Neuromuscular junction disorders

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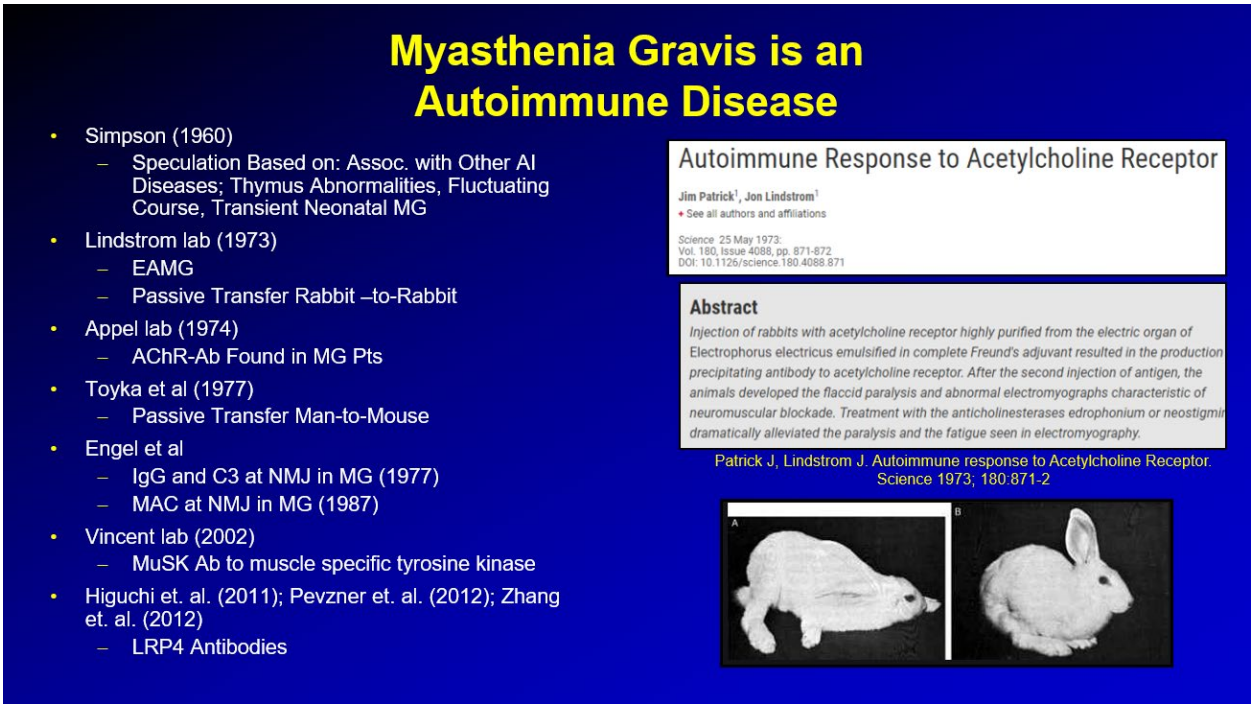
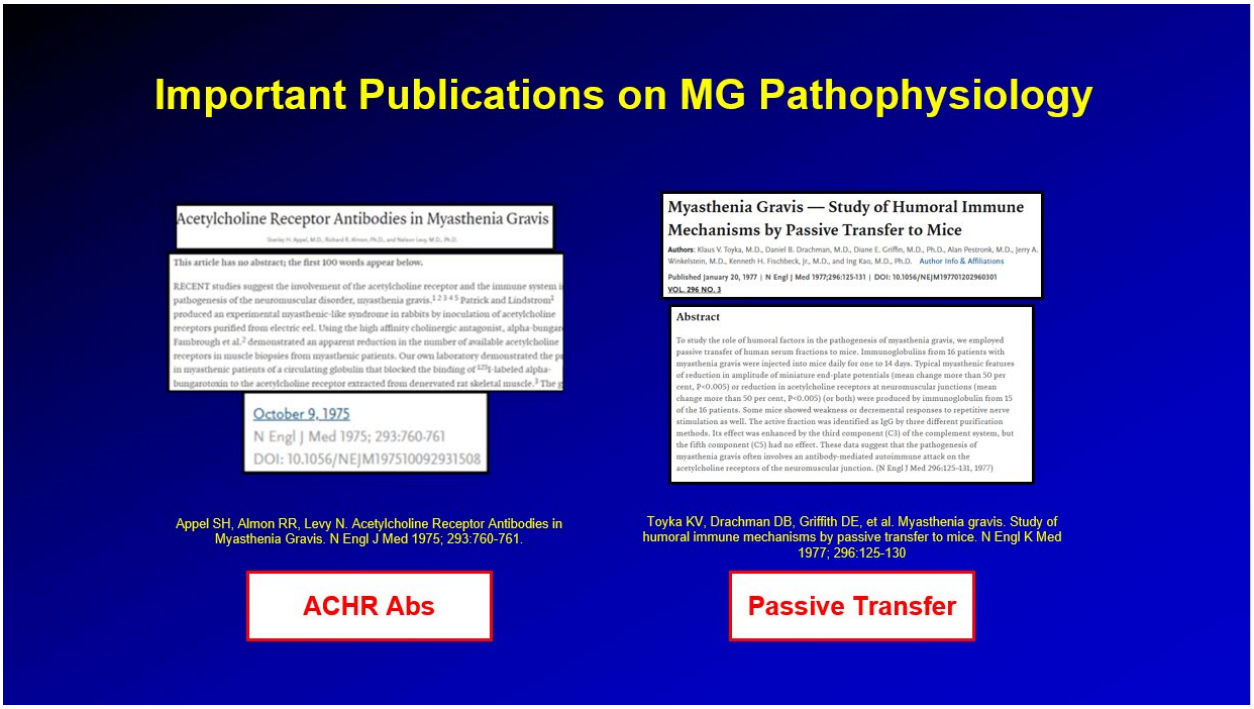
MG is an Autoimmune Disorder

Figure 1



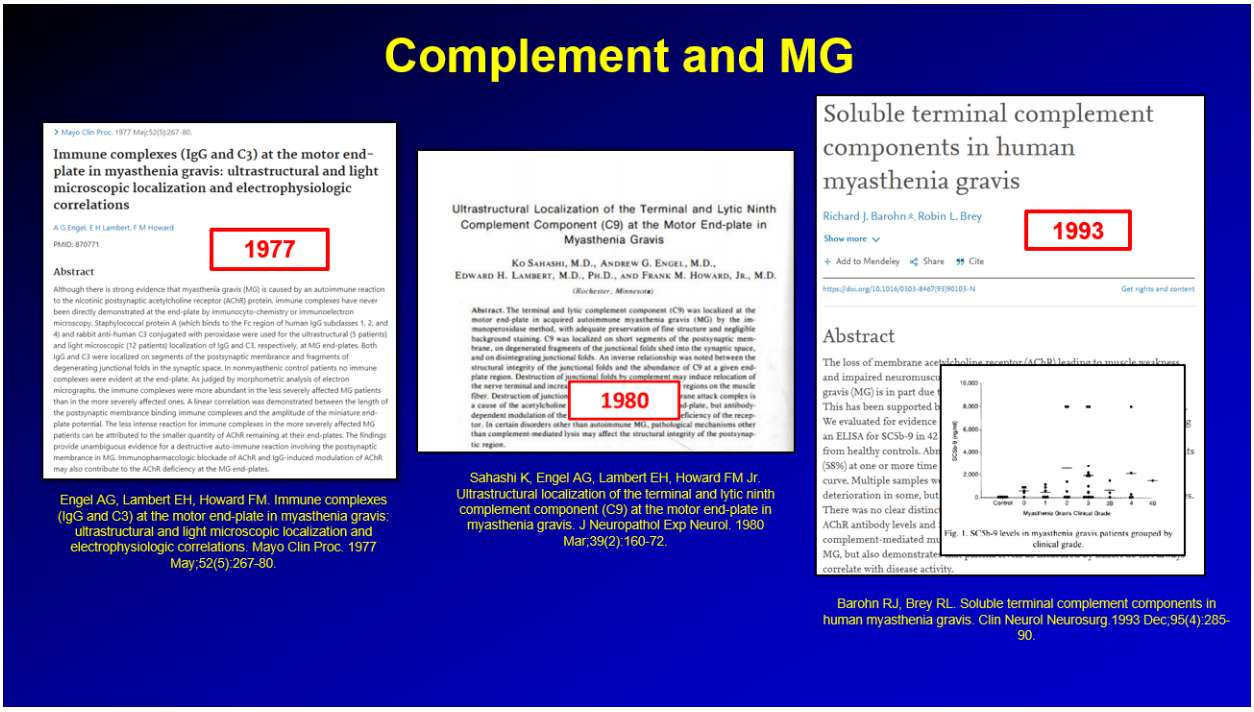
The concept that myasthenia gravis (MG) is autoimmune is relatively recent given how long we have known about the disease. It was speculated that MG was an autoimmune disease in 1960 by Dr. Simpson (Figure 1). His speculation was based on several observations that included the association of MG with other autoimmune diseases, thymus gland abnormalities, fluctuating course, and transient neonatal MG where infants born to MG mothers are weak at birth and then improved gradually. The real proof did not emerge until the early 1970s. In 1973 Dr. Jon Lindstrom, in his laboratory in California, produced the first experimental allergic MG model in rabbits. His group was able to passively transfer myasthenia from rabbit to rabbit. Dr. Stanley Appel was part of the team at Duke in 1974 that was first able to identify acetylcholine receptor antibodies (AChR-Ab) in MG patients. A couple of years later, Dr. Klaus Toyka and his team in Germany were able to passively transfer these antibodies from human to mouse (Figure 2).

Figure 2



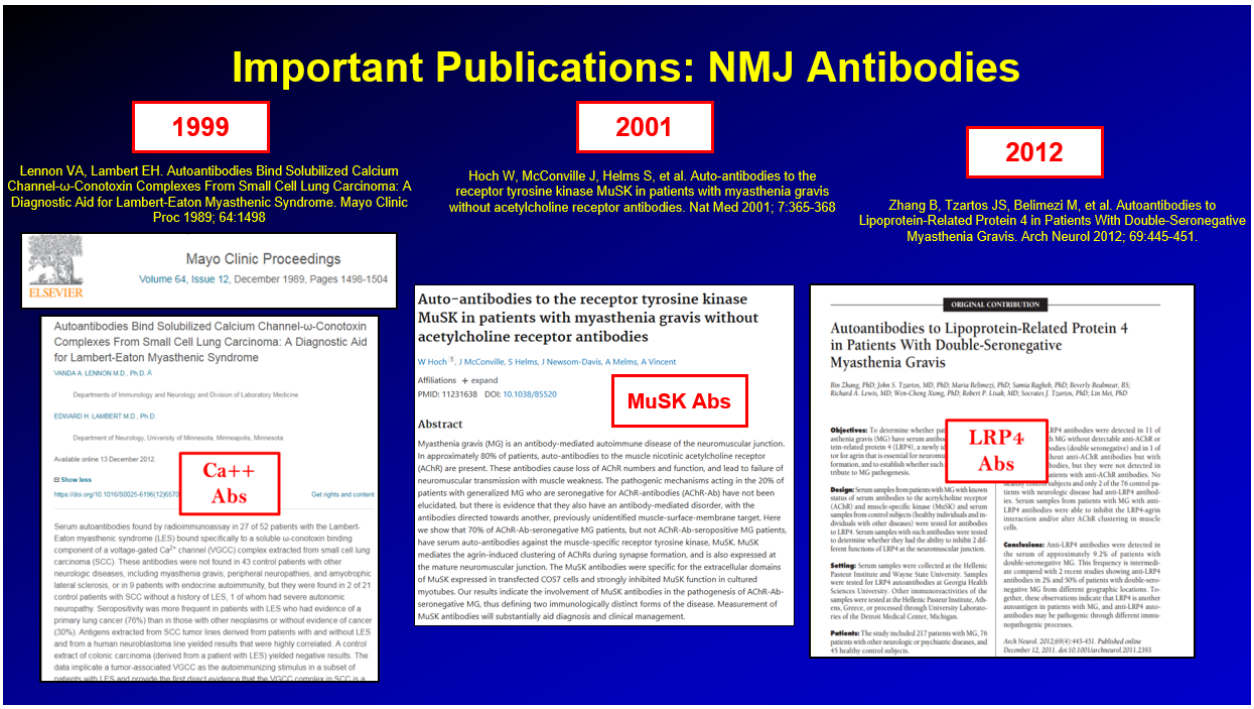
In 1977 at the Mayo Clinic, Dr. Andrew Engel and his team made the initial observations that in addition to the autoimmune antibodies, complement was important in MG pathophysiology at the neuromuscular junction. Our group was able to demonstrate complement elevation in the plasma of MG patients. The complement elevation was higher when the disease was more severe. The finding that complement was important in the development of MG ultimately led to the use of complement inhibitors for the treatment of MG (Figure 3).

Figure 3



The next big scientific breakthrough was in 1999 when Doctors Vanda Lennon and Edward Lambert discovered that the Lambert-Eaton myasthenic syndrome was due to antibodies directed against the presynaptic voltage-gated calcium channels at the neuromuscular junction. In 2001 Dr. Angela Vincent's lab in Oxford, England discovered antibodies directed against the muscle-specific tyrosine kinase (MuSK) at the neuromuscular junction in patients with MG who did not have AChR antibodies. In 2011 and 2012 several labs found low-density lipoprotein receptor-related protein 4 (LRP4) antibodies in a portion of MG patients who were seronegative to both AChR and MuSK. While there are other antibodies that are still being pursued in research labs, these three are now commercially available--AChR, MuSK, and LRP4.

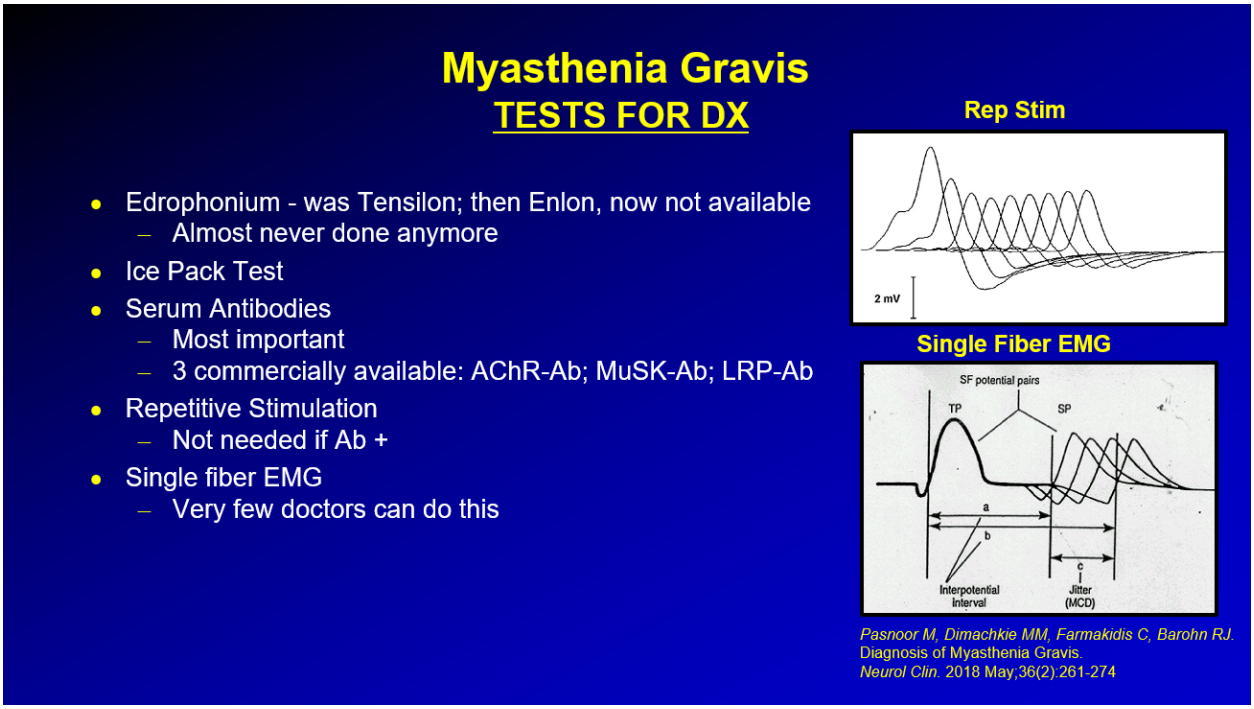
Figure 4



Diagnosis of MG

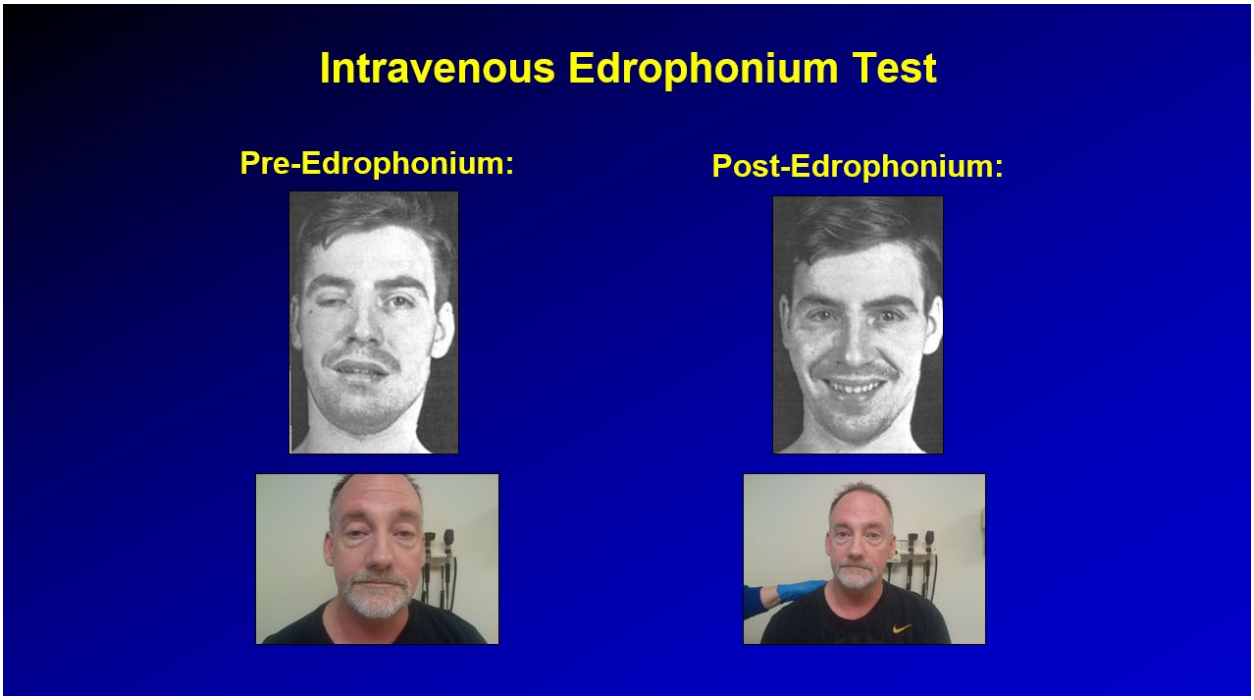
Edrophonium-chloride, previously known by the trade names Tensilon and Enlon, was developed in the mid-1950s to diagnose MG (Figure 5).

Figure 5



By injecting intravenously this acetylcholinesterase inhibitor, some symptoms and signs of MG could be improved or reversed, especially ptosis (Figure 6).

Figure 6



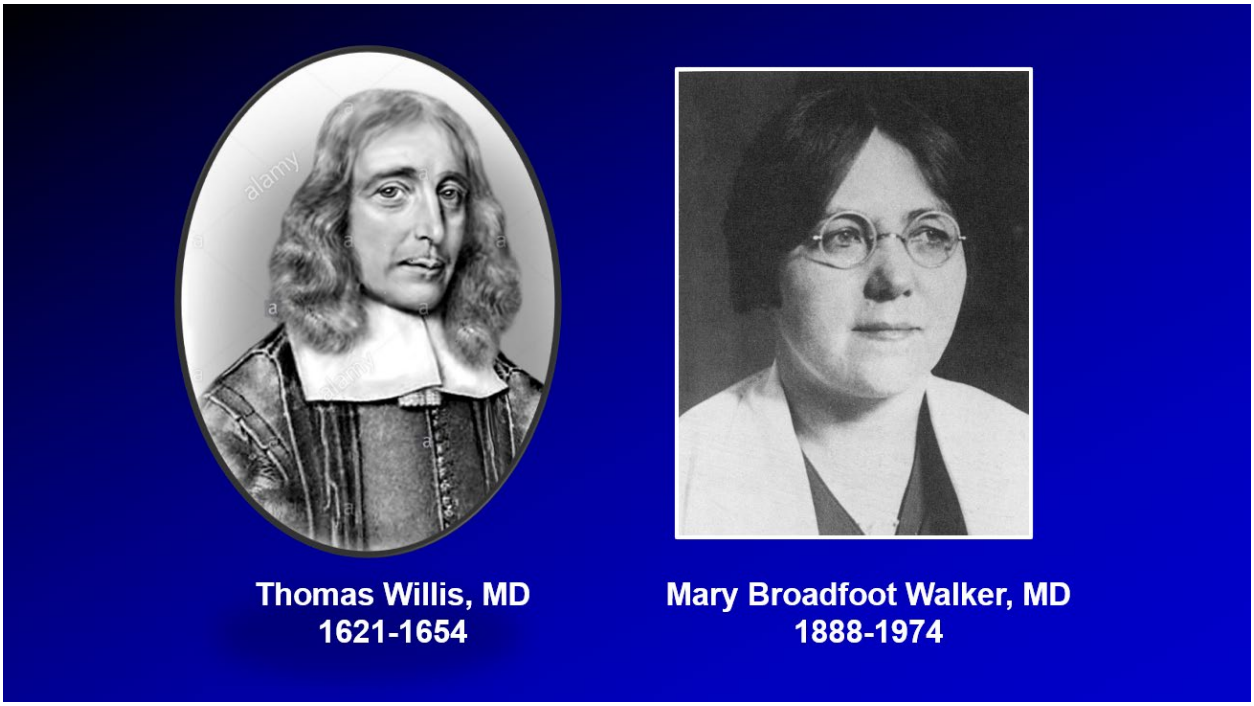
However, since 2018 edrophonium is no longer available in the United States. We hope that one day a drug company will bring edrophonium back on the market because we believe it is useful in the diagnosis of MG in both inpatient and outpatient settings when patients first present with symptoms and signs. In the absence of the ability to do edrophonium tests, an ice pack test can be performed by putting ice wrapped in a plastic bag over a patient's ptotic eye to see if the lid raises. This is not as effective as an edrophonium test. The pharmacologic basis for the ice pack test is that cold temperature slows down the activity of the enzyme acetylcholinesterase thus increasing the availability of the neurotransmitter acetylcholine at the neuromuscular junction to effect neuromuscular transmission. Serum antibodies are the most important diagnostic test and as mentioned above, there are now three commercially available serum antibodies: antibodies to AChR, MuSK, and LRP4. Repetitive stimulation is still a useful test to demonstrate neuromuscular junction pathophysiology. Figure 3 shows an example of an abnormal decremental response of an ulnar-innervated hand muscle when the

ulnar nerve was stimulated at 2 Hertz. In a patient who has the typical presentation of MG symptoms and signs, a positive antibody test to these components of the neuromuscular junction lessens the need to do repetitive stimulation as the diagnosis has already been confirmed.

Single fiber electromyography (EMG) is also a useful test to demonstrate neuromuscular junction dysfunction (Figure 3). It is more sensitive than repetitive stimulation. Single fiber EMG is most often used to document evidence of neuromuscular junction dysfunction in antibody-negative patients. However, single fiber EMG is a difficult test to perform that requires training and special equipment and it is not available at many medical centers.

Two historic figures that led to our understanding and treatment of MG

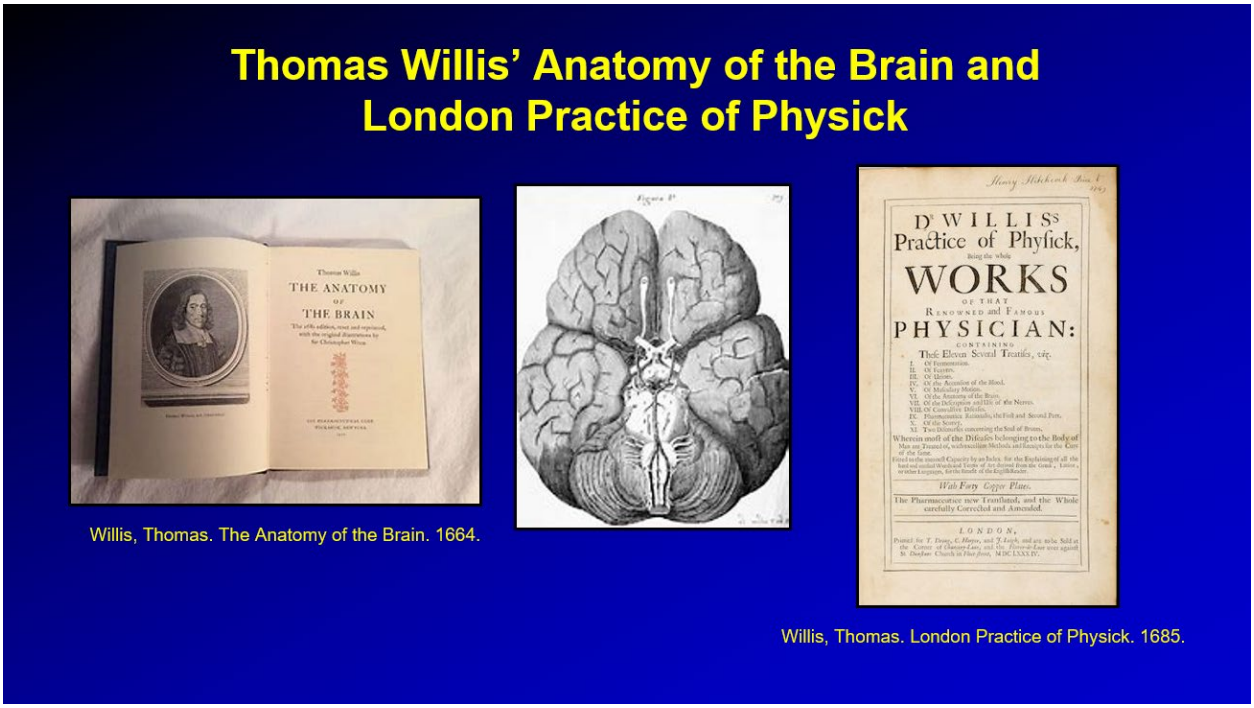
Figure 7



Who are these two individuals in Figure 7? The man on the left is Thomas Willis who was an important physician who practiced in England in the 1600s. He was primarily famous for publishing on the anatomy of the brain and describing the vasculature at its base which we now call the circle of Willis. He also was the first physician to describe the clinical features of MG in one of the many books that he published. 'De Anima Brutorum', published by Willis in London in 1672 and written in Latin, described patients who were well in the morning and fatigued toward noon and were unable to speak for a long time. This book was then translated into English in 1685 under the title 'The London Practice of Physick':

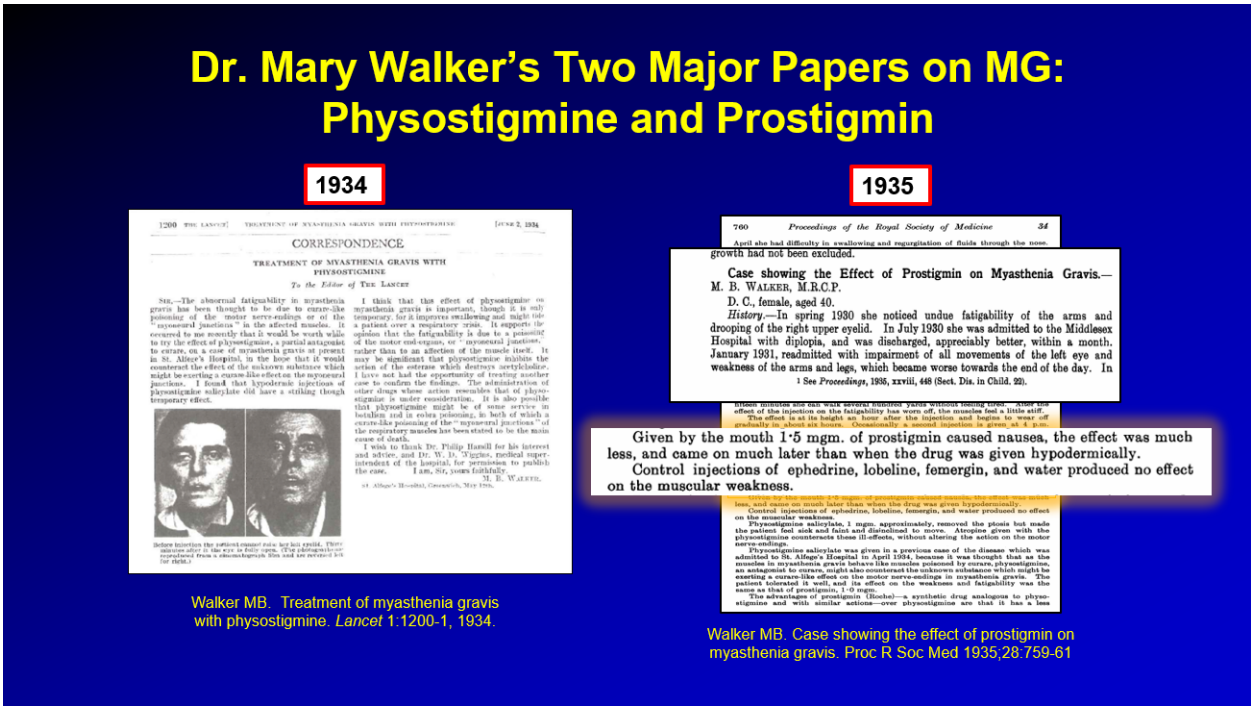
"in the morning [they] are able to walk firmly, to fling about their Arms hither and thither, or to take up any heavy thing, before noon the stock of Spirits being spent, which had flowed into the Muscles, they are scarce able to move Hand or Foot" (Figure 8).

Figure 8



The woman may not be as well known to many of you but she's one of the heroes in MG history and her name is Mary Broadfoot Walker. Dr. Walker first demonstrated that physostigmine and prostigmin were effective in treating MG. She published two papers, one in 1934 and one in 1935, that showed this beneficial effect.

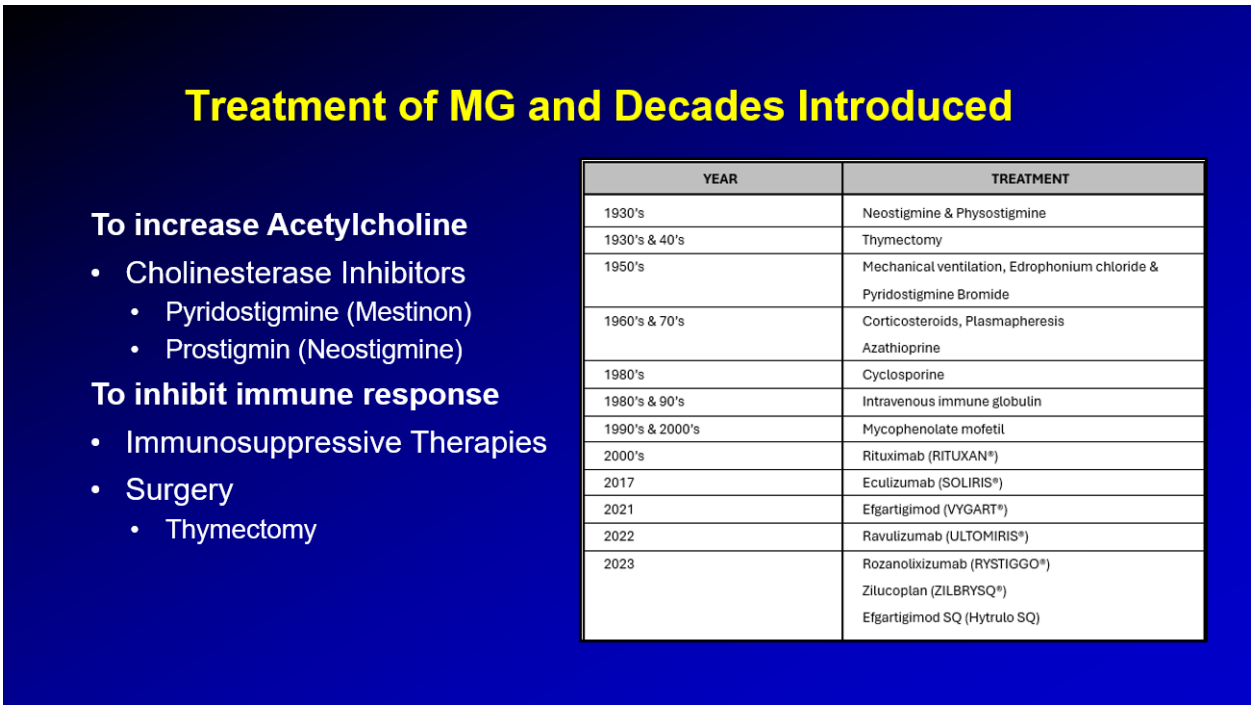
Figure 9



She saw similarities between the symptoms and signs of MG and curare intoxication. Curare poisoning was being treated with physostigmine, and based on this knowledge, she decided to use these drugs to treat MG-and it worked! This was a landmark discovery in the history of medicine. In the 1935 paper, she injected not only prostigmin (also known as neostigmine) but then injected water placebo and showed that the placebo did not work (see highlighted area in Figure 9). The observations of Dr. Walker were the biggest breakthrough in the treatment of MG in the early half of the last century.

The next major observation in the treatment of MG regarded the thymus gland. For years cases of MG had been observed with enlarged thymus glands or thymic tumors. In the 1930s and 40s thymectomy began being used for thymomatous and non-thymomatous MG by Dr. Alfred Blalock and others, and they reported improvement in the status of the patients (Figure 10).

Figure 10



YEAR	TREATMENT
1930's	Neostigmine & Physostigmine
1930's & 40's	Thymectomy
1950's	Mechanical ventilation, Edrophonium chloride & Pyridostigmine Bromide
1960's & 70's	Corticosteroids, Plasmapheresis Azathioprine
1980's	Cyclosporine
1980's & 90's	Intravenous immune globulin
1990's & 2000's	Mycophenolate mofetil
2000's	Rituximab (RITUXAN®)
2017	Eculizumab (SOLIRIS®)
2021	Efgartigimod (VYGART®)
2022	Ravulizumab (ULTOMIRIS®)
2023	Rozanolixizumab (RYSTIGGO®) Zilucoplan (ZILBRYSQ®) Efgartigimod SQ (Hytrulo SQ)

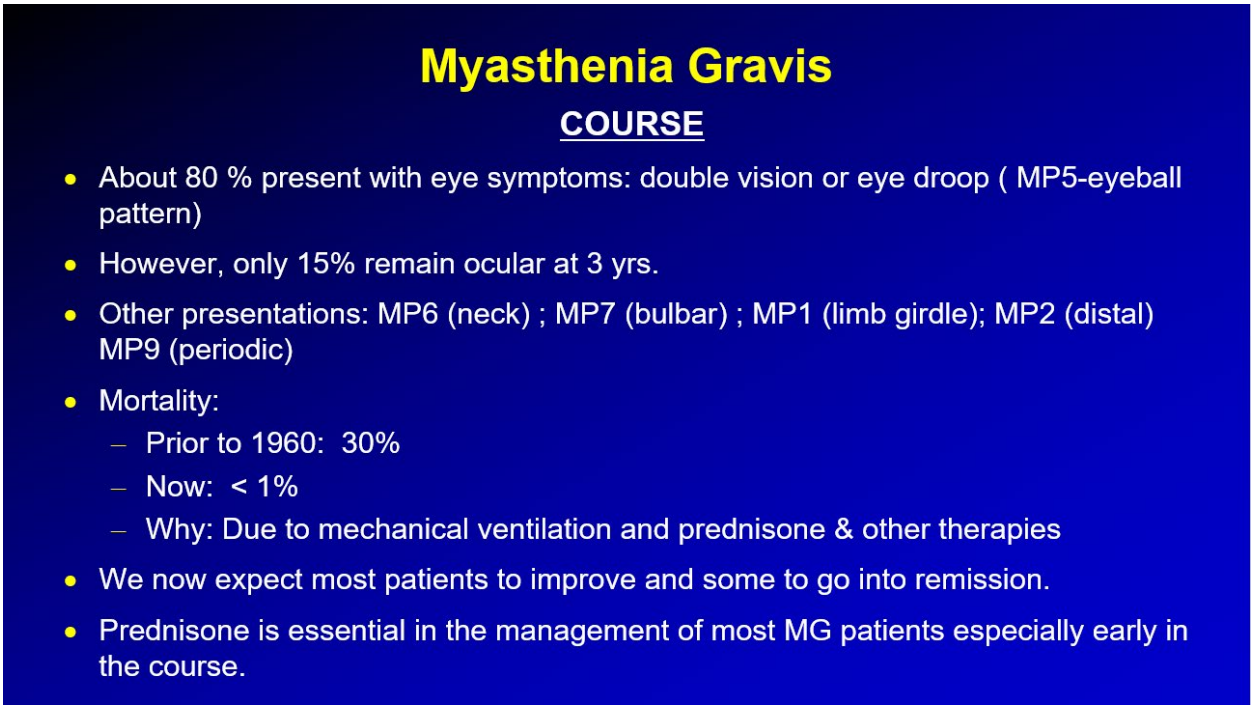
A major advance in the treatment of MG occurred in the 1950s when mechanical ventilators became available. As mentioned, edrophonium chloride became available in the 1950s, and then pyridostigmine bromide, which goes by the trade name of Mestinon, was developed in the mid-1950s and largely replaced the use of prostigmin (Neostigmine) due to fewer side effects. Pyridostigmine (Mestinon) became the first FDA-approved drug for MG in 1955. Corticosteroids and plasmapheresis were introduced in the 1970s. However, there were many reports in which ACTH was used for MG beginning in the 1950s which was really the first attempt of using corticosteroids for MG. The late 1960s and early 1970s ushered in an era of using drugs that were developed to prevent organ transplant rejection in autoimmune diseases such as MG. The first was azathioprine and the next was cyclosporine, and finally mycophenolate mofetil. In the 1980s and 90s, intravenous immune globulin (IVIG) began being used for MG.

Around 20 years ago, rituximab was first introduced as MG therapy. All of the above medications were approved for other disease states and were off label for MG. Finally, in 2017 the first FDA-approved

immunotherapy for MG was introduced-eculizumab--and subsequently several other drugs have been FDA-approved for MG, most notably efgartigimod in 2021.

Course of Disease and Patterns of Presentation

Figure 11



The course of MG is well known. Eighty percent are present with the ocular symptoms of either double vision or a droopy eyelid. This is the MP5 eyeball pattern discussed in the pattern recognition lecture published previously. However, only 15% of patients remain purely ocular at three years of disease duration. Other presentations include the MP6 neck drop pattern, the MP7 bulbar pattern, occasionally the MP1 limb-girdle pattern, and sometimes the MP2 distal pattern. Because many patients state that they get weaker with exercise, the MP9 pattern should be added to this list. Prior to all of the treatments that were just mentioned, MG was indeed a grave disease. The mortality rate prior to 1960 was 30%. However with our current therapies, the mortality rate should be well below 1%. Patients should not die of MG. When this does occur, it is usually due to complications from one or more of the therapies such as an overwhelming infection. The dramatic reduction in the mortality rate

in the 1960s and 1970s was most likely due to the introduction of mechanical ventilation and corticosteroids, but certainly other therapies played a role as well.

Time to Effectiveness of Each Therapeutic Modality

How long does it take these individual therapies to have a clinical effect? First it should be recognized that not all of these therapies will be effective in every patient. If they are effective, the time of onset to the improvement ranges from minutes to months depending on the therapy.

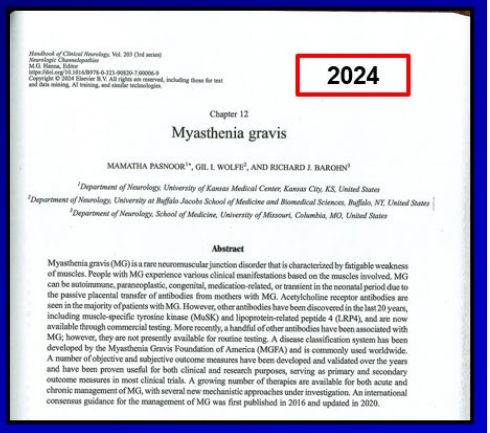
Figure 12

Treatment of Myasthenia Gravis

Typical Time to Clinical Effect After Initiating Therapy

Pasnoor, Wolfe, Barohn. Handbook of Clinical Neurology, 2024;203:185-203.

THERAPY	TIME
Pyridostigmine	Minutes
Plasmapheresis	1-14 days
IVIg	1-14 days
Prednisone Eculizumab Efgartigimod	2-8 weeks 2-8 weeks 2-8 weeks
Cyclosporine	2-6 months
Methotrexate	2-6 months
Mycophenylate	2-6 months
Azathioprine	12-18 months
Rituximab	months
Thymectomy	months to years



2024

Chapter 12

Myasthenia gravis

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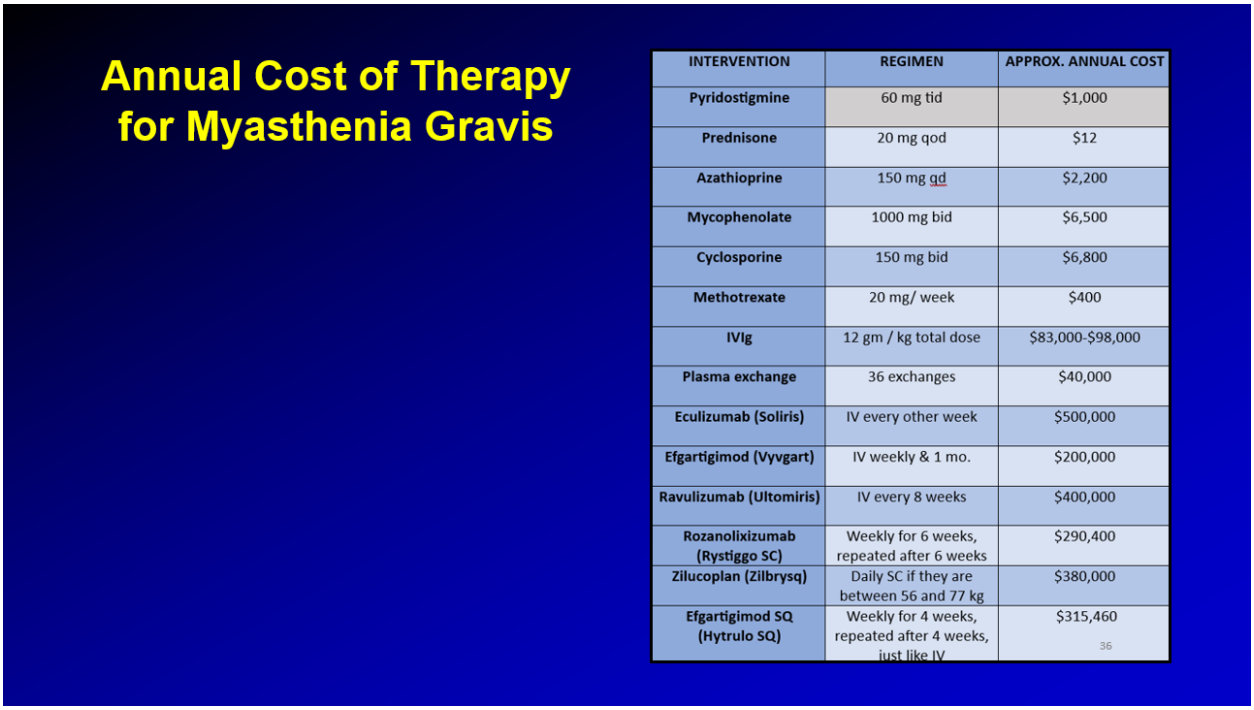
Abstract

Myasthenia gravis (MG) is a rare neuromuscular junction disorder that is characterized by fatigable weakness of muscles. People with MG experience various clinical manifestations based on the muscles involved. MG can be autoimmune, paraneoplastic, congenital, medication-related, or transient in the neonatal period due to the passive placental transfer of antibodies from mothers with MG. Acetylcholine receptor antibodies are seen in the majority of patients with MG. However, other antibodies have been discovered in the last 20 years, including muscle-specific tyrosine kinase (MuSK) and lipoprotein-related peptide 4 (LRP4), and are now available through commercial testing. More recently, a handful of other antibodies have been associated with MG; however, they are not presently available for routine testing. A disease classification system has been developed by the Myasthenia Gravis Foundation of America (MGFA) and is commonly used worldwide. A number of objective and subjective outcome measures have been developed and validated over the years and have been proven useful for both clinical and research purposes, serving as primary and secondary outcome measures in most clinical trials. A growing number of therapies are available for both acute and chronic management of MG, with several new mechanistic approaches under investigation. An international consensus guidance for the management of MG was first published in 2016 and updated in 2020.

Pyridostigmine works in a matter of minutes. Plasmapheresis and IVIG work in days. Prednisone and eculizumab work in 2 to 8 weeks. Cyclosporine, methotrexate, and mycophenolate mofetil, if they are going to have an effect, only start showing benefit after two to six months, sometimes longer. On the other hand, azathioprine, which does have an effect on MG, does not have an effect for 12 to 18 months. Rituximab, if it is effective, may take several months. Thymectomy surprisingly also seems to have an effect within several months.

Annual Cost of Individual Therapies

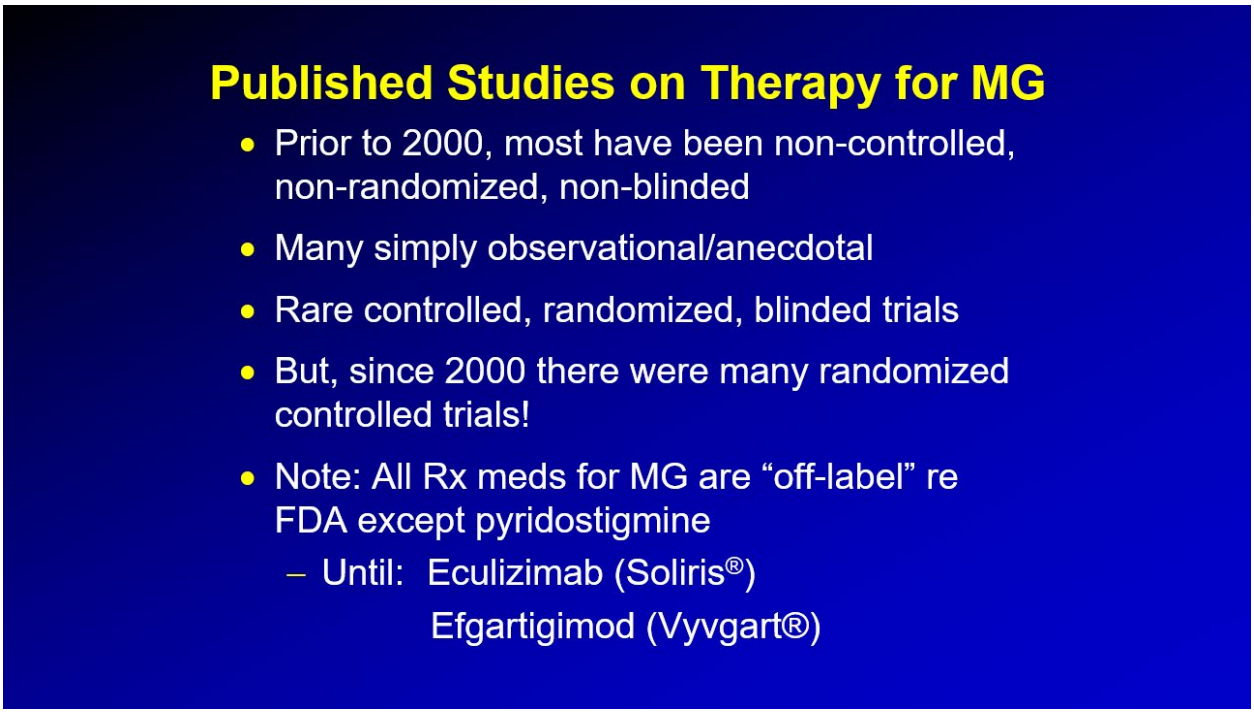
Figure 13



The cost of these drugs ranges from very inexpensive to staggeringly expensive and that is shown in Figure 13. If you can get prednisone for a dollar a month at your local Walmart, then the cost is $12 a year. After that, the drugs get increasingly more expensive. Methotrexate, which has been around since the 1950s, is relatively inexpensive compared to other oral immunosuppressive agents. On the other hand, IVIG and plasmapheresis have a large price tag. But the new biologics that either inhibit complement or Fc receptors are even more costly.

Published Studies on Therapy for MG

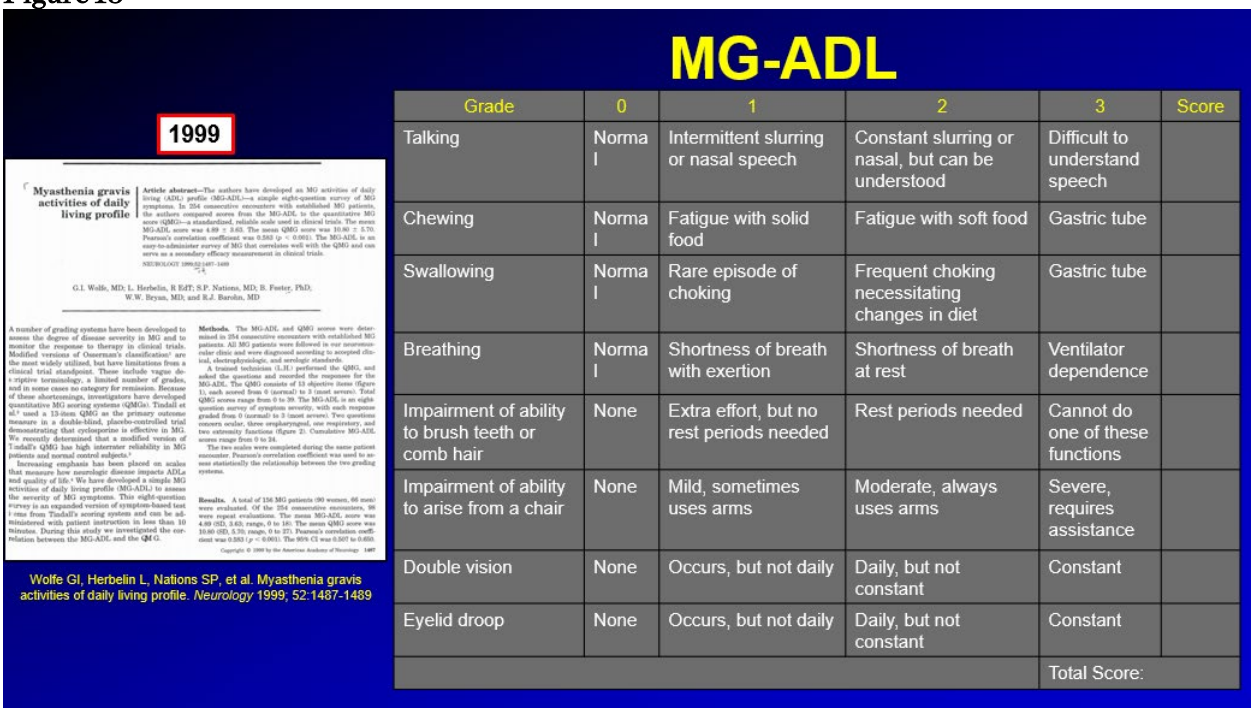
Figure 14



Prior to 2000 most MG studies were uncontrolled, nonrandomized, and unblinded with a few exceptions. There were many observational and anecdotal studies, particularly around thymectomy and prednisone. However, since 2000 there have been many published randomized controlled trials. We are currently in an exciting age of innovation regarding the treatment of MG. The list of FDA approved drugs in the biologic era continues to expand and now includes eculizumab, efgartigimod intravenous (IV), ravulizumab, rozanolixizumab, zilucoplan, and subcutaneous (SQ) efgartigimod.

MG Activities of Daily Living Scale

Figure 15



MG-ADL

Grade	0	1	2	3	Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
				Total Score:	

If you are going to be taking care of MG patients, then it is important to know about the MG activities of daily living scale MG-ADL which our team developed at University of Texas Southwestern in the 1990s. This scale was developed for research purposes, but it should now be routinely used to monitor the progress of MG patients. It is a very simple scale to use. A medical assistant can ask the patient the questions or the patient can fill it out on their own. In the office setting when a patient is first put in the waiting or the examination room, the MG-ADL can be completed. Therefore, when the physician walks in the exam room to begin the encounter the MG-ADL scale will have already been completed. The advantage of obtaining an MG-ADL at each clinic visit is that you have a quantitative score of the severity of the MG.

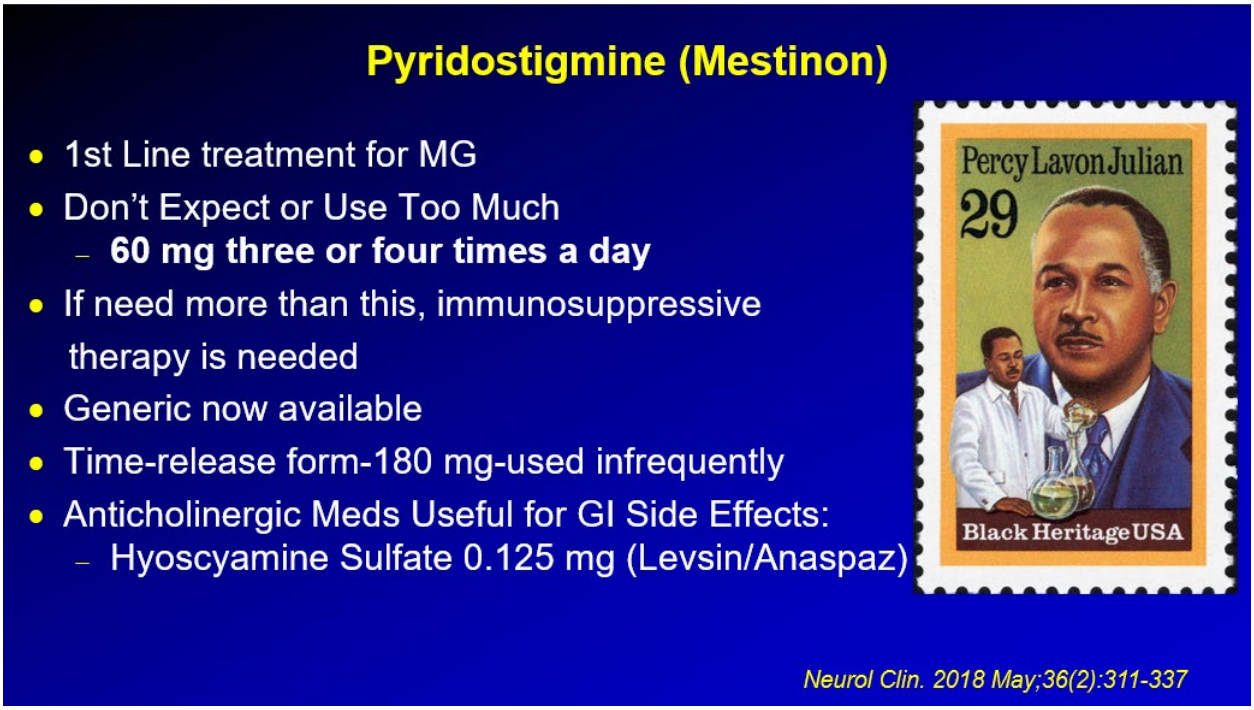
It is strongly encouraged that the MG-ADL be done routinely as a standard of care every time a MG patient is seen whether or not it is in a general neurologist's office or a tertiary care neuromuscular clinic.

Pyridostigmine

Pyridostigmine is the first-line treatment for MG. It also goes by the trade name Mestinon. The most important caveat with pyridostigmine is not expecting from or using it too much. If the patient is on 60mg three or four times a day and they are still symptomatic then it is time to go on to immunosuppressive therapy.

There is no need to increase the dose to 120mg every two or three or four hours. All this will do is cause more side effects such as increased bowel movements and sweating, and it will not improve the MG symptoms or signs any more than the effect of 60mg three or four times a day. Generic pyridostigmine is now available and it is just as effective as the trade drug. It is less expensive.

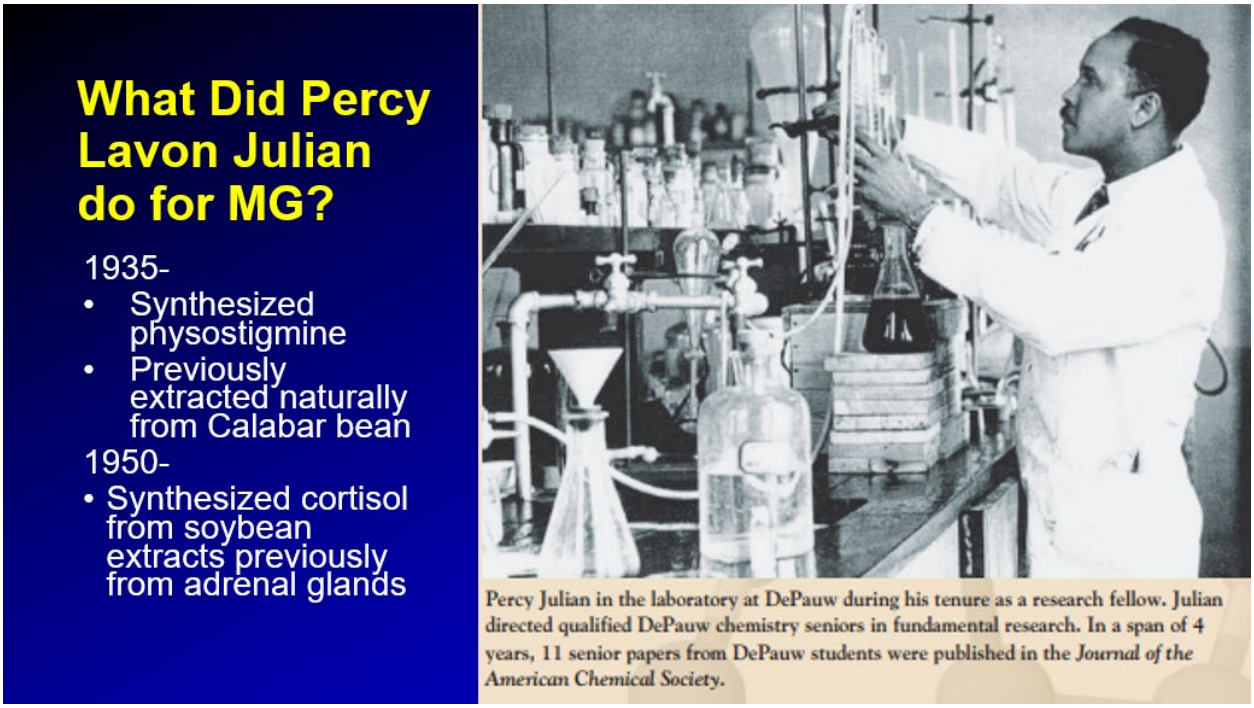
Figure 16



There is also a version called Mestinon Time Span which is a time release formulation. In general, we prefer not to use this formulation, as it gives a large pyridostigmine dose and absorption is erratic. However some patients take the time release tablet at bedtime presumably so they have fewer MG symptoms in the morning. Therefore, if a patient insists on using the time release capsule and believes they are benefiting we will agree with their decision as in these instances the patient is usually correct. If the patient does have loose stools on pyridostigmine, it should be treated with a muscarinic anticholinergic agent such as hyoscine sulfate 0.125mg that is taken with each pyridostigmine dose up to three times a day.

Percy Lavon Julian was a chemist who started his career at DePauw University and he and his team synthesized physostigmine.

Figure 17



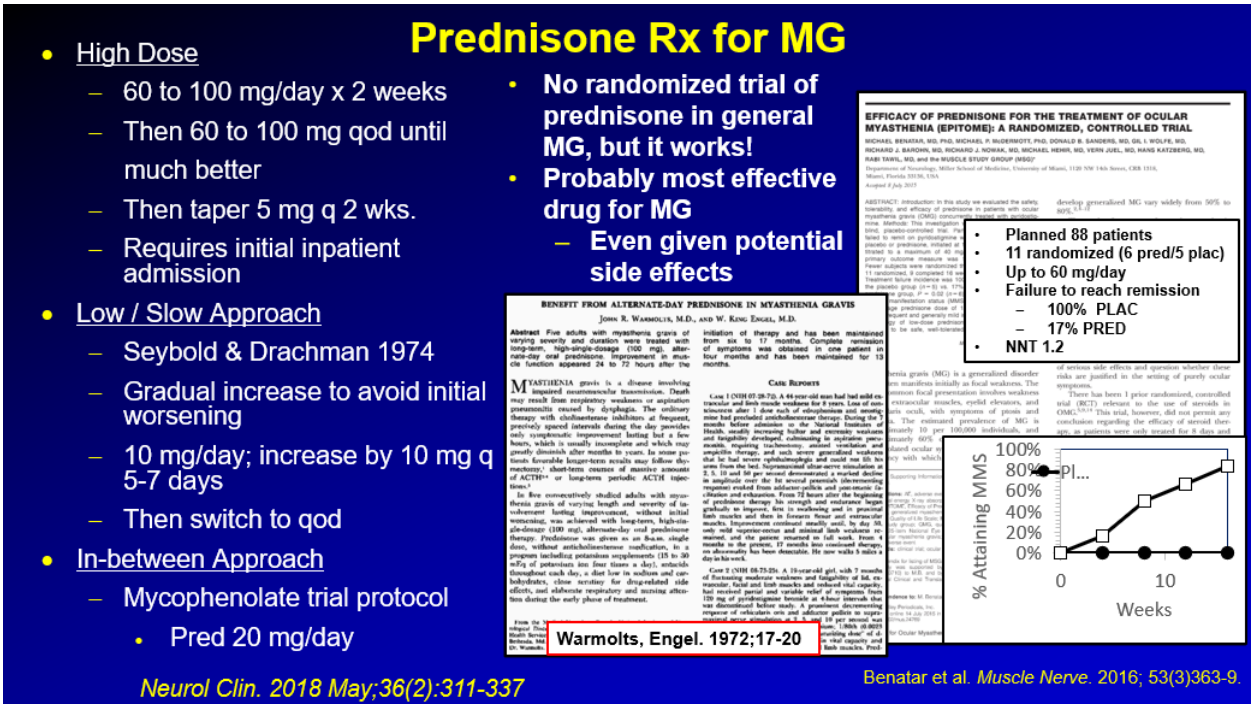
Prior to that, physostigmine had to be extracted naturally from Calabar beans which was the source of the drugs that Mary Walker used.

The use of corticosteroids for MG

The synthesis of acetylcholinesterase inhibitors by Dr. Julian's team was a huge breakthrough in MG. For this reason alone, he should be considered a hero in our understanding and treatment of MG. However, he should perhaps be even better remembered for the discovery in the 1950s in which his team synthesized cortisol from soybean extracts.

Previously cortisol had to be extracted from adrenal glands. His technique revolutionized the use of corticosteroids for many diseases.

Figure 18



While high-dose prednisone therapy is used to treat MG, it has been observed that if you put a generalized MG patient on high-dose prednisone therapy (60 to 100 mg a day), a small percentage of patients will have transient worsening during the first week of therapy.

Therefore, when an MG patient is placed on 60 to 100 mg a day of prednisone this should be done when they are in a hospital setting, and this usually is when they are in crisis on a ventilator or experiencing severe worsening that requires hospitalization. When starting prednisone as an outpatient, what has been used for decades is the go-low and slow escalation approach developed by Drs. Marjorie Seybold and Dan Drachman in the 1970s. In this approach, the patients start on 10 mg a day of prednisone, and every week you increase by 10 mg up to the target dose that you wish to reach. At some point, the patient can be switched to every other day to reduce the side effects. A third approach came out of our experience performing the Muscle Study Group mycophenolate mofetil trial

in MG. During that trial all new MG patients were placed immediately on 20 mg a day of prednisone and either mycophenolate mofetil or placebo.

We learned in this study that a patient can be put immediately on prednisone of 20 mg a day and a benefit could be achieved without increasing the dose in many patients.

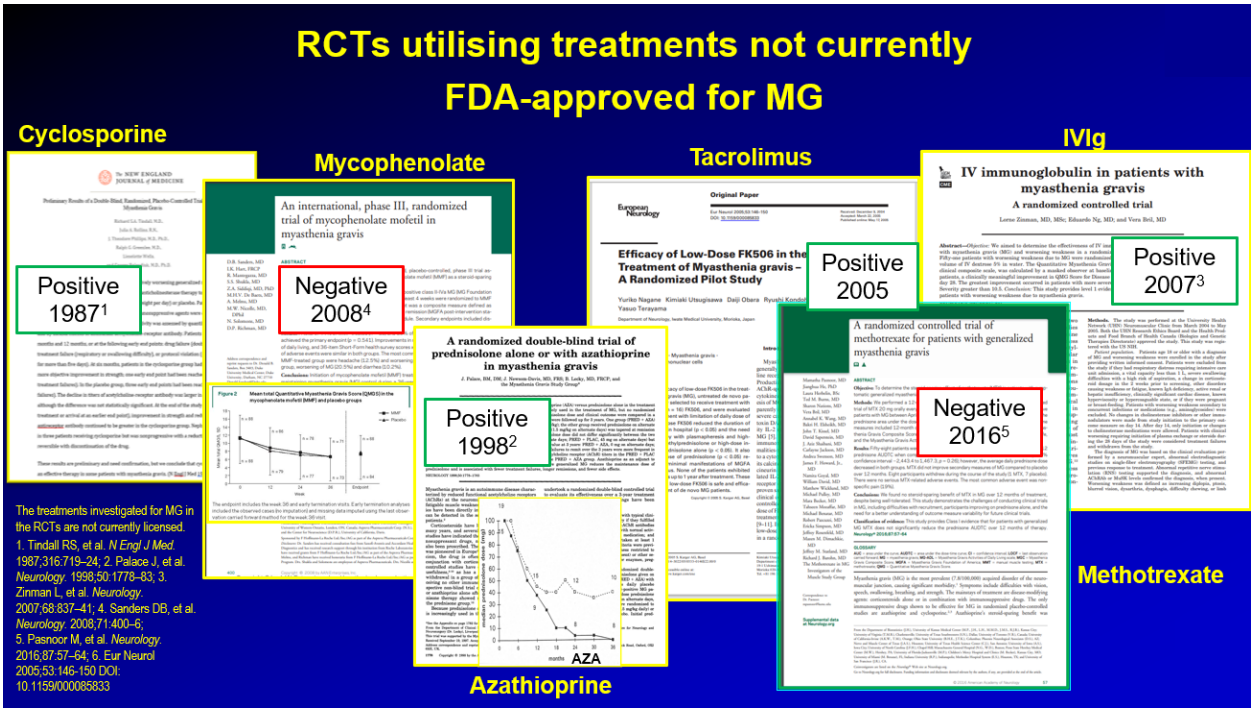
There are no randomized controlled trials of oral prednisone for generalized MG, but we all know from years of using the drug in MG that it is effective. We do have a small randomized controlled trial in ocular MG that was led by Dr. Michael Benatar and showed a dramatic effect of prednisone compared to a placebo in ocular MG patients (Figure 18). Essentially all of the ocular patients on prednisone got better but none of the patients on placebo improved.

The first paper that used high-dose prednisone in MG was authored by Drs. John Warmolts and King Engel at the NIH in 1972, and this was another landmark paper in the history of MG (Figure 18). The MG patients they reported improved dramatically even though this was not a placebo-controlled trial.

Other non-FDA approved immunosuppressive drugs for MG

Between the 1970s until the advent of the new biologic drugs a number of immunosuppressive drugs have been used to treat MG patients with varying degrees of success. A number of randomized control trials with these drugs have been performed and published (Figure 19).

Figure 19



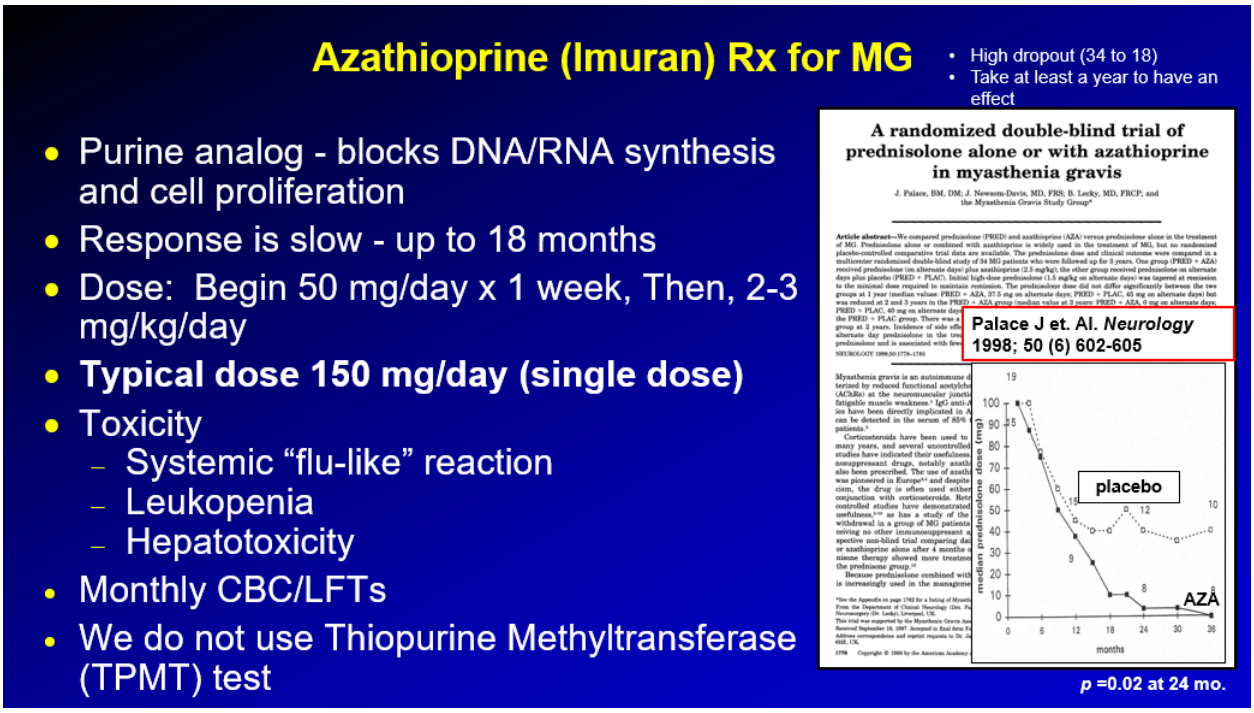
Azathioprine (Imuran)

Azathioprine is effective in MG, but the problem with the drug is that it does not have an effect for at least a year and does not have its maximal effect for 18 months after it is started (Figure 20). Therefore, it is not a drug that is used to improve MG patient symptoms in the near term. Azathioprine is used to decrease patient dependency on prednisone in the long term.

In general, we do not believe that a generalized MG patient and also an ocular MG patient can be managed without initially using prednisone. You can occasionally avoid prednisone in a small number of patients but generally, you have to use immunosuppressive therapy in the form of corticosteroids to see an initial improvement in a MG patient. Our view on this may change over time but currently, we use prednisone in all of our generalized MG patients once they get the maximum benefit from pyridostigmine. But we place greater emphasis now on trying to reduce prednisone to lower doses as

quickly and safely as possible with the help of other therapies as part of the goal of limiting corticosteroid-related side effects.

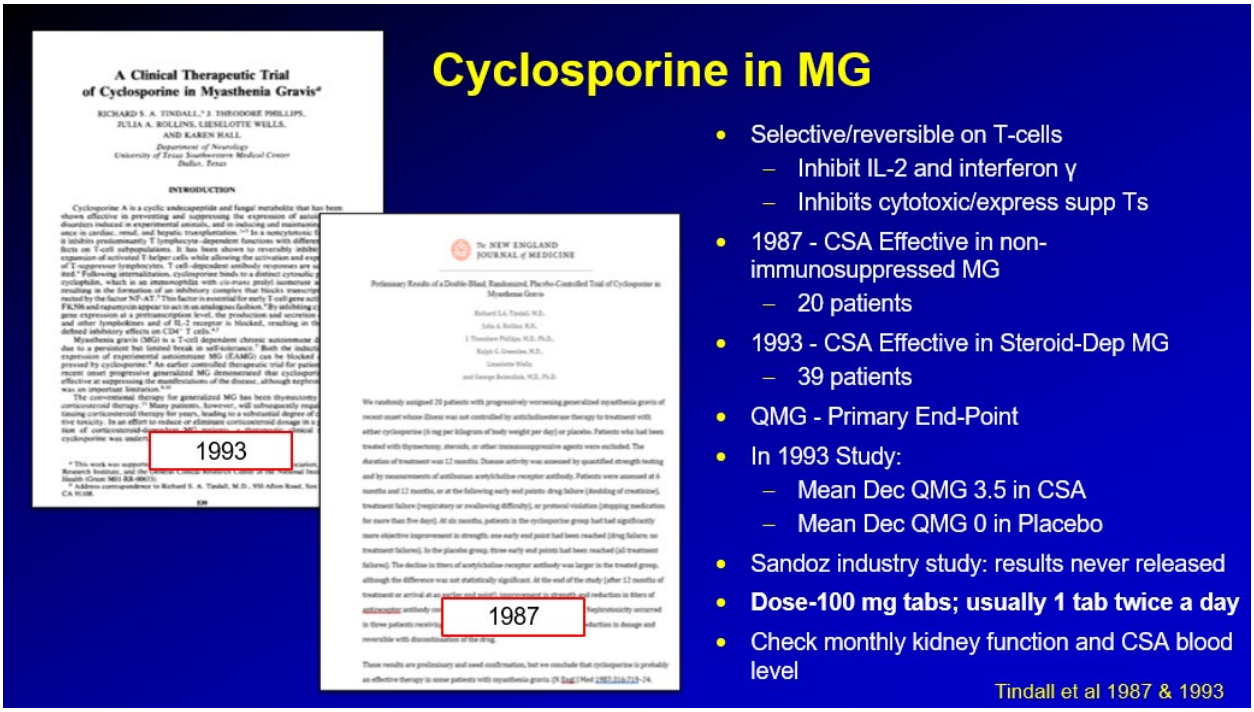
Figure 20



Cyclosporine and tacrolimus

The next drug after azathioprine that we began using as cyclosporine, again off label. Cyclosporine, like azathioprine, was first developed to suppress the immune system on patients undergoing organ transplantation. There were two cyclosporine randomized controlled trials for MG performed at University of Texas Southwestern, showing that cyclosporine was effective in improving patients with MG compared to placebo (Figure 21).

Figure 21

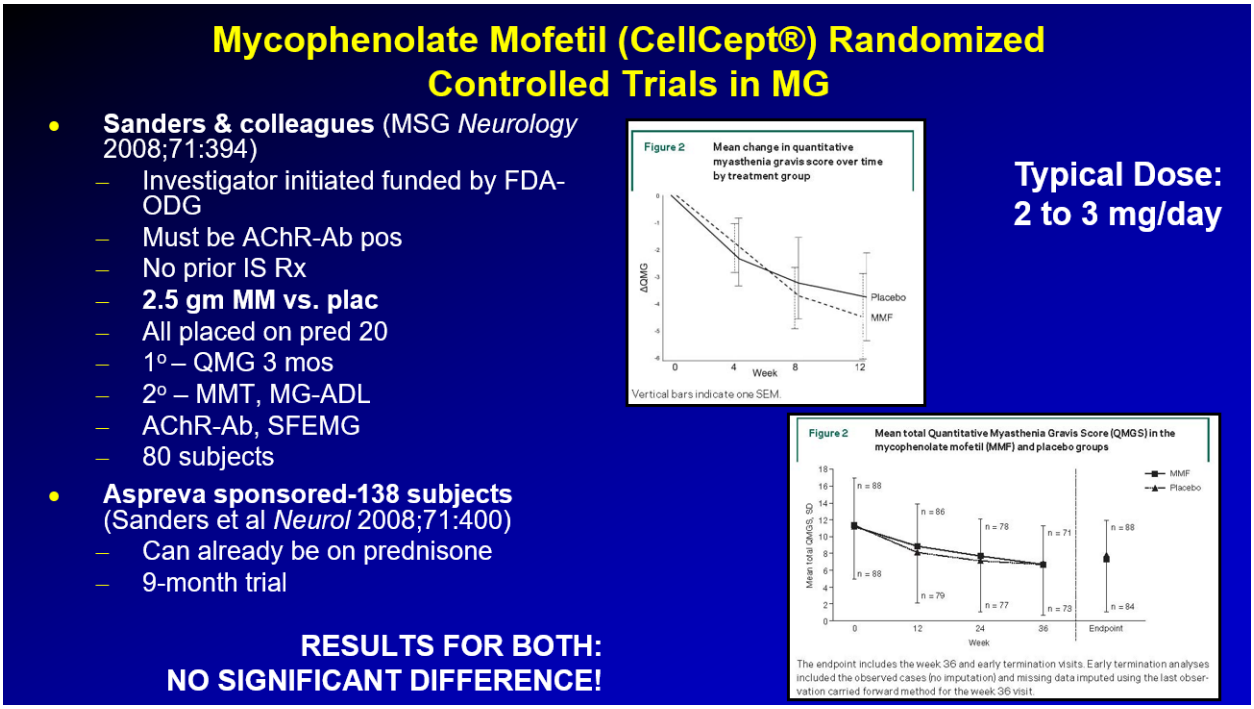


Therefore, in the mid and late 1980s and into the 1990s some of us were using a lot of cyclosporine for our MG patients. When it has an effect, this seems to occur in two to four months. Compared to others, it is a somewhat challenging drug to use because you have to monitor renal side effects, blood pressure and drug interactions very closely.

Mycophenolate Mofetil

Many of us stopped using cyclosporine as often in MG when the drug mycophenolate mofetil (CellCept) became available, primarily because it had fewer side effects and was easier to monitor (Figure 22).

Figure 22

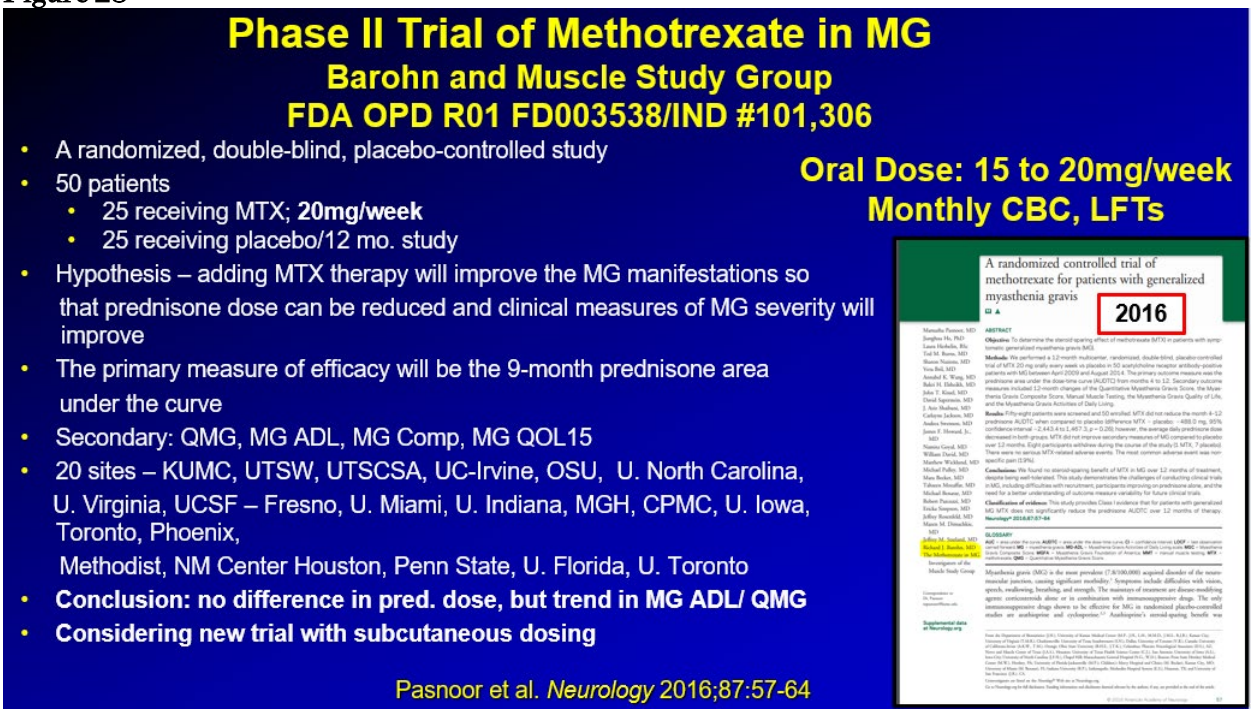


While mycophenolate mofetil is still used by many neurologists to treat MG, there have been two very good randomized controlled trials of mycophenolate mofetil in MG compared to a placebo. Both studies were negative; there was no hint of positivity at all in either study. So while this has dampened our enthusiasm for mycophenolate mofetil, it does not mean that we never use mycophenolate mofetil in MG, but in some clinics, it has lost its placement as a second-line drug for MG.

Methotrexate

When we had the results of the negative mycophenolate mofetil trials we then searched for another oral drug to test in MG, and we turned to the very old compound methotrexate which was originally developed in the 1940s for cancer treatment.

Figure 23



Many of us have been using methotrexate for years for dermatomyositis and polymyositis and we were comfortable using it. We thought that it could be effective in MG. We and others had anecdotal experience of MG patients improving on methotrexate. Our team designed a trial, randomizing patients to methotrexate versus placebo. It was a one-year trial in which patients received methotrexate 20 mg or placebo once a week. In this trial we used oral methotrexate, but subcutaneous methotrexate is also an option and probably produces higher blood levels and may be more effective. In the research trial, we enrolled 50 patients at 20 sites in the US and Canada. We made a decision to use as our primary endpoint the cumulative prednisone dose the patient received during the trial. Our secondary endpoints were the MG-ADL score described earlier and the quantitative MG (QMG) score, an objective measure of strength.

To our disappointment, the study was negative using our primary endpoint of prednisone dose. In other words, patients on methotrexate did not have lower prednisone requirements than those on placebo.

On the other hand, our secondary endpoints were very close to nearing statistical significance. We believe that if we would have chosen the MG-ADL score as our primary endpoint we would have had a better chance of demonstrating that methotrexate was effective in MG. Many of us still believe that methotrexate is effective in some MG patients. In the future we hope to investigate further the use of methotrexate in MG and perhaps to use the subcutaneous delivery method.

Intravenous Immunoglobulin (IVIG)

The MG community began using IVIG for MG in the 1990s. This was about the same time we began using IVIG for Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), and dermatomyositis. IVIG is still not FDA-approved for MG. There has been one well-designed randomized control trial from Canada which showed IVIG was more effective than placebo in MG patients (Figure 24).

Figure 24

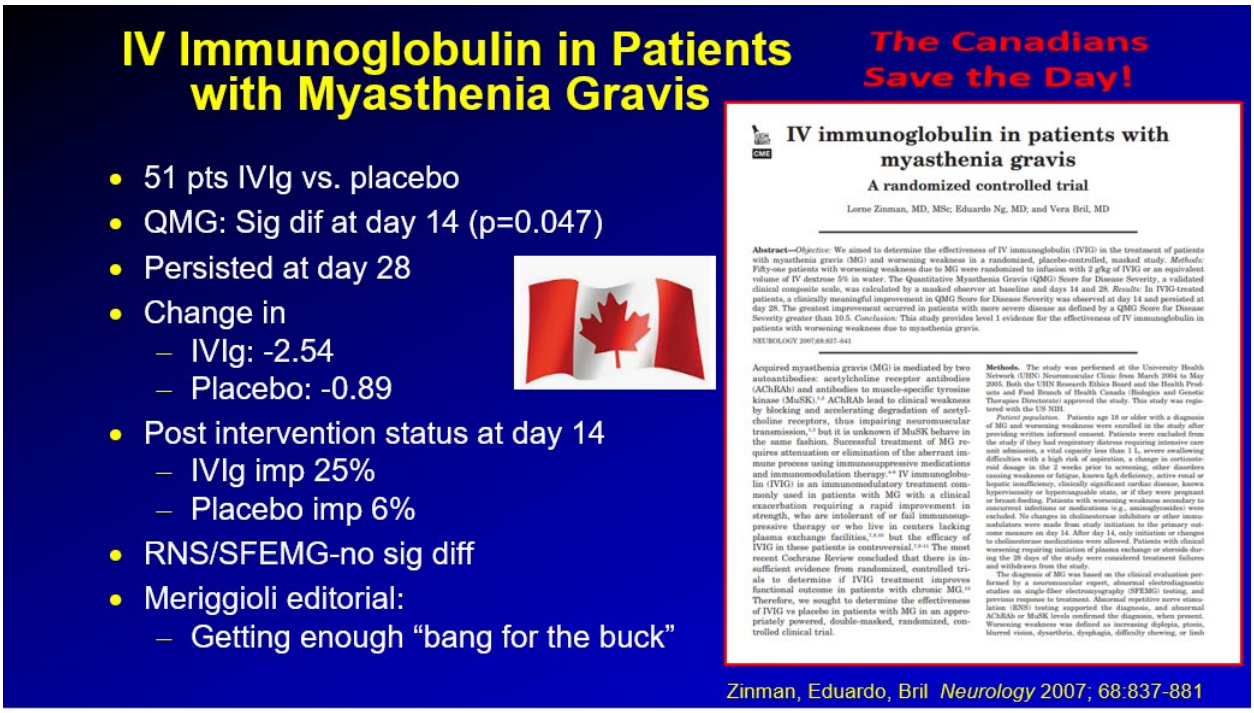
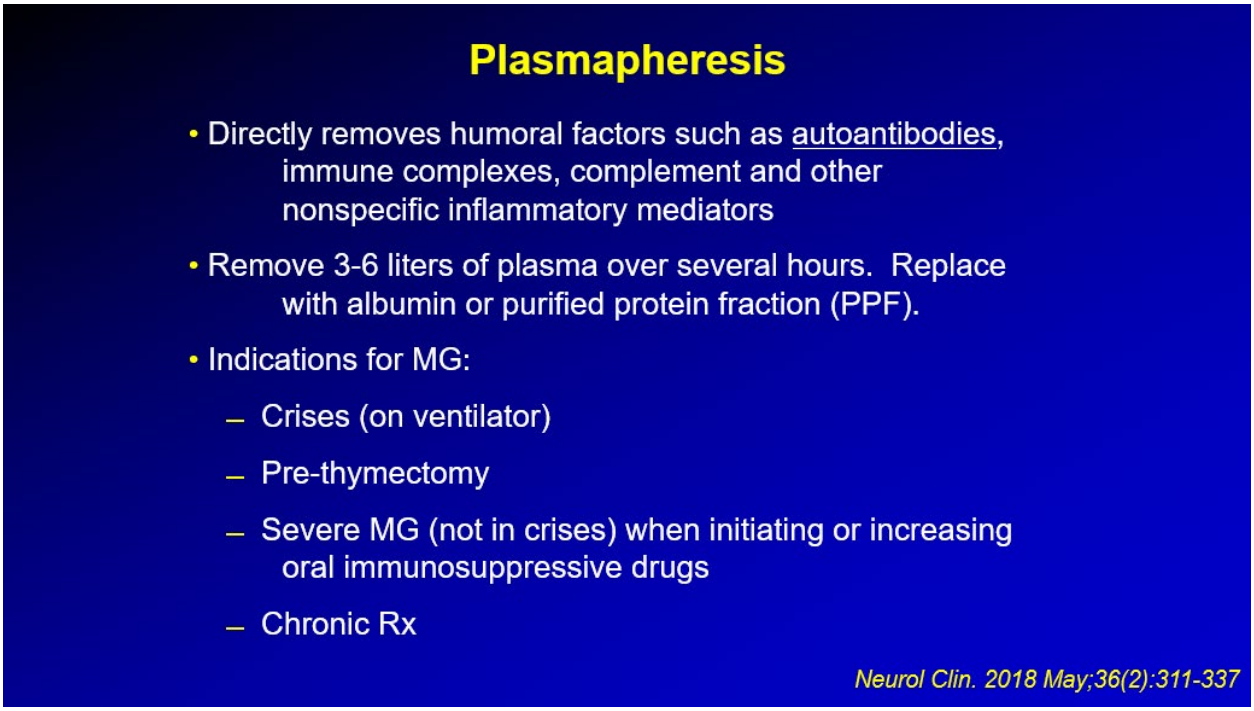


Figure 24 shows a very important article for you to know about. This is the results of the research trials which showed that IVIG is more effective than placebo in a well-designed randomized control trial. It is the best information available to make the case to insurance companies when you are trying to convince them to cover the cost of IVIG in a MG patient. The use of IVIG for MG is similar to the dosing used in CIDP. There is a 2 gram per kilogram loading dose followed by monthly doses of one gram per kilogram. The biggest mistake we have observed by practitioners using IVIG is that they do not continue the chronic maintenance therapy monthly after the loading dose. We recommend monthly maintenance therapy continue for six months and then the patient may be reevaluated to see if the drug has been effective and if it needs to be continued. Usually if the drug has been effective it does need to be continued for even a longer period of time and stopping the drug will often result in a relapse of symptoms.

Plasmapheresis

Plasmapheresis is a technique in which antibodies are removed from the patient's body by removing their plasma. If the patient's plasma contains harmful antibodies such as those directed against the AChR or MuSK causing MG, then removing the antibodies can result in improvement of MG symptoms and signs.

Figure 25

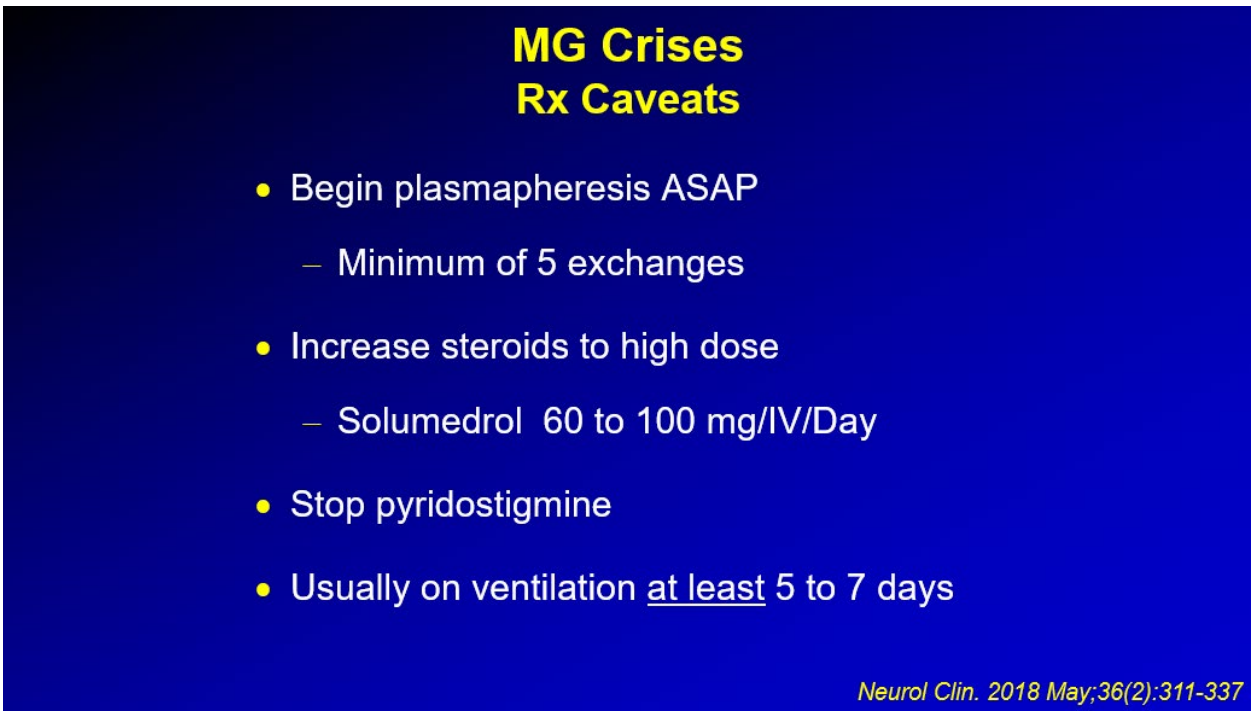


Each plasmapheresis treatment removes 3 to 6 liters of plasma over several hours. Plasmapheresis is most often used in MG when a patient is in crisis and on a ventilator or if the patient is nearly in crisis but not yet on a ventilator, and they are admitted to the hospital for a course of plasmapheresis to avoid further worsening. Occasionally we use plasmapheresis prior to a thymectomy to make the patient stronger in preparation for surgery. However, in the modern era it is less common to use plasmapheresis preoperatively because we try to optimize the patient's status using prednisone and other drugs before the thymectomy.

When we admit the patient for plasmapheresis this generally involves 5 to 10 courses of plasmapheresis over 10 to 20 days. During this time there are other MG medications that are optimized so that when the patient is discharged they will not have to be readmitted when the effect of the plasmapheresis wears off after a few weeks. There are a very small number of patients who require chronic plasmapheresis once or twice a month, particularly MG patients with MuSK antibodies.

We still prefer to use plasmapheresis for our patients in crisis on a ventilator rather than IVIG. We believe plasmapheresis is probably more effective than IVIG in the crisis situation but there is really no comparative effectiveness data on this topic. If your hospital has the ability and experience to use plasmapheresis when an MG patient is in crisis, we would suggest that course of therapy. However, if you are in a hospital that does not have access to plasmapheresis, then loading a patient with IVIG is another option (Figure 26).

Figure 26



A minimum of five plasmapheresis treatments should be performed, but usually if a patient is in crisis they will require more and perhaps up to ten. The plasmaphereses are usually performed every other day to allow time for the patient's clotting factors to reaccumulate between exchanges.

While the patient is on the ventilator, corticosteroids should be given in the form of Solu-Medrol IV up to 60 to 100mg a day. Also, while the patient is on a ventilator, one should stop the pyridostigmine, as it will cause excessive oral secretions and complicate airway management. Pyridostigmine does not have

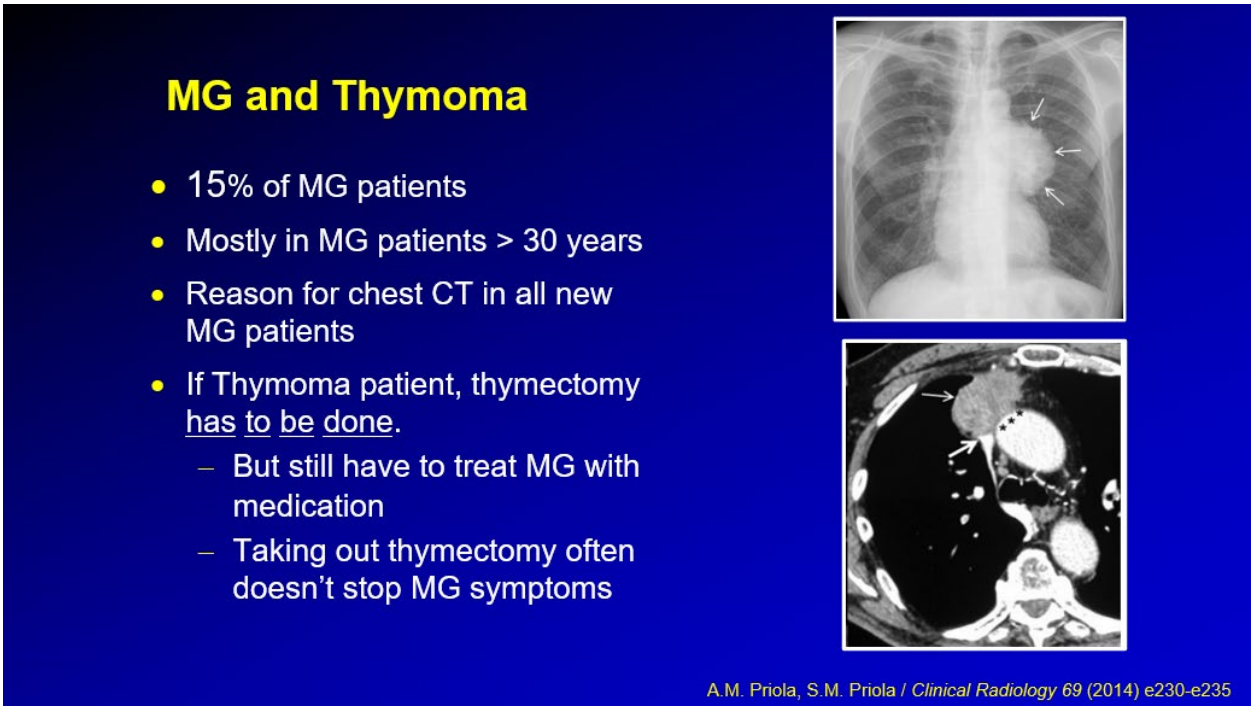
a role in MG crisis. You can restart the pyridostigmine orally when they are extubated and taking oral medications. A myasthenic patient is generally on a ventilator for at least five to seven days in the intensive care unit (ICU).

If the ICU doctors are advocating taking the patient off the ventilator after two to three days when they seem to be improving, there is a need to convince them that the patient needs to be rested on a ventilator for at least five to seven days before attempting extubation.

MG, thymoma, and thymectomy

Thymoma occurs in 15% of MG patients. The reason a chest CT is obtained on all new MG patients, both ocular and generalized, is to search for thymoma. The chest CT is not performed to look for so-called thymic hyperplasia which is a judgement call by the radiologist and can frequently be overinterpreted. The only reason to obtain a chest CT in a MG patient is to look for a thymoma. While a routine chest x-ray can occasionally show a thymoma it is usually only revealed once the thymoma has grown to a large size as shown in Figure 27.

Figure 27



The chest CT is used to demonstrate the presence of a thymoma in its early stages. Figure 27 shows a thymoma visualized on a chest CT. If a thymoma is identified it is mandatory to do a thymectomy as soon as possible. Before the thymectomy is performed the patient should be put on pyridostigmine, and usually they need to also start prednisone and other drugs to improve their status and stabilize them prior to the thymectomy.

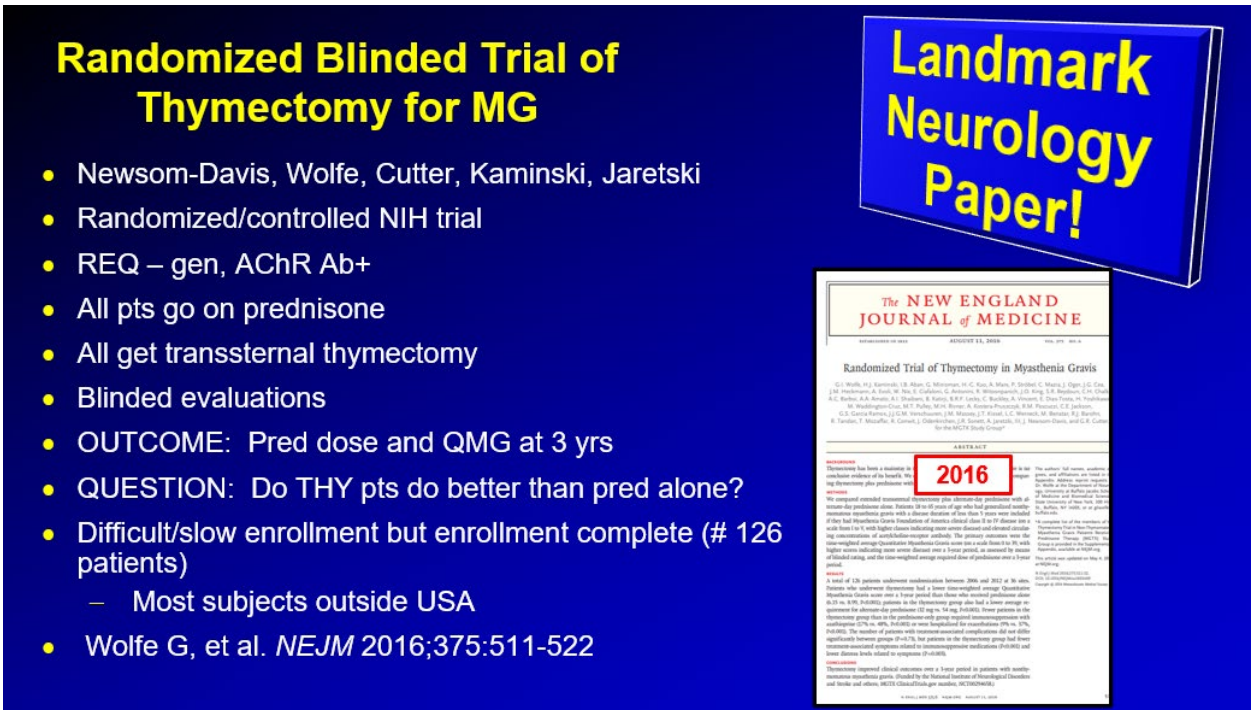
Thymoma is a mandatory reason to have a thymectomy. Thymectomy is also done for MG patients as a form of therapy if they do not have thymoma. This is called non-thymomatous MG and is the most common form of MG. A decision to do a thymectomy is not based on the chest CT in a non-thymomatous patient but based on data discussed below.

Until recently we did not have a randomized controlled trial of thymectomy in MG; now we do.

This is another landmark neurology publication, similar to the initial paper describing plasmapheresis treatment for Guillain-Barré syndrome. We consider both to be landmarks in neuromuscular

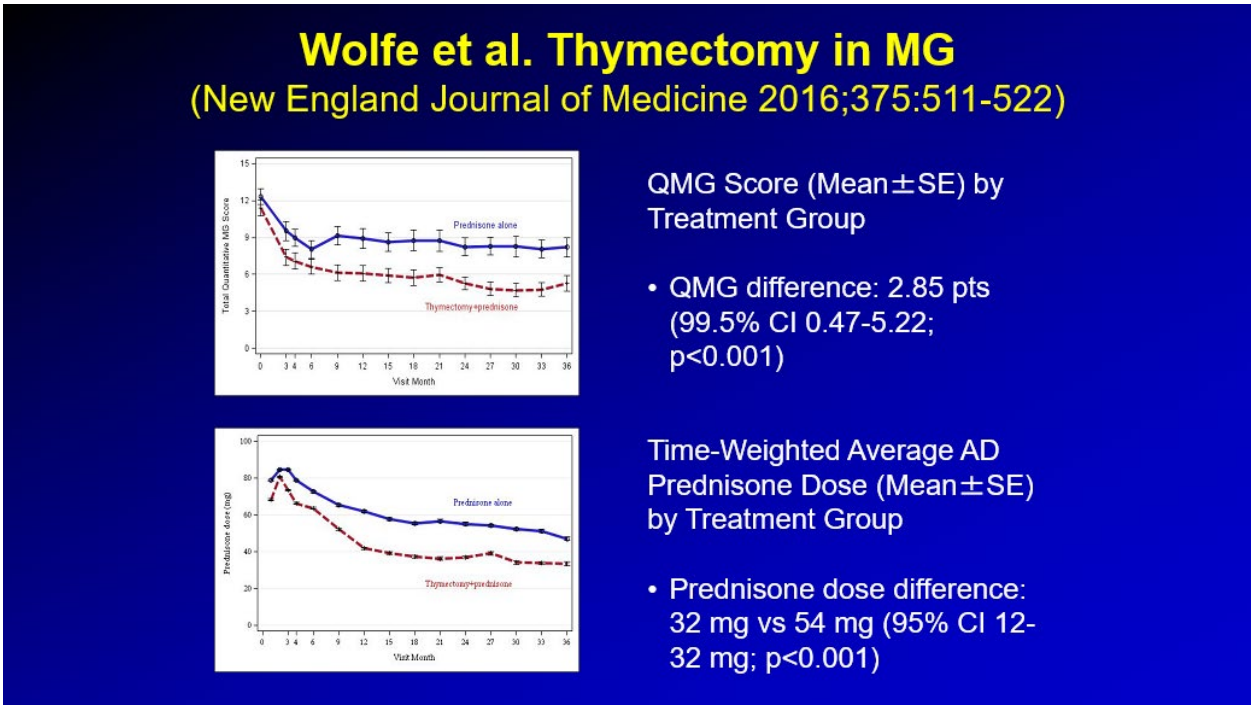
neurology publications as the result of large multicenter trials that led to a consensus and really changed how we managed patients.

Figure 28



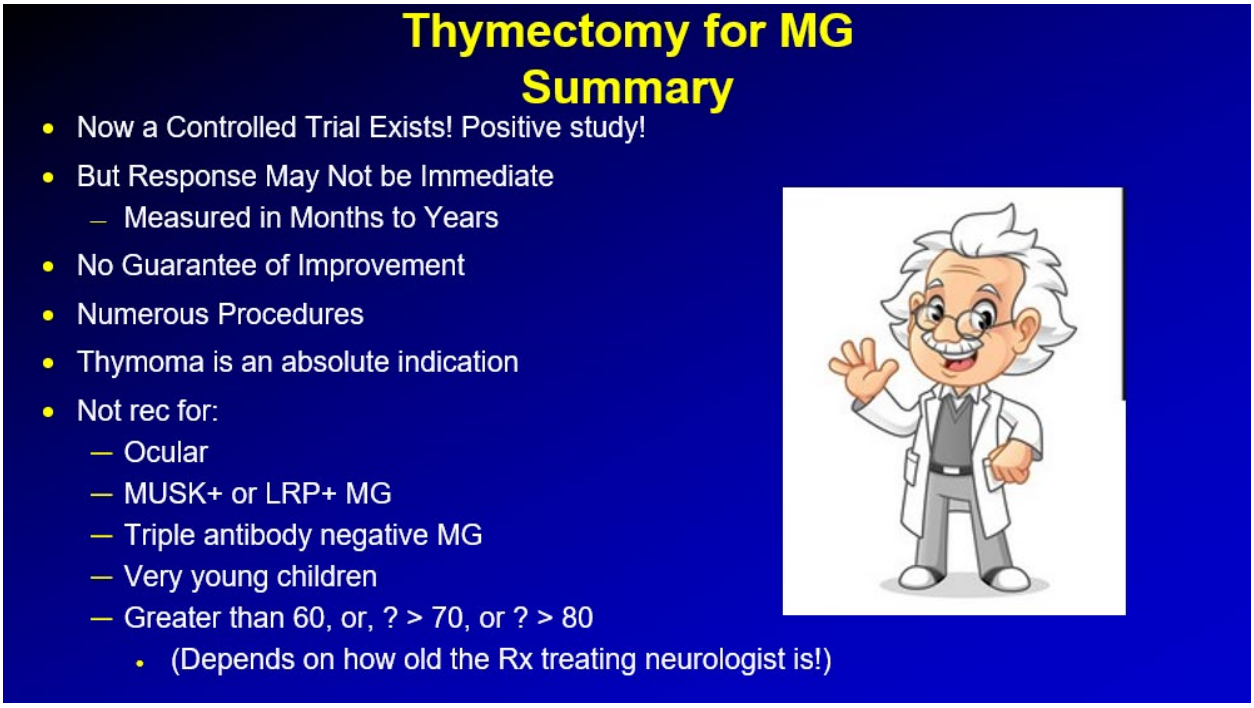
In this international trial, the MG community came together and enrolled over 100 patients and randomized them to either thymectomy or medical treatment. All patients were put on a prednisone-dose protocol and when the patients improved the prednisone was tapered per standardized protocol. What this important study showed was that at four months we can start seeing that patients who receive a thymectomy had a lower prednisone daily dose and also had a lower QMG score indicating improved MG (Figure 29). This data held up in a follow-up study of the same population at five years. Therefore, we now have a controlled trial of thymectomy in MG and to the surprise of many, the study was dramatically positive.

Figure 29



When you advise patients regarding whether or not they want to have a thymectomy, you do need to tell them that the response may not be immediate and that there's no guarantee that the thymectomy will result in an improvement, even though the study showed that overall patients who get a thymectomy are more likely to improve (Figure 30).

Figure 30



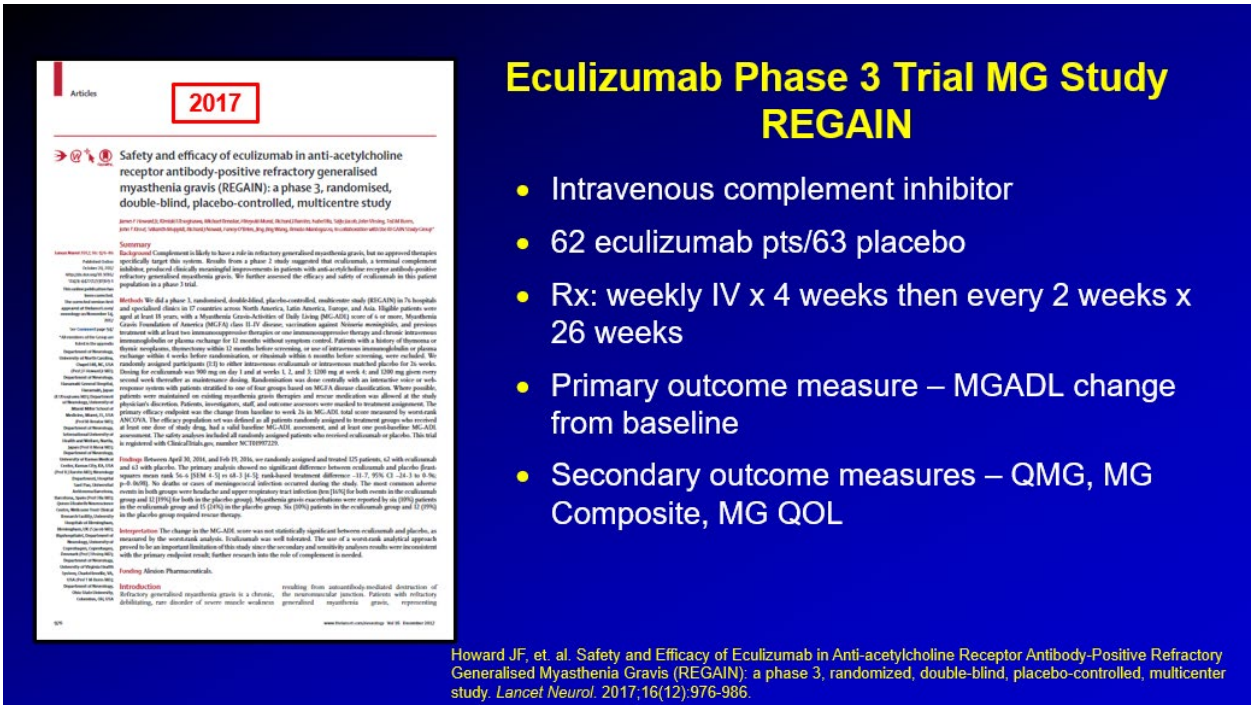
The type of procedure that is done for a thymectomy is variable. In the study that we just referred to all patients received identical extended transsternal thymectomies. However, transsternal thymectomies are not done very often today in the age of robotic surgery, so most patients now receive robotic or minimally invasive thymectomy surgery. We do not believe that there is ever going to be a comparative effectiveness research study comparing the various types of thymectomy.

We do not routinely recommend thymectomy for triple antibody-negative MG, but again this is somewhat debatable. We do not do thymectomies in young children who are under the age of two. Over the years there has been a belief that you should not do thymectomies in someone who is elderly. But the question is what is the upper age at which you would not do a thymectomy and the answer is not known. In the thymectomy study, patients were allowed to be enrolled up to age 65. But if an MG patient is a healthy 73 year-old should they get a thymectomy? We simply do not know the answer based on data and therefore the decision is left to the physician and the patient.

Complement inhibitors in MG

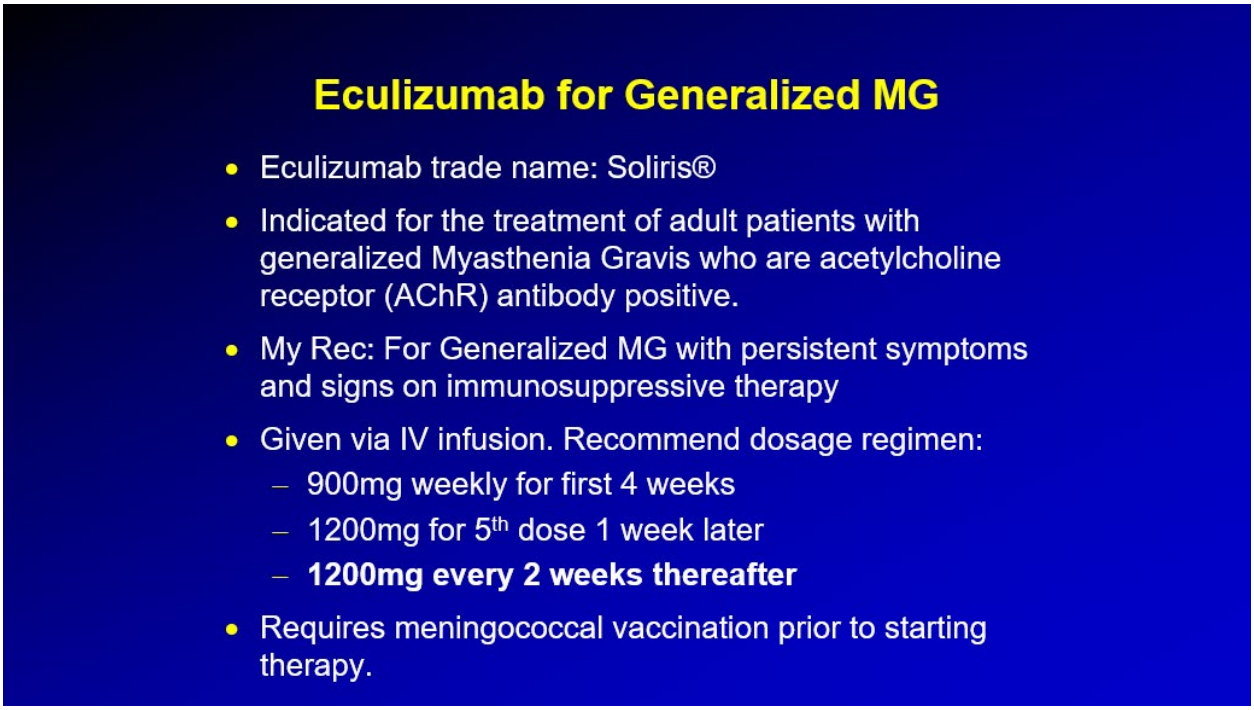
As we mentioned earlier in this presentation, Dr. Andrew Engel and the group at Mayo Clinic first showed how important the role of complement was at the neuromuscular junction in MG (Figure 3). These early pivotal papers were published in the 1970s and 1980s. As mentioned earlier, one of us (Dr. Barohn) performed a study in the 1990s that measured serum terminal complement levels in MG patients and was able to show that not only were they elevated but the magnitude of increase correlated with disease severity. The recognition of the role of complement in MG ultimately led to the pharmaceutical development industry having an interest in trying complement inhibitors as a therapy for MG. Eculizumab had previously been FDA approved for paroxysmal nocturnal hemoglobinuria (PNH) and hemolytic uremic syndrome (HUS). The pharmaceutical company that developed eculizumab for PNH and HUS then performed phase 2 and phase 3 trials for MG.

Figure 31



These trials were successful and showed that patients who received intravenous complement inhibitors had improved MG-ADL scores, and other secondary outcome measures including QMG score. Many believe that the development of complement inhibitors for MG is the biggest breakthrough in MG therapy over the last 50 years. This drug is now FDA-approved under the trade name Soliris. The labeling indication says it is indicated for the treatment of adult patients with AChR antibody positive generalized MG. However, the labeling indication approved by the FDA perhaps may be too wide and currently the neuromuscular community uses eculizumab therapy for generalized MG patients that still have persistent signs on immunosuppressive therapy or when immunosuppressive therapy has previously failed.

Figure 32



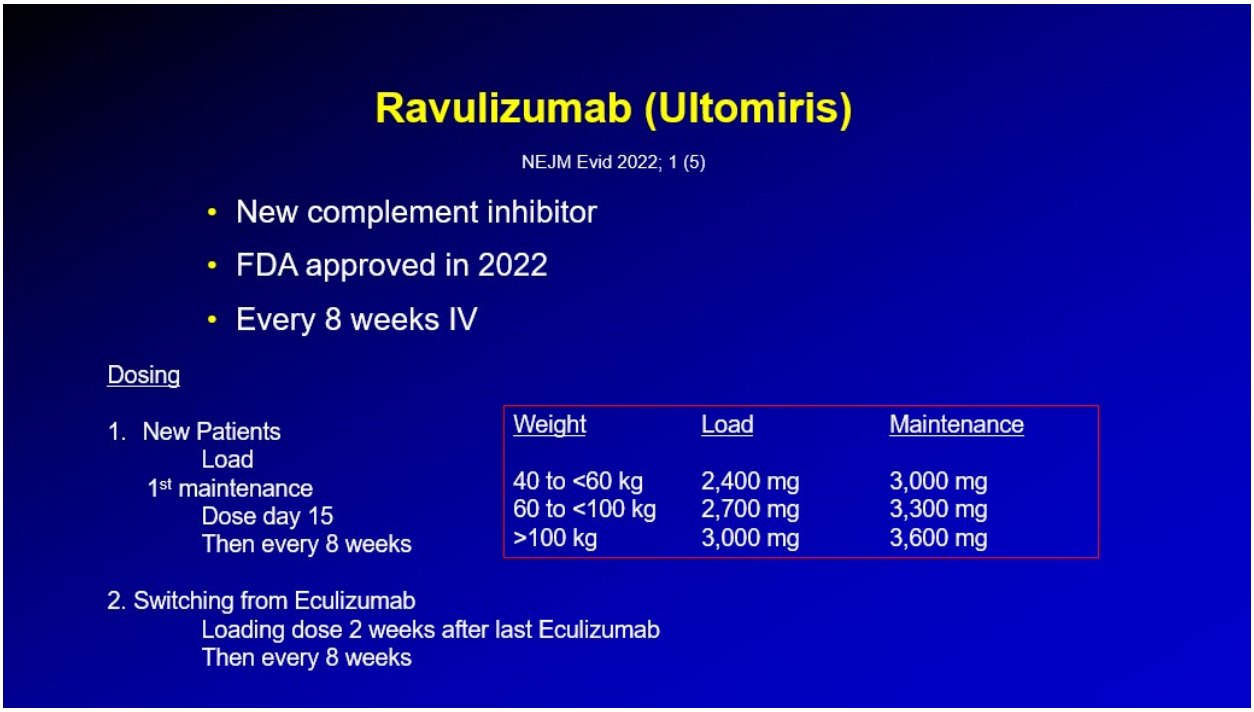
Before a patient receives eculizumab they need to have completed a full meningococcal vaccination regimen.

For the first month, eculizumab is administered weekly and after that, the infusions are given every two weeks. These can be done either in an outpatient hospital setting or at home.

After the release of eculizumab the same pharmaceutical company released ravulizumab (tradename Ultomiris). The major advantage of ravulizumab is that it can be administered every 8 weeks intravenously (Figure 33). Figure 33 shows the recommended loading and maintenance doses for ravulizumab. More recently, zilucoplan (Zilbrysq), another complement inhibitor, was FDA approved (Figure 13). The advantage of zilucoplan is that the drug is self-administered subcutaneously as a quick injection daily. Immunization guidelines for meningococcus have been recently updated by the Advisory Committee on Immunization Practices (ACIP) and should be closely followed for patient safety. In addition to meningococcus vaccination, clinicians should be aware that the late 2024 ACIP

recommendation is not to start complement inhibitors until after a full immunization series with 3 doses of the meningococcus B vaccine which takes 6 months, or in patients who cannot wait for 6 months, they should receive antibiotic prophylaxis. The 2024 ACIP recommendations state: "Persons on complement inhibitor therapy likely remain at substantially increased risk for meningococcal disease, even if they are fully vaccinated or taking antimicrobial prophylaxis...Persons not up to date with meningococcal vaccinations for whom urgent complement inhibitor therapy is indicated should be provided antimicrobial prophylaxis. Few data are available to guide decision-making regarding the optimal duration of antimicrobial prophylaxis; therefore, the duration of prophylaxis should be determined based on clinical judgment. Providers could consider treating patients with antimicrobial prophylaxis for the duration of complement inhibitor treatment."

Figure 33



Rituximab in MG

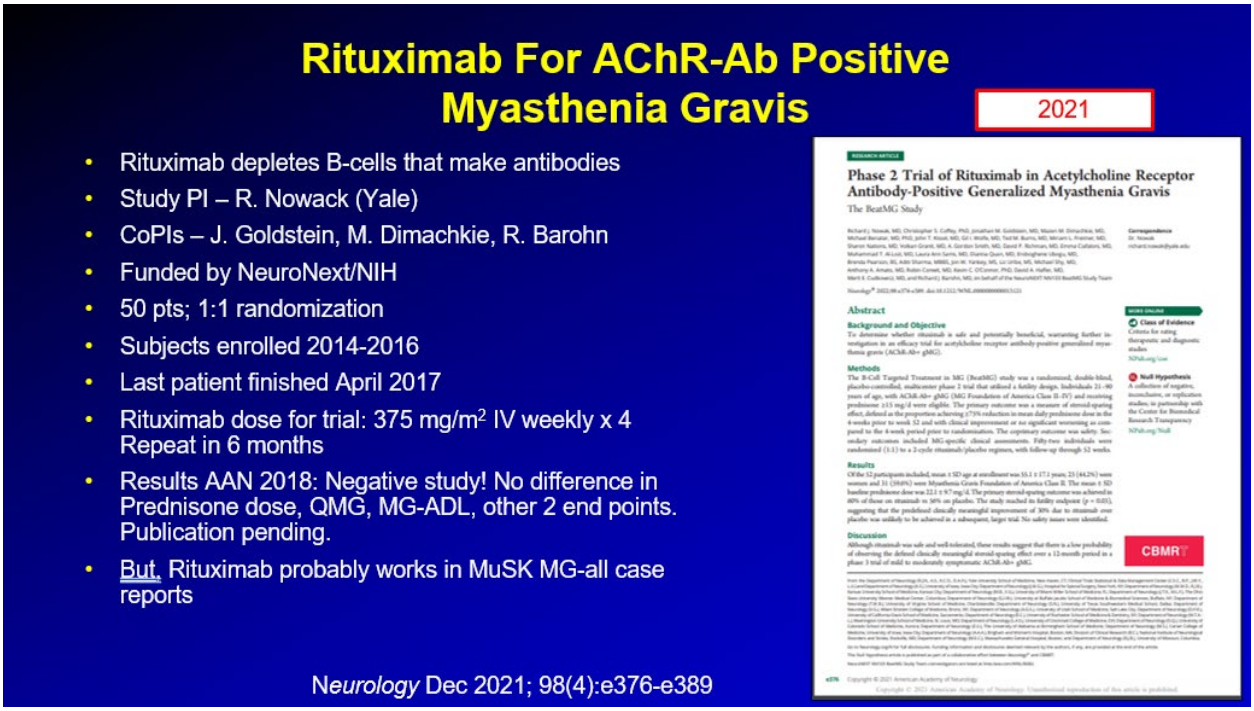
Rituximab was developed as a treatment for hematologic tumors because it eliminates B-lymphocytes. Due to this action, rituximab was applied to MG and other autoimmune diseases. It is generally believed that rituximab is very effective for patients with MUSK MG even though a randomized controlled trial has never been done in this rare patient population.

We all believe rituximab probably works for most MG patients, but MUSK MG is so rare that a randomized controlled trial may never be performed.

Many in the MG community believe that rituximab is effective in AChR-Ab positive MG based on anecdotal experience. This led to a randomized controlled trial in MG with rituximab in MG and generalized AChR antibody MG (Figure 34).

To our disappointment, the study was negative and did not show any steroid sparing effect compared to placebo.

Figure 34



Moore recently, a rituximab study out of Sweden suggested that there might be a benefit in recent onset AChR antibody positive MG.

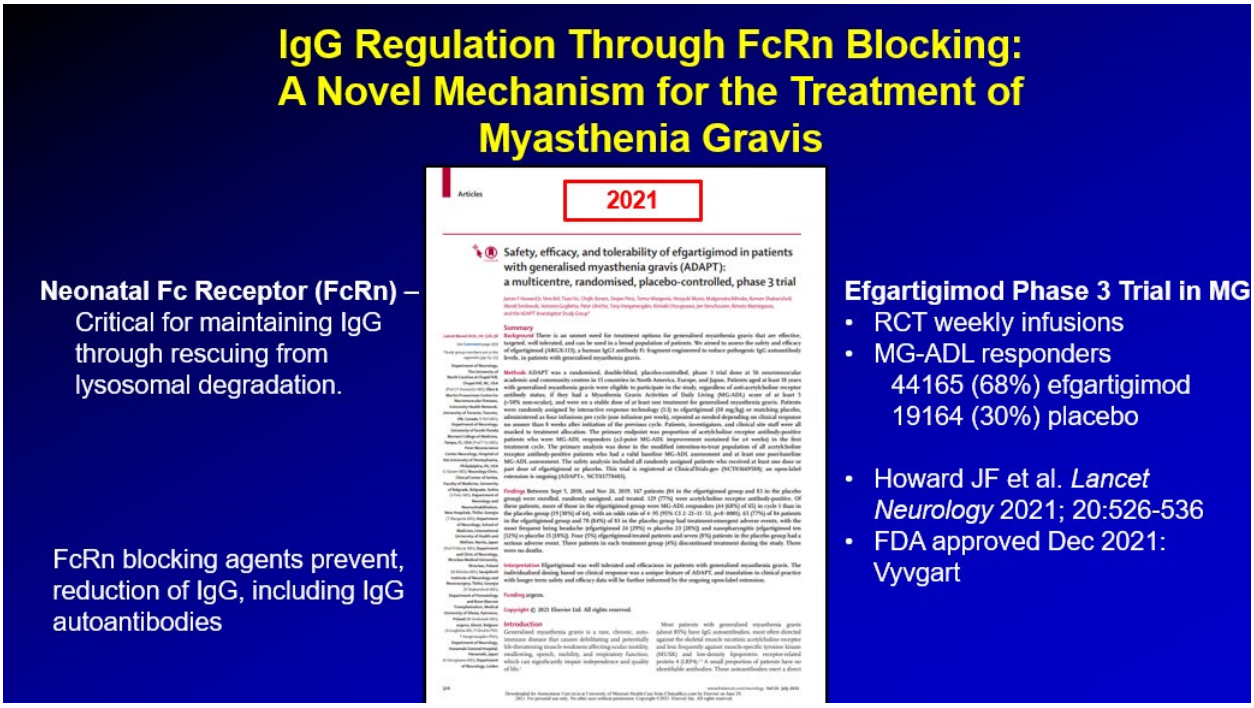
Fc receptor blockers

Another new class of drugs that has shown to be effective in MG is neonatal Fc receptor blockers. Efgartigimod decreases the level of all IgG that a human produces through blocking the FcRn receptor (Figure 35). This novel mechanism of action promotes intracellular lysosomal degradation of IgG. The FcRn is critical for maintaining IgG through rescuing IgG from lysosomal degradation and allowing it to exit the cells after entry as part of normal IgG recycling. Therefore, by blocking the FcRn receptorendogenous IgG levels decrease.

A phase 3 trial with this drug in MG was positive and led to FDA approval. As mentioned above, the generic name for the drug is efgartigimod with the tradename Vyvgart (Figure 13). The intravenous

preparation of this drug is on average given as 4 weekly cycles followed by a break for about 4 weeks, but this is also dependent on the patient's response to therapy. Recently a subcutaneous preparation for this drug has also been FDA approved, efgartigimod SQ, with tradename Vyvgart Hytrulo SQ, as well as another subcutaneous FcRn blocking agent, rozanolixizumab (Rystiggo).

Figure 35



Treatment recommendations for MG

Figure 36

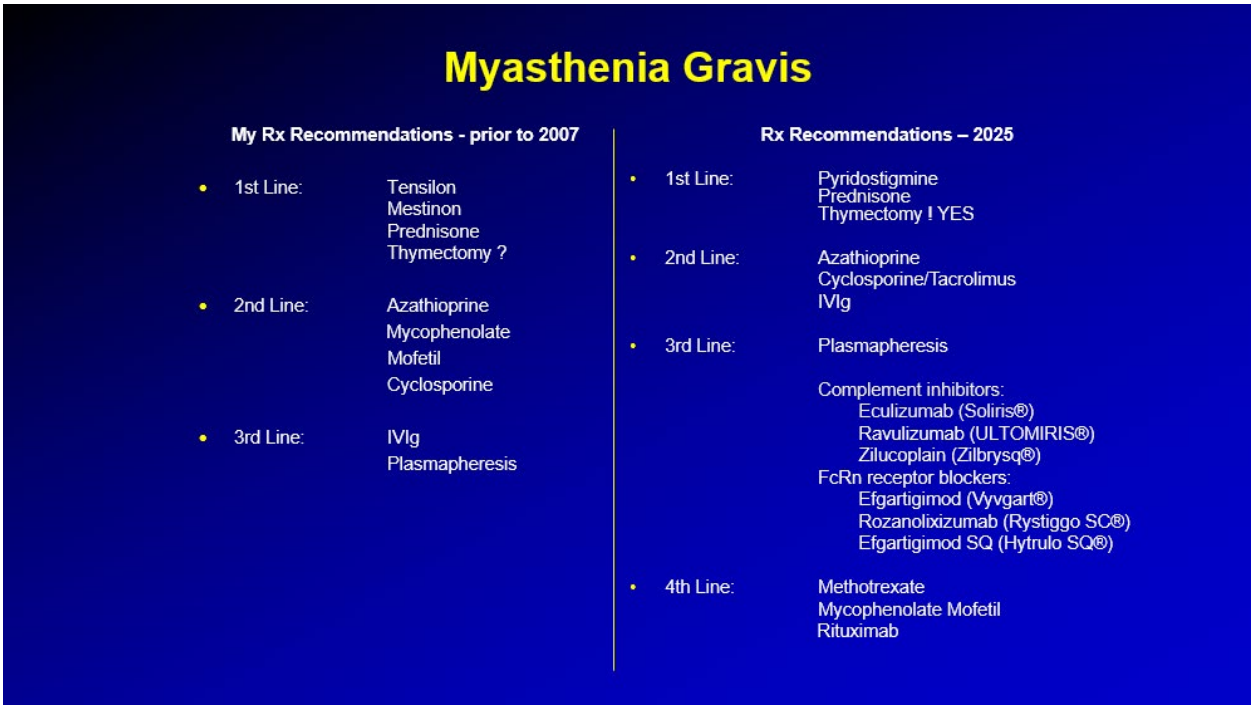


Figure 36 shows what our recommendations for MG were in 2007 compared to what they are now in 2024. This figure shows us how far we have come in the field of MG.

The first line treatment is pyridostigmine and we now have a generic form.

Prednisone is still the first line immunosuppressive treatment. Thymectomy is also a first line treatment, but usually patients are stabilized first on prednisone.

Second line treatment consists of traditional immunosuppressive drugs that have shown to be positive in randomized controlled trials: azathioprine, tacrolimus, and IVIG although all are off label.

Third line treatment is plasmapheresis, and the new class of FDA approved drugs that either suppress complement or the FcRn receptor blockers.

The fourth line category includes drugs that still have not been shown to be effective in randomized controlled trials such as methotrexate, mycophenolate mofetil, and rituximab.

These drugs may work in selected patients, but they are in the fourth line category as the randomized controlled trials with these drugs so far have been negative. Now, there is extensive discussion among the physicians and patients in the MG community whether the complement inhibitor and FcRn receptor blocking drugs can be used as first or second line therapy. In many instances this is now being done but the practice is somewhat restricted because often insurance companies require that at least two traditional immunosuppressive drugs have been used before one of these new classes of drugs can be tried. We suspect that over time as more data accumulates the newer drugs will be used as first and second line therapy.

Emerging Therapies

Chimeric antigen receptors T (CAR-T) cell therapy has revolutionized the care of patients with many advanced malignancies. CAR-T therapies and other related advanced cell therapy approaches are in clinical trials for autoimmune neuromuscular diseases, including MG. The antigenic targets of CAR-T are either the B-cell maturation antigen (BCMA, a marker of plasmablasts and plasma cells) or the CD19 surface cell marker (expressed on plasmablasts and earlier B-cell lineage cells). The goals are to reset the immune system targeting BCMA+ or CD19+ cells, to revert to a naïve B-cell phenotype and to impact pathogenic autoantibody production. Steps in these studies include leukapheresis to remove white blood cells from the patient, cell manufacturing (for T-cell enrichment, followed by virus-based transfection of enriched T cells, then cell expansion), and finally by reinfusion under a controlled setting into the patient. Therefore, this autologous approach requires close collaboration and care coordination between neurology, oncology and cell therapy to manage these complex studies. This is to closely monitor for any adverse event such as cytokine-release syndrome and for immune effector cell-associated neurotoxicity syndrome. The aim from these studies is to assess whether these approaches are safe in MG and ultimately whether patients can reach prolonged drug-free disease remission.

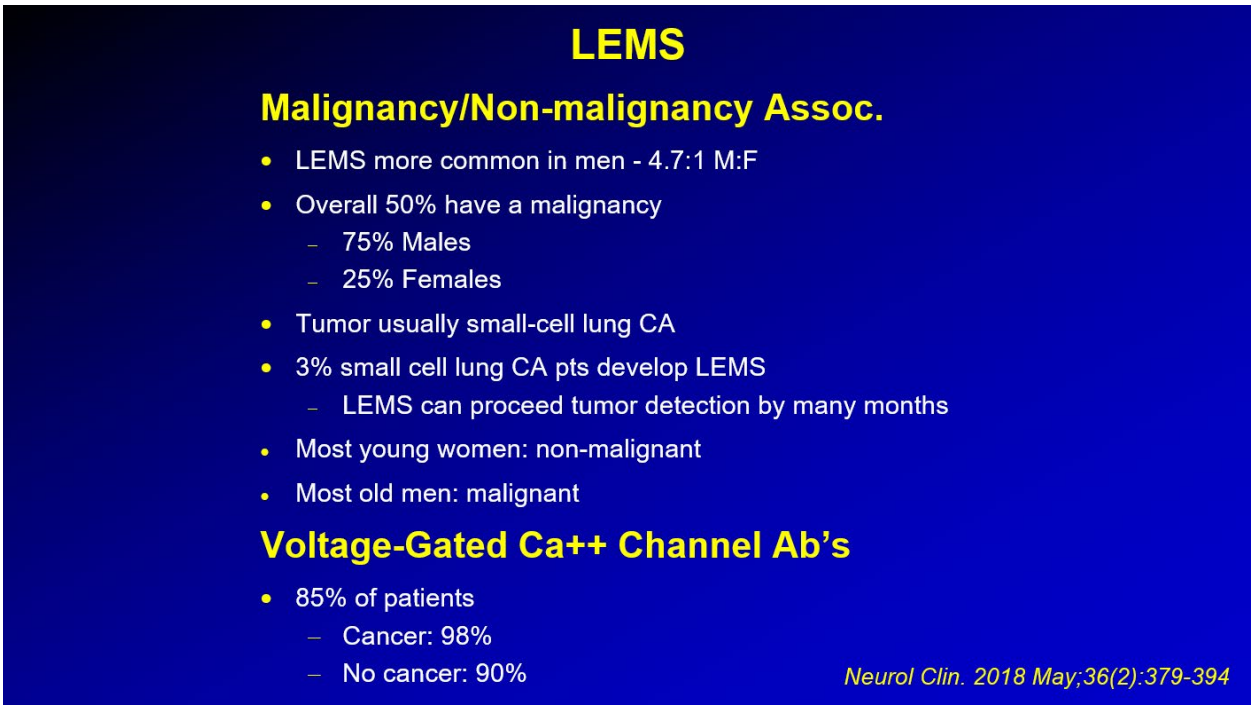
Lambert-Eaton myasthenic syndrome

Lambert-Eaton myasthenic syndrome (LEMS) basically comes in two categories: those patients that have cancer and those who do not have cancer.

The cancer patients are usually older men and the non-cancer patients are generally younger women, although of course there are many exceptions.

Both groups have voltage gated calcium channel antibodies in the blood that are directed against the presynaptic terminals and prohibit the release of acetylcholine into the synaptic cleft. The detection of voltage gated calcium channel antibodies is not specific for LEMS. The diagnosis of LEMS requires electrophysiologic confirmation. This can be done even before the voltage gated calcium channel antibody results are obtained.

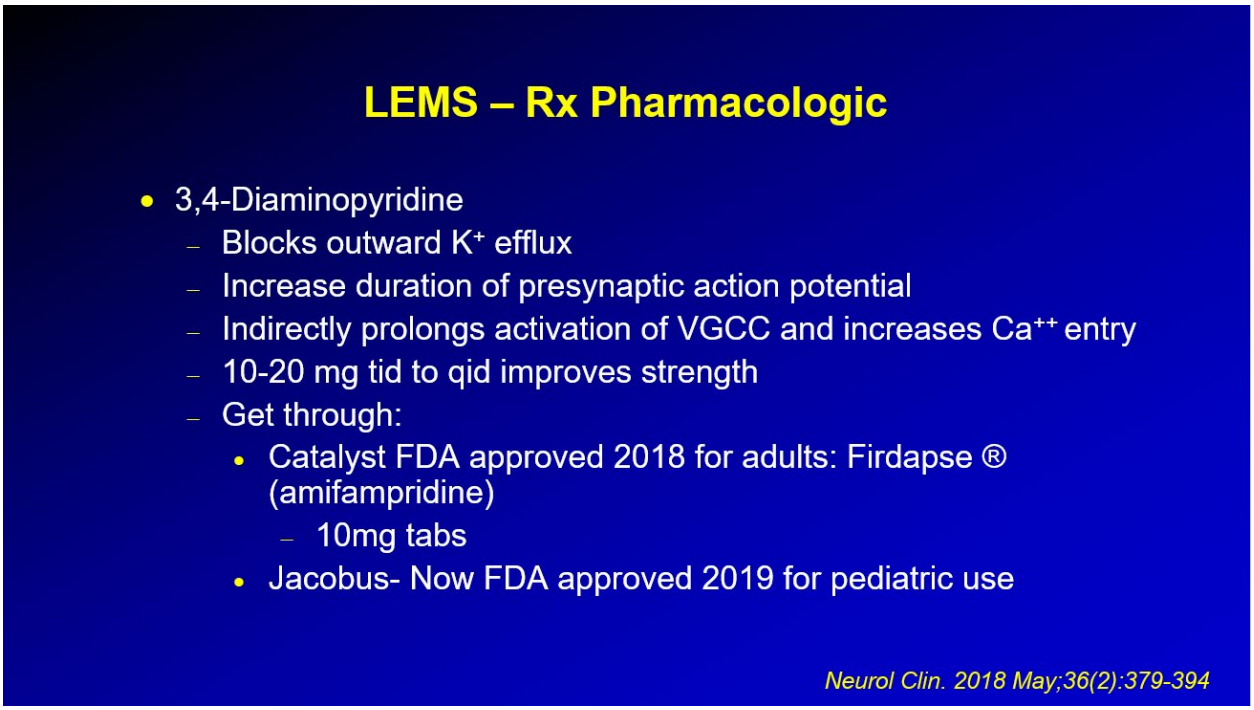
Figure 37



Electrophysiological evidence is obtained via nerve conduction studies when one can show a dramatic increment in the size of the compound muscle action potential either by doing a brief 10 seconds of exercise or by performing 50 Hertz repetitive stimulation.

The treatment of LEMS is twofold: there is symptomatic treatment and there is immunosuppressive treatment. The symptomatic treatment involves giving 3,4 diaminopyridine (Figure 38).

Figure 38



3,4-Diaminopyridine blocks the outward potassium efflux and increases the duration of the presynaptic action potential and thereby indirectly prolongs the activation of voltage gated calcium channels and increases calcium entry.

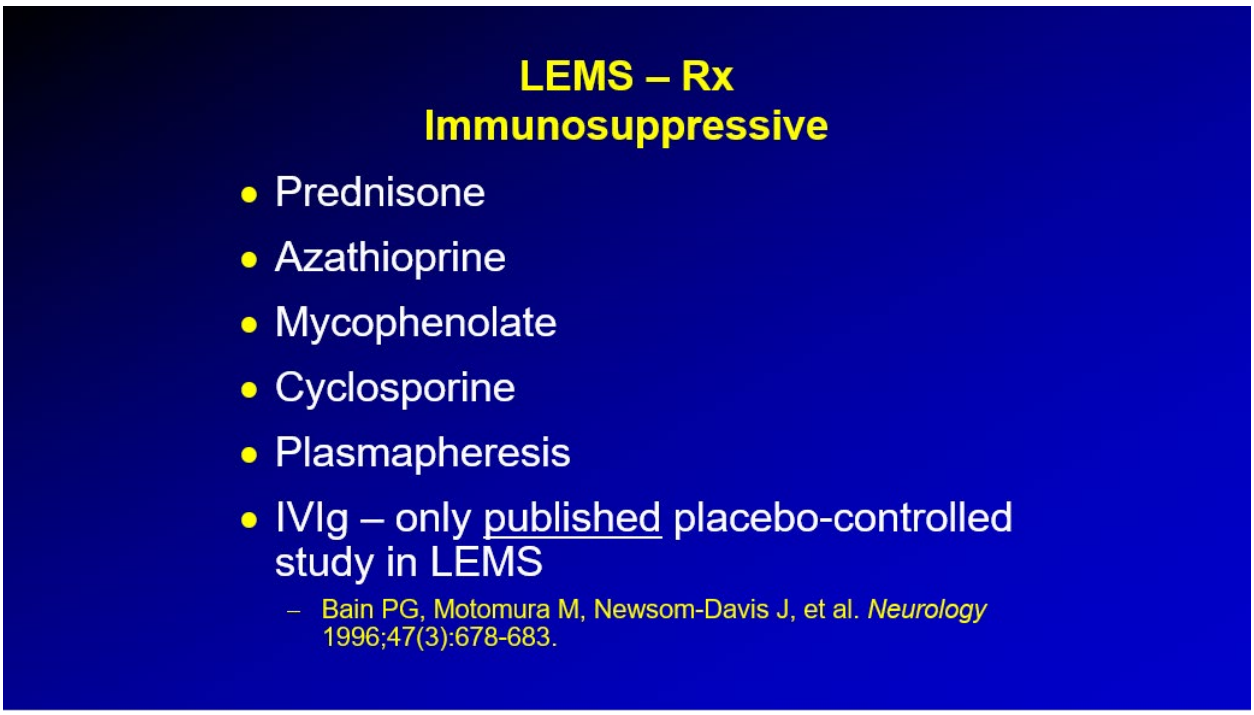
In essence, it increases the presynaptic release of acetylcholine vesicles into the neuromuscular junction.

This is very effective symptomatic treatment for LEMS patients and improves their strength.

The typical dose is 10 to 20 mg three to four times a day.

There were two FDA-approved forms: one is by Catalyst, and it is called Firdapse; the other was made by Jacobus, but that drug is no longer on the market. In the past we could obtain 3,4 diaminopyridine through compounding pharmacy but this is no longer an option now that an FDA-approved drug exists. Even when you put a patient on 3,4-diaminopyridine you usually still have to treat them with immunosuppressive treatment for LEMS and this involves the same traditional drugs that we use in MG (Figure 39).

Figure 39



In general, we do not believe that LEMS can be treated without prednisone. Other traditional immunosuppressive treatments can be used including azathioprine, mycophenolate mofetil and cyclosporine. Plasmapheresis and IVIg are also effective in LEMS.

Amazingly there is a placebo-controlled trial of IVIG in LEMS done by the British in the 1990s which showed a positive benefit of the drug compared to placebo.

Therefore, there are a number of treatment options. The bottom line is even if patients have cancer, you as the treating neurologist have to treat LEMS with 3,4-diaminopydridime because treating the cancer alone will not improve the weakness from LEMS.

Many of the patients who have small cell cancers and LEMS will die in a matter of months. Therefore, the goal of the neurologist is to keep them as strong as possible as long as possible so they can enjoy the remaining days that they have.

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