MG patients in the Dutch-Belgian MG registry, may have led to a selection bias. However, given the absence of differences in baseline characteristics between patients who filled out the survey and patients who did not respond, this limitation appears to be minimal. Second, this study does not provide information on the causality of the reported side effects and the use of pyridostigmine. Third, recall bias may have affected results, especially for patients who were asked to report side effects for medication that was discontinued several years ago. Finally, all collected data on net benefit, effectiveness and side effects were patient reported and therefore cannot be related to commonly used quantitative outcome measures such as the QMG and the MG-ADL. Although the observational design brings about some limitations, it is the most common way of obtaining evidence on effectiveness and side effects for medication that has gained market approval.

Another limitation in this study is that patients were actively queried about a list of 30 potential side effects. It has been shown that patients report more side effects when asked to check off a list, than when they are asked to spontaneously name them [23]. We tried to minimize this effect by comparing the side effect profile in the currently using group to the reported symptoms in a control group, which consisted of patients not using pyridostigmine in the period queried (the past seven days).

It may have been challenging for patients (and physicians) to distinguish whether their muscle weakness or fatigue were caused by MG or by pyridostigmine. However, as our results show that the reported frequency of fatigue and muscle weakness did not differ significantly between the group currently using pyridostigmine and the group not using pyridostigmine, we believe that the potential inability to distinguish the causes of these symptoms did not affect the main conclusions of this paper.

In this cross-sectional questionnaire study, longitudinal data on comorbidity and comedication was not available. It is possible that patients who stopped using pyridostigmine were more susceptible to side effects due to certain comorbidities or comedications.

Remarkably, only a small number of patients experienced a very good effect of pyridostigmine on their symptoms. This is surprising since 19% report using pyridostigmine as monotherapy and are apparently satisfied with its effect. The use of distigmine was somewhat more common than expected. It appears to have been prescribed by a single neurologist in the Netherlands (now retired) and used mainly as an add-on to pyridostigmine. Medication to treat side effects was used in 20% of all patients. The Dutch national myasthenia gravis consensus guideline contains the following recommendation: “consider starting atropine in patients with muscarinic side effects such as abdominal cramps and diarrhea and hypersalivation”, leaving considerable leeway for different traditions and habits among treating neurologists in the approach towards side effects. This may have influenced the prevalence and severity of the observed side effects. There is no influence of reimbursements on the prescription of these medications since all medications are fully reimbursed in the Netherlands.

Fatigue is a frequent and disabling symptom of MG [24]. Immunomodulatory drugs might improve fatigue, as suggested by a small number of studies. In our study, pyridostigmine resulted in only a limited improvement of fatigue. This suggests that the contribution of neuromuscular transmission disturbances to the development of fatigue is limited. Indeed, previous studies have suggested that the pathophysiology of fatigue is likely multifactorial [25].

In contrast to two previous small studies [26,27] and expert opinion [28–30], we found no difference on the patient’ reported effectiveness on ptosis and diplopia compared to generalized weakness.

Twenty-six percent of all patients reported side effects as the main reason for lowering or discontinuing pyridostigmine, which is higher than reported in previous studies [11,12].

It has been hypothesized that the risk of cholinergic side effects increases after prolonged treatment with pyridostigmine or with increasing age [12]. In our study, we found no significant correlation between the number and severity of side effects and age or disease duration. Moreover, in the discontinued group, younger patients reported more side effects than older patients. We therefore recommend that pyridostigmine be used in all patients regardless of age or disease duration.

5. Conclusion

Almost all international guidelines recommend pyridostigmine as the first step in the treatment of MG [1,31,32]. Our data do not support a change in these guidelines, although the observed effectiveness was relatively modest and side effects occurred frequently. Nonetheless, pyridostigmine remains a drug that is readily available at low cost and has a very favorable long term safety profile [33]. In addition, the majority of patients do experience a positive effect on their symptoms, and potential side effects are generally mild and reversible. However, our results can be used to guide shared decision making, prior to starting symptomatic treatment for MG, as they provide a nuanced quantification of its expected effectiveness and side effects. To further aid patient education, we have summarized the main results of this study in an easy-to-read patient leaflet that can be handed out with the prescription (Supplementary Fig. 3 in the Appendix).

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Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.nmd.2022.09.002](https://doi.org/10.1016/j.nmd.2022.09.002).

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