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Testosterone Therapy is Associated With Depression, Suicidality, and Intentional Self-Harm: Analysis of a National Federated Database

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ABSTRACT

Background: Long-term use of testosterone can be associated with mood destabilizing effects. Most studies investigating psychiatric complications of anabolic steroids have used small samples, but a comprehensive assessment of the risk of developing mental health disorders after testosterone use has not been performed at the population level.

Aim: To determine whether testosterone therapy is associated with major depressive disorder or suicide attempts in men.

Methods: We conducted a retrospective cohort study of 70.3 million electronic health records collected from 46 healthcare organizations encompassing flagship hospitals, satellite hospitals, and outpatient clinics since 2008 to determine whether testosterone use is associated with major depressive disorder and suicide attempts in a large population. We included men 18 or older who either used testosterone or did not, defined by reported use, insurance claim, or prescription use of testosterone documented in the electronic health record. We propensity-score matched by age, race, ethnicity, obesity, and alcohol-related disorder. Additionally, a sub-group analysis was performed in testosterone deficient (<300 ng/dL) men comparing those with TD on testosterone therapy to a control group of men with TD who are not using testosterone.

Outcomes: We determined measures of association with a new diagnosis of major depressive disorder and suicide attempt or intentional self-harm following testosterone use within 5 years.

Results: A total of 263,579 men who used testosterone and 17,838,316 men who did not were included in the analysis. Testosterone use was independently associated with both Major Depressive Disorder (OR 1.99, 95% CI 1.94−2.04, $P < .0001$) and Suicide Attempt/Intentional Self-Harm (OR 1.52, 95% CI 1.40-1.65, $P < .0001$). Results remained significant in testosterone deficient sub-group analysis.

Clinical Implications: Men who use testosterone should be screened for and counseled about risks of depression and suicidality.

Strengths and Limitations: Strengths of this study include a large sample size, the ability to account for chronology of diagnoses, the use of propensity score matching to control for potentially confounding variables, and the consistency of results with sub-group analyses. Limitations include the potential for incorrect coding within the electronic health record, a lack of granular information regarding testosterone therapy adherence, the possibility that unrecorded testosterone or anabolic steroid use were prevalent but not captured within the control group, and a lack of data regarding testosterone withdrawal.

Conclusion: Testosterone use is independently associated with new-onset mental health disorders. Future studies are necessary to elucidate the role that androgen withdrawal plays and whether a causal relationship exists.

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INTRODUCTION

Synthetic derivatives of testosterone known as anabolic-androgen steroids (AAS) have been developed to maximize the anabolic effects, which has led to the substantial abuse of this class of drugs.[1] While AAS were mainly abused in the past for athletic gain by professional athletes, today's average user is a young male trying to optimize his personal appearance.[2–4] Commonly abused AAS include synthetic androgens such as nandrolone and stanozolol, however, commercial formulations of testosterone are increasingly found among the list of AAS implicated in abuse.[5] Testosterone therapy (TT) has long been used as a successful treatment for the signs and symptoms of testosterone deficiency (TD) which include decreased muscle mass, osteoporosis, diminished energy, and low libido.[6] While testosterone is often used appropriately in this setting, many of the men using testosterone do so without clinical diagnosis or even appropriate diagnostic testing.[7]

Studies have demonstrated a multitude of adverse effects from AAS use including cardiovascular toxicity, long-term cognitive defects, HPG axis dysfunction, and long-term testosterone deficiency upon discontinuation among others.[8] In addition to these medical comorbidities, a host of psychiatric conditions have been associated with AAS use, including mood disorders, aggressive behavior,[4] depression, and suicidality.[9,10] In fact, mental health disorders such as body image dysmorphia may be an underlying impetus for AAS use from the beginning.[11] After discontinuation, withdrawal from these drugs can lead to depression, and suicidality.[9]

Given the increasing usage of testosterone in the United States, both appropriate and inappropriate,[5,12] it is imperative that we evaluate whether an increased prevalence of mental health disorders exist with testosterone use as they do with other AAS use. In this study, we hypothesized that men receiving testosterone therapy have a higher prevalence of mental health diagnoses than the general male population, regardless of an appropriate indication of testosterone deficiency.

MATERIALS AND METHODS

Data Source and Study Design

We utilized electronic health record data stored within the TriNetX Research Network to conduct a retrospective cohort analysis. For this study, 46 HCOs were accessed, which include information for 70.3 million patients. The TriNetX database has a waiver from the Western Institutional Review Board; all patient data is de-identified, and TriNetX takes measures to protect patient privacy in the cases of small cohort sizes. Information regarding demographics, diagnoses from International Classification of Disease (ICD) codes, medications, and laboratory values are all recorded and used for analysis. Medication data is obtained from prescriptions, orders, inpatient medication reconciliations, and charted medications.

Cohorts

To evaluate the risk of mental health disorders with testosterone use, we constructed 2 cohorts of adult men, aged 18 or older, with history of an ambulatory visit, and without history of gender dysphoria (F64, Z87.890). The men had either (i) history of documented testosterone use, or (ii) no history of testosterone use (controls). We defined testosterone use as recorded use, insurance claim, or prescription of any commercial testosterone formulation captured within patient medical records.

Outcomes

We assessed all outcomes as events that occurred between 1 day and 5 years after index event. Index event was a visit to a healthcare organization and use of testosterone. Our primary outcome was a new diagnosis of MDD (F32–F33). Secondary outcome was a first-time suicide attempt (SA) or intentional self-harm (ISH) event (T14.91, X71–83, T36–65, and T71 ISH codes).[13] Patients who had an instance of each outcome prior to the analysis window were excluded at analysis.

Statistical Analysis

We measured associations between testosterone use and MDD or SA/ISH by comparing all men aged 18 or older with a history of testosterone use against all men aged 18 or older without a history of testosterone use. Confounding variables were controlled for through propensity score matching, a statistical technique that utilizes logistic regression to build cohorts of equal size based on covariates of interest.[14] We used 1:1 greedy nearest-neighbor propensity score matching to control for confounding variables through the TriNetX platform. Statistical analysis was powered through Python and R software. We determined that the 2 groups had minimal differences after balancing when standardized differences between propensity scores were less

than 0.1.[15] We accounted for confounding variables known to be associated with a risk of mood disorders or symptoms through propensity score matching by logistic regression for age, race,[16] ethnicity, obesity (E66), or alcohol-related disorder (F10).[17] Values for each propensity-match variable before and after matching in each cohort are included in Supplementary Tables 1 and 2. Additional confounding variables were considered but the complexity of propensity score matching for more variables with the sample size used exceeded the computing capabilities of the software.

Sub-Group Analysis

As TD is associated with symptoms that can mimic major depression,[18] we conducted a sub-group analysis to evaluate associations between testosterone use and MDD or SA/ISH in men with TD (<300 ng/dL).[19] Men with TD and testosterone use were compared against a control cohort of patients with TD who did not use testosterone. Odds Ratios (ORs) were calculated by comparing rates of new-onset MDD and SA/ISH outcomes that occurred between 1 day and 5 years after the index event in the testosterone use cohorts against the no testosterone cohort. We accounted for the same confounding variables as the primary analysis to maintain consistency in analysis.

Kaplan-Meier Analysis

To better understand the time course with which patients are normally diagnosed with MDD or SA/ISH following testosterone use, we additionally conducted a Kaplan-Meier analysis using the TriNetX platform. All analyses were conducted following propensity score matching for age, race, ethnicity, obesity, and alcohol use. Groups were compared using the log-rank test.

Sensitivity and Time Frame Analysis

To account for the possibility that patients with pre-existing MDD were diagnosed during immediate follow-ups to the onset of testosterone therapy, we conducted an additional sensitivity analysis where all outcomes were assessed at 1−5 years after index event. In doing so, we eliminated all patients that may have been diagnosed within the 1st year of testosterone therapy. We additionally sought to assess time course to the best of our ability by determining aOR at the following time intervals: 1 day to 1 year, 1−2 years, 2−5 years. To calculate the average time-to-diagnosis, we determined the monthly number of diagnoses in the TD cohorts for each month following index event up to 5 years. We then calculated a weighted average months to diagnosis based on the population within each month.

RESULTS

We analyzed 263,579 men aged 18 or older who used testosterone, and 17,838,316 men who did not. Men who used testosterone were generally older (54.1 ± 14.2 vs 45.4 ± 20.3 years), more frequently Caucasian (78% vs 63%) and were more commonly obese (11% vs 1%) (Table 1).

Table 1. Baseline characteristics, men aged 18−50 with, and without testosterone use.

Variable	No Testosterone	Testosterone use (total)
Number in cohort	17,838,316	263,579
Age (y)	45.4 ± 20.3	54.1 ± 14.2
Race		
White	63%	78%
Black	11%	7%
Asian	3%	1%
Native American	<1%	<1%
Unknown	22%	14%
Ethnicity		
Hispanic	7%	4%
Non−Hispanic	59%	75%
Unknown	34%	21%
Cerebral Infarction (I63)	<1%	1%
Ischemic Heart Diseases (I20−I25)	1%	9%
Overweight or obese (E66)	1%	12%
Mood Disorders (F30−39)	1%	11%
Body Dysmorphic Disorder (F45.22)	<1%	<1%
Alcohol disorder (F10)	1%	2%
Nicotine Dependence (F17)	2%	6%

All diagnosis codes are International Classification of Disease, Clinical Modification, Tenth Revision (ICD-10-CM). Age in years is represented in mean and standard deviation.

Prior to propensity-score matching, we found that 9.4% of men who used testosterone developed new-onset MDD within 5 years, as opposed to 3.8% in the control group (Table 2). Men who used testosterone also had higher rates of SA/ISH (0.5% vs 0.3%). Both before and after controlling for confounding variables through propensity score matching, testosterone use was independently associated with all psychiatric outcomes that we studied (MDD aOR 1.99, 95% CI 1.94−2.04, $P < .0001$, SA/ISH aOR 1.52, 95% CI 1.40−1.65, $P < .0001$, Table 2).

On sub-group analysis investigating psychiatric outcomes in men aged 18 or older with a diagnosis of TD, testosterone use was still associated with MDD (aOR 1.28, 95% CI 1.23−1.33, $P < .0001$) and SA/ISH (aOR 1.41, 95% CI 1.25−1.59, $P < .0001$) at 5 years both before and after controlling for confounders such as age, race, ethnicity, obesity, or alcohol use when compared to the control cohort of men with TD not on testosterone therapy (Table 2). Our sensitivity analysis accounting for pre-existing mental health diagnoses that may have been missed and only assigned during the first year following testosterone therapy additionally showed significant independent associations with MDD (Total aOR 1.87, 1.82−1.93, $P < .0001$; TD aOR 1.34, 1.28−1.40, $P < .0001$) and SA/ISH (Total aOR 1.48, 1.34

Table 2. Measures of association between testosterone use and new-onset MDD or SA/ISH at 5 years in total population and TD sub-group*.

Outcome	Analysis	Number with outcome in Testosterone use cohort (Risk %)	Number with outcome in No Testosterone Use Cohort (Risk %)	Unbalanced OR (95% CI)	Number with outcome in Testosterone use cohort after matching (Risk %)	Number with outcome in No Testosterone Use Cohort after matching (Risk %)	Balanced aOR (95% CI)
MDD	Total	22,191 (9.40%)	659,729 (3.82%)	2.61 (2.58–2.65) $P < .0001$	22,191 (9.40%)	12,914 (4.98%)	1.98 (1.93–2.02) $P < .0001$
SA/ISH		1,393 (0.52%)	59,200 (0.34%)	1.54 (1.47–1.64) $P < .0001$	1,393 (0.52%)	975 (0.36%)	1.44 (1.32–1.56) $P < .0001$
MDD	TD	7,301 (10.09%)	13,559 (7.42%)	1.40 (1.36–1.44) $P < .0001$	7,301 (10.08%)	6,079 (7.77%)	1.33 (1.29–1.38) $P < .0001$
SA/ISH		650 (0.73%)	1,040 (0.51%)	1.44 (1.31–1.59) $P < .0001$	650 (0.73%)	501 (0.56%)	1.30 (1.16–1.47) $P < .0001$

*All comparisons made against control cohort without testosterone use. MDD = Major Depressive Disorder; SA = Suicide Attempt; ISH = Intentional Self-Harm; TD = Testosterone Deficiency; OR = Odds Ratio; aOR = adjusted Odds Ratio; CI = Confidence Interval. Chi-square tests were used to assess statistical significance.

−1.64, $P < .0001$; TD aOR 1.34, 1.16−1.55, $P < .0001$) between 1 and 5 years after onset of testosterone therapy (Table 3). With the exception of SA/ISH outcomes for the TD cohort at <1 year and 1−2 years, all other time frame analyses were statistically significant (Table 4). Average time to MDD was 36.5 ± 14.8 months in the TD cohort on testosterone therapy and 29.6 ± 11.9 months in the TD cohort not on testosterone therapy.

We additionally conducted a Kaplan-Meier analysis to compare the MDD-free and SA/ISH-free time for patients using testosterone vs patients who did not use testosterone (Figure 1). All results were statistically significant for both MDD-free (Chi-square = 2044.9, df = 1, $P < .0001$) and SA/ISH-free (Chi-square = 36.8, df = 1, $P < .0001$) time.

DISCUSSION

The use of AAS has been linked to mood imbalance and psychotic behavior,[20,21] but the full scale of psychiatric complications in men who use androgens such as commercially available testosterone formulations is not completely understood. To characterize the association between testosterone and mental health complications, we compared rates of MDD, and SA/ISH between large populations of men who have or have not used

Table 3. Sensitivity and time course analysis with measures of association between testosterone use and new-onset MDD or SA/ISH from 1 to 5 years in total population and TD sub-group.

Outcome	Analysis	Number with outcome in Testosterone use cohort (Risk %)	Number with outcome in No Testosterone Use Cohort (Risk %)	Unbalanced OR (95% CI)	Number with outcome in Testosterone use cohort after matching (Risk %)	Number with outcome in No Testosterone Use Cohort after matching (Risk %)	Balanced OR (95% CI)
MDD	Total	11,442 (5.08%)	368,286 (2.17%)	2.41 (2.37–2.46) $P < .0001$	11,442 (5.08%)	7,035 (2.78%)	1.87 (1.82–1.93) $P < .0001$
SA/ISH		899 (0.34%)	37,620 (0.22%)	1.58 (1.48–1.69) $P < .0001$	899 (0.34%)	611 (0.23%)	1.48 (1.34–1.64) $P < .0001$
MDD	TD	4,282 (6.17%)	7,851 (4.43%)	1.42 (1.37–1.47) $P < .0001$	4,282 (6.17%)	3,541 (4.68%)	1.34 (1.28–1.40) $P < .0001$
SA/ISH		451 (0.51%)	700 (0.34%)	1.49 (1.32–1.68) $P < .0001$	451 (0.51%)	338 (0.38%)	1.34 (1.16–1.55) $P < .0001$

All comparisons made against control cohort without testosterone use. MDD = Major Depressive Disorder; SA = Suicide Attempt; ISH = Intentional Self-Harm; TD = Testosterone Deficiency; OR = Odds Ratio; aOR = adjusted Odds Ratio; CI = Confidence Interval. Chi-square tests were used to assess statistical significance.

Table 4. Time course analysis to determine the association between testosterone use and MDD and SA/ISH at different time intervals in the total cohort and testosterone deficient cohort.

		Adjusted Odds Ratio at each time interval		
Outcome	Analysis	1 d to 1 y	1–2 y	2–5 y
MDD	Total	2.10 (2.03–2.17) $P < .0001$	2.10 (2.00–2.20) $P < .0001$	1.73 (1.66–1.80) $P < .0001$
SA/ISH		1.31 (1.14–1.50) $P < .0001$	1.47 (1.25–1.75) $P < .0001$	1.49 (1.31–1.70) $P < .0001$
MDD	TD	1.30 (1.23–1.37) $P < .0001$	1.27 (1.19–1.37) $P < .0001$	1.48 (1.24–1.77) $P < .0001$
SA/ISH		1.23 (1.00–1.51) $P = 1.0540$	1.14 (0.90–1.44) $P = .2738$	1.38 (1.30–1.46) $P < .0001$

All comparisons made against control cohort without testosterone use. MDD = Major Depressive Disorder; SA = Suicide Attempt; ISH = Intentional Self-Harm; TD = Testosterone Deficiency; OR = Odds Ratio; aOR = adjusted Odds Ratio; CI = Confidence Interval. Chi-square tests were used to assess statistical significance.

testosterone. As we hypothesized, men who use testosterone were at an increased risk of developing depression, suicidality, and self-harm over the subsequent 5 years. To our knowledge, our study represents the largest sample in which testosterone use, and mental health complications have been associated. The strong associations identified in this study indicate that men who use testosterone should be screened for mental health issues and counseled regarding their potentially increased risk. Future studies are necessary to elucidate whether a dose-response association exists, whether withdrawal from testosterone plays a role, and whether patient selection or preventative measures can mitigate the risk.

Our findings are consistent with previous investigations associating AAS and psychiatric comorbidities. Several small-scale studies in athletes have detected significantly higher rates of mood disorders,[21] body dysphoria,[22] and suicidality or violent death,[23] primarily through cross-sectional surveys or retrospective reviews. These studies were typically small in scale, but they revealed a concerning pattern of mental health complications that we also saw in our study. Although not specifically investigated in the present study, aggressive behavior has also been associated with testosterone use, which may be related to patterns of dysphoria or self-harming behavior.[24] One population-based study of 10,259 adolescents found that AAS users had more anger issues, anxiety, depression, low self-esteem, and, alarmingly, suicide attempts compared to non−users.[10] The study, however, was restricted to high school students only, possibly limiting the generalizability to middle aged, and older men.

A simple but significant confounder in the evaluation of testosterone use and psychiatric conditions is the overlap of symptoms between depression and testosterone deficiency, leading to the opportunity for misdiagnosis, and incorrect treatment. For example, a patient presenting with depression symptoms may be treated for testosterone deficiency, and given testosterone as a treatment rather than correctly being diagnosed with MDD. In order to effectively control for this scenario, we performed a subgroup analysis in patients with a history of testosterone deficiency comparing patients who did or did not receive testosterone. Here, the associations between testosterone use and MDD and suicidality remained strong, implicating testosterone use as a contributor to development of these psychiatric conditions.

Another complicating factor in the association between testosterone use and psychiatric comorbidities are analyses that demonstrate a positive effect on some mild depressive symptoms for men who initiate prescribed testosterone therapy.[25,26] However, the benefits of testosterone in depressive disorders is controversial,[27] with many studies failing to differentiate psychiatric disorders or use strict diagnostic criteria for patient selection. In fact, 2 randomized controlled trials with a strict inclusion criteria of

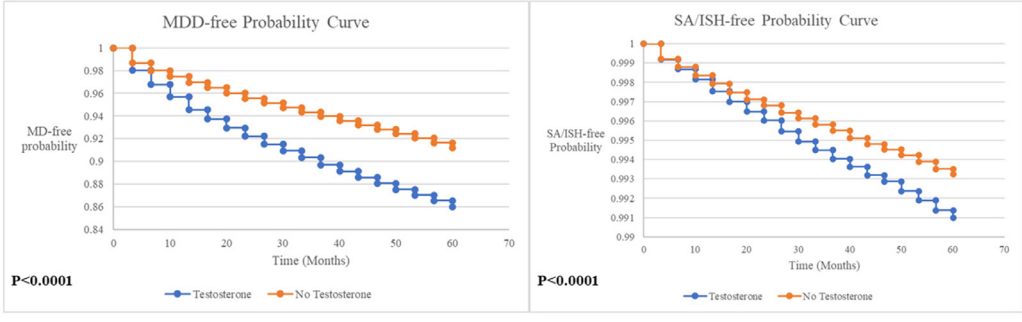

Figure 1. Kaplan-Meier analysis to evaluate time free from MDD and SA/ISH in patients using testosterone compared to patients not using testosterone. MDD = Major depressive disorder; SA/ISH = Suicide attempt or Intentional Self-Harm.

MDD failed to show that testosterone improved depression symptoms over placebo.[28,29] Our analysis not only failed to demonstrate a reduction in the development of MDD and suicidality after the initiation of testosterone in testosterone deficient men, but even demonstrated a modest increase in these psychiatric comorbidities. These findings highlight the need for physicians to screen patients presenting with symptoms of testosterone deficiency for MDD and suicidality, as well as appropriately counsel patients prior to starting testosterone, and actively monitor for development of symptoms while on therapy.

Our study is not without strengths and limitations. Strengths of this study include a large sample size, the ability to assess clinical diagnoses as outcomes, robust statistical techniques to control for confounding variables, high strength of associations, and the ability to assess chronology of diagnoses. As with all studies examining electronic medical records, analysis was limited by the potential for incorrect coding. There is potential for underreporting of testosterone use in the database, since men who use testosterone without a prescription may be reluctant to report it to their physician. Furthermore, patients in the database may receive care at additional facilities that do not contribute data to the TriNetX platform, and the database does not track whether or not prescriptions for medications are filled, so there is potential for errors related to medication reconciliation that could limit our findings. Additionally, we were unable to assess precise duration of testosterone use or evaluate length of time from initiation of testosterone use to diagnosis of MDD or SA/ISH. TriNetX does not provide granular time-to-diagnosis data, and we are therefore unable to determine average time-to-diagnosis values when the monthly diagnoses fall below 10, such as in the SA/ISH cohort. Another limitation of the study was our inability to account for other social factors that can influence mood disorders, such as abuse, social environments, family instability, or financial status. Although several additional diagnoses are known to be associated with depression, we were not able to include them in the analysis because additional variables would have exceeded the propensity score matching capabilities of the software with the sample size we used. One critical component of the relationship between testosterone and mood disorders is the potential for withdrawal to cause symptoms, which we could not assess within the confines of this database. While our findings were statistically significant, the absolute risk differences between the overall testosterone use and no testosterone use groups were 5.15% for MDD and 0.18% for SA/ISH, which may have limited clinical significance.

While the present study could not entirely capture the implications of long-term use of testosterone, it may be that associations with depression are due to an extended period of dependence. Furthermore, the effect of testosterone withdrawal may play an important role in the onset of psychiatric symptoms,[23,30] but we could not assess the effects of withdrawal as our data represent prescriptions and reported use without specific information on adherence.

CONCLUSION

Testosterone use is independently associated with mental health comorbidities. Typically, when patients are prescribed testosterone, they are counseled regarding the risks of polycythemia, gynecomastia, infertility, and physiologic dependence, but our study reveals that men who use testosterone should also be screened for and counseled about risks of depression and suicidality. As this study could only establish an association rather than true causation, future studies are necessary to investigate potential dose-response relationships, whether withdrawal from testosterone plays a role, and whether patient selection or preventative measures can mitigate the risk.

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STATEMENT OF AUTHORSHIP

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SUPPLEMENTARY MATERIALS

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