Depression

Depressive Syndromes in Men With Hypogonadism in the TRAVERSE Trial: Response to Testosterone-Replacement Therapy

Bhasin S *et al. J Clin Endocrinol Metab* 2024; doi: 10.1210/clinem/dgae026.

Background

- TTh has been associated with modest but significant improvements in depressive symptoms in a variety of studies in men with hypogonadism, and may be particularly effective in men with LG-PDD and hypogonadism
- The **TRAVERSE trial** was designed to determine the effects of TTh on the incidence of MACE among middle-aged and older hypogonadal men with either pre-existing CVD or who were at high CV risk; the **TRAVERSE Depression substudy** evaluated the effects of TTh for improving depressive symptoms in hypogonadal men with and without depressive symptoms enrolled in the TRAVERSE trial

Study type

- Phase 4, multicentre, randomised, double-blind, placebo-controlled, non-inferiority, event-driven trial (NCT03518034)

Patients

- Men were aged 45–80 years with pre-existing CVD or elevated CV risk, reporting symptoms of hypogonadism plus two fasting testosterone levels <300 ng/dL (<10.4 nmol/L); 3 cohorts were evaluated: i) men with rigorously defined, late life-onset LG-PDD (n=49); ii) men with significant depressive symptoms (PHQ-9 score >4; n=2643); and iii) all TRAVERSE study participants (N=5204)
- 316 clinical trial sites in the USA

Interventions

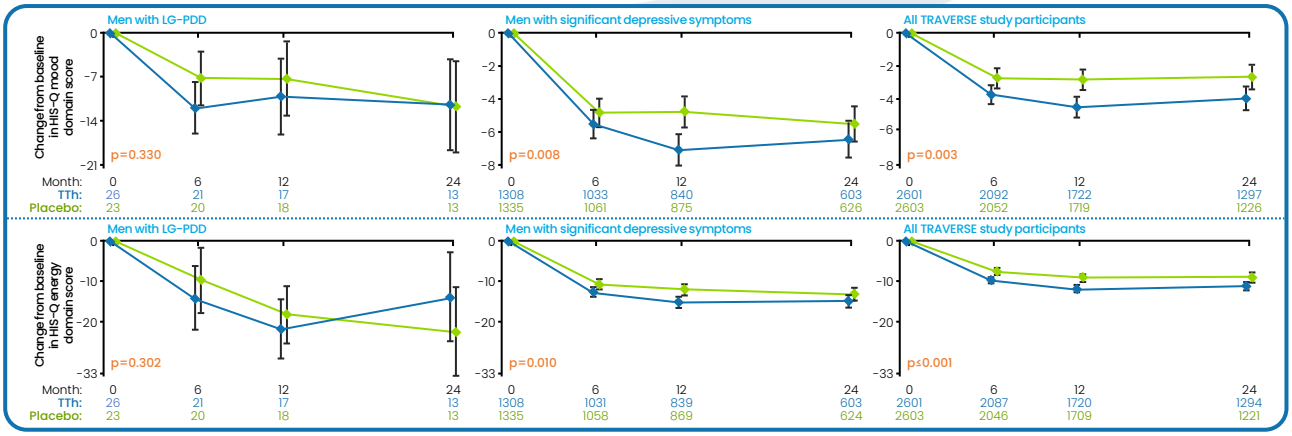
- Randomisation 1:1 to daily transdermal 1.62% testosterone gel (n=2601), dose adjusted to maintain testosterone levels between 350–750 ng/dL (12.1–26.0 nmol/L), or matched placebo gel (n=2603) (**note:** a maximum dose of 101.25 mg was used, which is above the licensed maximum dose)

Depression substudy outcome measures and analysis

- **Primary endpoint:** effect of TTh for inducing remission and improving depressive symptoms in men with hypogonadism and LG-PDD, versus placebo
- **Secondary endpoints included:** efficacy of TTh for improving depressive symptoms, energy, sleep quality and cognition in men with hypogonadism who had significant depressive symptoms (defined as PHQ-9 score >4) but who did not meet all LG-PDD criteria, and also in all TRAVERSE participants, irrespective of depressive status

Findings

- Among men with LG-PDD, the relative risk ratio for LG-PDD remission did not differ significantly between TTh and placebo groups (p=0.197), and changes from baseline in PHQ-9, GDS-15 and HIS-Q mood (**Figure**), energy, cognition or sleep domain scores, while numerically greater with TTh than placebo, also did not reach significance (all p>0.05); these findings likely reflected the small sample size precluding meaningful conclusions being made
- In men with significant depressive symptoms and in all randomly assigned TRAVERSE study participants, TTh was associated with modest but significantly greater improvements in mood and energy (**Figure**), but not cognition or sleep quality (p>0.05 for both HIS-Q domain comparisons), versus placebo



Conclusions

Depressive symptoms are common in middle-aged and older men with hypogonadism, but LG-PDD is uncommon

Among middle-aged and older men with hypogonadism, established CVD or multiple risk factors for incident cardiac events, with or without depressive symptoms, TTh for up to 2 years was associated with small improvements in mood and energy, versus placebo

Implications for the field

- Middle-aged and older men with hypogonadism should be evaluated for depressive symptoms because of their high prevalence in this population, but TTh does not appear to be an effective treatment option for most men with clinical depressive disorders; the findings of the TRAVERSE Depression substudy support guidelines on TTh for male hypogonadism, with respect to its positive effects on mood

Abbreviations

CV, cardiovascular; CVD, cardiovascular disease; GDS-15, 15-item Geriatric Depression Scale; HIS-Q, Hypogonadism Impact of Symptoms Questionnaire; LG-PDD, low-grade persistent depressive disorder (previously 'dysthymia'); MACE, major adverse cardiovascular events; PHQ-9, Patient Health Questionnaire-9; TRAVERSE, Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men; TTh, testosterone therapy.

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