## TREATMENT OPTIONS

### Table 7. Testosterone Products for the Treatment of TDS[5,98,434,435]

| Compound | Starting or standard dose | Advantages | Disadvantages |
|---|---|---|---|
| **Oral agents** | | | |
| Testosterone undecanoate | 120-240 mg TID | Oral convenience<br>Modifiable dosage | Serum T levels and clinical responses vary<br>Must be taken with fatty food |
| **Intramuscular agents** | | | |
| Testosterone enanthate | 250 mg q2-3 weeks | Low cost<br>Self injection for some men | Wide fluctuations in circulating T levels, occasionally symptomatic<br>Multiple injections<br>Pain and redness at injection site<br>Relative higher risk of polycythemia |
| Testosterone cypionate | 200 mg q2-3 weeks | Low cost<br>Self injection for some men | Wide fluctuations in circulating T levels, occasionally symptomatic<br>Multiple injections<br>Pain and redness at injection site<br>Relative higher risk of polycythemia |
| Testosterone propionate | 100 mg q2 days | Low cost<br>Self injection for some men | Wide fluctuations in circulating T levels, occasionally symptomatic<br>Multiple injections<br>Pain and redness at injection site<br>Relative higher risk of polycythemia |
| **Transdermal agents** | | | |
| Testosterone patch | 5 to 10 mg/day | Mimics T circadian rhythm<br>Simple administration | Skin irritation, occasional allergic contact dermatitis<br>Daily administration |
| Testosterone gel 1% | 40 to 80 mg/day | T levels within normal range<br>Flexible dose modifications<br>Easy to apply<br>Readily absorbed<br>Skin irritation less common | Possible transfer during intimate contact<br>Skin irritation at application site in a small number of men<br>Daily administration |
| Testosterone solution 2% (for underarm application) | 60 to 120 mg/day | T levels within normal range<br>Skin irritation less common | Possible transfer during intimate contact<br>Daily administration |

The following products are not marketed in Canada:
Testosterone undecanoate injection in castor oil (long-acting IM injection)
Testosterone buccal system (mucoadhesive)
Testosterone pellets for subcutaneous administration (implantation)
Testosterone gel 1.62%, 2%

## Table 8. Testosterone Preparations: Approximate Cost Per Month

| Compound | Availability and cost | Cost of usual or maximum recommended dose: 30 days' supply (not including pharmacy markup and professional [dispensing] fee) |
|---|---|---|
| **Oral agents** | | |
| Testosterone undecanoate | $0.564 per 40 mg capsule[a] | 6 capsules (240 mg)/day; 180 capsules = $101.52 |
| **Intramuscular agents** | | |
| Testosterone enanthate | $50.65 per 5 mL vial; 200 mg/mL[a] | 200 mg (1 mL) q2weeks; 2 mL/month; $20.26 |
| Testosterone cypionate | $28.59 per 10 mL vial; 100 mg/mL[a] | 200 mg (2 mL) q2weeks; 4 mL/month; $11.436 |
| **Transdermal agents** | | |
| Testosterone patch | $2.0929 per 12.2 mg patch[a]<br>$4.1858 per 24.3 mg patch[a] | One 24.3 mg patch (equivalent to 5 mg testosterone) per day; 30 patches; $125.574 |
| Testosterone gel 1% | $2.23 per 2.5 g tube[a]<br>$3.9533 per 5 g tube[a] | One 5 g tube daily; 30 tubes; $118.299 |
| Testosterone gel 1% | $133.98 per 2 x 90 mL pump[b] (1.25 g per actuation, 60 actuations per pump) | 5 g (4 actuations)/day;<br>2 x 90 mL (120 actuations); $133.98 |
| Testosterone gel 1% with pentadecalactone | $3.6030 per 5 g tube[a] | One 5 g tube daily; 30 tubes; $108.09 |
| Testosterone solution 2% (for underarm application) | $138.86 per 90 mL pump[b]; (30 mg per actuation, 60 actuations per pump) | 120 mg (4 actuations)/day; 2 x 60 mL; $277.72 |

Cost information (June 2014):

a. Ontario Drug Benefit Formulary/Comparative Drug Index lists the "Drug Benefit Price" for nine generic and brand testosterone products (available: https://www.healthinfo.moh.gov.on.ca/formulary/ accessed 2014 June 14). Not all available products are reimbursed by this program and product cost and/or coverage in other provinces may be different.

b. Price obtained from manufacturer's or pharmaceutical wholesaler's price list

## CARDIOVASCULAR DISEASE

### Table 9. Investigations of Cardiovascular Surrogate Measures

| Ref | Population and study design | Surrogate measure or outcome(s) of interest | Results |
|---|---|---|---|
| [188] | 26 hypogonadal men, treated with IM T for 1 year | Markers of blood coagulation (plasma free tissue factor pathway inhibitor antigen [TFPI Ag] and TF-induced thrombin generation *ex vivo* | Markers were unchanged |
| [190] | Retrospective chart review, Veterans Affairs database, total T checked in 2008; n=1479 | Framingham risk scores for developing hard coronary heart disease | Framingham score was negatively associated with total T ($P$<0.0001) and FT ($P$=0.03) |
| [436] | 12-week double-blind RCT in men with stable angina; T patch (n=22) or placebo patch (n=24) | Time to 1-mm ST-segment depression during the Bruce treadmill exercise test | T patch group increased at 4 and 12 weeks ($P$=0.02); greater magnitude of change with lower baseline levels of BAT ($P$=0.024) |
| [437] | Men aged 19-72 y, community based, single-sample survey; n=1891 | N-terminal pro-B-type natriuretic peptide (NT-proBNP) | Increasing NT-proBNP levels related to decreasing cFT and increasing SHBG |
| [438] | 9-week open-label study in men with MetS + TD (n=30), men with MetS (n=25), and healthy controls (n=25); IM T q3 weeks to men with MetS + TD | NT-proBNP | TRT had no significant effect on NT-proBNP |
| [439] | 6-month trial in hypogonadal men age 50-64 with isolated arterial erectile dysfunction; T gel 2% (n=30), not treated due to contraindications to TRT (n=20) | Markers of endothelial dysfunction (blood endothelial progenitor cells [EPCs] and endothelial microparticles [EMPs]) | EPCs and EMPs were significantly higher in men in the T group |
| [440] | 12-month single-arm study in symptomatic men between 40 and 70 years old; 29 hypogonadal men received open-label T gel 1%, 17 eugonadal were not treated | Circulating EPC levels | No difference at baseline; treated men showed significant increase at 3, 6, and 12 months |
| [191] | 12-month RCT in hypogonadal men with stable angina pectoris; long-acting T IM (n=7) or placebo IM (n=6) | Exercise-induced ischemia, lipid profiles, carotid intima media thickness (CIMT), and body composition | TRT: significant improvements in exercise-induced ischemia, BMI and triglycerides; nonsignificant reduction in CIMT; no change in total cholesterol and HDL-cholesterol |
| [189] | 24-month double-blind double-dummy RCT in hypogonadal men, 1000 mg T IM q12 weeks (n=40) or placebo gel (n=10) | HOMA-IR, CIMT, high-sensitivity C-reactive protein (hsCRP) | T group: HOMA-IR, CIMT and hsCRP significantly reduced at 12 but not at 24 months |

| | | | |
|---|---|---|---|
| [441] | Survey of 195 community-living men ≥70 years old, to measure endogenous sex hormones and CIMT in 1996 and in 2000 | Progression of CIMT | FT inversely related to mean progression of age-adjusted CIMT; total T not related to progression |
| [442] | A single survey in 403 community-living men aged 73 to 94 years | CIMT | Age-adjusted serum T, estrone, and free IGF-1 were inversely related to CIMT |
| [192] | 9-week open-label study in men with MetS + TD (n=30), men with MetS (n=25), and healthy controls (n=25); IM T q3 weeks was given to men with MetS + TD | Heart-rate variability (HRV) by 24-hour Holter monitor | At baseline, all time-domain and most frequency-domain HRV parameters were significantly lower in MetS + TD versus controls; TRT improved HRV parameters; they did not reach control values |
| [443] | 3 trials (106 men) comparing T vs placebo in men with intermittent claudication or critical leg ischemia; meta-analysis | | TRT produced no significant improvements |
| [444] | Double-blind, cross-over RCT; 12 men received 60 mg T or placebo via the buccal route | Central hemodynamics monitored over 6 hours, using a pulmonary flotation catheter | Acute increase in cardiac output, apparently via reduction of left ventricular afterload |
| [445] | Measure of T in men 30 to 85 years old with recent (within 6 to 12 hours) myocardial infarction (MI, confirmed by troponin I level) (n=60), versus matched controls (n=60) | The relationship of total T in men with a recent MI versus matched controls | Strong inverse relationship between T in men with recent MI compared with controls |
| [446] | 18 hypogonadal males and 12 matched controls; transdermal T gel 1%, 90-day trial | Arterial stiffness, as assessed by pulse wave velocity | Normalizing T improved arterial stiffness |

## Table 10. Testosterone Replacement Compared to Placebo for Adult Men with Testosterone Deficiency Syndrome

**Patient or population:** Adult men with TDS
**Settings:**
**Intervention:** TRT
**Comparison:** Placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) | Ref |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo | Testosterone Replacement | | | | |
| **MedDRA classified cardiac events** Examination by physician, review of medical records, physician notification and self-report Follow-up: <12 to 24 weeks | **Study population** | | **OR 5.4** (2 to 14.9) | 209 (1 study) | **Low**[1,2,3,4,5,6] | 205,206 |
| | **49 per 1000** | **216 per 1000** (93 to 432) | | | | |
| | **Moderate** | | | | | |
| **Risk of hospitalization for MI** Claims data Medicaid Services beneficiaries. Follow-up: mean 1495 days[7] | **13 per 1000** | **11 per 1000** (9 to 13) | **HR 0.84** (0.69 to 1.02) | 25431 (1 study) | **Very low** | 209 |
| **All cause mortality** Follow-up: 6 – 36 months | **Study population** | | **RR 1.21** (0.7 to 1.81) | 476 (5 studies) | **Low**[4,8,9,10] | 140,447-451 |
| | **107 per 1000** | **129 per 1000** (75 to 194) | | | | |
| | **Moderate** | | | | | |
| | **50 per 1000** | **61 per 1000** (35 to 90) | | | | |
| | **High** | | | | | |
| | **200 per 1000** | **242 per 1000** (140 to 362) | | | | |
| **Coronary bypass surgery** Follow-up: 3 – 36 months | **Study population** | | **RR 1.35** (0.26 to 6.96) | 158 (2 studies) | **Very low**[4,11,12] | 436,449,450 |
| | **25 per 1000** | **34 per 1000** (7 to 176) | | | | |
| | **Moderate** | | | | | |
| **Myocardial infarction** Follow-up: 3 – 36 months | **Study population** | | **RR 0.91** (0.29 to 2.82) | 1054 (7 studies) | **Very low**[8,13,14] | 124,140,436,448-453 |
| | **10 per 1000** | **9 per 1000** (3 to 28) | | | | |
| | **Moderate** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Note: CI = confidence interval; RR = risk ratio; OR = odds ratio; HR = hazard ratio

[1] Cardiovascular-related events included serious cardiovascular adverse events and events of uncertain cardiovascular significance such as elevated blood pressure, tachycardia with fatigue, peripheral edema, LV strain pattern during exercise testing, ectopy on ECG. When only the life-threatening and serious cardiovascular events were included, there was not a significant difference between the intervention and treatment groups. Furthermore, based on the adverse events, the trial was stopped early. Finally, most of the patients were recruited from one site, which may also have influenced the results.

[2] The results of this trial are not in keeping other meta-analyses and systematic reviews such as those conducted by Carson et al. 2012,[454] Fernández-Balsells et al. 2010[140] and Haddad et al. 2007.[203] Additionally, systematic review and meta-analyses evaluating the use of T in high-risk patients such as those with congestive heart failure did not demonstrate significant adverse cardiovascular events.

[3] Although the confidence intervals are wide, the imprecision of the estimate is less relevant as the lower limit of the confidence intervals are 2.0.

[4] No explanation was provided.

[5] Sensitivity analyses were conducted for potential sources of confounding and did not change the results significantly.

[6] Secondary analyses were done of the sera of men who had had cardiovascular events in the intervention and placebo arm. Logistic regression performed in these 25 subjects showed a potential association between free T levels and the odds of a cardiovascular event as defined in this study. The estimate for the OR (95% CI) for this association was 1.07 (1.00 to 1.15). This inference is limited by the small numbers and the limits of the confidence interval.

[7] 1495 days in the intervention arm and 1193 days in the control arm.

[8] Allocation of concealment, blinding and loss to follow-up not consistently reported between studies. Most of the study numbers were small, varying from 40 to 221.

[9] The RR was 1.12, with a confidence interval varying from 0.70 to 1.81. The results of the pooled data are therefore inconclusive with the true effect ranging from a 30% reduction or an 81% increase in the risk of mortality with T replacement therapy.

[10] Given the small size some of these studies it is quite possible that the groups would not be well balanced in regards to potential confounders despite randomization. It is however, difficult to determine the direction of influence on the RR.

[11] Trial numbers are small and event rates were low, resulting in very wide confidence intervals.

[12] English et al. 2000.[436]The placebo group potentially had a higher incidence of risk factors for CAD, This may therefore have contributed to a lower than expected RR.

[13] Individual RR of T therapy in the included studies varied from 0.27 to 1.96.

[14] Wide confidence intervals around the pooled estimate of 0.91, varying from 0.29 to 2.82

## DIABETES MELLITUS and OBESITY

**Table 11. Evidence Profile of Studies Evaluating the Metabolic Effects of TRT in Patients with Type 2 Diabetes**

| Quality Assessment | | | | | | | Study details | Quality | Ref |
|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | | | |
| **Glycemic Control (follow-up 3 to 52 weeks; measured with: Laboratory tests; Better indicated by lower values)** | | | | | | | | | |
| **5** | Randomised trials | No serious risk of bias[1] | Serious[1] | No serious indirectness | No serious imprecision | None | N=323. A1c was lower in T treated groups compared with placebo. Pooled mean difference for 4 studies was -0.87 (-1.31, -0.42) %, and mean difference for the 5th study was -0.20 (-0.34, -0.05) % at 18 weeks and -0.11 (-0.34, 0.13) at 30 weeks. | MODERATE | 234,235,250,251,260 |
| **Blood Pressure (follow-up mean 3-12 weeks; assessed with: Clinical Examination)** | | | | | | | | | |
| **4** | Randomised trials | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | None | N=277. No significant difference in BP in T treated group versus placebo. | HIGH | IMPORTANT 231,233,234,250,260 |

| Lipids (follow-up mean 3-30 weeks; assessed with: Laboratory Measurement) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **5** | Randomised trials | No serious risk of bias | Serious[3] | No serious indirectness | No serious imprecision | None | N=427 Total cholesterol was improved in the T treated group in one study by -0.21(-0.44-0.01) mmol/L at 30 weeks, with no significant change in the other lipid fractions. In the pooled results for the remaining four studies, the triglyceride level was improved in the T treated group by -0.35 (-0.62, -0.07) mmol/L, however there was no difference for the other lipid fractions. | MODERATE | IMPORTANT [233-235,250,251] |

[1] The effect size was small and not consistent for the duration of the longer trials suggesting that the improvent may be transient.

[2] Variable changes in anthropometric parameters according to the baseline testosterone level.

[3] Results not consistent across trials. Very small changes noted in lipid parameters of questionable clinical significance.

## MONITORING RESPONSE

### Table 12. Recommendations for Monitoring

| Parameter | Baseline | 3 months | 6 months | Annually for the duration of TRT | Intermittently |
|---|---|---|---|---|---|
| CBC | X | X | X | X | |
| Testosterone | X | X (see note) | X | X | |
| PSA | X | X | X | X | |
| DRE | X | | X | X | |

Note: Or sooner, to ensure physiological replacement and to allow dose titration (depending on the formulation of testosterone used).

## METHODOLOGY

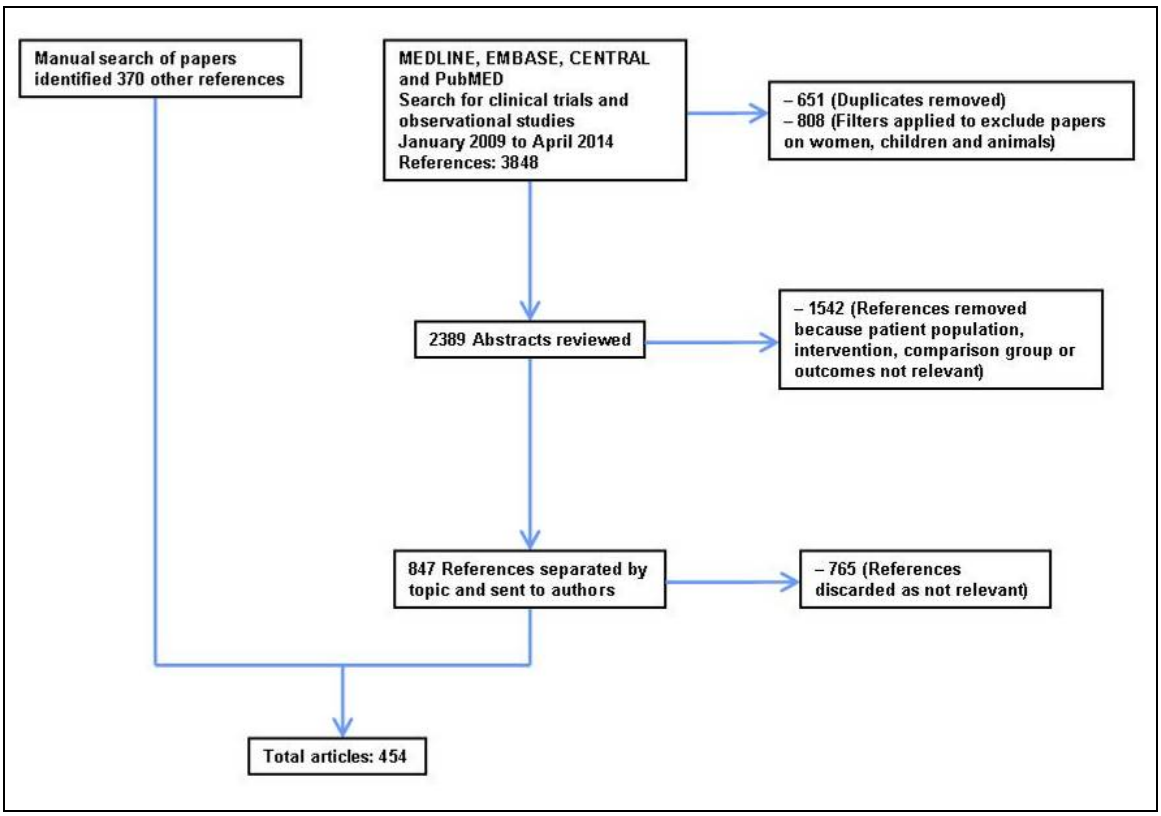


**Figure 1. Study Selection Flow Diagram**

**DIAGNOSTIC ALGORITHM**

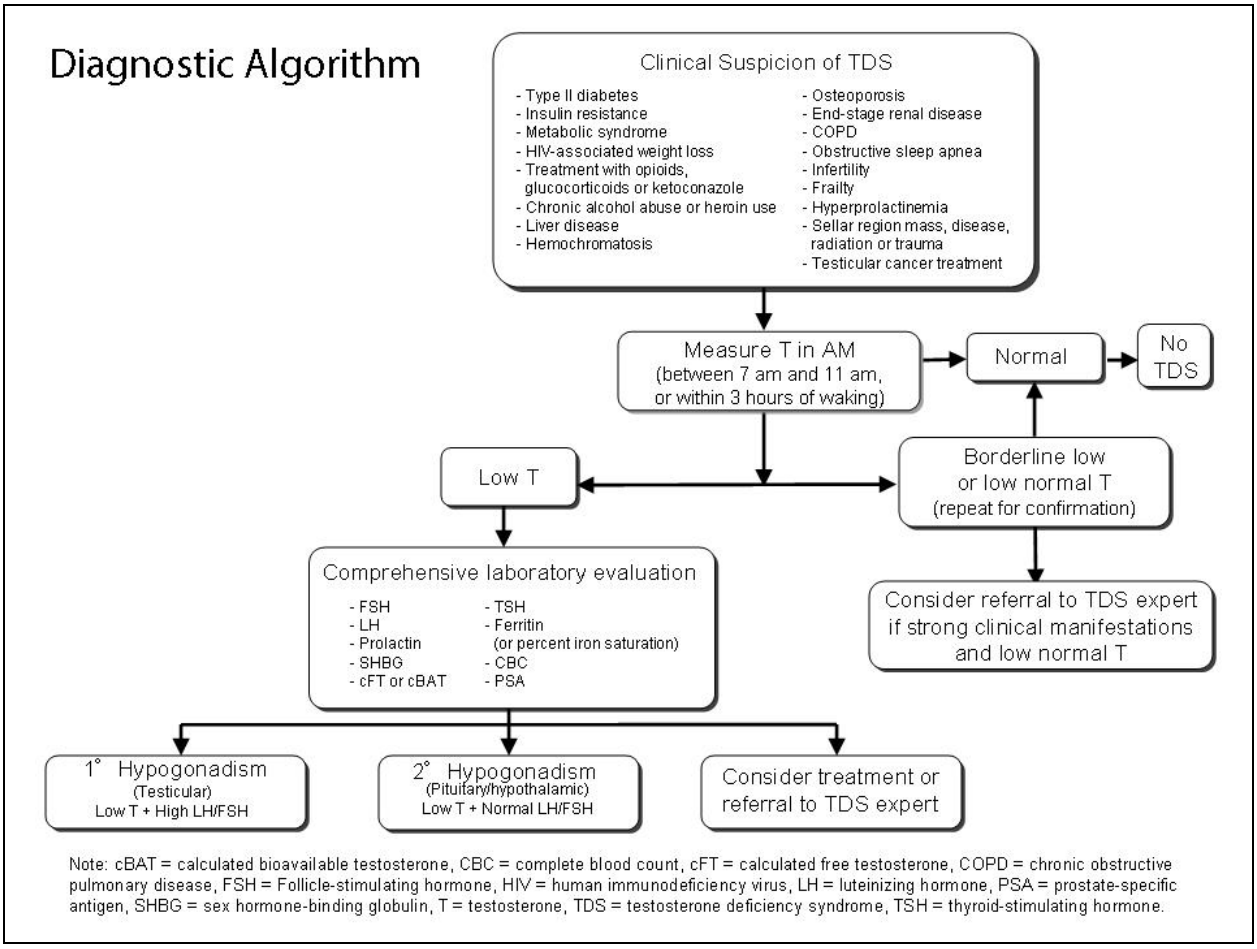


**Figure 2. Clinical Decision Making Algorithm for the Diagnosis of Testosterone Deficiency Syndrome.**

**THERAPEUTIC ALGORITHM**

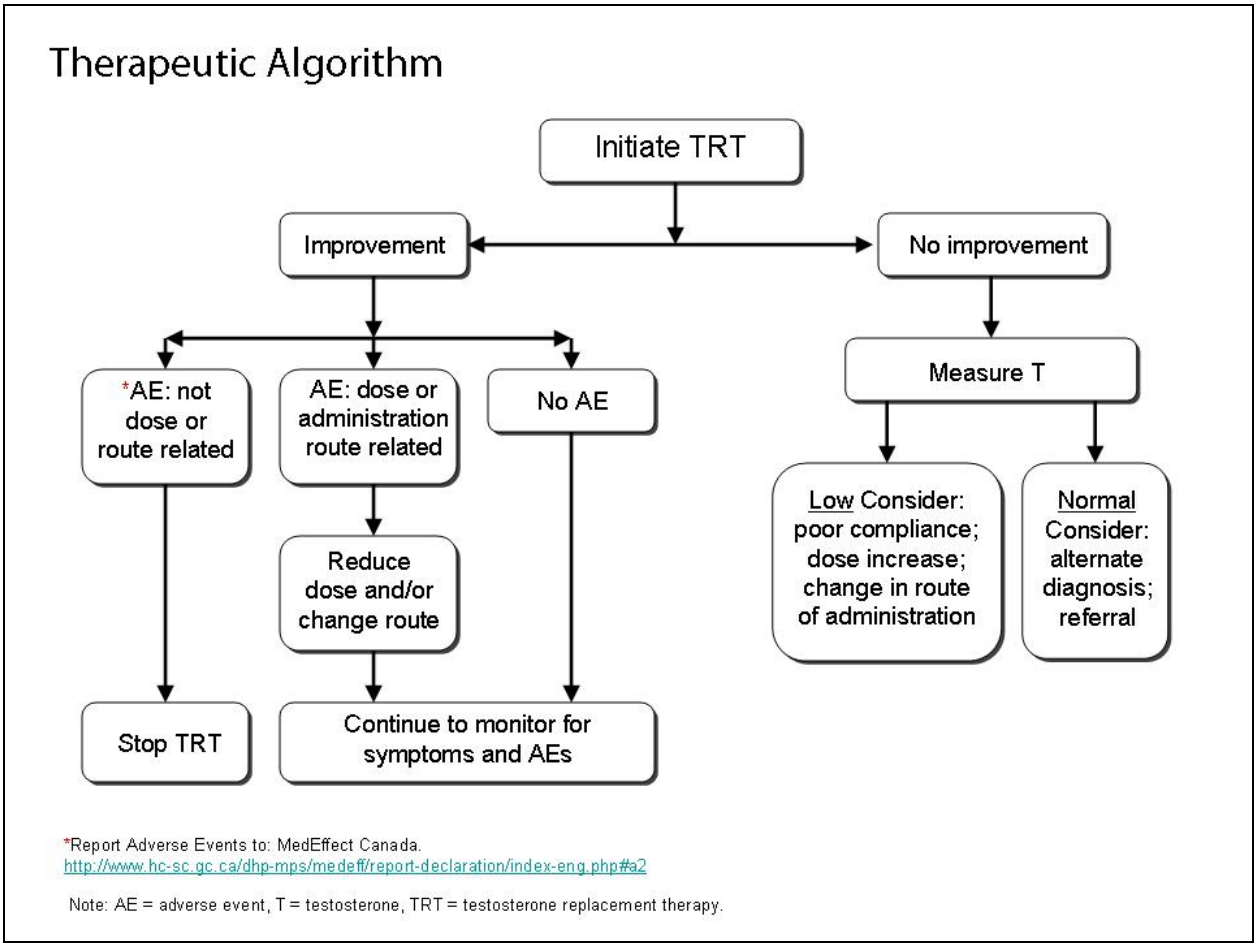


**Figure 3. Clinical Decision Making Algorithm for the Treatment of Testosterone Deficiency Syndrome.**

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