# Bicalutamide as an anti-androgen in transfeminine people: a cross-sectional study

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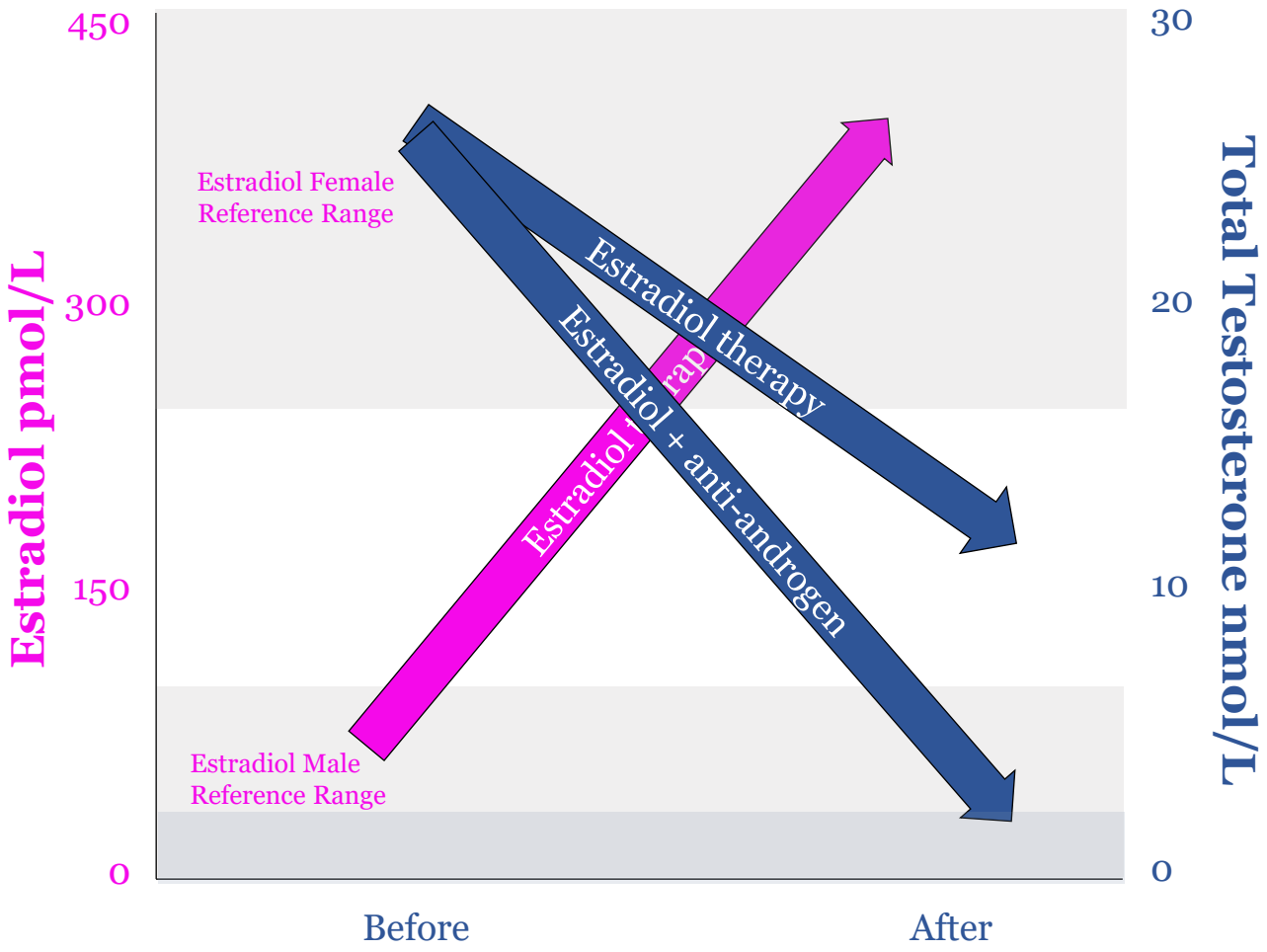
# Background 1: Feminising hormone therapy



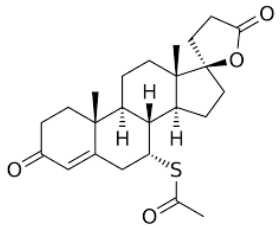

- Most guidelines recommend a target serum total testosterone <2 nmol/L
- But **androgen activity**, rather than measured serum total testosterone is more important for clinical feminisation

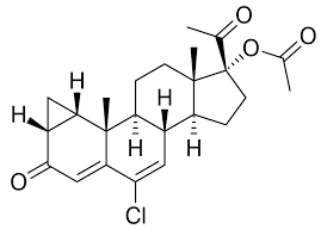
# Background 2: Anti-androgens

Decrease the actions and/or synthesis of testosterone

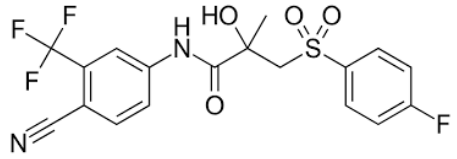
- **Androgen receptor antagonism/blockade**
- Suppression of gonadotrophins
- Inhibition of testosterone biosynthesis

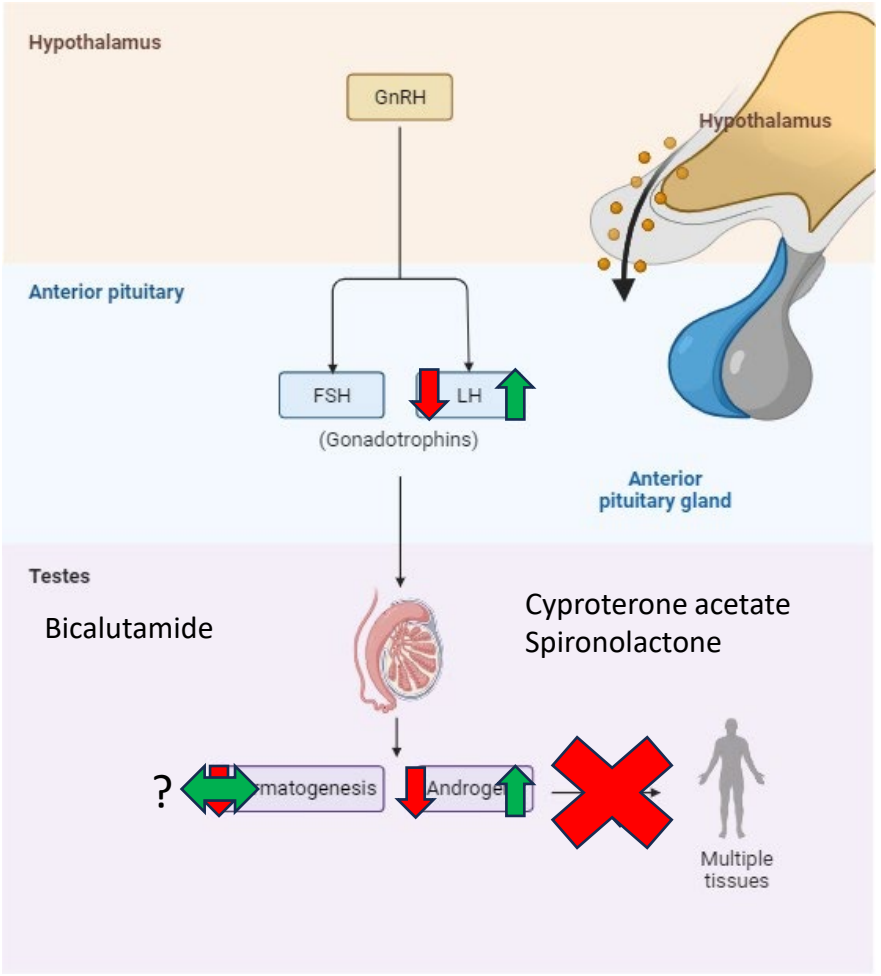
- Steroidal
  - Spironolactone: progesterone receptor, mineralocorticoid receptor
  - Cyproterone acetate: progesterone receptor





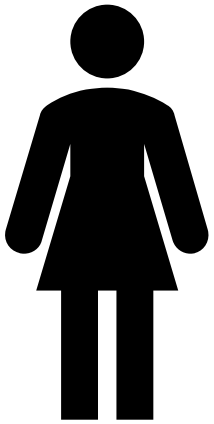
- Non-steroidal
  - Bicalutamide, enzalutamide, apalutamide etc.
  - No off-target effects





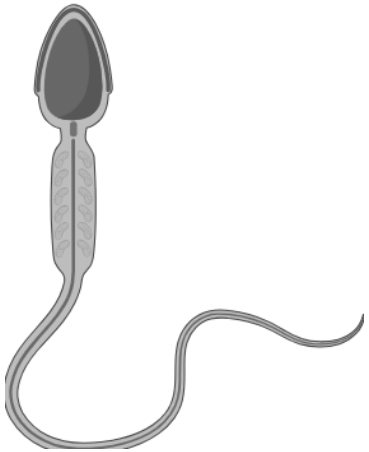

Angus et al. *Clin Endocrinol (Oxf) 2020;94(5):743-52*

# Background 3: theoretical advantages



Increased feminisation?

Less side effects?



Preservation of fertility?

# Background 4: Increased feminisation?

1. Case series of 13 trans girls treated with bicalutamide 50mg daily
   - 84.6% had breast development within 6 months
   - Testosterone range 18.2 – 28.5 nmol/L
   - Estradiol range  <70 – 224 pmol/L
   - Normal liver function tests

2. Gynaecomastia occurred in ~80% of men with prostate cancer treated with bicalutamide 150mg daily

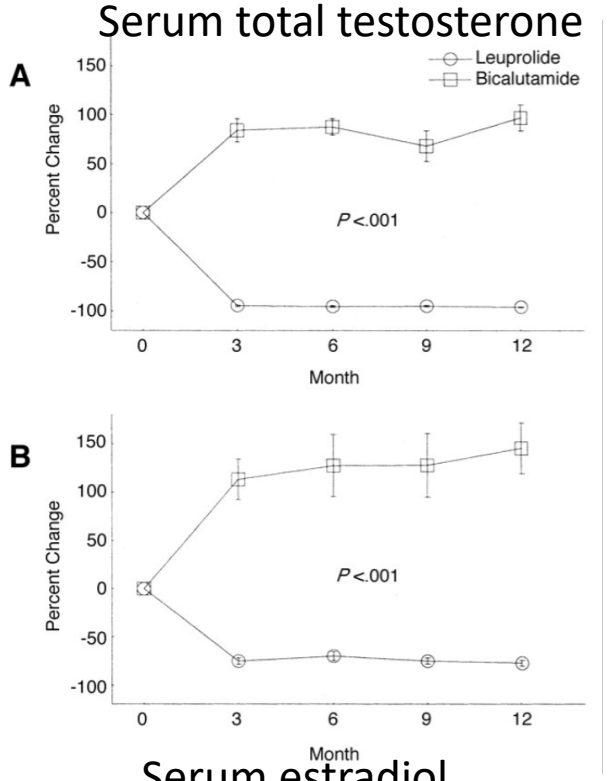
3. COCP + Bicalutamide 50mg daily resulted in significantly improved hirsutism in women with PCOS

Neyman et al. *J Adolesc Health* 2019 Apr;64(4):544-6
Tyrrell et al. *Int J Radiation Oncology Biol Phys* 2004;60(2):476-83
Moretti et al *J Clin Endocrinol Metab* 2018;103:3):824-38

# Background 5: less side effects?

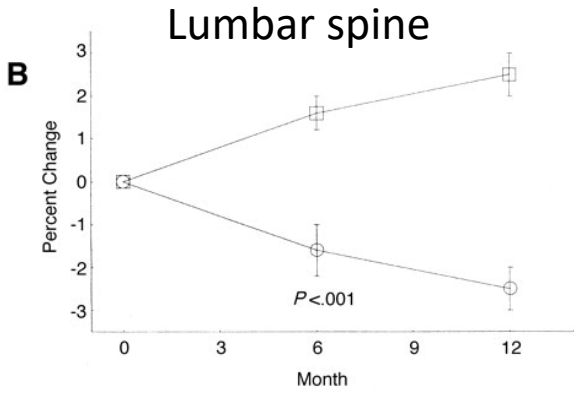
Bicalutamide 150mg daily preserved bone density in men with prostate cancer over 12 months (vs GnRH analogue)

Serum total testosterone

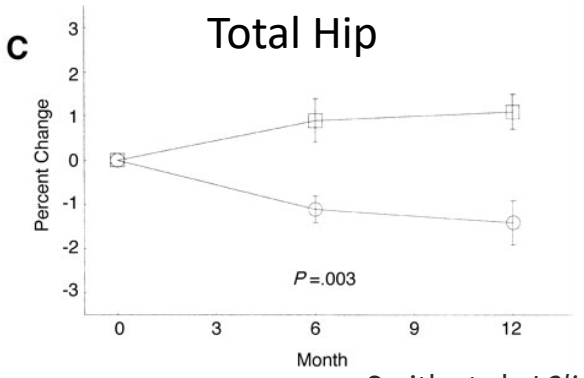



Serum estradiol

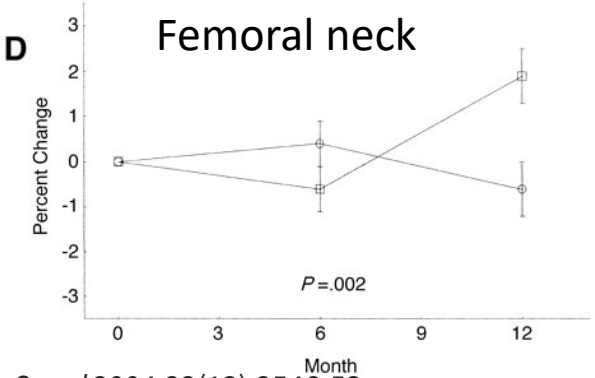
Lumbar spine




Total Hip



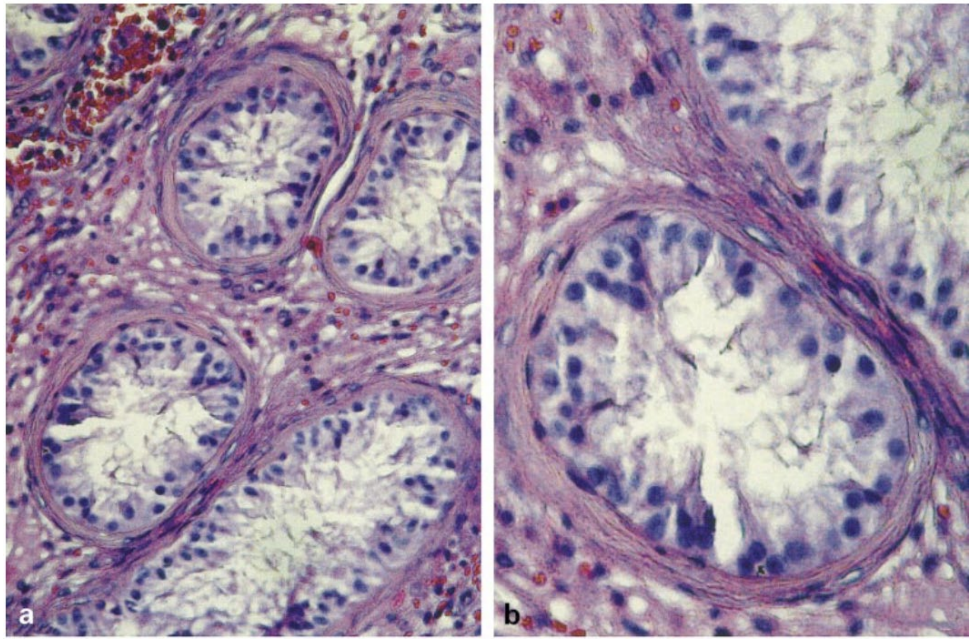

Femoral neck



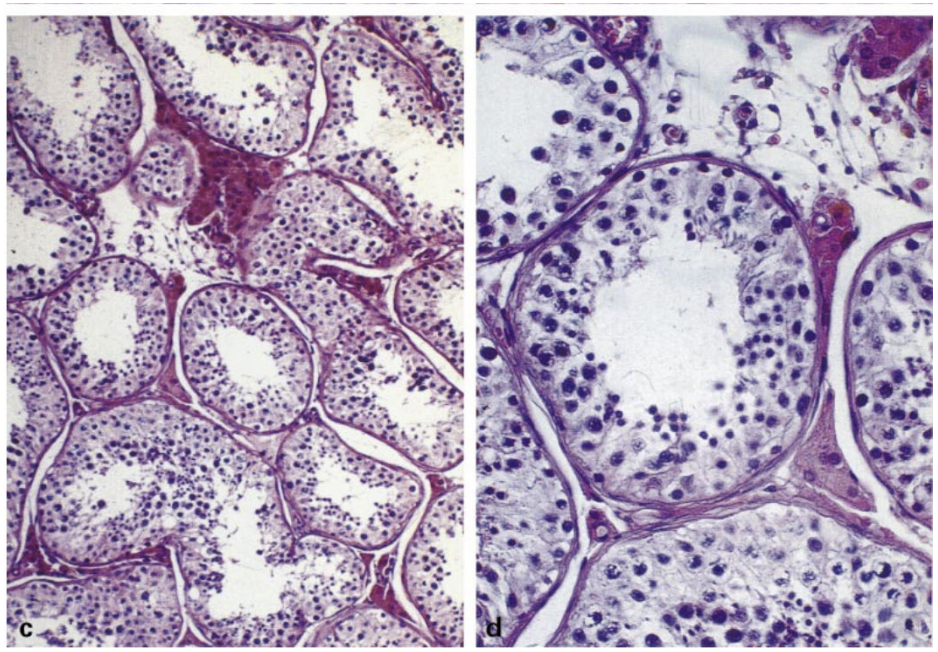

Smith et al. *J Clin Oncol* 2004;22(13):2546-53

# Background 6: preservation of fertility?

Histopathological examination of testes post-orchidectomy after 4 years of bicalutamide 50mg daily (x2 patients) showed normal spermatogenesis




Normal testis



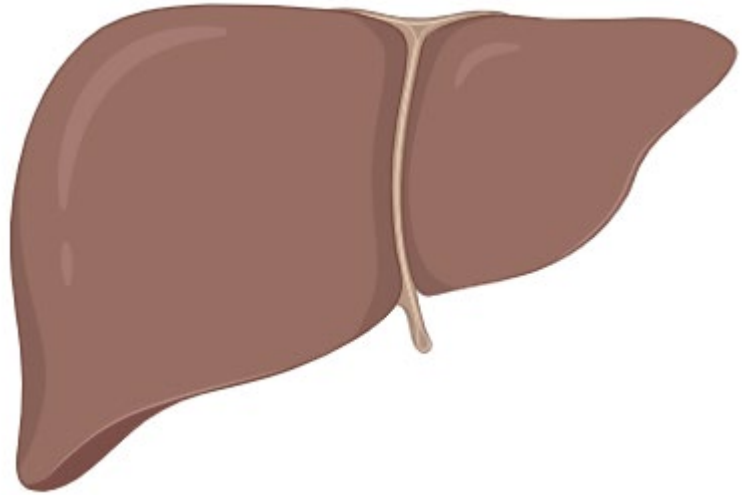

Bicalutamide

Morgante et al. *Histopathology* 2001 Mar;38(3):195-201

# Background 7: potential hepatotoxicity?

- Flutamide was associated with numerous cases of fatal hepatotoxicity (now seldom used)

- Bicalutamide
  - transient elevations in transaminases in 6% of patients
  - ~6 case reports of liver injury and 1 death (doses 50-150mg daily)



Gretarsdottir et al. *Cas Rep Gastroenterol* 2018;12(2):266-70
LiverTox: Clinical and research information on drug-induced liver injury (Internet)

# Methods 1

**AIM**: To assess the effect of bicalutamide on serum sex steroids and ALT compared to conventional treatment

**HYPOTHESIS**: Bicalutamide will result in higher serum total testosterone levels than use of estradiol alone or with spironolactone or cyproterone acetate

# Methods 2

Cross-sectional study of patients treated with bicalutamide >6 months attending the Austin Gender Clinic and private endocrinologists

Comparison to historical cohorts treated with estradiol alone ± spironolactone or cyproterone acetate

Outcomes

- Serum total testosterone
- Serum estradiol
- Serum ALT

# Results 1

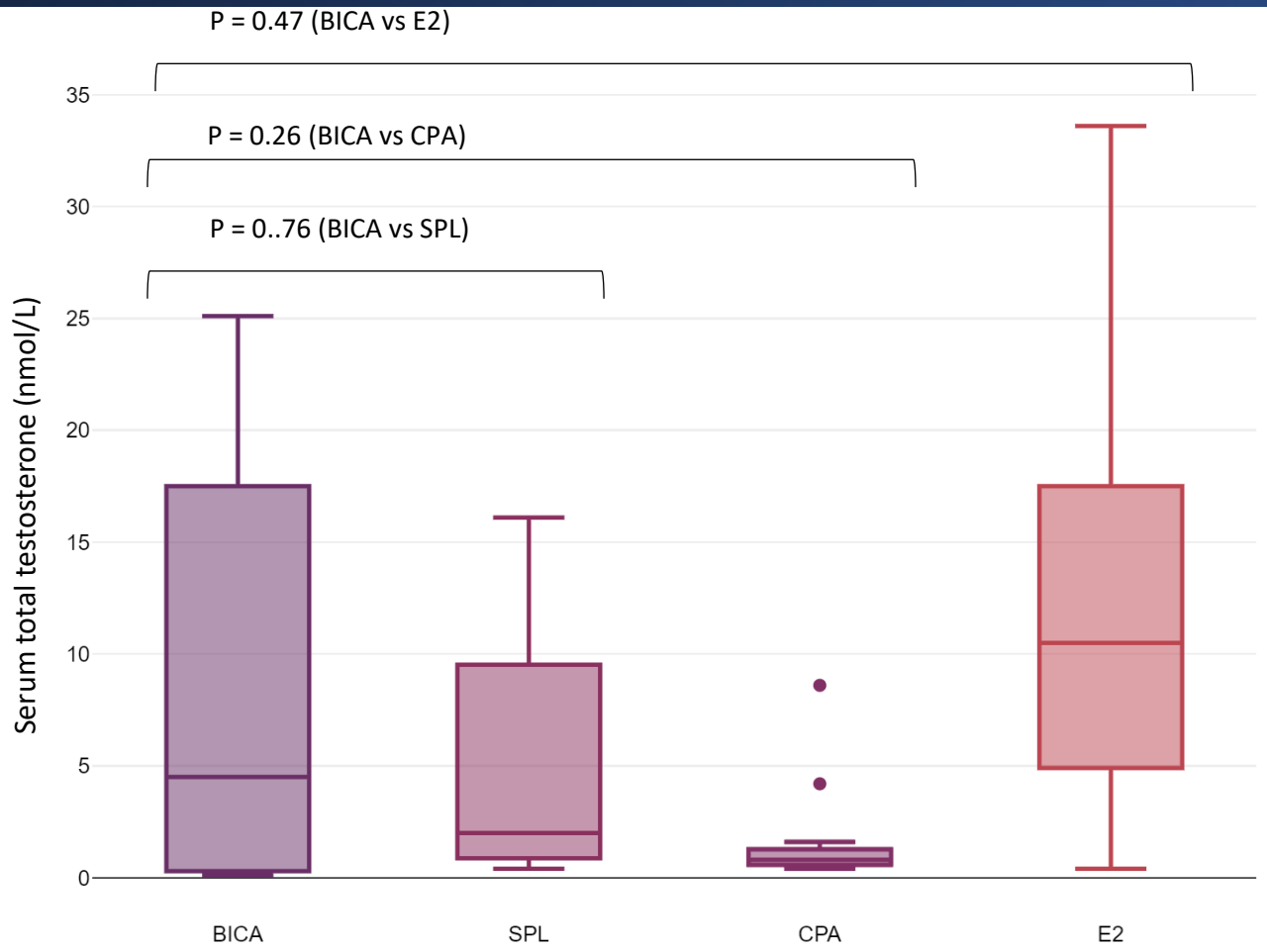



**Figure 1**: Serum total testosterone by group

| | Bica | SPL | CPA | E2 | Overall P (<0.05) |
|---|---|---|---|---|---|
| **N** | 14 | 38 | 21 | 21 | |
| **Serum total testosterone (nmol/L)** | 4.5 (0.5 – 17.8) | 2.0 (0.9 – 9.4) | 0.8 (0.6 – 1.2) | 10.5 (4.9 – 17.2) | |
| **Serum estradiol (pmol/L)** | 375 (300 - 477) | 279 (233 - 384) | 279 (149 - 334) | 256 (119 - 408) | 0.09 |
| **ALT (IU/L)** | 15 (10 - 26) | 19 (15 – 24) | 23 (15 – 29) | 21 (15 - 28) | 0.53 |

Median bicalutamide dose 25 (25-50) mg

**Table 1**: Serum total testosterone, estradiol and ALT by group

# Results 2

| Anti-androgen naive bicalutamide users (N=5) | |
|---|---|
| **Gender identity** | |
| **Female** | 4 (80) |
| **Non-binary** | 1 (20) |
| **Age - years** | 22 (20 – 30) |
| **Estradiol therapy** | |
| **Duration – months** | 13 (6 – 14) |
| **Formulation** | |
| **Oral tablet** | 2 (40) |
| **Sublingual tablet** | 2 (40) |
| **Transdermal patch** | 0 (0) |
| **Transdermal gel** | 0 (0) |
| **Intramuscular injection** | 1 (20) |
| **Bicalutamide therapy** | |
| **Duration – months** | 6 (2 – 14) |
| **Dose – mg/day** | 25 (25 – 50) |

| Anti-androgen naive bicalutamide users (N=5) | |
|---|---|
| **Biochemistry** | |
| **Total testosterone - nmol/L** | 34.2 (16.6 – 47.7) |
| **Luteinising hormone - IU/L** | 5.0 (2.8 – 7.8) |
| **Estradiol - pmol/L** | 285 (235 – 404) |
| **Alanine transferase - IU/L** | 13 (10 – 23) |

**Categorical variables are reported as N (%) and continuous variables median (interquartile range) unless otherwise stated**

# Summary

- Bicalutamide *may* have advantages over conventional anti-androgens in terms of feminisation and side effects
- In this cross-sectional analysis and case series of transfeminine people taking bicalutamide, there was:
  - Significant variation in serum total testosterone levels
  - No evidence of hepatotoxicity

# Conclusions

- Use of bicalutamide in transfeminine people appeared safe and had variable effects on serum total testosterone with short-term follow up
- Further research is needed to assess the effectiveness and safety of bicalutamide for feminisation

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