Alternative management of hypogonadism
Tamoxifen

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What hypogonadism is?
What hypogonadism is?
It is an empty glass
The two possible strategies to fill the glass

• From outside → SUPPLEMENTATION

• From inside → RESTORATION
Understanding the glass
From outside
The first choice treatment for hypogonadism
# Testosterone

## Table 1. Testosterone Replacement Therapies Approved for Use in the U.S.\(^1\)

<table>
<thead>
<tr>
<th>Delivery System (Drug)</th>
<th>Route of Delivery</th>
<th>Standard Dosage for Androgen Deficiency</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Estimated Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone esters</td>
<td>IM</td>
<td>100 mg every week or 200 mg every 2 weeks</td>
<td>Inexpensive; administered every 2 weeks</td>
<td>Roller-coaster pharmacokinetics; requires injection</td>
<td>$100</td>
</tr>
<tr>
<td>Testosterone enanthate</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Testosterone cypionate</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Testosterone pellets</td>
<td>SC</td>
<td>Two to six 75-mg pellets every 3 to 6 months</td>
<td>Convenient 6-month biological duration</td>
<td>Expensive; requires small incision; high rate of extrusion; available only through manufacturer</td>
<td>$150</td>
</tr>
<tr>
<td>Buccal testosterone</td>
<td>Buccal</td>
<td>30 mg BID</td>
<td>Testosterone levels within physiologic range</td>
<td>Expensive; twice-daily dosing; possible oral irritation</td>
<td>$250</td>
</tr>
<tr>
<td>Testosterone patch</td>
<td>Noncrotal topical</td>
<td>5 mg/day</td>
<td>Mimics circadian rhythm</td>
<td>Expensive, daily administration; skin irritation</td>
<td>$250</td>
</tr>
<tr>
<td>Testosterone gel</td>
<td>Topical</td>
<td>5 g/day</td>
<td>Testosterone levels within physiologic range</td>
<td>Expensive; daily administration; possible transference to intimate contacts</td>
<td>$300</td>
</tr>
</tbody>
</table>

Adapted with permission from Edelman D, Doba A, Basaria S. Emerging drugs for hypogonadism. Expert Opin Emerg Drugs. 2006;11(6):685-707.\(^1\)
Testosterone

<table>
<thead>
<tr>
<th>Compound</th>
<th>Half-Life</th>
<th>Injection Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone Propionate</td>
<td>2-3 days</td>
<td>2-3x/wk</td>
</tr>
<tr>
<td>Testosterone Cypionate</td>
<td>8-10 days</td>
<td>1-2x/wk</td>
</tr>
<tr>
<td>Testosterone Enanthate</td>
<td>8-10 days</td>
<td>1-2x/wk</td>
</tr>
<tr>
<td>Nebido (Testosterone Undecanoate)</td>
<td>&gt;12wks</td>
<td>1x/every 90 days</td>
</tr>
</tbody>
</table>

*Injectable Options for TRT*
<table>
<thead>
<tr>
<th>Time</th>
<th>Recommended Steps*</th>
</tr>
</thead>
</table>
| Base line        | Determine base-line voiding history or use standardized questionnaire.  
                  | Determine history of sleep apnea.  
                  | Perform digital rectal examination.  
                  | Perform blood tests for base-line testosterone levels, PSA, and hematocrit or hemoglobin.  
                  | Perform prostate biopsy if PSA level is above 4.0 ng/ml or digital rectal examination is abnormal. |
| Follow-up        | Perform efficacy evaluation with dosage adjustment for suboptimal response at 1 to 2 mo.  
                  | Perform monitoring evaluation with repeated testing every 3 to 6 mo for the first year and annually thereafter.  
                  | Assess urinary symptoms and presence or exacerbation of sleep apnea or gynecomastia.  
                  | Perform digital rectal examination.  
                  | Perform blood tests for testosterone, hematocrit or hemoglobin, and PSA.  
                  | Perform prostate biopsy if the digital rectal examination shows change or there is a substantial increase in PSA. |
Effect on testis

- Reduced testis size
- Reduced spermatogenesis
T as contraceptive


**Male Hormonal Contraception**

Mara Y. Roth, MD
RESTORATION: A CLINICAL CASE
Who is he?

Filippo 42 years old (October 2013)
- Education: secondary school
- Clerk
- Very happy for the current situation
- Never smoke
- Rare alcohol consumption
- Normal pubertal development
- Negative familiar history
- Medical history negative
Who is she?

- Margherita, 31 years old, relationship span more than 10 years
- Good coupler relationship
- Good general health
- Normal sexual desire
- Normal orgasmic functioning
- Previous diagnosis of PCOS
- Good intimacy
Sexual function?

• Erection complete and sufficient for penetration in 60% incomplete but sufficient for penetration in 40%
• The problem started > 2 years ago, gradually
• Mild impaired sleep related erections
• No masturbation
• Mild hypoactive sexual desire
• normal orgasmic functioning
• Reduced perceived ejaculate volume
• frequency of intercourse 4-5/month
• no ejaculatory problems
• no IPP
Ho you name it?

• Erection complete and sufficient for penetration in 60%
  incomplete but sufficient for penetration in 40%
• The problem started > 2 years ago, gradually
• Mild impaired sleep related erections
• No masturbation
• Mild hypoactive sexual desire
• Normal orgasmic functioning
• Reduced perceived ejaculate volume
• Frequency of intercourse 4-5/month
• No ejaculatory problems
• No IPP
In the absence of erectile dysfunction—defined as a continuous or repetitive inability to achieve or maintain an erection sufficient for satisfying sexual activity—SED is diagnosed when at least one major and two minor of the following criteria are met:

(a) Major criteria
   1. During the last 6 months, to have had non-occasional trouble getting an erection before intercourse begins
   2. During the last 6 months, to have had non-occasional trouble maintaining an erection once intercourse has begun
   3. During the last 6 months, to have experienced non-occasional reduction in erection intensity

(b) Minor criteria
   1. Distressed by the condition
   2. Dissatisfaction with sexual relationship with present partner(s)
   3. At least one partner dissatisfied with the sexual performance
   4. Reduced sexual relationships due to fear of erectile failure

Note that here “continuous/repetitive” is used when the condition occurs on >25% of occasions, “non-occasional” for occurrence between 10% and 25% of occasions, and “occasional” for <10% of occasions.
What the couple was looking for

Looking for pregnancy for 6 years
Clinical examination

- Weight = 88 Kg
- Height = 172 cm
- Waist circumference = 106 cm
- BMI = 39.8 Kg/m2
- Right testis = 12 mL (NV>15)
- Left testis = 12 mL (NV>15)
- No varicocele
- Normal prostate at DRE
- No thyroid problems
- BP = 130/80 mmHg
Laboratory exams

Total Testosterone = 10.5 nmol/L (10-30)
SHBG = 27 nmol/L (12.9-61.7)
Calculated free T = 223 pmol/L (>225)
TSH = 3.5 mU/L (0.3-5)
LH = 2.3 mU/L (0.6-7)
PRL = 4.2 mU/L (<15)
Glycemia = 99 mg/dL (60-110)
Total Cholesterol = 201 mg/dL
HDL Cholesterol = 44 mg/dL
Triglycerides = 101 mg/dL
PSA = 0.4 ng/ml (<4)
SEMEN ANALYSIS

- Volume: 1.3 > 1.5 ml
- pH: 7.3 ≥ 7.2
- Concentration: 12x10^6 > 15x10^6 /ml
- Total number: 15.6x10^6 > 39x10^6
- Motility
  - total: 38 > 40%
  - progressive: 28 > 32%
- Morphology: 15 > 4%
- Vitality: 60 > 75%
- WBC: 0 < 1x10^6/ml
- MAR test: Neg < 10%
Structured interview on erectile dysfunction (SIEDY©): a new, multidimensional instrument for quantification of pathogenetic issues on erectile dysfunction

L Petrone, E Mannucci, G Corona, M Bartolini, G Forti, R Giommi and M Maggi

Andrology Unit, Endocrinology Unit, Radiology Units; and Department of Clinical Physiopathology, University of Florence and International Institute of Sexology, Florence, Italy

S.I.E.D.Y© Multidomain SIEDY scores

- Scale 1 = organic domain
  - Filippo’s score = 3/12 (<4)
- Scale 2 = relational domain
  - = 2/12
- Scale 3 = intrapsychic domain
  - = 1/18
IIEF  International Index of Erectile Function

Score

22-25 no ED
17-21 Mild ED
12-16 Mild-moderate ED
8-11 Moderate ED
7-5 Severe ED

Score = 20

Repeated exams

Total Testosterone = 10.3 nmol/L (10-30)
SHBG = 28 nmol/L (12.9-61.7)
Calculated free T = 223 pmol/L (>225)

Pituitary MRI normal

- Volume: 1.4 ml (> 1.5 ml)
- pH: 7.4 (≥ 7.2)
- Concentration: 10x10^6 /ml (> 15x10^6 /ml)
- Total number: 14x10^6 (> 39x10^6)
- Motility:
  - total: 31 (> 40%)
  - progressive: 18 (> 32%)
- Morphology: 8 (> 4%)
- Vitality: 60 (> 75%)
- WBC: 0 (< 1x10^6 /ml)
- MAR test: Neg (< 10%)
Our suggestions

• Tamoxifen 20 mg/daily
• Referral to assisted reproductive centre
Restorative Alternatives

- **PERIPHERAL**
  - Gonadotropins
    - hCG
- **CENTRAL**
  - Aromatase inhibitors
    - Anastrozole
    - Letrozole
  - Selective ER Modulators
    - Clomid
    - Tamoxifen
SERMs

Advantages:
1. Simple,
2. Cheep
3. Oral administration

Disadvantages
1. Off label
2. Useful only in metabolic forms
3. If pure anti-estrogens: estrogen deficiency

Buvat et al., J Sex Med. 2013;10:245
Effects of letrozole (2.5 mg/week x 6 months) in 12 obese subjects (BMI>35.0 kg/m²)
the use of oestrogen antagonists as empiric medical therapy for idiopathic male infertility with oligo and/or asthenoteratozoospermia through meta-analysis of randomized controlled trials
### Testosterone levels

**Significant elevation of serum testosterone**

(WMD 54.59; 95% CI 15.92, 93.27; p = 0.006)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experimental</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.1.1 Clomiphene 25mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sokol 1988</td>
<td>473.19</td>
<td>276.47</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>11</td>
<td>8.66</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.81 (P &lt; 0.00001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.1.2 Clomiphene 50mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ronnberg 1980</td>
<td>20</td>
<td>13.5647</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>27</td>
<td>11.9088</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.55 (P &lt; 0.00001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.1.3 Tamoxifen 20-30mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cakan 2009</td>
<td>86.4</td>
<td>32.6399</td>
</tr>
<tr>
<td>Krause 1992</td>
<td>3</td>
<td>4.0705</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>142</td>
<td>62</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 4378.36; Chi² = 210.89, df = 1 (P &lt; 0.00001); I² = 100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.05 (P = 0.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>180</td>
<td>100</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 1195.55; Chi² = 251.45, df = 3 (P &lt; 0.00001); I² = 99%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.77 (P = 0.006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 21.67, df = 2 (P &lt; 0.0001), I² = 90.8%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Study or Subgroup

#### 8.1.1 Clomiphene 25mg
- Sokol 1988
  - Mean: 18.9
  - SD: 15.8
  - Total: 11
- Subtotal (95% CI): 11
  - 4.4%
  - 16.11 [6.64, 25.58]
  - Heterogeneity: Not applicable
  - Test for overall effect: Z = 3.33 (P = 0.0009)

#### 8.1.2 Clomiphene 50mg
- Micic 1985
  - Mean: 6.3
  - SD: 3.6055
  - Total: 56
- Ronnberg 1980
  - Mean: 6.3
  - SD: 8.7706
  - Total: 27
- Subtotal (95% CI): 83
  - 27.5%
  - 5.08 [3.86, 6.30]
  - Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
  - Test for overall effect: Z = 8.65 (P < 0.00001)

#### 8.1.3 Tamoxifen 20-30mg
- Cakan 2009
  - Mean: 3.7
  - SD: 4.0707
  - Total: 103
- Krause 1992
  - Mean: 0.5
  - SD: 0.3124
  - Total: 39
- Subtotal (95% CI): 142
  - 26.6%
  - 3.50 [2.07, 4.93]
  - Heterogeneity: Tau² = 2.01; Chi² = 4.15, df = 1 (P = 0.04); I² = 76%
  - Test for overall effect: Z = 2.09 (P = 0.04)

#### Total (95% CI)
- Mean: 4.19
- SD: 2.40
- Total: 236
- 100.0%
- 4.19 [2.05, 6.34]
- Heterogeneity: Tau² = 3.98; Chi² = 20.62, df = 4 (P = 0.0004); I² = 81%
- Test for overall effect: Z = 3.83 (P = 0.0001)
- Test for subgroup differences: Chi² = 10.06, df = 2 (P = 0.007), I² = 80.1%\n
**FSH levels**

Chua et al., Andrology. 2013;1:749
Pregnancy rate per couple randomized

Significant increase in sperm concentration (WMD 5.24; 95% CI 2.12, 88.37; p = 0.001) and per cent sperm motility (WMD 4.55; 95% CI 0.73, 8.37; p = 0.03)

Statistically significant increased pregnancy rate compared with controls (pooled OR 2.42; 95% CI 1.47-3.94; p = 0.0004)
Advantages of tamoxifen vs other antiestrogens (anastrazole)

- Better cholesterol levels
- Much lower osteoporotic effect
- Less joint disorders (arthritis, arthrosis, arthralgia)
- Less pathological fractures
- Less carpal tunnel syndrome
- No differences in CV safety
The couple had FIVET with negative results and they are waiting for new cycle.

The hormonal and sperm parameters were improved but ED worsen especially during the scheduled week for the pick up.

Estrogens may be as or even more important for male libido than testosterone. Driving estrogens to very low levels with aromatase inhibitors may risk affecting libido and sexual performance. This is not so frequently seen using SERMs. (Finkelstein et al. NEJM, 2013)
**Laboratory exams**

Total Testosterone = 12.2 nmol/L (10-30)
SHBG = 26 nmol/L (12.9-61.7)
Calculated free T = 280 pmol/L (>225)

- Volume: 2.0 > 1.5 ml
- pH: 7.4 ≥ 7.2
- Concentration: 14x10^6 > 15x10^6 /ml
- Total number: 28x10^6 > 39x10^6
- Motility
  - total: 38 > 40%
  - progressive: 28 > 32%
- Morfology: 6 > 4%
- Vitality: 60 > 75%
- WBC: 0 < 1x10^6/ml
- MAR test: Neg < 10%

**SEMEN ANALYSIS**
WHAT IS THE IMPACT OF INFERTILITY ON MALE SEXUAL FUNCTION?
Phosphodiesterase Type 5 Inhibitor Therapy for Sexual Dysfunction Induced by Male Infertility

Emmanuele A. Jannini, MD; Francesco Lombardo, MD, PhD; Pietro Salacone, MD; Loredana Gandini, BSc; Andrea Lenzi, MD

Infertility is considered a chronic stress factor for couples, and the stress itself may have a negative effect on spermatogenesis and fertility rate.

The American Journal of Urology Review

September 2004 • Vol 2 • No 9
Stress, sexual dysfunctions, and male infertility

A. Lenzi*, F. Lombardo*, P. Salacone*, L. Gandini*, and E.A. Jannini**
Our suggestions

- Tamoxifen 20 mg/daily
- Sildenafil 50 mg on demand
Our suggestions

I read these drugs could cause possible sperm problems
Treatment of sexual dysfunctions secondary to male infertility with sildenafil citrate

FERTILITY AND STERILITY®
VOL. 81, NO. 3, MARCH 2004

Emmanuele A. Jannini, M.D. a
Francesco Lombardo, M.D., Ph.D. b
Pietro Salacone, M.D. b
Loredana Gandini, B.Sc. b
Andrea Lenzi, M.D. b
Efficacy of IVF.

Erectile function is normal without PDE5i.

SERMS seem the most logical choice for men of reproductive age looking for reproduction, because they elevate endogenous LH and FSH, stimulating BOTH Leydig cell and germinal epithelium in the most physiologic manner. (Ross, Fertil Steril, 2014)
Man with Testosterone Deficiency
Signs and/or symptoms AND repeatedly low testosterone level

Assess possible contraindications
*Prostate and breast cancers or suspicion*
and cautions to be taken in use of testosterone therapy
*Polycythemia, severe bladder outlet obstruction, severe sleep apnea syndrome, severe heart failure, tumoral hyperprolactinemia*

If obese or overweight, advise losing weight
Exercise, low calorie diet

Interested in fatherhood

Therapy that stimulates endogenous T secretion
(if LH is not elevated)
- human Chorionic Gonadotropins [+ FSH]
- Anti-estrogens

Follow-up at 3 months

Not improved
ED: try combination with PDE5-I
Other cases: consider discontinuation
Search for other causes/treatments

Improved
Continue (bi)annual follow-up including after age 40 annual DRE

Not interested in fatherhood

Testosterone therapy