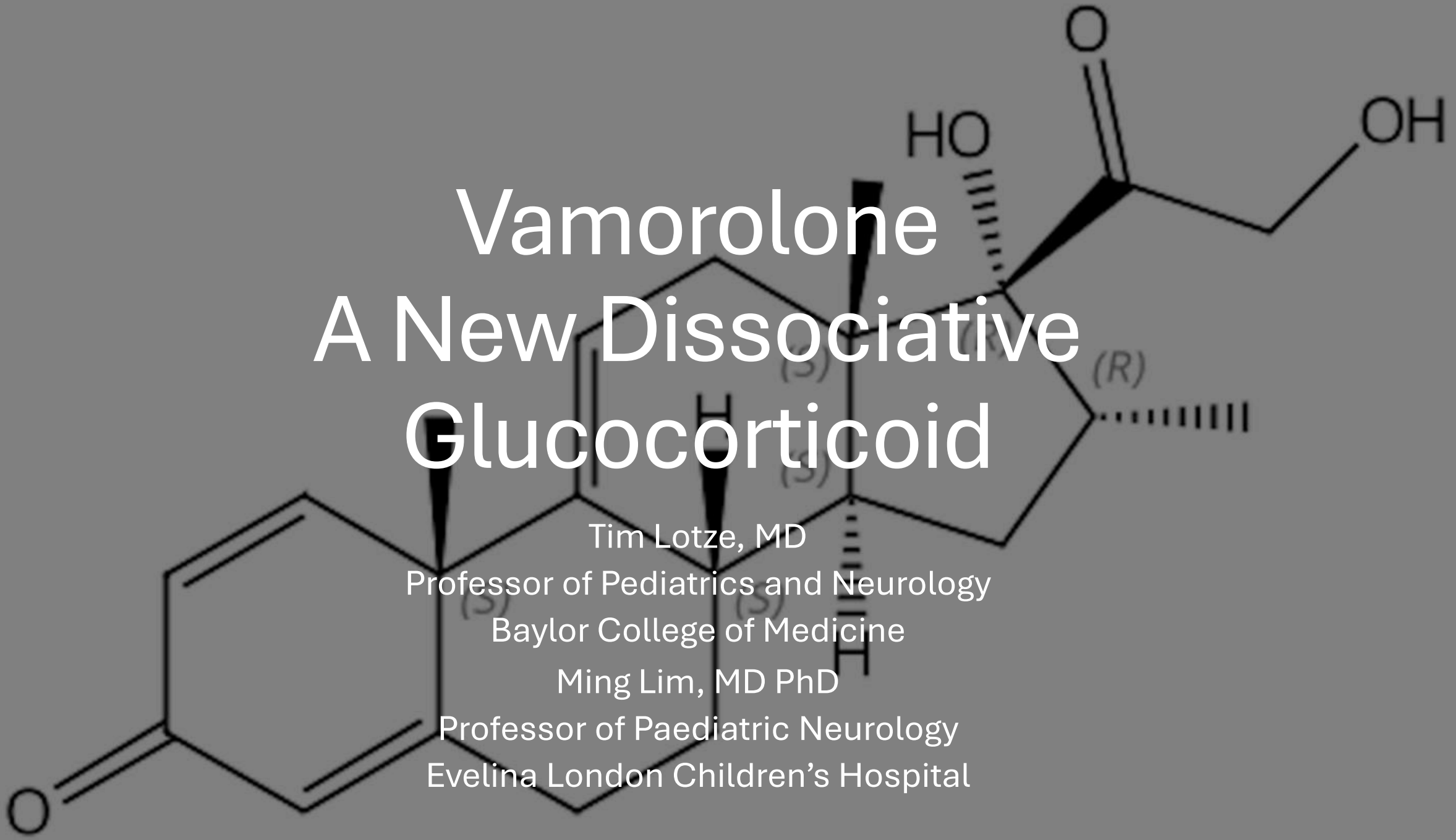
Vamorolone
A New Dissociative Glucocorticoid



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Overview

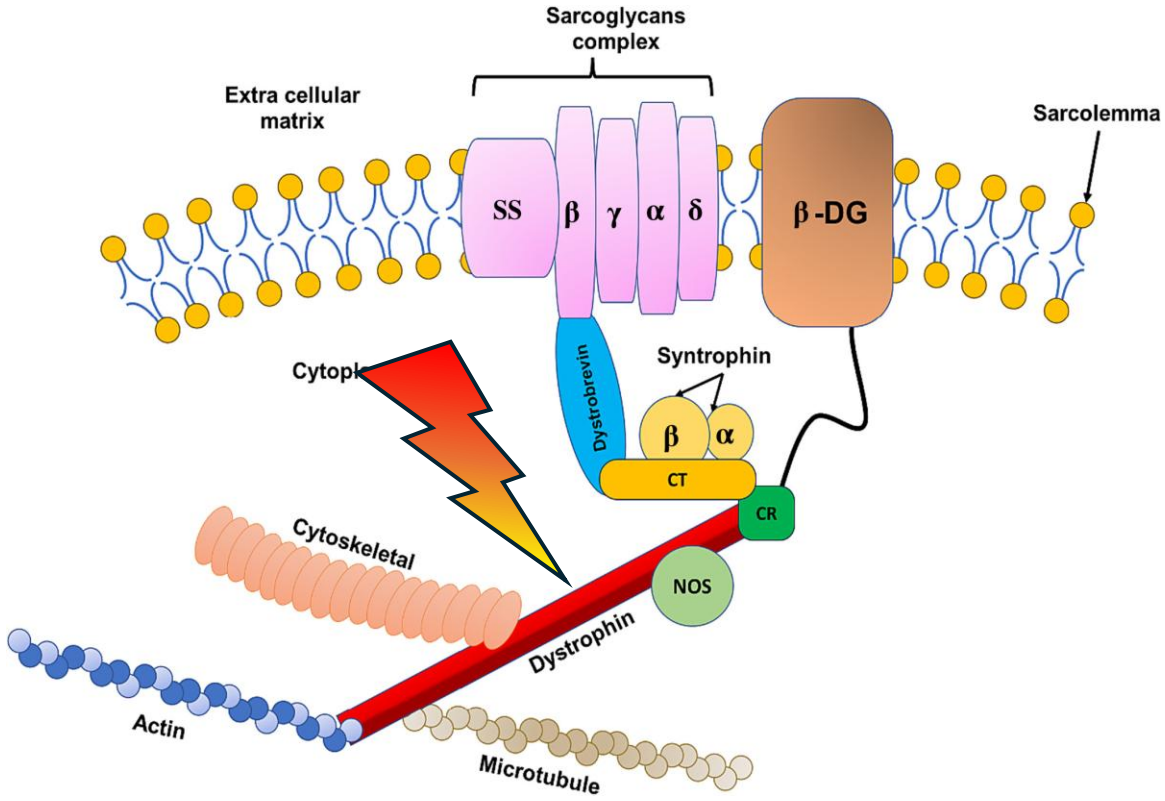
- Review of Duchenne Muscular Dystrophy
- Pathology of DMD
- Current treatments
- Vamorolone mechanism of action
- Vamorolone studies in DMD
- Package insert and adverse events
- Real world experience incl cost and insurance

Duchenne Muscular Dystrophy (DMD)

- Most common and severe of inherited muscular dystrophies
  - Incidence is 1 in 3600 male
- Muscle degeneration and weakness starting < 5 years of age
  - Loss of ambulation by 12 years of age
- Mutation in Dystrophin gene, Xp21
  - X-Linked out-of-frame
  - 30% spontaneous mutation
- Lifespan 20s+

Becker MD

- X-linked in-frame
- Symptom onset > 10 years of age
- Loss of ambulation in 30-40s
- Lifespan 50-60s



Dystrophin provides mechanical support during muscle contraction

Cytoskeleton, Volume: 81, Issue: 6-7, Pages: 269-286, First published: 15 January 2024, DOI: (10.1002/cm.21826)

The “almost always right” reading frame rule

NUCELOTIDES	**1 2 3**	**4 5 6**	**7 8 9**	**10 11 12**	**13 14 15**	**16 17 18**	**19 20 21**
AMINO ACIDS	T H E	B I G	D O G	H A S	O N E	R E D	E Y E

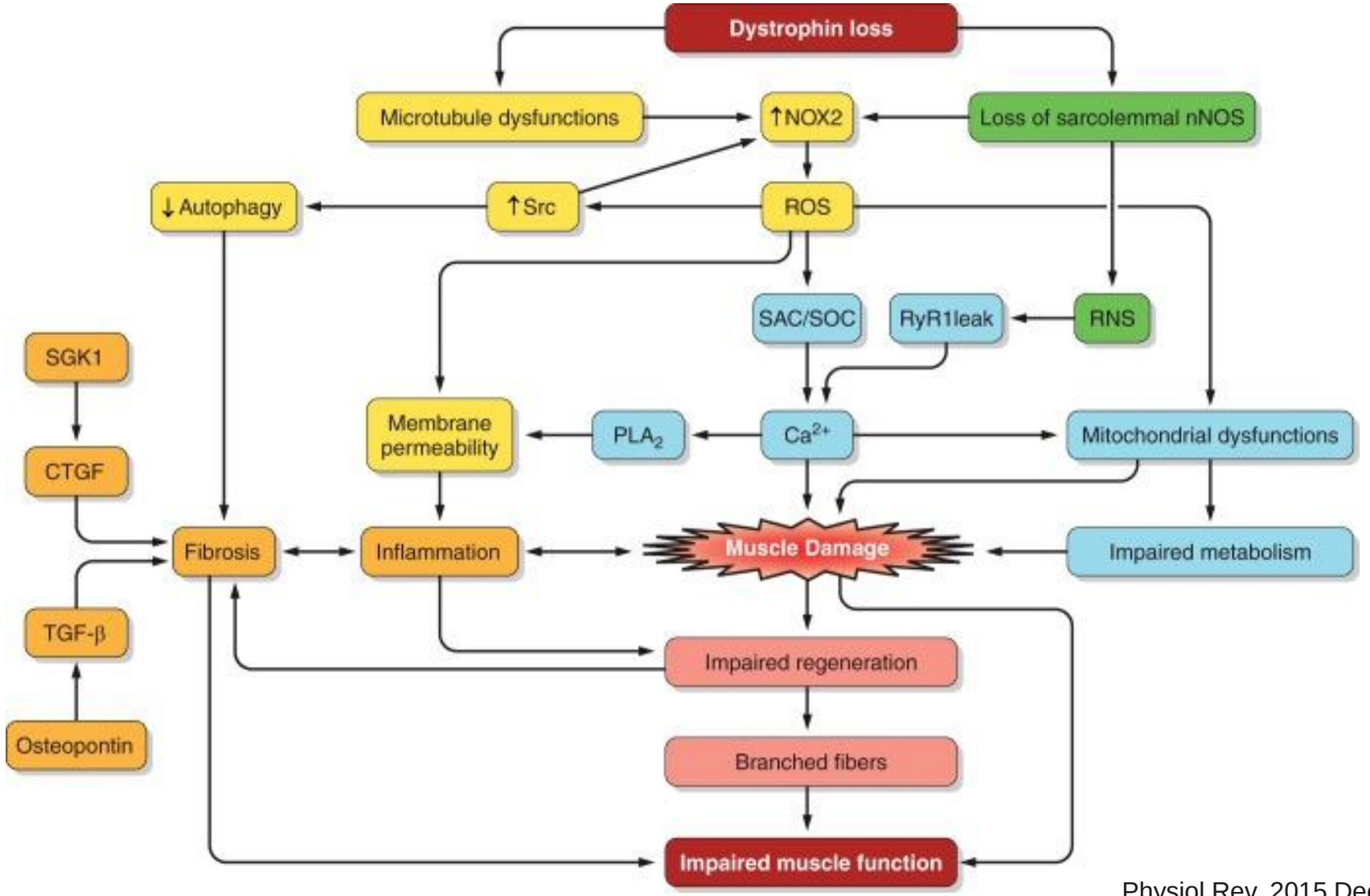
OUT-OF-FRAME DELETION @ 5 = **DUCHENNE MD**

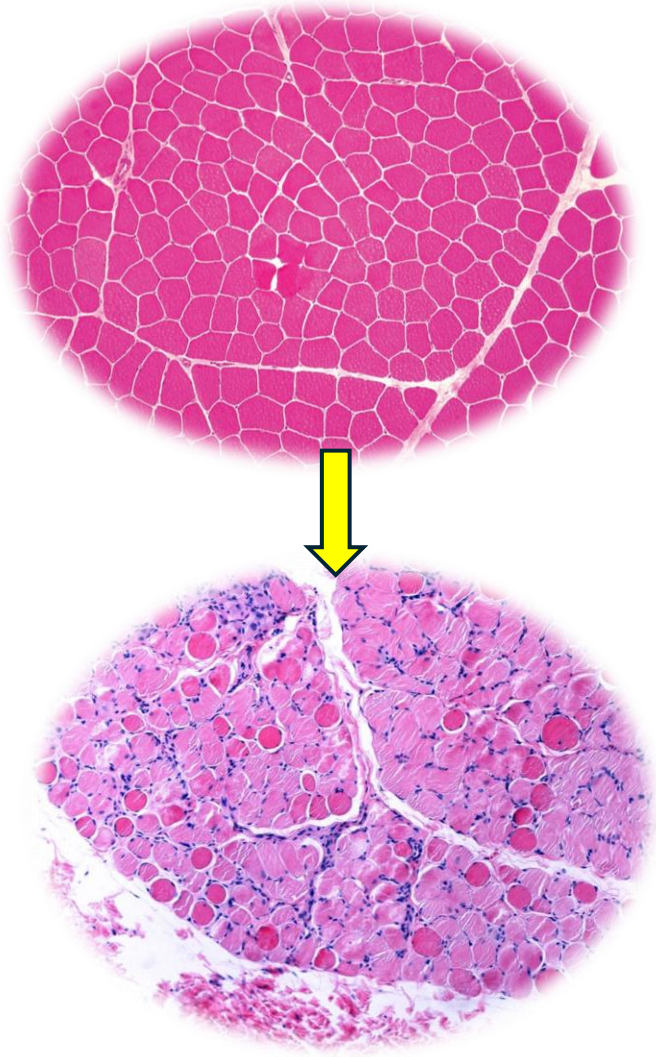
1 2 3	**4 6 7**	**8 9 10**	**11 12 13**	**14 15 16**	**17 18 19**	**20 21 22**
T H E	B G D	O G H	A S O	N E R	E D E	Y E X

IN-FRAME DELETION @ 4,5,6 = **BECKER MD**

1 2 3	**7 8 9**	**10 11 12**	**13 14 15**	**16 17 18**	**19 20 21**
T H E	D O G	H A S	O N E	R E D	E Y E

Pathology of Duchenne Muscular Dystrophy





Physiol Rev. 2015 Dec 16;96(1):253–305. doi: 10.1152/physrev.00007.2015

Current Treatments for DMD

- Glucocorticoids: prednisone, deflazacort, vamorolone
- Exon-skipping agents: eteplirsen, golodirsen, casimirsen,
- Anti-sense oligonucleotide @ nonsense variants: ataluren
- Myogenic repair: givinostat
- Trans-gene therapy: delandistrogene moxeparvovec
- Multi-disciplinary care

Glucocorticoid Mechanisms of Action

Transactivation (steroid side effects; GC-GR **dimer**)

Transrepression ☺ (GC-GR **monomer**)

Physicochemical effects on cell membranes

Synchronization of cell division and tissue remodeling

Cross-reaction with other steroid hormone receptors (mineralocorticoid receptor)

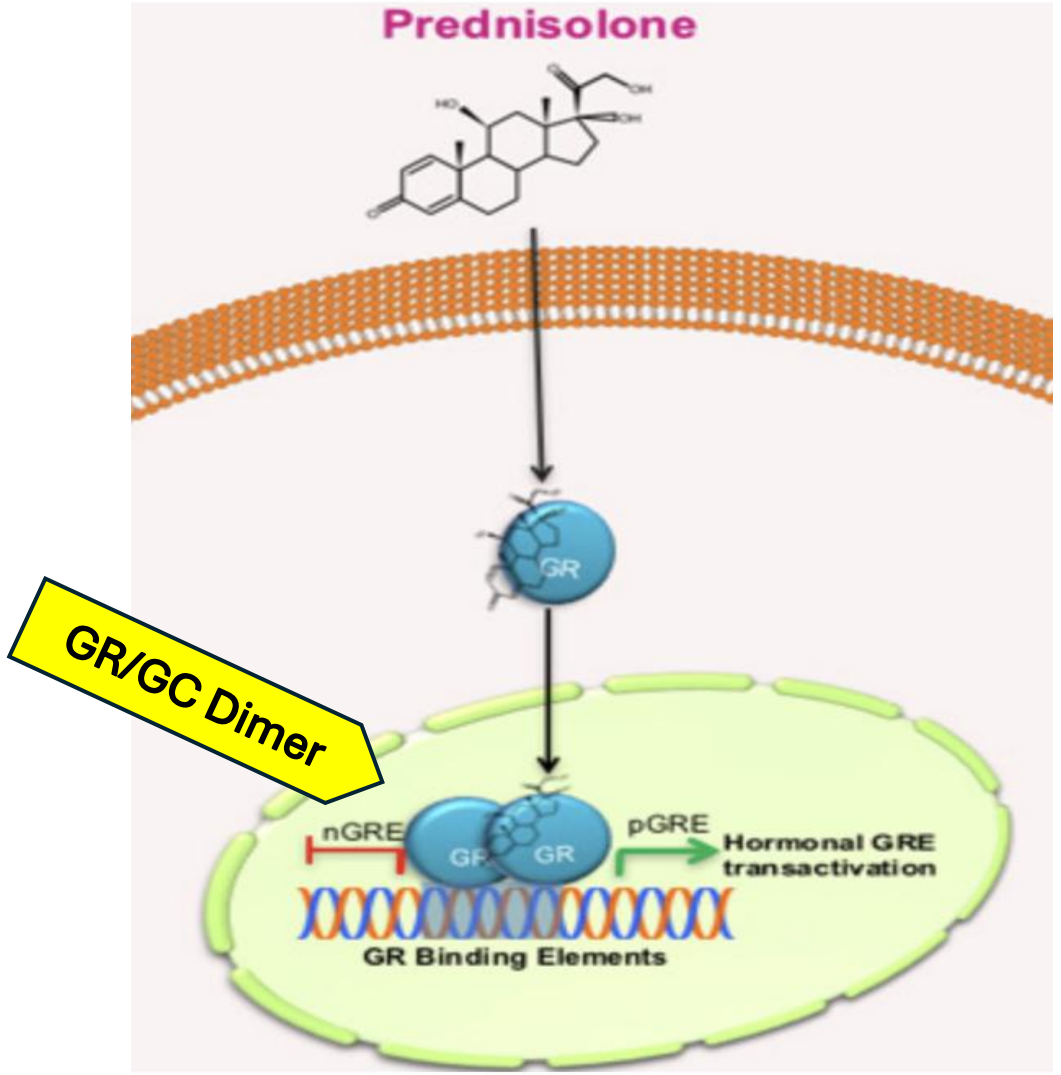
Glucocorticoid Transactivation

Steroid binds to cytoplasmic nuclear hormone receptor (glucocorticoid receptor [GR] for prednisone and cortisol)

Receptor ligand complex translocates to nucleus binding to specific GC response elements (GRE) on genes

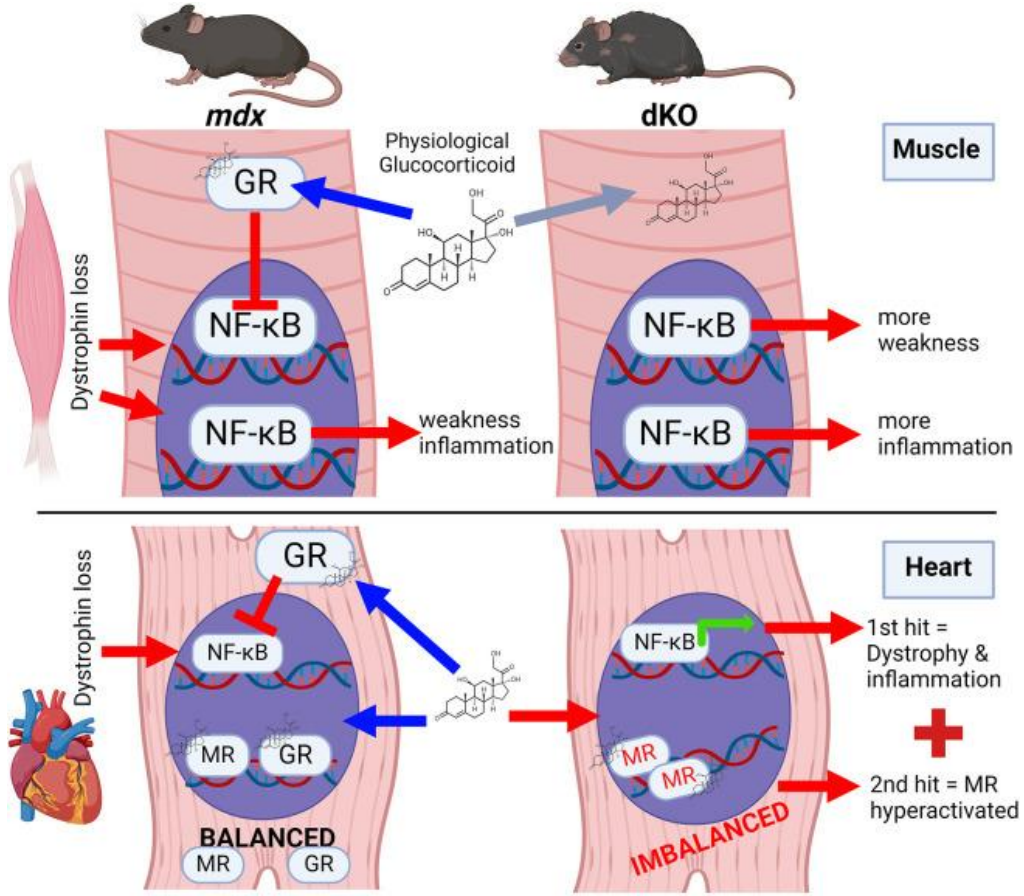
Activates gene transcription in a dose dependent manner

(Pharmacodynamic transcription outlasts PK of GC by several hrs)



Glucocorticoid Transrepression (and other benefits in DMD)

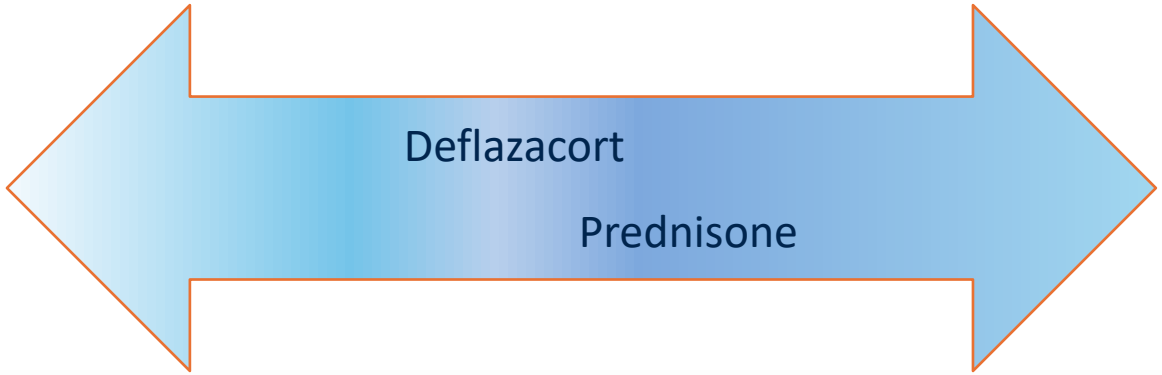
Anti-inflammatory effect via NF-κB inhibition (PD=PK)
Inhibit muscle proteolysis
Stimulate myoblast proliferation
Stabilize muscle fiber membranes
Increase myogenic repair
Reduce cytosolic [Ca++]
Up-regulate utrophin
Differential regulation of other genes



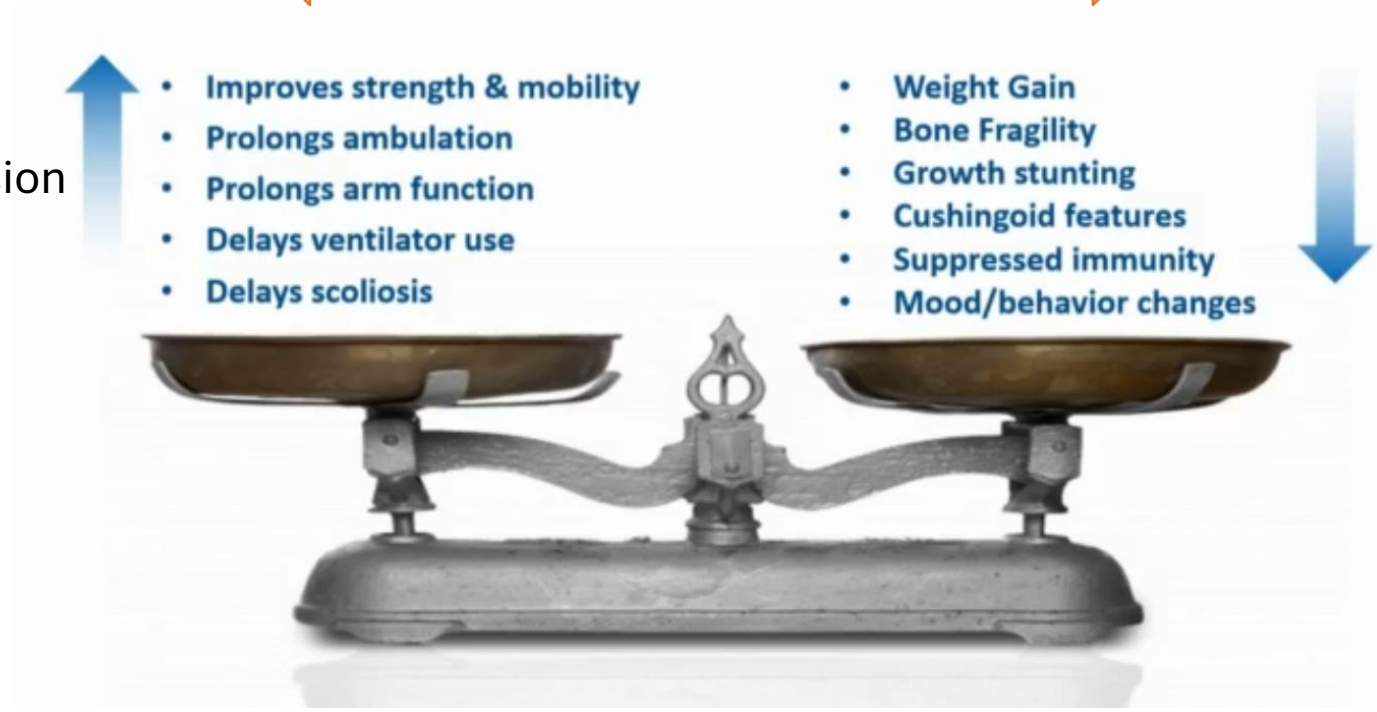
Matthews, Emma et al. “Corticosteroids for the treatment of Duchenne muscular dystrophy.” *The Cochrane database of systematic reviews* vol. 2016,5 CD003725. 5 May. 2016, doi:10.1002/14651858.CD003725.pub4

Oliver, Trinitee et al. “The glucocorticoid receptor acts locally to protect dystrophic muscle and heart during disease.” *Disease models & mechanisms* vol. 17,5 (2024): dmm050397. doi:10.1242/dmm.050397

Corticosteroid use in DMD



Transrepression

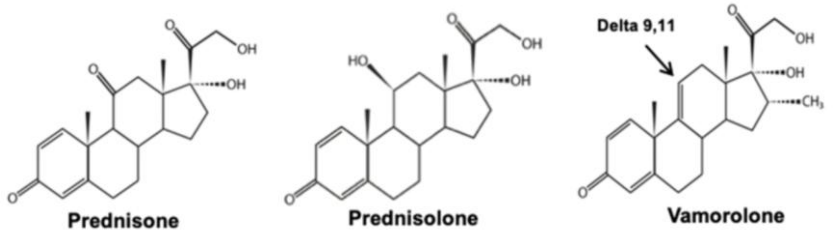


Transactivation

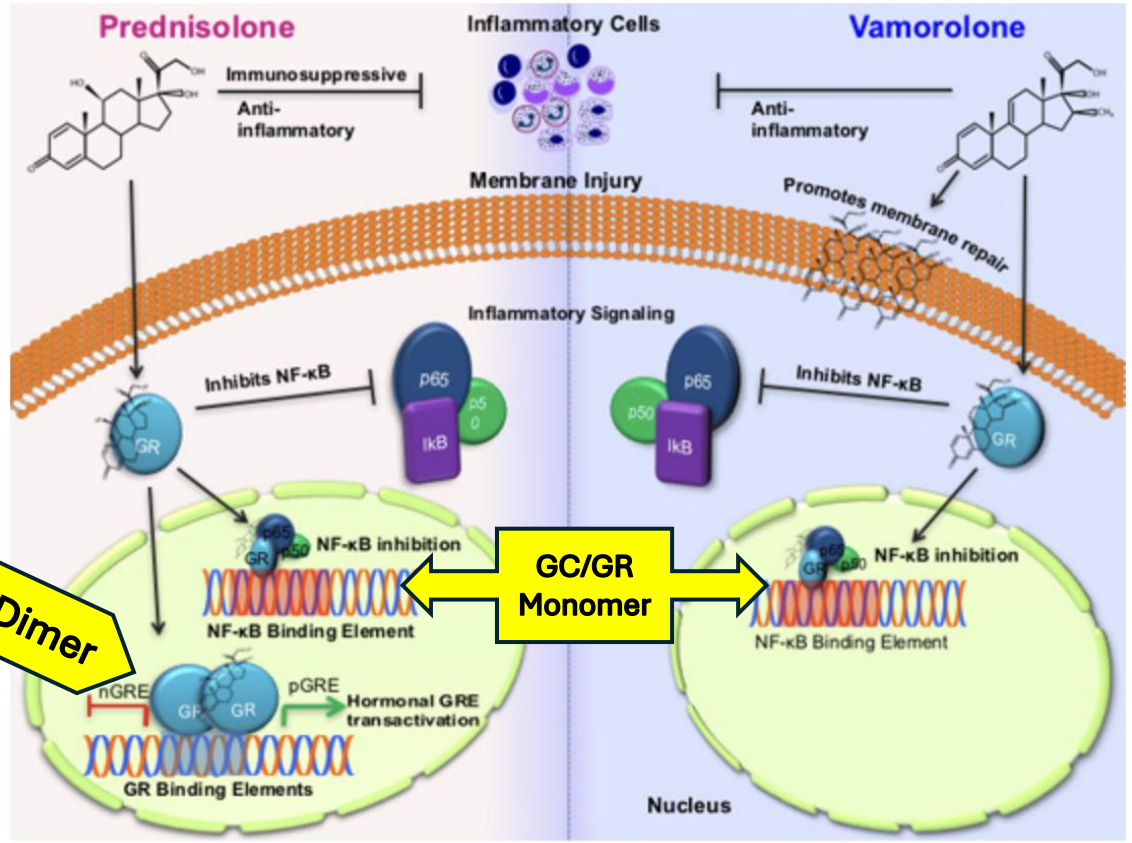
Steroid comorbidity costs up to $29K/yr

Roy, Runia et al. “Acute serum protein and cytokine response of single dose of prednisone in adult volunteers.” *Steroids* vol. 178 (2022): 108953. doi:10.1016/j.steroids.2021.108953

Vamorolone



- Dissociative steroid
- Differs from other GCs- lacks contact site with target glucocorticoid receptor (GR) altering activity
  - relative loss of transactivation activities, but retention of transrepression activities,
  - Inhibits NF-kB activity (anti-inflammatory)
- Potent antagonist of the mineralocorticoid receptor
- Improved myogenic repair and stabilization of muscle membranes

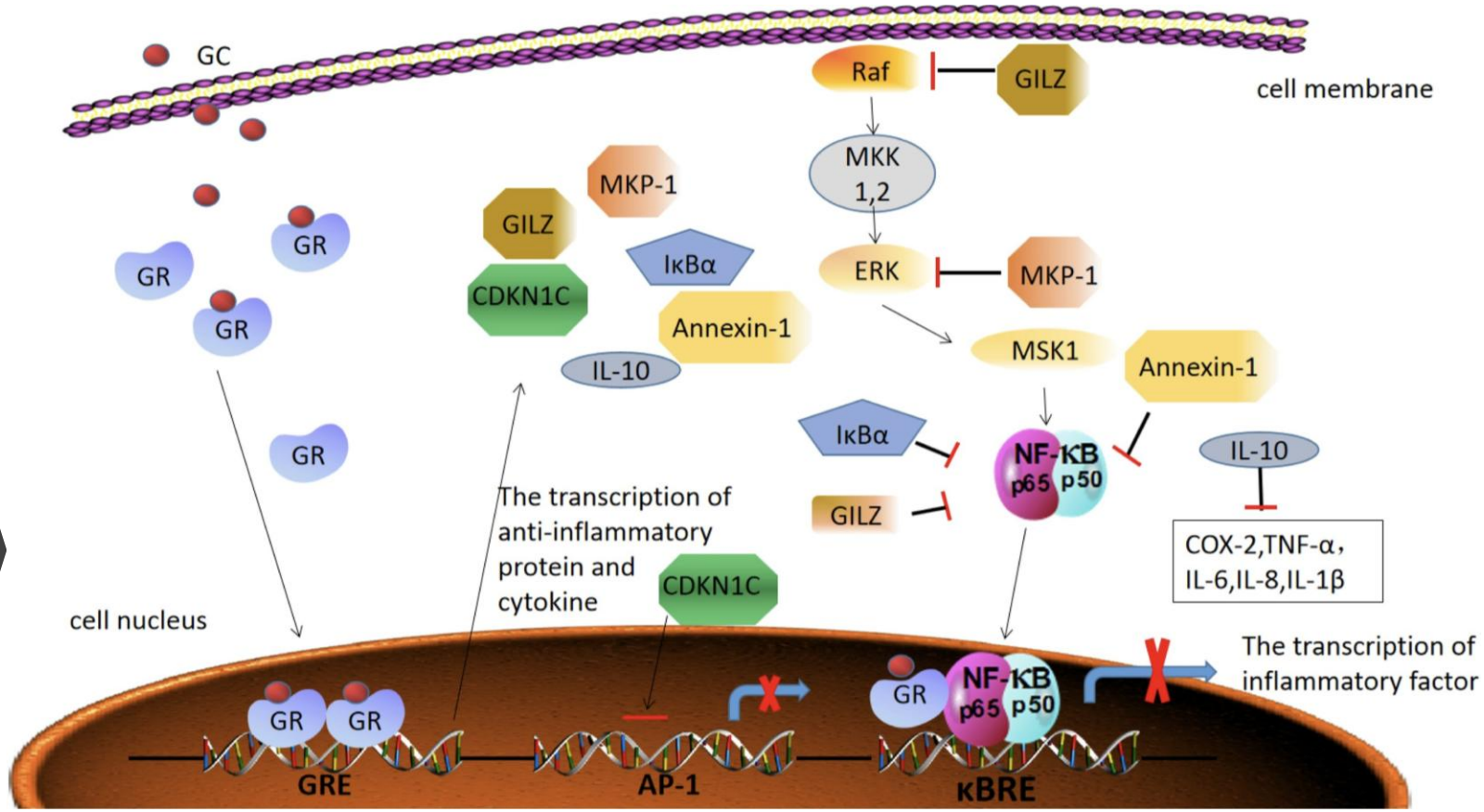


Mah JK, Clemens PR, Guglieri M, et al. Efficacy and Safety of Vamorolone in Duchenne Muscular Dystrophy: A 30-Month Nonrandomized Controlled Open-Label Extension Trial. *JAMA Netw Open*. 2022;5(1):e2144178. Published 2022 Jan 4. doi:10.1001/jamanetworkopen.2021.44178

Heier, Christopher R et al. "VBP15, a novel anti-inflammatory and membrane-stabilizer, improves muscular dystrophy without side effects." *EMBO molecular medicine* vol. 5,10 (2013): 1569-85. doi:10.1002/emmm.201302621

Grounds MD, Lloyd EM. Considering the Promise of Vamorolone for Treating Duchenne Muscular Dystrophy. J Neuromuscul Dis. 2023;10(6):1013-1030. doi: 10.3233/JND-230161. PMID: 37927274; PMCID: PMC10657680.

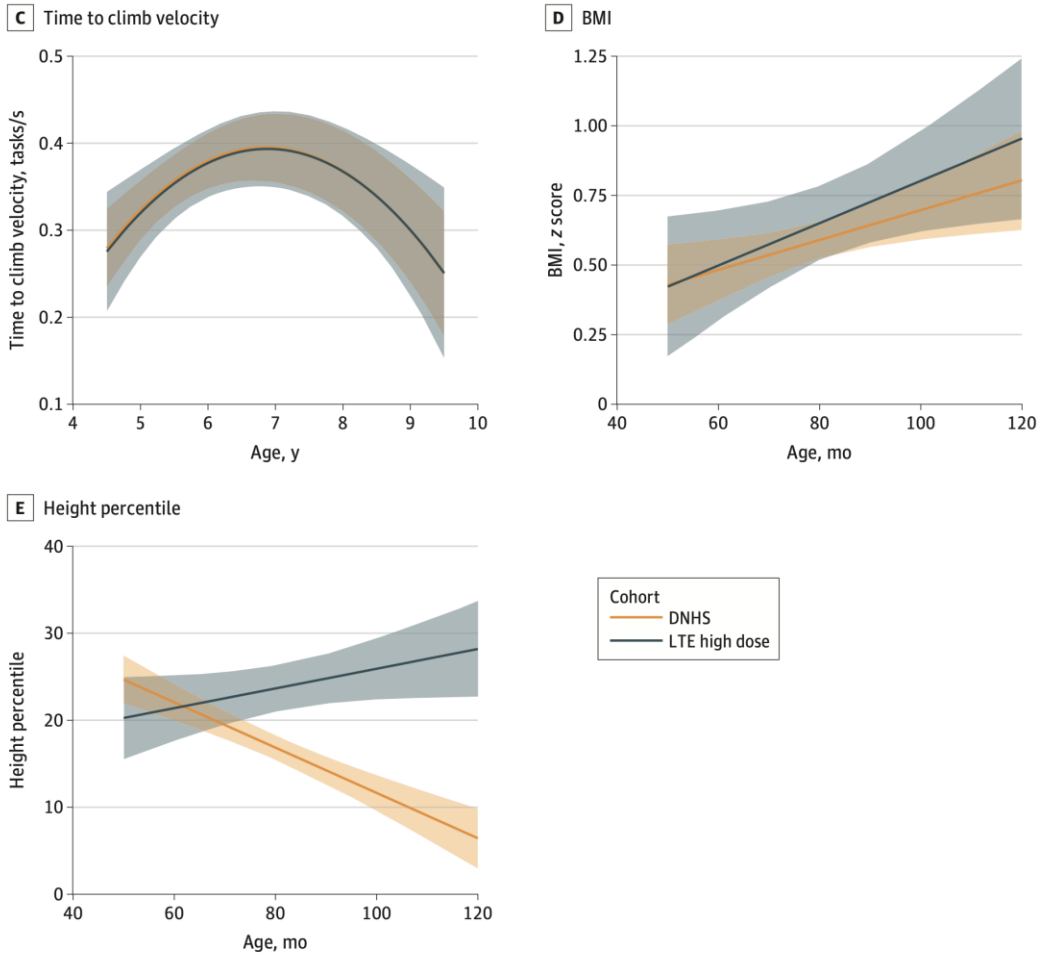
Are dimers all bad?...Some evidence GC/GR Dimers transactivate genes of ANTI-INFLAMMATORY proteins



Mei Yang, Jingyu Chen, Wei Wei. Dimerization of glucocorticoid receptors and its role in inflammation and immune responses. Pharmacological Research. Volume 166, 2021, https://doi.org/10.1016/j.phrs.2020.105334.

Vamorolone 30-month outcomes in DMD

- Similar efficacy to traditional glucocorticoids in maintaining strength over 30 months in DMD
- Improved height velocity compared to traditional GC
- Minimal bone age delay
- BMI z score was not significantly different to GCs
- Less insulin resistance vs GC
- Risk of adrenal suppression



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Possible Reduced Behavioral Side Effects vs other glucocorticoids…?

Table 3. Incidence of physician-reported adverse events.

Study	Treatment	*n*; mean age in years (SD)[1]	Cushingoid	Weight gain	Hypertrichosis/hirsutism	Behavior change
Vamorolone	6.0 mg/kg/day vamorolone	*n* = 38; 4. 9 (0.9)	2.6%	13.2%	0%	0%[2]
Griggs et al. 2016 [20]	0.9 mg/kg/day deflazacort	*n* = 68; 8. 8 (2.5)	60.3%	27.9%	35%	9%
	0.75 mg/kg/day prednisone	*n* = 63; 8. 9 (2.9)	77.8%	34.9%	44%	14%
CINRG DNHS [18]	Deflazacort	*n* = 94	72%	63%	NR	33%
	Prednisone	*n* = 80	50%	67%	NR	30%

Physicians reported fewer other corticosteroid-associated safety concerns in vamorolone-treated participants compared to published studies of deflazacort- and prednisone-treated DMD patients, including

- Cushingoid appearance
- Behavior change (mood disturbance)
- Hirsutism
- Weight gain

Smith, Edward C et al. “Efficacy and safety of vamorolone in Duchenne muscular dystrophy: An 18-month interim analysis of a non-randomized open-label extension study.” *PLoS medicine* vol. 17,9 e1003222. 21 Sep. 2020, doi:10.1371/journal.pmed.1003222

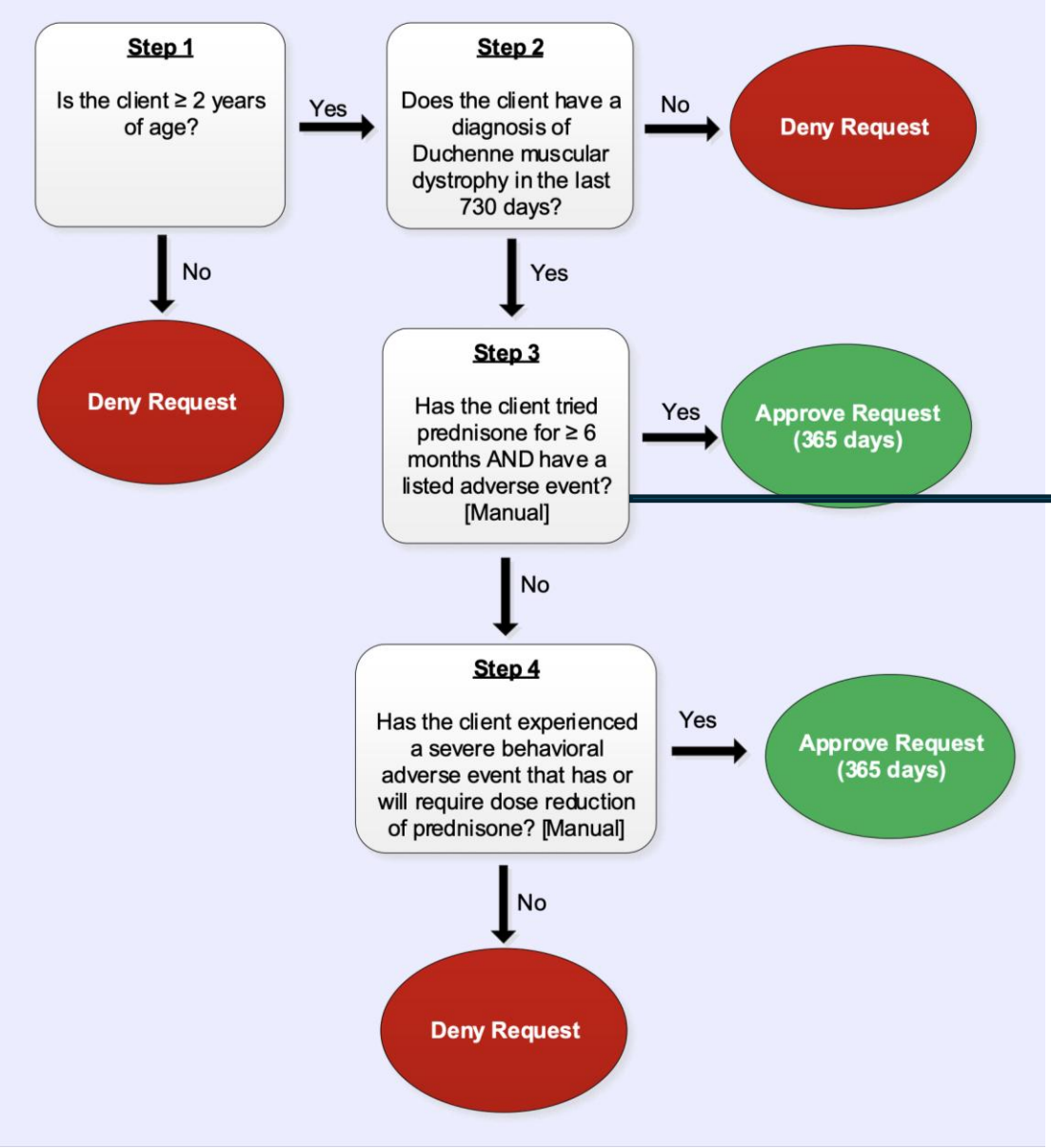
AEs in Vamorolone 24-Week Study Results

Table 1: Adverse Reactions in Patients with DMD that Occurred in ≥ 5% of Patients Treated with AGAMREE and More Frequently than in Patients Who Received Placebo During 24 Weeks (Study 1)

Adverse Reaction	AGAMREE 2 mg/kg/d (N=30) %	AGAMREE 6 mg/kg/d (N=28) %	Placebo (N=29) %
Cushingoid Features	7	29	0
Psychiatric disorders [1]	7	21	14
Vomiting	17	14	7
Weight increased	0	11	3
Vitamin D deficiency	7	11	0
Cough	10	7	3
Headache	7	7	3

Hoffman, Eric P et al. “Vamorolone trial in Duchenne muscular dystrophy shows dose-related improvement of muscle function.” *Neurology* vol. 93,13 (2019): e1312-e1323. doi:10.1212/WNL.0000000000008168

Insurance Approval Texas Medicaid



Listed Adverse Events

a. Cushingoid appearance
b. Central (truncal) obesity
c. Undesirable weight gain (defined as greater than or equal to [≥] 10% body weight gain over a 6-month period)
d. Diabetes and/or hypertension that is difficult to manage according to the prescribing physician
e. Inhibition of growth and/or concerning osteoporosis markers

How much do GCs cost (in the US)?

- Dexamethasone = $30 for ten 4 mg tablets ~ $400/yr
- ACTHar Gel = $40K/5 mL vial @ 80 iu/mL
- Vamorolone = $10K/100 mL ~ $275,000 / year (for DMD…not immunosuppressive dosing)

Challenges for usage in paediatric neuroinflammatory condition

- Company focus on more common conditions - asthma etc
- All early safety data only performed in healthy adult males and subsequent trials in boys
- Quite a lot of work to be done still re actual equivalent anti-inflammatory effect
- Proof of Concept Trial of Vamorolone in Pediatric Ulcerative Colitis (NCT04348890) been withdrawn - probably because of inadequate anti-inflammatory dose equivalent

Corticosteroid Comparison Chart

	Equivalent Glucocorticoid Dose (mg)	Potency relative to Hydrocortisone: Anti-Inflammatory	Potency relative to Hydrocortisone: Mineral-Corticoid	Half-Life: Plasma (minutes)	Half-Life: Duration of Action (hours)
Short Acting					
Hydrocortisone (Cortef, Cortisol)	20	1	1	90	8-12
Cortisone Acetate	25	0.8	0.8	30	8-12
Intermediate Acting					
Prednisone	5	4	0.8	60	12-36
Prednisolone	5	4	0.8	200	12-36
Triamcinolone	4	5	0	300	12-36
Methylprednisolone	4	5	0.5	180	12-36
Long Acting					
Dexamethasone	0.75	30	0	200	36-54
Betamethasone	.6	30	0	300	36-54
Mineralocorticoid					
Fludrocortisone	0	15	150	240	24-36
Aldosterone	0	0	400 +	20	- -

Reference: Adrenal Cortical Steroids. In Drug Facts and Comparisons. 5th ed. St. Louis, Facts and Comparisons, Inc.:122-128, 1997

Commonly Prescribed Replacement Steroid Equivalents

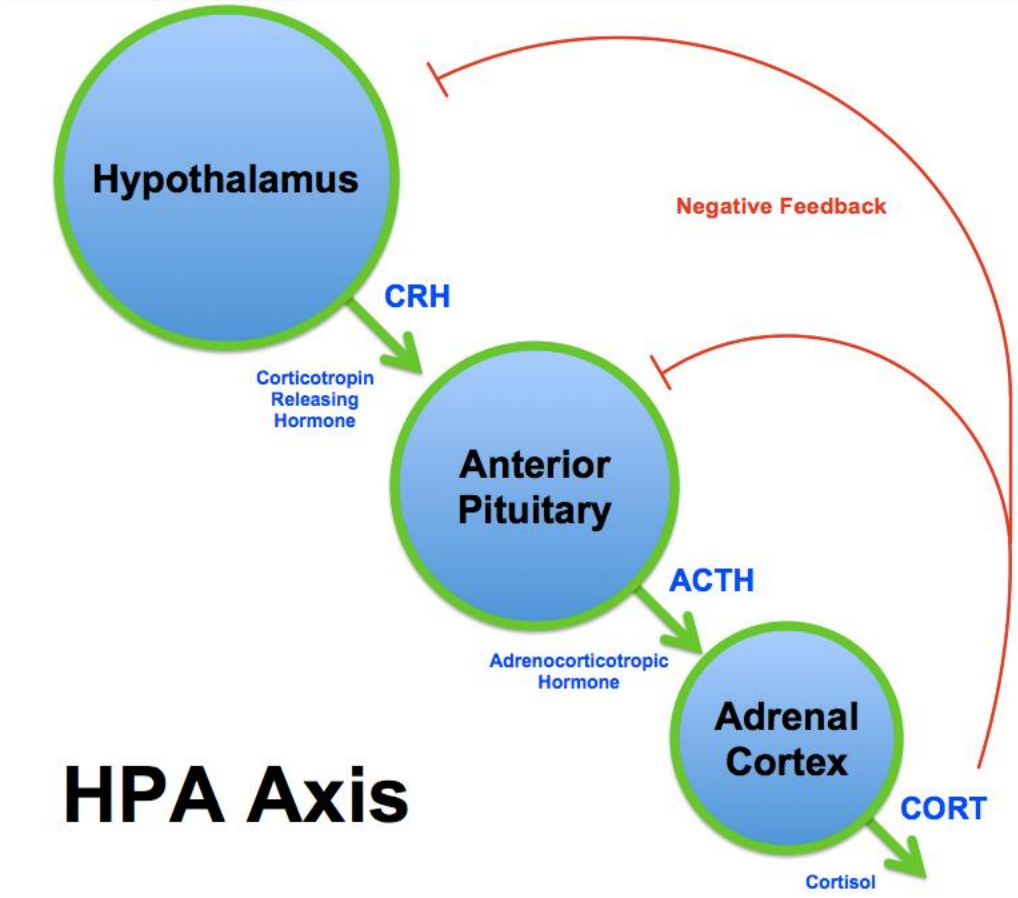
Prednisone		Cortisone		Dexamethasone		Hydrocortisone (Cortef)
5 mg	=	25 mg	=	0.75 mg	=	20 mg


REGNANTE CAROLO

Acute serum protein and cytokine response of single dose of prednisone in adult volunteers

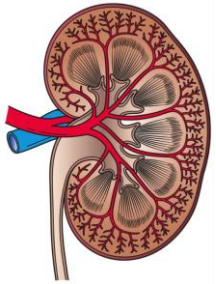
Runia Roy [a], Steven J. Soldin [b], Brian Stolze [b], Marissa Barbieri [c], Shefa M. Tawalbeh [a,1], Nicole Rouhana [d], Ann E. Fronczek [d], Kanneboyina Nagaraju [c], John van den Anker [e], Utkarsh J. Dang [f,2], Eric P. Hoffman [a,c,*]

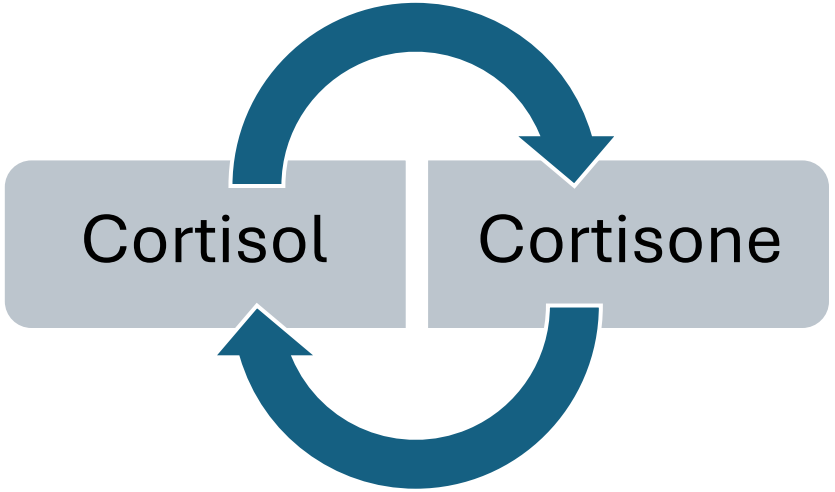
Roy, Runia et al. “Acute serum protein and cytokine response of single dose of prednisone in adult volunteers.” *Steroids* vol. 178 (2022): 108953. doi:10.1016/j.steroids.2021.108953



HPA Axis

11-β– hydroxysteroid dehydrogenase 2





11-β– hydroxysteroid dehydrogenase 1