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Adverse Side Effects Associated with Corticosteroid Therapy: A Study in 39 Patients with Generalized Myasthenia Gravis

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Background: The tolerability of high-dose oral corticosteroids in patients with generalized myasthenia gravis (gMG) has not been systematically assessed. We evaluated adverse side effects (ASEs) of corticosteroid treatment in patients with gMG.





Material/Methods: Retrospective analysis was conducted of ASEs reported as being related to corticosteroid treatment in 39 patients with gMG who were treated with oral corticosteroids for ≥ 1 year.

Results: Median (interquartile range [IQR]) age was 60 (21) years, 53.8% of patients were women, and 66.7% were aged ≤ 65 years. Median (IQR) prednisone treatment duration was 14 (2) months; median (IQR) daily dose was 40 (15) mg. The median number of ASEs reported as corticosteroid-related was 2/patient (IQR, 1). Pre-diabetes and weight gain were most common (each 43.6% of patients). Bruising, insomnia, and osteoporosis were more prevalent in patients aged >65 years, while irritability, osteopenia, and pre-diabetes were more common in patients aged ≤ 65 years, although differences were not statistically significant. Irritability and weight gain were more prevalent in women ($P=0.010$ for irritability); osteoporosis and pre-diabetes more common in men ($P=0.015$ for osteoporosis). ASEs were generally more common in the high-dose prednisone group (>30 mg/day), but were only statistically significant for irritability ($P=0.001$).

Conclusions: Corticosteroid-related ASEs were common in patients with gMG. Some of these ASEs can have serious medical consequences, and certain ASEs appeared to be associated with specific patient characteristics. Demographics and comorbidities of patients with gMG must be carefully considered before corticosteroid initiation. Potential ASEs, such as unanticipated osteoporosis in men, require extra vigilance.

Keywords: **Myasthenia Gravis • Prednisone • Risk Factors • Safety • Steroids**

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Background

Myasthenia gravis (MG) is a rare autoimmune disorder caused by autoantibodies that target elements of the neuromuscular junction [1,2]. The resulting muscle weakness can be localized (ocular or oculobulbar), but in most cases (approximately 85%) it is generalized, affecting the trunk and proximal muscles of the extremities [2]. Most patients with MG have autoantibodies against the acetylcholine receptor (AChR) [1]. Other autoantibodies involved in this condition include those targeting muscle-specific tyrosine kinase, agrin, and low-density lipoprotein receptor-related protein 4 [1,3]. The estimated prevalence and incidence of MG are 78 cases per million persons and 5.3 cases per million person-years, respectively, although results vary considerably between studies [4].

Acetylcholinesterase (AChE) inhibitors are the standard of care for the symptomatic treatment for MG and are supplemented with immunomodulating agents as necessary [3]. The latter include corticosteroids, azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, and tacrolimus [3]. More recent additions include the monoclonal antibodies rituximab (anti-CD20 antibody) and eculizumab (a terminal complement inhibitor) [5-7]. Plasma exchange and intravenous immunoglobulin are frequently used to manage acute exacerbations of MG [3]. Of all these treatments, only eculizumab [8] and pyridostigmine (an AChE inhibitor) [9] are licensed in the United States to treat MG.

Corticosteroids have been used for their anti-inflammatory and immunosuppressant effects in a wide range of conditions since the 1940s [10]. A number of small studies in the 1950s and 60s described their beneficial effects in patients with MG, and their use was associated with a reduction in MG-related mortality to less than 10% from the 1960s onward, compared with 30% in 1955 [11,12]. Steroids' immunosuppressive mechanism of action, relatively fast onset of action (compared with the slow onset of alternative immunosuppressants used in this setting), wide availability, low cost, and, as highlighted above, extensive track record across disciplines account for their continued place in therapy [10,13-15]. However, there are very few controlled studies evaluating their efficacy in MG [13]. Despite this, international consensus guidelines for the management of MG advocate the use of corticosteroids (or non-steroidal immunosuppressants) in all patients who do not meet treatment goals after an adequate trial of the AChE inhibitor pyridostigmine [16]. They also recommend gradual tapering of the corticosteroid dose once treatment goals are reached, noting that long-term use of low-dose corticosteroids can be appropriate in some patients [16].

Given their widespread use, the side effect profile of corticosteroids is well established. Adverse side effects (ASEs) range from mild to serious and affect a diverse range of body

systems, including musculoskeletal (eg, osteoporosis and myopathy), metabolic and endocrine (eg, hyperglycemia, Cushing syndrome, weight gain, and hirsutism), immunologic (eg, infections), cardiovascular (eg, hypertension and arrhythmias), gastrointestinal (eg, gastric ulcers and bleeding), neuropsychiatric (eg, altered mood and psychosis), ophthalmologic (eg, glaucoma and cataract) and laboratory abnormalities (eg, hypokalemia) [15,17]. Corticosteroid-related ASEs, particularly in patients on high-dose and/or long-term regimens, can have a negative impact on patients' quality of life [12] and require monitoring for the duration of steroid treatment [15]. Age, comorbidities, and concomitant use of immunosuppressants are other risk factors for corticosteroid-related ASEs [15].

Despite, or perhaps as a consequence of, the well-established ASE profile of corticosteroids, there is a lack of systematic evaluation of their tolerability in patients with MG. In retrospective long-term studies conducted in the 1980s and 90s [18-21], at least one ASE was observed in 52% of patients with MG treated with corticosteroids, including osteoporosis, diabetes mellitus, infection, and gastric ulcers [13]. More recently, small studies have evaluated the safety profile of corticosteroids in patients with ocular MG [22,23]. One of these followed 83 patients for a median of 58 months and documented a low rate of serious complications [22]; however, the median dose was tapered to 5 mg/day following initial treatment with higher doses. The authors highlighted that patients should be monitored to detect "relatively common but less serious complications" [22]. Another recent, large retrospective study that evaluated infections in patients with neuromuscular autoimmune conditions – including 358 corticosteroid-treated patients with MG – found a significant association between infection and corticosteroid use in a multivariate analysis, as well as an infection rate of 19.3% in patients with MG [24].

The objectives of the current study were to describe ASEs reported as being corticosteroid-related in a cohort of patients with MG and to determine potential risk factors for these ASEs.

Material and Methods

This was a retrospective analysis of data from patients with MG (aged ≥ 18 years) who were treated at a single center in the United States between January 2014 and December 2015. Patients were eligible for inclusion if they had been diagnosed with generalized MG (gMG), namely weakness of non-ocular muscles with or without ocular muscle weakness (Myasthenia Gravis Foundation of America [MGFA] Classes 2-4), had been treated with oral corticosteroids for their gMG symptoms for ≥ 1 year, and had ≥ 1 year of follow-up. They also had to have a decremental response on low-frequency repetitive nerve stimulation or abnormal jitter on single-fiber electromyography.

Table 1. Individual patient data.

Patient no.	Age (years)	Sex	Race	Daily prednisone dose (mg)*	Side effect(s)**	Concomitant treatments for MG
1	26	F	W	40	Pre-diabetes, insomnia, acne, weight gain 40 lb	PS, MMF
2	30	F	W	30	Insomnia, acne, pedal edema	PS, MMF
3	38	F	W	10	Irritability	PS
4	65	F	W	30	Pre-diabetes, irritability	PS, Aza
5	70	M	W	40	Osteoporosis, insomnia	PS, MMF
6	72	F	W	45	Weight gain 30 lb	PS, MMF
7	55	M	W	40	Weight gain 35 lb, diabetes	PS, MMF, IVIg q4 weeks
8	60	M	W	35	Pre-diabetes, osteopenia	PS, Aza
9	65	M	W	50	Diabetes, osteoporosis	PS, MMF, IVIg q3 weeks
10	62	F	W	30	Insomnia, weight gain 20 lb, pedal edema	PS, MMF
11	64	F	W	30	Bruising, irritability	MMF
12	50	M	AA	50	Osteoporosis, bruises, pre-diabetes, recurrent infections	PS, MMF, IVIg q4 weeks
13	20	F	W	20	Weight gain 15 lb, acne, striae, bruises	PS, MMF
14	24	F	W	30	Insomnia, irritability, weight gain 15 lb	PS, MMF
15	80	M	W	50	Pedal edema, bruises, worsened diabetes requiring insulin	PS, MMF, IVIg q4 weeks
16	26	M	W	40	Pre-diabetes, weight gain 35 lb	MMF
17	55	M	W	30	Pre-diabetes	PS, MMF
18	57	F	W	45	Hypertension, weight gain 20 lb, pedal edema	PS, MMF
19	67	F	H	35	Bruising, pre-diabetes	PS, MMF
20	68	F	W	40	Recurrent upper respiratory tract infection, weight gain 40 lb	PS, MMF
21	69	M	W	40	Weight gain 35 lb	PS, MMF
22	70	M	W	30	Pre-diabetes	PS, MMF
23	77	M	W	40	Osteopenia, bruises	PS, MMF, IVIg q4 weeks
24	68	M	W	35	Pre-diabetes, insomnia	PS, MMF
25	69	F	W	30	Irritability, weight gain 20 lb	PS, MMF
26	54	M	AA	50	Pre-diabetes, weight gain 30 lb	PS, MMF
27	43	F	H	30	Weight gain 15 lb	PS, Aza
28	58	M	W	40	Pre-diabetes, osteopenia, pedal edema	PS, MMF
29	60	F	W	40	Pre-diabetes, osteopenia	PS, MMF
30	64	F	W	30	Pre-diabetes, osteopenia, insomnia, irritable mood	PS, MMF
31	43	F	W	10	Irritability, striae	PS
32	48	M	W	15	Pre-diabetes	PS

Table 1 continued. Individual patient data.

Patient no.	Age (years)	Sex	Race	Daily prednisone dose (mg)*	Side effect(s)**	Concomitant treatments for MG
33	54	F	W	30	Pre-diabetes, pedal edema	PS, IVIg q4 weeks
34	69	M	W	30	Weight gain 20 lb, insomnia	PS, MMF
35	72	M	W	50	Osteoporosis, pedal edema	PS, MMF
36	61	F	W	50	Pre-diabetes, osteopenia, pedal edema	PS, MMF
37	48	F	W	45	Osteopenia, weight gain 35 lb	PS, MMF, IVIg q4 weeks
38	78	M	W	50	Pre-diabetes, bruises, osteoporosis, pedal edema, weight gain 20 lb, insomnia	PS, Aza
39	59	F	W	40	Weight gain 40 lb, recurrent skin infections, bruises	PS, MMF

* Based on the last recorded value in the patient's medical charts; ** weight gain was rounded to the nearest 5 lb. AA – African-American; Aza – azathioprine; F – female; H – Hispanic; IVIg – intravenous immunoglobulin; M – male; PS – pyridostigmine; q – every; W – white.

Patients with muscle-specific tyrosine kinase antibodies were not included, as prednisone is not routinely the treatment of choice for these patients at our clinic.

The following information was extracted from each patient's electronic medical record: sex, age, and race; MGFA class; pre-existing comorbidities; prednisone dose; AEs that the treating physician judged to be steroid related (based on their own clinical experience and knowledge); other medications for MG; and Myasthenia Gravis – Activities of Daily Living (MG-ADL) scores. Non-fixed variables were based on the last recorded value in the patient's chart. Differences in steroid doses according to sex (male vs female) and age (≤ 65 vs >65 years) were analyzed using a Mann-Whitney test.

Steroid-related AEs were summarized in aggregate and subdivided according to patient age (≤ 65 vs >65 years), sex (male vs female), and steroid dose [25] (moderate [≤ 30 mg/day] vs high [>30 mg/day]). As the prednisone dose was not normally distributed, differences in the incidence of each AE according to age, sex, and steroid dose were analyzed using Fisher's exact test. No adjustments were made for multiplicity.

The study was approved by the University of Missouri Independent Review Board (approval number 2019523 MU). Patient consent was not required for this retrospective chart review.

Results

Data were obtained from 39 patients, of whom 21 (53.8%) were female; the median age (interquartile range [IQR]) was

60 (21) years, 26 (66.7%) patients were aged ≤ 65 years, and 35 (89.7%) were white. Individual patient data are provided in **Table 1**, and a summary of patients' clinical characteristics is presented in **Table 2**. Overall, 35 patients (89.7%) had AChR antibody-positive MG and at the time of data collection, over 60% were categorized as MGFA disease class 2A or 2B (ie, they had mild weakness of the non-ocular muscles \pm ocular weakness of any severity). Overall, 37 patients (94.9%) had comorbid conditions and 25 (64.1%) had ≥ 2 comorbidities (**Table 2**). The most common comorbid conditions were hypertension and chronic obstructive pulmonary disease. The median (IQR) MG-ADL score was 7 (1) and the range was 2 to 11 (out of a maximum possible score of 24).

The mean duration of prednisone treatment was 14.3 months (median, 14 months; IQR, 2 months) and the mean daily dose was 36.0 mg (median, 40 mg; range 10–50 mg; IQR 15 mg). Median (IQR) daily doses in non-elderly (≤ 65 years) and elderly (>65 years) patients were 32.5 (10) mg and 40 (10) mg, respectively ($P=0.178$). In men and women, the median (IQR) daily doses were 40 (15) mg and 30 (10) mg, respectively ($P=0.035$).

Corticosteroid-related AEs in the overall patient population are summarized in **Figure 1**. All patients experienced at least one corticosteroid-related AE; the mean number of AEs per patient was 2.3 (median, 2; IQR, 1); the greatest number of AEs experienced by an individual patient was six. AEs were reported at all prednisone doses, including 10 mg. Pre-diabetes (ie, elevated glucose concentration, but not high enough to be diagnosed with diabetes) was one of the most common AEs, reported in 17 patients (43.6%); in addition, diabetes was reported in two patients, and worsening diabetes (monitored via

Table 2. Summary of patients' clinical characteristics* (n=39).

Characteristic	No. of patients (%)
Positive AChR antibody test result	35 (89.7)
MGFA class	
2A	14 (35.9)
2B	13 (33.3)
3A	8 (20.5)
3B	3 (7.7)
4A	1 (2.6)
Pre-existing comorbidities	
Anemia	2 (5.1)
Asthma	8 (20.5)
Atopic dermatitis	1 (2.6)
Benign prostatic hypertrophy	1 (2.6)
COPD	16 (41.0)
Coronary artery disease	2 (5.1)
Coronary heart disease	1 (2.6)
Depression	4 (10.3)
Diabetes	5 (12.8)
Gastroesophageal reflux disease	8 (20.5)
Hyperlipidemia	4 (10.3)
Hypertension	22 (56.4)
Hypothyroidism	6 (15.4)
Lung cancer	1 (2.6)
Pre-diabetes	1 (2.6)
Prostate cancer	1 (2.6)
Stroke	4 (10.3)
Vitamin D deficiency	1 (2.6)
None	2 (5.1)
Number of comorbidities	
None	2 (5.1)
1	12 (30.8)
2	9 (23.1)
3	9 (23.1)
≥4	7 (17.9)
MG-ADL score	
2	3 (7.7)
3	0
4	0
5	1 (2.6)
6	4 (10.3)
7	11 (28.2)
8	15 (38.5)
9	3 (7.7)
10	1 (2.6)
11	1 (2.6)

* Based on the last recorded value in the patient's medical charts. AChR – acetylcholine receptor; COPD – chronic obstructive pulmonary disease; MG-ADL – Myasthenia Gravis – Activities of Daily Living; MGFA – Myasthenia Gravis Foundation of America.

HbA1c concentrations) was reported in one patient. Weight gain was also reported in 17 patients (43.6%); in over half of these cases, weight gain was ≥30 pounds (13.6 kg).

Corticosteroid-related AEs according to age, sex, and prednisone dose are shown in **Figure 2A-2C**. Bruising, insomnia, and osteoporosis were more prevalent in elderly patients (those aged >65 years), while irritability, osteopenia, and pre-diabetes were more prevalent in younger patients (aged ≤65 years), although the differences were not statistically significant. In women, the incidence of irritability was significantly higher than in men ($P=0.010$), while the incidence of weight gain was numerically higher. In men, the incidence of osteoporosis was significantly higher than in women ($P=0.015$), and the incidence of pre-diabetes was numerically higher. AEs were generally more common in the high-dose prednisone group, with the exception of insomnia and irritability, which were more frequent with the low dose; only the incidence of irritability was statistically significantly higher in the lower-dose group.

Discussion

Although the general AEs profile of corticosteroids is well established, there is a lack of published information on their tolerability in patients with MG. The current study provides some interesting insights into corticosteroid-related AEs in a cohort of patients with gMG treated in routine clinical practice. All patients experienced at least one AE commonly associated with corticosteroids; the mean number of such AEs per patient was 2.3, with one patient having six AEs. The ubiquitous nature of AEs in this population indicates that healthcare providers should be mindful when prescribing steroids for prolonged periods. It is also interesting that infection, a well-recognized potential consequence of corticosteroid treatment, was reported in only 3/39 patients (7.7%), a much lower incidence than that observed in the retrospective study by Prior et al (69/358, 19.3%), which was specifically designed to evaluate infection over a 10-year period [24].

Age is a risk factor for corticosteroid-related AEs and in the current study, some AEs (bruising, insomnia, and osteoporosis) were numerically more common in older (>65 years) than in younger patients (≤65 years). However, other AEs (irritability, osteopenia, and pre-diabetes) were numerically more common in the younger subgroup. Whether these differences relate to the median prednisone dose being numerically higher in the older subgroup (40 mg vs 32.5 mg in younger patients) is difficult to say. Perhaps one of the most unexpected findings was the difference in the type of corticosteroid-related AEs between men and women. Osteoporosis was reported only in men, whereas irritability was reported only in women. Pre-diabetes was numerically more common in men than

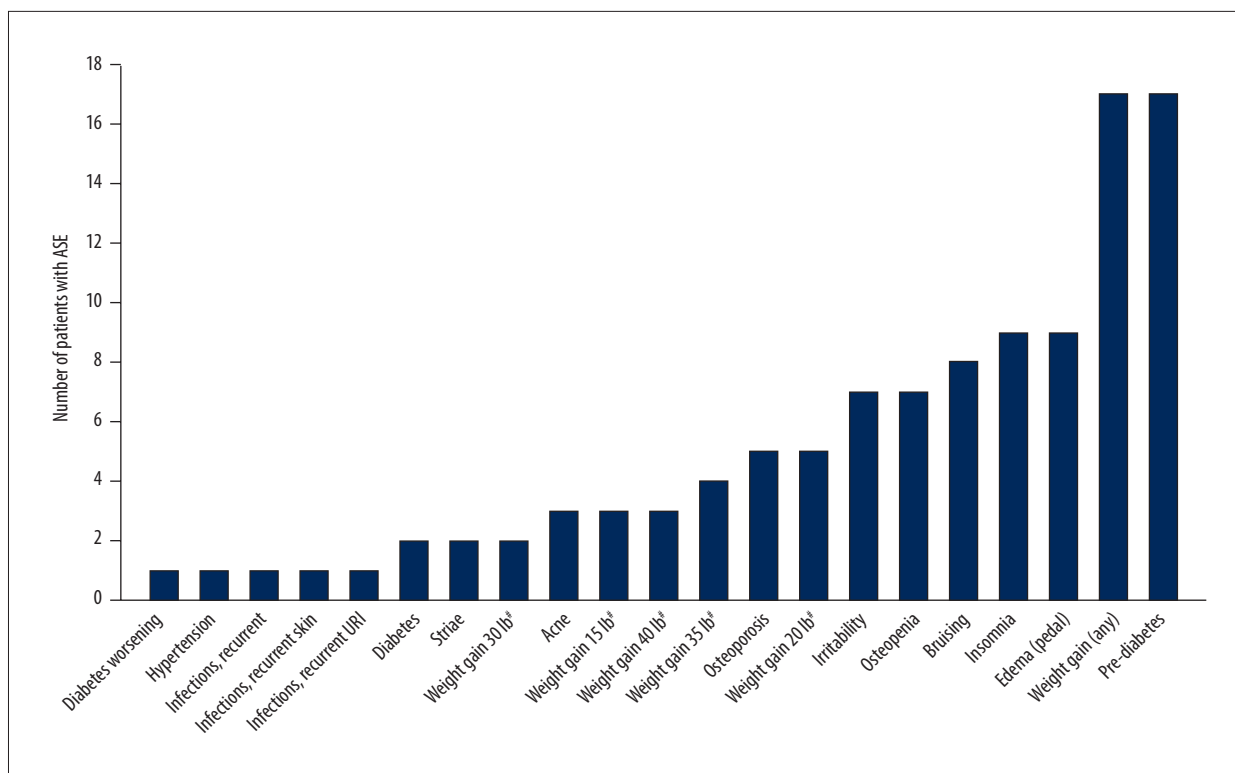


Figure 1. Corticosteroid-related AEs reported in patients with myasthenia gravis (n=39). * Weight gain was rounded to the nearest 5 lb. ASE – adverse side effect; URI – upper respiratory tract infection. Figure was created using Adobe Illustrator version 25.3.1 (Adobe, Inc.).

women, while weight gain was numerically more common in women than men. The finding that osteoporosis was reported as a corticosteroid-related ASE in men but not in women is interesting. It may reflect an ASE attribution bias, but warrants further investigation in a larger study in which other possible confounding factors are controlled for. If supported, it would suggest the need to maintain a higher index of suspicion for osteoporosis in male patients treated with corticosteroids. Most patients in the study were treated with high prednisone doses (≥ 30 mg/day), and, as expected, the frequency of most ASEs was numerically greater in these patients than in those treated with lower doses. Exceptions were insomnia and irritability; the reasons for this are unclear, although for irritability, it may reflect the preponderance in younger patients, who were treated with lower doses. The possibility of confounding inter-relationships between age, sex, and dose was not controlled for in the statistical analysis. The relatively small number of patients in the current study means that the results should be interpreted with caution. The small sample number may also have compromised the ability to detect statistically significant differences between subgroups.

It is anticipated that some of the ASEs identified in the current study (eg, insomnia, irritability, and weight gain) could affect patients' quality of life [26-28]. In an online survey of

approximately 600 patients being treated with glucocorticoids for various conditions, weight gain, insomnia, and 'moon face' (a symptom of Cushing syndrome) were ranked as the most important ASEs [29]. Other ASEs identified in the present study could have potentially serious consequences (eg, weight gain, pre-diabetes/diabetes, and osteoporosis) [30-32]. Weight gain and pre-diabetes are of particular concern given their prevalence in the current sample, the magnitude of the observed weight gain, pre-existing risk factors, including hypertension, hyperlipidemia, and coronary artery disease, in some of the patients, and their well-recognized complications [33,34].

Various strategies have been used to manage the ASEs of corticosteroids. These include alternate-day treatment [12,13], dose tapering/de-escalation [12,16], and concomitant use of steroid-sparing treatments [12,14,35]. In a small, single-blind, 2-year study in patients with gMG, methotrexate had greater steroid-sparing effects than did azathioprine [35], but it is notable that methotrexate failed to show a steroid-sparing effect in a double-blind, placebo-controlled, 1-year study [36], although the lack of statistical power and short duration of the study have led to the conclusions being questioned [37]. Results of small case series suggest that eculizumab [38] and cyclosporine [39] may also have steroid-sparing effects. The beneficial effects of eculizumab have been confirmed in a recent analysis of data

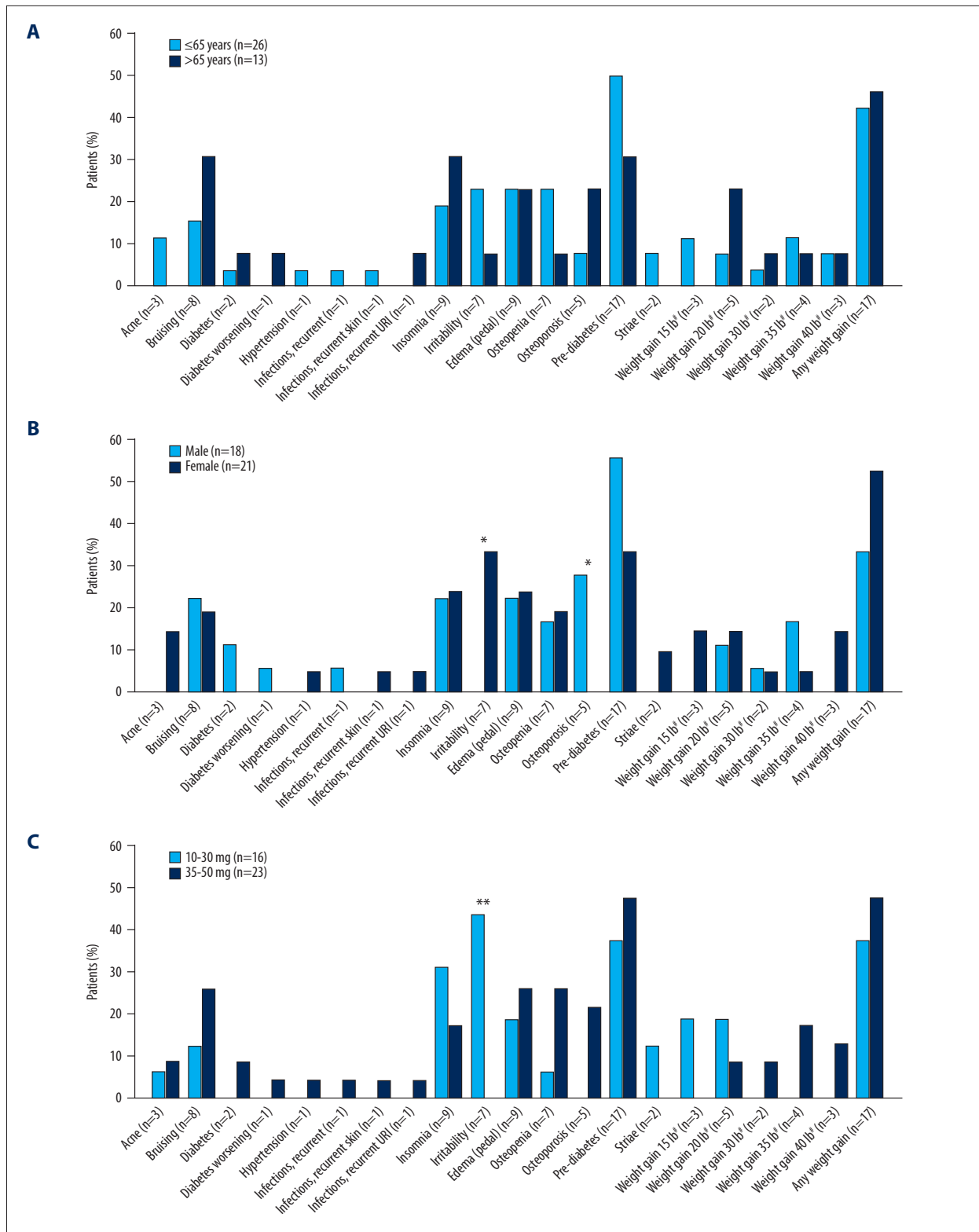


Figure 2. Corticosteroid-related adverse side effects in patients with myasthenia gravis according to (A) age, (B) sex, and (C) prednisone daily dose. n values on x axis represent the number of events reported; most patients reported more than 1 event. * $P < 0.05$, ** $P < 0.01$. # Weight gain was rounded to the nearest 5 lb. URI – upper respiratory tract infection. Figure was created using Adobe Illustrator version 25.3.1 (Adobe, Inc.).

from the open-label extension (OLE) of the phase 3 REGAIN study, in which 117 patients received eculizumab for up to 4 years. At the OLE baseline, most patients (90 [76.9%]) were receiving prednisone; at the last assessment, there was a significant reduction in prednisone dose ($P=0.0335$) and 10 patients had stopped prednisone completely [40].

The primary limitations of this study include the relatively small sample size and limitations associated with retrospective chart-based data extraction. In addition, all patients were receiving at least one other medication to treat gMG, and it is possible that these contributed to the AEs observed. Nevertheless, the results may provide useful information for clinicians who manage patients with gMG in terms of dosing, counseling, and monitoring according to patient age and sex.

Conclusions

In this study of patients being treated with prednisone for gMG, corticosteroid-related AEs were ubiquitous, some with potentially serious medical consequences, and certain AEs appeared

to be associated with patient characteristics. Although steroids have a role to play in managing MG, these results highlight the importance of considering patients' demographic and comorbid conditions before initiating treatment and the need to consider the various strategies for monitoring and managing corticosteroid-related AEs.

Statement

The work reported was conducted at the Department of Neurology, University of Missouri Health Care, Columbia, MO.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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