Myasthenia Gravis Contraindicated Medication List with Clinical Notations and Full References

Myasthenia Gravis Hope Foundation

Please Note:

This list serves as a cautionary tool to promote safer care and improve clinical outcomes. Various drugs have been linked to exacerbating Myasthenia Gravis (MG) in all its subtypes. It's important to note that these drug associations do not automatically rule out their use for MG patients, as many reports are context-dependent.

Also, some of these drugs may be clinically necessary for a patient's treatment and should not be automatically discarded. Therefore, some of these drugs should not necessarily be considered "off limits" for MG patients. Careful thought needs to go into decisions about all prescription interventions and management. It is advisable that patients and physicians recognize and discuss the possibility that a particular drug might worsen the patient's MG.

If this risk is moderate to significant, a careful monitoring period with rescue measures in place should be carefully understood by all parties. Both parties should also consider, when appropriate, the pros and cons of an alternate treatment, if available. It is critical that the patient notify his or her medical team right away if the symptoms of MG worsen after starting any new medication. This list is compromised of the more common prescription drugs with the strongest evidence suggesting an association with worsening MG. ***This list should in no way be considered exhaustive.***

It is always important to discuss medications with your established practitioner before making any changes to your care regimen.

Autoimmune Myasthenia Gravis (MG) is a rare neuromuscular disease due to an autoimmune attack against components of the neuromuscular junction. MG is a multifactorial disease resulting from a combination of genetic predisposition and environmental risk factors [1]. The disease can be classified according to the severity of the symptoms, age of onset, antigenic targets, and thymic-associated abnormalities. MG is characterized by fluctuating muscle weakness that can affect different muscles. Two major forms of the disease are described: an ocular form (15%) and a generalized form (85%). Symptoms of the ocular form are restricted to the eyes, causing ptosis and/or diplopia. Generalized MG involves ocular, bulbar, limb, facial, and respiratory muscles. A respiratory crisis is the main life-threatening event that occurs in MG patients and leads to hospitalization [2]. Disease exacerbation without crisis can also lead the patient into the hospital to seek interventional or bridging therapies. It is important that both clinician and patient does not wait until a crisis is presenting itself before intervening. It is also important to note that a severe exacerbation without respiratory crisis can present in multi-factorial ways and does not limit itself to a singular presentation. Additionally, patients can have severe symptoms including bulbar and respiratory manifestation without significant limb or ocular weakness. It is imperative to look at all possible co-factors that might exacerbate the disease (ie., electrolyte imbalances, dehydration, low protein, acidosis, hormone or thyroid imbalances, severe stress, infection or inappropriate mediation regimens).

Ongoing research shows that Myasthenia Gravis continually changes its presentation even within the same individual and it is critical the clinical teams evaluate the variability of symptom manifestation without bias or presumption against the individual.

Alpha-Interferons (studies have reported inducement of MG with this treatment and sporadic case studies also report disease worsening with unknown frequency or severity of exacerbation. Caution and alternatives are recommended unless otherwise unavoidable.)

Analgesics: (Can be used quite safely in most patients but it is considered appropriate to monitor the patient during initial administration**.** Opioid medications such as Buprenorphine, Fentanyl, Hydromorphone, Methadone, Morphine, Oxycodone and Oxymorphone are commonly used as sedatives and management of acute and chronic pain, and are generally well tolerated in patients with MG, although high doses can suppress respiratory function. Fentanyl and Propofol have been successfully used in conjunction with non-depolarizing neuromuscular blockers in surgical procedures on MG patients, including during thymectomy.)

Antibiotics: Most antibiotics that have been identified as harmful to patients with MG interfere with neuromuscular transmission. In normal neuromuscular transmission, acetylcholine is released into the neuromuscular junction after a nerve impulse is sent from the brain. Acetylcholine crosses the junction and attaches to a receptor site on the muscle, depolarizing the muscle and allowing it to contract. In patients with MG, the number of receptor sites is reduced, preventing proper contraction and resulting in generalized muscle weakness. The addition of certain antibiotics can further hinder neuromuscular transmission and create life-threatening consequences. [5]

As infection can cause a myasthenic exacerbation or crisis, it should be treated swiftly while taking care to avoid additional therapeutic patient harm. Certain antibiotic agents should be avoided, if possible, in patients with MG. Antibiotics can impede neuromuscular transmission by blocking the release of acetylcholine presynaptically, competitively binding with the acetylcholine receptors post synaptically, or acting at both sites in combination. [1,2]

Most notably, aminoglycosides, fluoroquinolones, macrolides, and telithromycin may interfere with neuromuscular transmission and lead to worsening muscle weakness. When this occurs, clinical deterioration typically begins within 24 to 48 hours after the new antibiotic is begun; however, there have been cases in which clinical decline occurs within minutes. [2,3]

The severity of the reaction also varies, with patients experiencing mild to severe weakness requiring differing levels of clinical intervention. Additionally, patients with no known history of MG have been reported to first experience myasthenic weakness after antibiotic use. Therefore, all providers should be aware that in addition to the potential for antibiotics to aggravate existing MG, antibiotics may also unmask undiagnosed MG. [2,4]

- *Fluroquinolines and Macrolides* full classes are considered high risk with definite ADR.

- *Aminoglycosides* exhibits neuromuscular transmission impairment pre and post synaptically. ADR considered probable.

- *Penicillins* exhibits neuromuscular transmission of unknown severity. Animal models and reported exacerbations classifies this as a probable ADR of unknown severity. It is recommended that the patient is closely monitored with the initiation of this treatment.

- Amikacin, Amoxicillin, Augmentin, Blaxin, Cinoxacin, Chloroquine, Ciprofloxacin, Clarithromycin, Clindamycin, Doxycycline, Eradicil, Erythromycin, Gentamicin, Hydroxychloroquine, Kanamycin, Ketek, Levofloxacin, Lymecycline, Minocycline, Moxifloxacin, Nalidixic Acid, Neomycin, Netilmicin, Norfloxacin, Ofloxacin, Oxytetracycline, Penicillins (mildest risk among this list), Polymyxin, Rosoxacin, Streptomycin, Tobramycin, Tetracycline, Zithromax.

- High caution and continued observation strongly recommended when these medications are necessary. Not an exhaustive list of all drugs within these known classes.

- ***Cephalosporins, Clindamycin, Nitrofurantoin, Polymyxin B, sulfa drugs (including trimethoprim/sulfamethoxazole), and tetracyclines and have no or rare reports of exacerbation and are considered good alternatives.***

Anti Convulsants: (Barbiturates, Dilantin, Gabapentin and Phenytoin. Several Myasthenia-like symptoms are listed in the Gabapentin monograph as low-frequency adverse events, increasing the possibility that Gabapentin is associated with unmasking or worsening Myasthenia Gravis in clinical trials. Gabapentin and similar medications should be used with caution in patients with Myasthenia Gravis, and clinicians are cautioned to be aware of the potential risks of this therapy. ADR is probable but severity risk remains moderate.)

Antihistamines and Decongestants: (Benadryl, Claritin D., Sudafed. - *All* diphenhydramine agents pose the risk of inhibiting acetylcholine post synaptically and decreasing muscle function in MG. Use as a pre-medication for certain intravenous therapies can be initiated with careful observation.)

Anthelmintics (produces a depolarizing-type neuromuscular blockade.)

Antiemetics: (Meclizine, Metoclompramide, Promethazine. Anti-cholinergic properties with varying reports of exacerbation and ADR risk. Ondansetron is generally well tolerated. Management with this class of drugs can be tricky depending on the clinical context of use, however it is possible to use these medications carefully with ongoing observation when needed.)

Antimuscarinic Drugs: (*medicines for Parkinson's*; Orphenadrine, Procyclidine, Trihexiphenidyl)

Antimuscarinic Drugs: (f*or urinary incontinence*; Oxybutynin, Tolterodine Trospium)

Atropine: (sometimes used to reverse a cholinergic crisis. **Robinul** may be considered a safer cholinergic reversal by comparison only but may not be available in emergencies.)

Botox (Presynaptic reduction in ACh release. ADR is considered definite. Avoid if possible, may be offered with caution and slow dose titration to patients with mild/stable MG who also have blepharospasm or cervical dystonia.)

β-adrenergic blockers (classified ADR as possible. General recommendation is considered acceptable risk for patients with stable disease course. Monitoring recommended.)

Cardiovascular Drugs Generalized: (Beta Blockers, Bretylium, Calcium Channel Blockers, Propafenone, Quinidine, Quinine. Cardizem is considered a more benign alternative. Monitor carefully with any introduction of these medications.)

L type Calcium Channel Blockers (unclear severity on neuromuscular transmission. Considered appropriate in stable patients but monitor closely for adverse response.)

Class Ia anti arrhythmics (Chloroquine, Hydroxychloroquine, Procainamide, Propafenone, Quinidine and Quinine exhibit significant impairment of neuromuscular transmission, pre and postsynaptic levels. Considered a likely ADR with significant risk.

- There have been no known reports of class Ib antiarrhythmics, such as Flecainide, potassium channel blockers (such as Amiodarone and Dofetilide), and Moricizine causing worsening of symptoms in MG patients.

Corticosteroids (Oral prednisone or prednisolone are now one of the main first line immunosuppressant treatments for ocular and generalized MG. However, high doses of steroids may result in paradoxical MG exacerbation or crisis especially in the first 2 weeks after starting the treatment. The frequency of steroid-induced MG exacerbation has been estimated between 25 and 75%. Initiating steroid therapy at low therapeutic doses and slowly increasing is appropriate to avoid drug induced exacerbation. MG exacerbation and induced weakness can also occur when steroid agents are titrated too rapidly. It is important to consider the adrenals and MG when adding or reducing steroid therapy.)

CT Dye/Contrast/Iodinated Radiographic Contrast: (Lothalamic Acid, Diatrizoate Meglumine, Diatrizoate Methyl-sulfate. Older contrast agents have higher association of exacerbation.)

D-L-carnitine (but *not* L-carnitine. ADR severity unknown. Severe weakness has been noted in studies with improvement following discontinuation.)

General Anesthetics: (Atracurium, Cisatracurium, Doxacurium, Gallamine, Mivacurium, Pancuronium, Pipecuronium, Rocuronium, Tubocurarine, and Vecuronium. These agents have been shown to inhibit/ Interfere with neuromuscular transmission. To be used in extreme caution. MG patients are potentially more sensitive to sedatives and anesthetics. It is important to note that timing of anesthesia and surgical procedures are also important. MG patients ideally should be the first case of the day due to optimized strength for the patient, new anesthesia tubing and other materials so no gas residuals remain from previous cases that can negatively impact the patient and timing with ongoing home therapeutics to increase stability preoperatively, are critical.)

- Agents such as Desflurane, Enflurane, Halothane, Isoflurane, Nitrous Oxide and Sevoflurane are used for intubation as well as maintenance of anesthesia. Myasthenic patients require smaller amounts of these agents than normal, but the effects on neuromuscular transmission do not extend beyond the discontinuation of the agent, thus permitting rapid post-operative extubation of patients with Myasthenia Gravis. Drugs such as Propofol and opioids in therapeutic concentrations are considered to be less risky for patients with defects of neuromuscular transmission.

Hyoscine (used to treat bladder spasms)

Hormones: (Estrogen, Progesterone, Birth Control Pill. <u>It is important to note that levels can and should be corrected when low, but keep in mind that replacement can still exacerbate. Elevated levels have a more significant risk of disease exacerbation.)</u>

H-2 Receptor Antagonists (research is unclear on the risk rate and frequency of exacerbation. Some studies have noted an unmasking of latent MG with initiation of therapy.)

Immune Checkpoint inhibitors (T cell activation, Increased ratio of T effector to T regulatory cells, B cell activation, autoantibody production, cytokines such as IL-17. Avoid after emergence of life-threatening MG. Considered high risk in unstable and high disease burden patients. Risk for ADR is considered definite.)

Local Anesthetics (Lidocaine, Procaine, etc... Carbocaine is considered the safest in this family as it is shorter acting. These mediations can be safely used but careful monitoring is key, especially in peri and post operative conditions. Watch for increased lethargy, generalized weakness and changes to respiratory status.)

Lithium (Presynaptic: reduction in ACh synthesis and release; postsynaptic: reduction in number of AChRs. Reported to cause de novo MG. ADR seen as probable in limited studies, however stable patients with close monitoring are considered candidates for treatment.)

Magnesium and Magnesium Products (be especially mindful of gi preps and epsom salts. pre and post synaptic impairment. Caution and close monitoring are advised in magnesium replacement -specially parenteral- in MG patients. Elevated concentrations either natural or synthetic - unless deficient in biochemistry - can also significantly and rapidly increase systemic weakness acutely. Replacement has been shown in some case studies to still cause significant exacerbation. Slower replacement -recommendation 25ml/hr if well tolerated- than typical protocol is considered key, especially intravenously.)

Muscle Relaxants (even in cases of intubation, it is best to avoid whenever possible. ADR definite with significant severity in moderate to severe presentations. Limited case studies show exacerbation of varying degrees in stable presentations.)

Neuromuscular Blocking Agents (Postsynaptic neuromuscular blockade. ADR definite and typically significant. Non-depolarizing NMBs and inhalation anesthetics better be avoided; if used, observe close postoperative monitoring. Alternatives to consider: using acetylcholinesterase inhibitor and Sugammadex.)

Opthalmalic Drugs: (Acetazolamide, Betaxolol, Echothiophate, Hydrochloride, Proparacaine, Timolol, Tropicamide. *ALL dilators are anticholinergic!*)

Psychotropic Drugs: (Lithium, Phenothiazine, tricyclic antidepressants like Amitriptyline)

Rheumatologic Drugs: (Cholorquine, D-Penicillamine, Hydroxychloroquine, Procainamide)

Statins (known for inducing myopathies even in patients without Myasthenia Gravis. Use alternatives whenever possible. ADR probable. Recommendation is to discontinue in cases or exacerbation. There is accumulating evidence suggesting that statins may cause MG-like symptoms, MG exacerbation, and induction of de novo MG.)

Tyrosine kinase inhibitors (Inhibition of neuromuscular transmission. ADR considered probable with Tandutinib.)

It is important to note that this list is not exhaustive. It is imperative that all medications are carefully checked to see if they are anti-cholinergic or have known synaptic inhibition regardless of their status on this or any other contraindicated list. The MG Hope Foundation strongly recommends to all providers to track patient responsiveness to all medications whenever feasible to help develop accurate data and create safer outcomes for future generations of patients.

Please note your patient's subtype, age, severity and status pre and post interventions to facilitate more accurate clinical pictures for all patients and future research.
Thank you for your patience and care for your MG patients!

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