

Testosterone therapy for
adolescents/adults with sex
chromosome aneuploides:
What's available and what's new?

Alan D. Rogol MD, Ph.D

Professor, *Emeritus*

University of Virginia

Disclosures

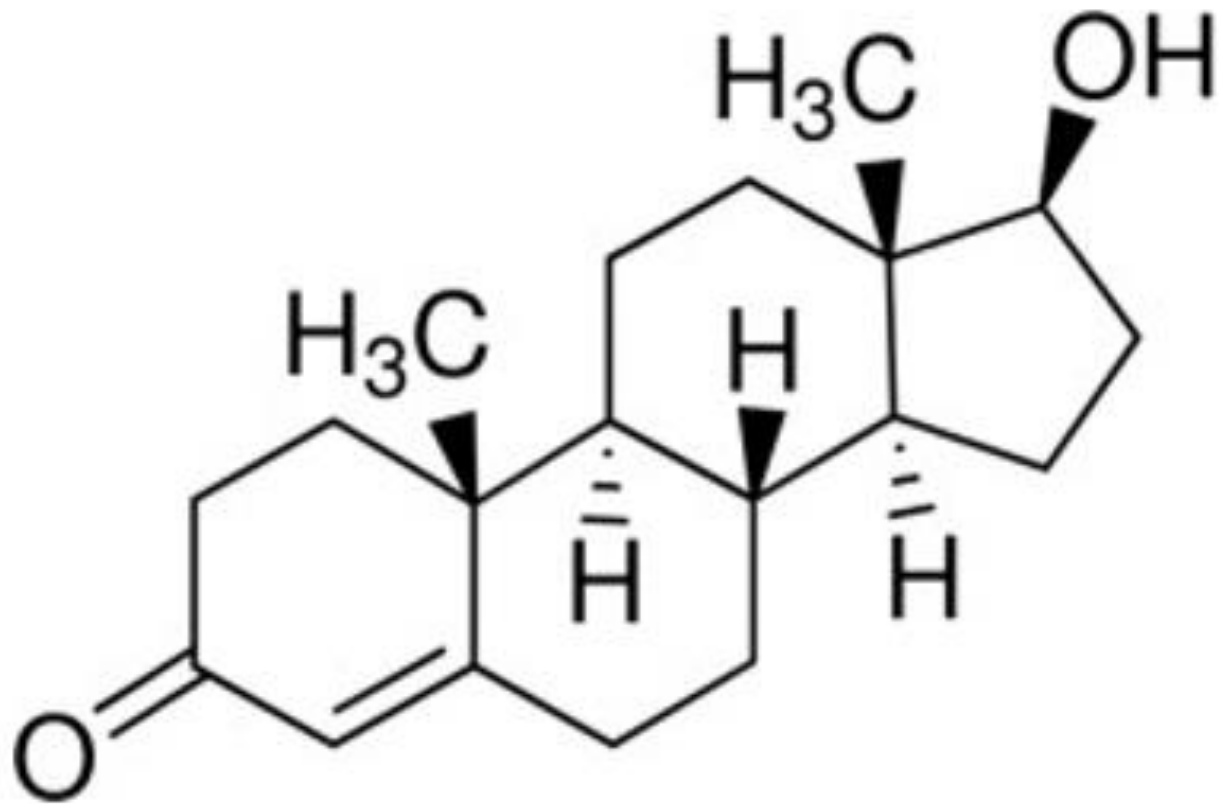
- Consultant to and scientific advisory board
 - Acerus Pharma
 - Aytu BioScience

Both market nasal testosterone gel

Outline

- Testosterone preparations
 - Injectable
 - Transdermal
 - Intra-nasal
 - Buccal
 - Implantable
 - Oral
- Time course
- Advantages and disadvantages
- Adverse events
- Cost

Testosterone



Testosterone preparations

- Injectable
 - Cypionate and enanthate (generic and branded)
 - Undecanoate (**Aveed**[®])
- Transdermal
 - Patch (**Androderm**[®])
 - Gel (branded and generic)
- Intranasal
 - **Natesto**[®]
- Buccal
 - **Testim**[®]
- Implantable
 - **Testopel**[®]
- Oral

FDA Thresholds for Testosterone Products

Table 1.

Observed serum total testosterone C_{max} FDA thresholds

Observed C_{max} Limit (ng/dl)	Success Criteria (% participants)
1,500 or Less	85% or Greater
1,800–Less than 2,500	5% or Less
2,500 or Greater	None

1 nmol/L = ~ 30 ng/dL

Testosterone Preparations

- Oral
 - Alkylated (methyl T)
 - Undecanoate
 - oxandrolone
- Transdermal
 - scrotal patch
 - Non-scrotal patch
 - gel (packets and pump)

Testosterone Preparations (cont.)

- Oral androgens
 - T (unmodified)
 - 17 α -alkylated
 - Hepatotoxic
 - \uparrow transaminases
 - Cholestasis
 - *Peliosis hepatis*

Testosterone Preparations (cont.)

- Oral androgens (cont.)
 - Undecanoate
 - 17 β -ester, absorbed in lymph
 - high inter-individual variability in absorption, time-to-peak, maximal concentration
 - multiple doses per day with fatty meal
- Not approved in the US, although several companies working on new formulations

Testosterone Preparations (cont.)

- Oral androgens (cont.)
 - Oxandrolone
 - Nonaromatizable
 - treatment
 - boys with CDGP
 - girls with Turner syndrome

Testosterone Preparations (cont.)

- Injectable
 - short- and long-acting esters
- Longer-acting preparations
 - microcapsules (Testopel)
 - buciclate

Testosterone Preparations (cont.)

- Injectable
 - Propionate
 - unsuitable because of short half-life
 - Enanthate
 - ~200-250 mg every 2 weeks leads to *virtually* physiological levels of T with peaks just above the upper limit of normal and nadirs just below the lower limit of normal
 - Cypionate
 - indistinguishable from enanthate

Testosterone enanthate or cypionate

- Dose
 - 75 to 100 mg/week
 - 150 to 200 mg/2 weeks
- Testosterone levels rise to supraphysiological range and then decline into the hypogonadal range before the next dose
- Cost: ~\$12 to ~\$18/month + (perhaps) administration fee, 2/mo

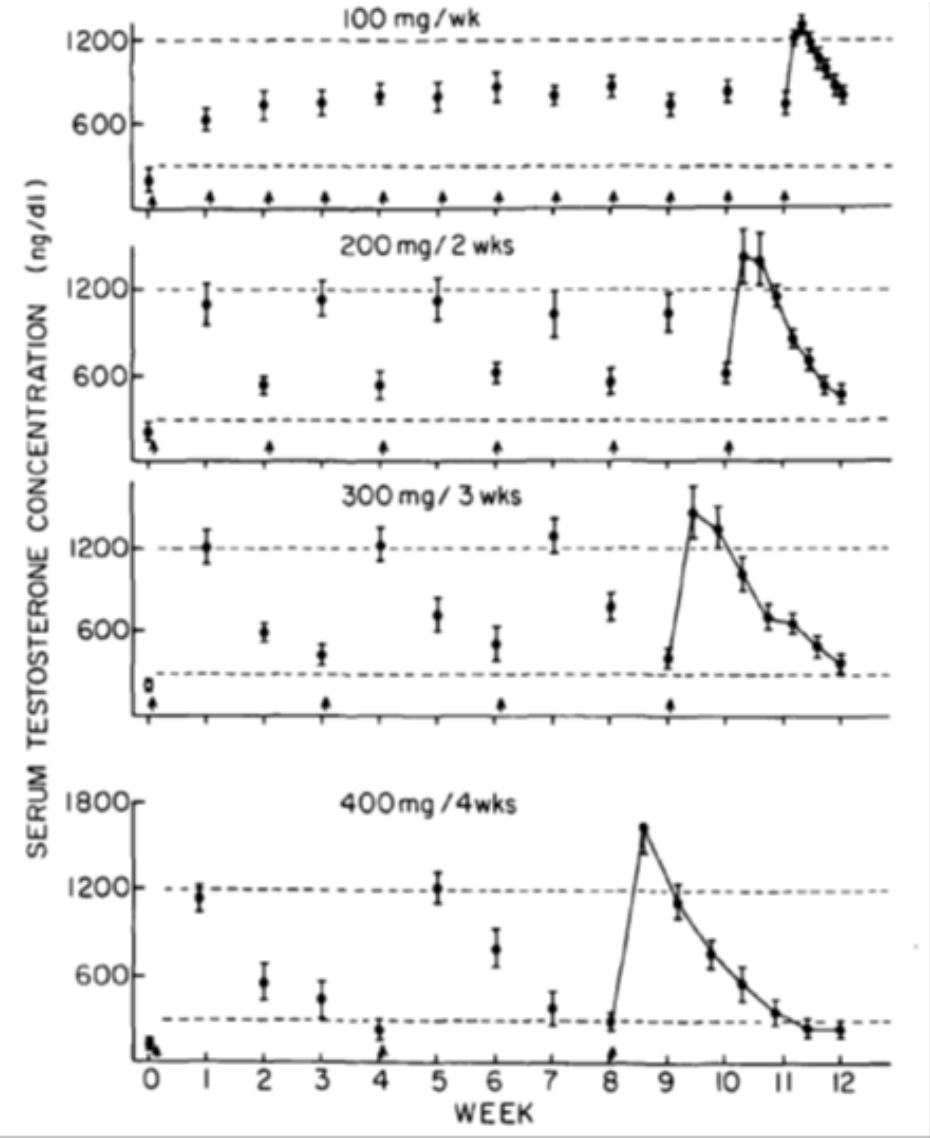
Testosterone (implantable pellets)

- 3 to 6 (75 mg) pellets
 - Testosterone peaks at about 1 month and remains within the normal range for 3-6 months
- Adverse events—surgical incision (trocar) and potential extrusion

Testosterone Preparations (cont.)

- Subdermal
 - Pellets
 - effective modality for more than 50 y
 - newer formulations (100 and 200 mg)
 - multiple pellets per implantation
 - highly reproducible and dose-dependent time course for circulation total and free T
 - 6 month intervals

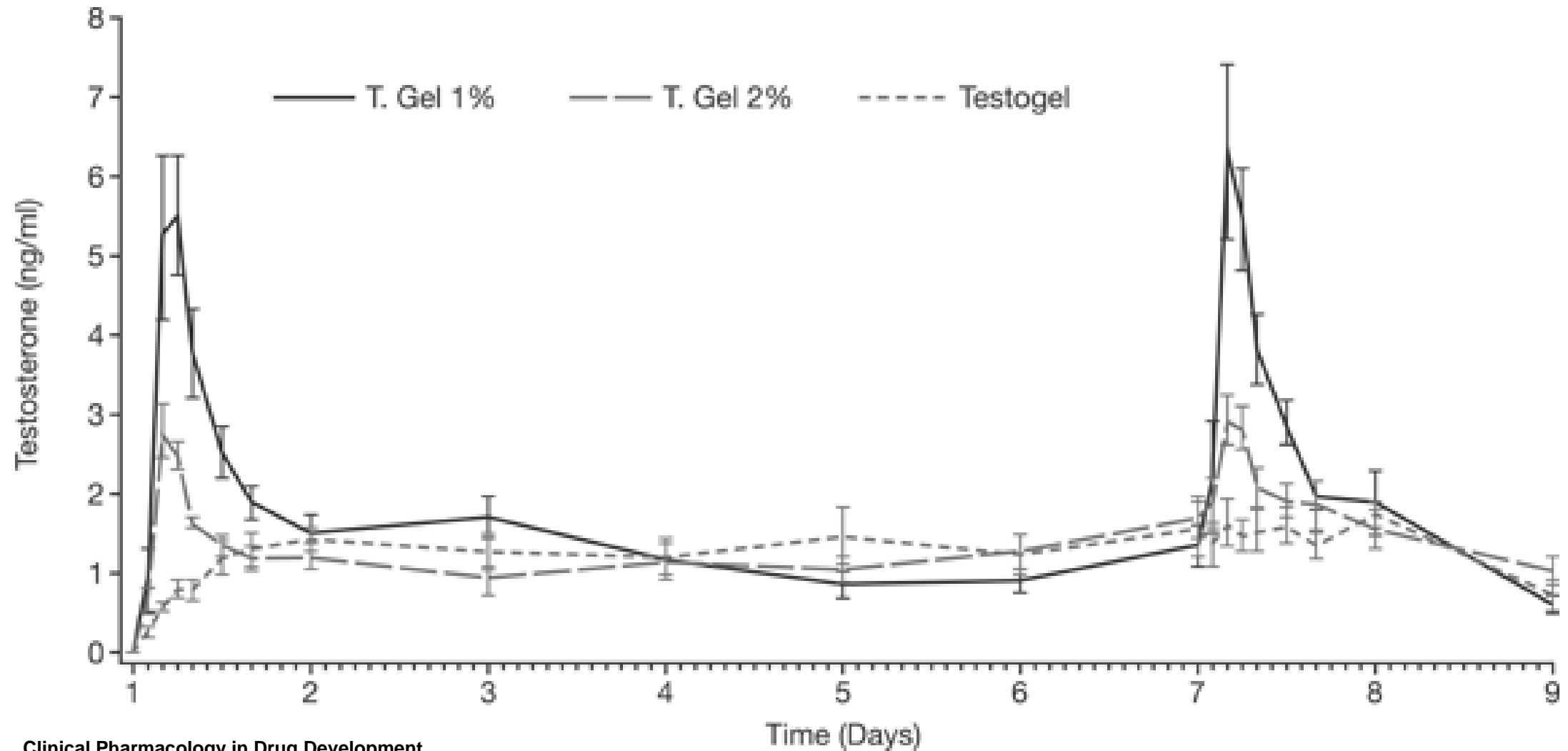
Testosterone enanthate or cypionate (im)



Testosterone gel (various strengths)

- Available in sachet packets, tubes and by pump
 - 5-10 g/day T gel containing 50 to 100 mg testosterone
- Restores T and estradiol levels to the physiologic range
- Adverse events
 - Potential for transfer to a partner or child
- Cost: branded *versus* generic

Pharmacokinetics and bioavailability of a new testosterone gel formulation in comparison to Testogel® in healthy men



Clinical Pharmacology in Drug Development

Volume 3, Issue 5, pages 358-364, 8 MAY 2014 DOI: 10.1002/cpdd.110

<http://onlinelibrary.wiley.com/doi/10.1002/cpdd.110/full#cpdd110-fig-0001>

Testosterone Preparations (cont.)

- Transdermal
 - scrotal patch
 - highest rate of steroid absorption
 - high concentration of 5α -reductase
 - problem-to deliver 5-15 mg T/day
 - stable levels of T, DHT, E_2 with daily application

Testosterone Preparations (cont.)

- Transdermal (cont.)
 - nonscrotal patch
 - enhancers to facilitate sufficient T passage through the skin (drug delivery system)
 - skin irritation-up to 60% (alcoholic enhancer and occlusive nature of system)

Testosterone Preparations (cont.)

- Transdermal (cont)
 - gel (packets and pump)
 - hydroalcoholic gel to contain 25 to 50 mg T in 2.5 or 5 g doses
 - physiologic levels of T, DHT, E₂

Testosterone Preparations (cont.)

- Transdermal (cont.)
 - gel (packets and pump)
 - advantages
 - ability to deliver T dose to low, mid or high physiologic range
 - lower incidence of skin irritation
 - ease of application
 - invisibility of dried gel
 - disadvantages
 - transfer to women and children

Testosterone (transdermal patch)

- One or two patches to deliver 5 to 10 mg Testosterone per day
- T:DHT and T:E2 within the physiologic range
- Adverse events-skin irritation is common

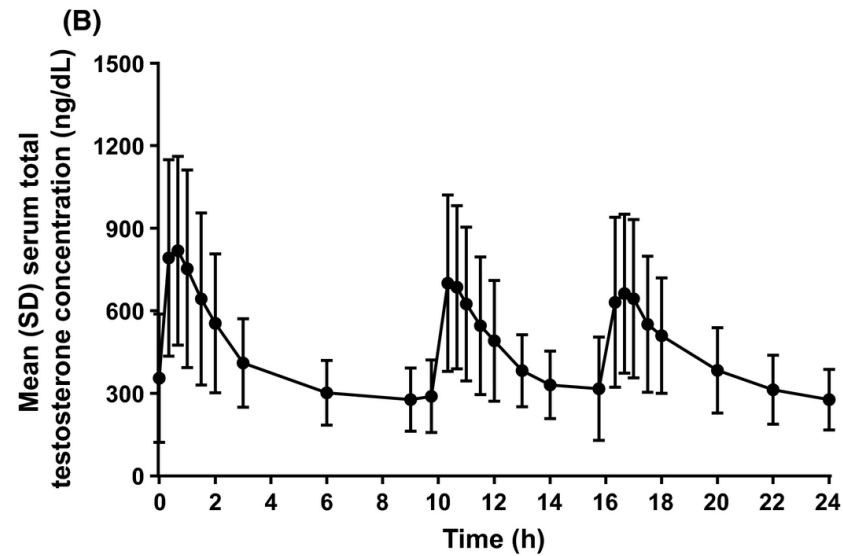
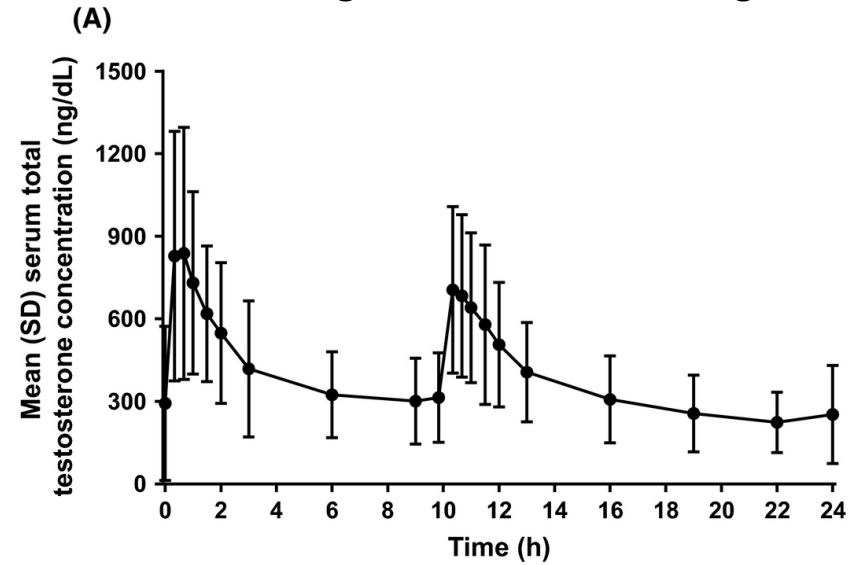
Testosterone (buccal adhesive)

- 30 mg controlled release twice daily
- Normalizes T, DHT and E2 levels
- Adverse events- gum irritation in ~ 16 %

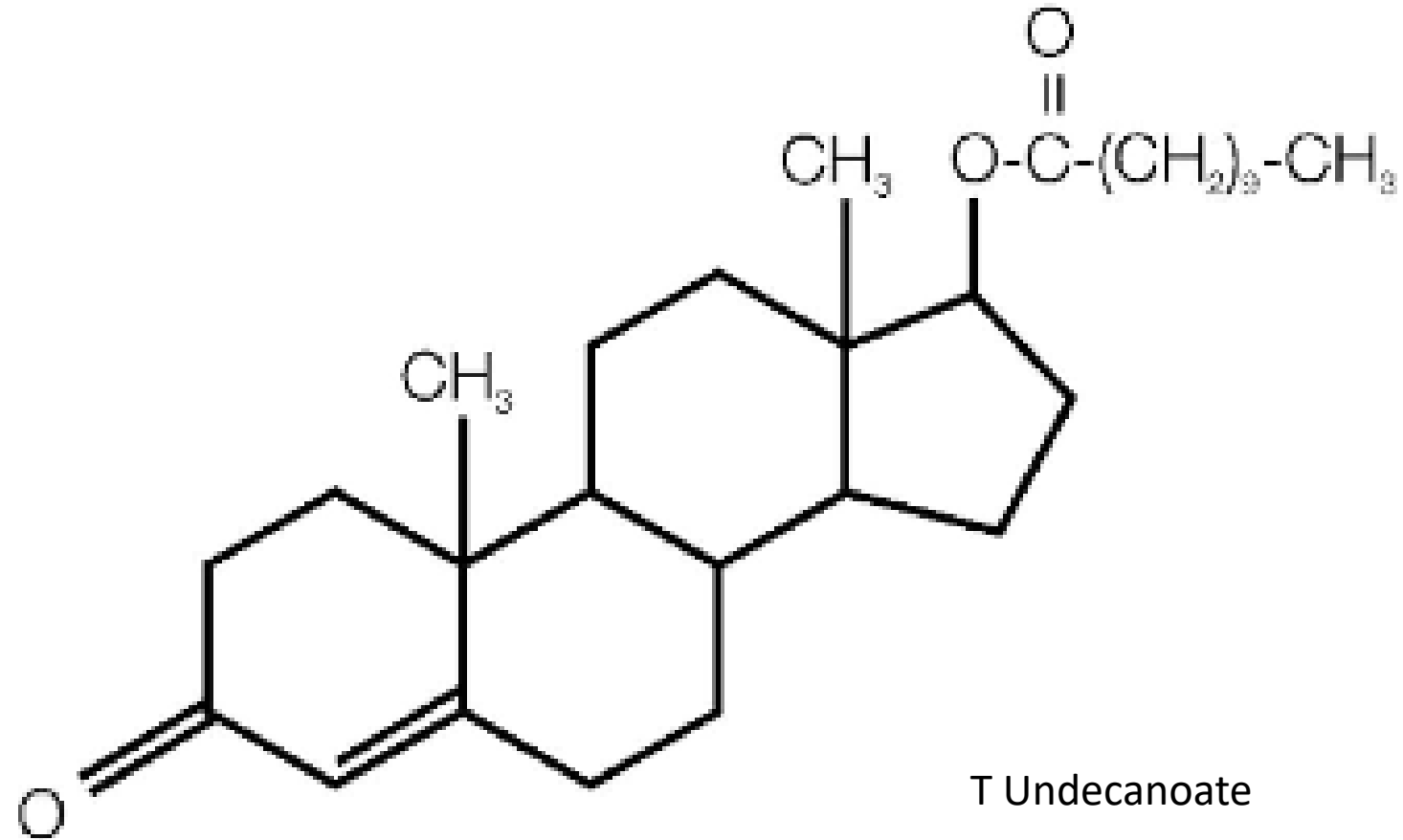
Testosterone (nasal gel)

- 22 or 33 $\mu\text{g}/\text{day}$ given twice or three times
- Relatively low total dose because it is directly absorbed
 - Very short acting
- Adverse events
 - No transfer to partners or children
 - ? Ameliorative effect with rhinitis

Natesto™, a novel testosterone nasal gel, normalizes androgen levels in hypogonadal men



Testosterone undecanoate



Testosterone undecanoate (injectable)

- 750 to 1,000 mg at 0 and 6 weeks
- 750 to 1,000 mg every 10 to 14 weeks
- Levels of T, DHT, E2 mainly within the physiologic range
- Adverse events-injection of a large volume (4 mL) and lipid droplets in lungs (cough)

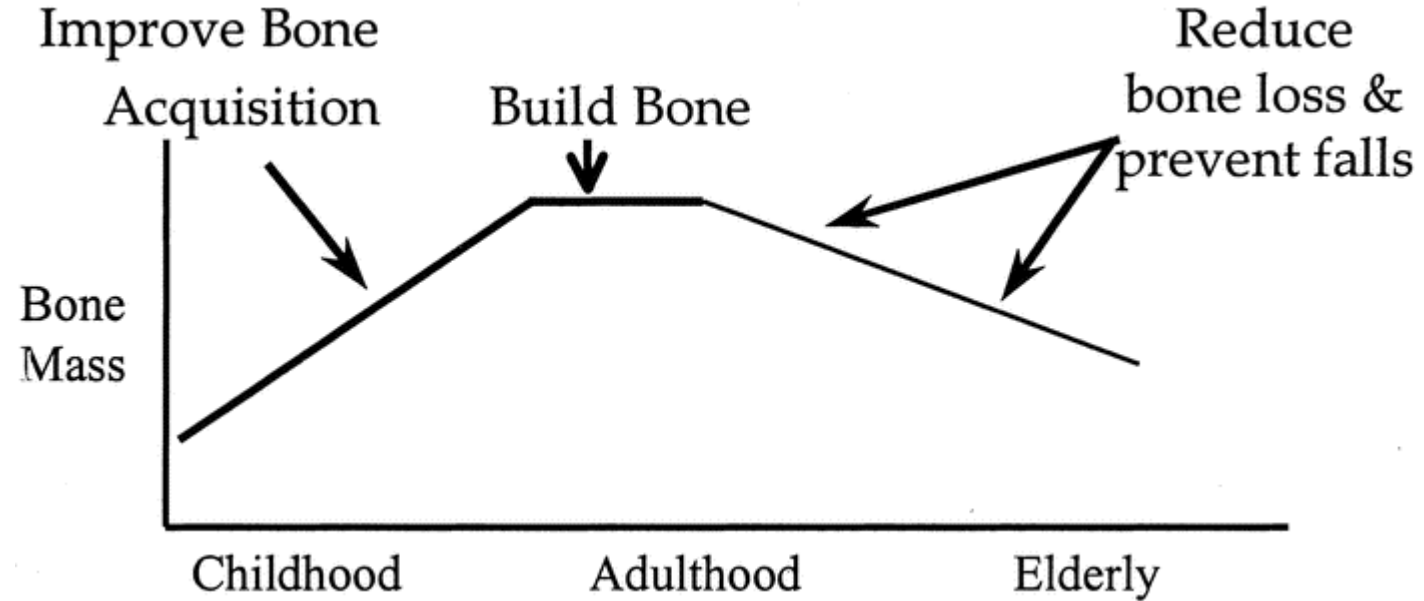
Testosterone undecanoate (injectable)

- 1000 mg deep IM initial
- Second dose 6 weeks later of 1000 mg
- Then 1000 mg every 10 to 14 weeks
- Caution that oil can travel to lung or be associated with anaphylaxis (0.4 cases per 10,000 men)

Monitoring Testosterone Treatment

- Adolescent development
 - testicular size
- Height velocity
- Serum testosterone level

Bone Mass



Testosterone Pharmaceuticals (1)

Form	Cost/month (without markup)	Dosing Interval	Adverse Events	Advantages	Disadvantages
Injectable					
propionate		~3 da			
Cyp/enanthate	~\$25-50	1-2 wk	Pain and redness at injection site; relatively higher risk of polycythemia	Longer dosing interval	Wide fluctuations in T levels
Undecanoate	~\$900/3 mo	~10-12 wk	Lipid in lung; anaphylaxis	Long dosing interval	Difficult to change dosing
Implant					
Testopel	~\$950/10 pellets	Mult pellets 4-6	extrusion	Long dosing interval	Surgical

Testosterone Pharmaceuticals (2)

Form	Cost	Dosing Interval	Adverse Events	Advantages	Disadvantages
Transdermal					
Gel/other	~\$5-600/mo (no discount); ~150 with discount	daily	2 ^o exposure [BBW]	Mimics morning T peak; simple administration	Transference; daily administration
patch	~\$550/mo (no discount); ~\$125 with discount	daily	Cutaneous inflammation	Mimics morning T peak	Skin irritation; may not stick
buccal	~\$600/mo (no discount)	2/da	Gum/mouth irritation	Ease of use; rapid kinetics	In mouth 12 h
nasal	~\$250-750/mo (no discount)	2-3/da	Nasal symptoms	Ease of use; rapid kinetics	3x/da

Testosterone Pharmaceuticals (3)

Form	Cost/month	Dosing Interval	Adverse Events	Advantages	Disadvantages
Oral					
oxandrolone	~\$60-120	daily	Hepatic AE's	Oral convenience	Hepatic AE's
Undecanoate (not available US)	\$50-100	tid		Oral convenience; modifiable dose	Very variable responses; taken with a fatty meal

THANK YOU