



Anabolic androgen use in the management of hereditary angioedema Not so cheap after all

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ABSTRACT

Background: Hereditary angioedema due to C1 inhibitor deficiency (HAE) is a rare, life-threatening disease that imposes a significant burden on affected patients. 17 α -alkylated androgens (anabolic androgens) decrease attack frequency and severity but carry the risk of potentially serious dose-related adverse effects. Despite the emergence of targeted therapies for HAE, continued anabolic androgen use has been driven in part by their low cost.

Objective: To examine the hidden cost of anabolic androgen use related to the risk of developing non-HAE comorbidities.

Methods: Patients with HAE were identified in the Southern California Kaiser Permanente database using clinical and laboratory findings compatible with HAE. These patients were stratified into anabolic androgen exposed and nonexposed groups. Matched controls were selected from the Kaiser database who did not have HAE or anabolic androgen exposure. Using multivariate analysis, we determined the number of non-HAE comorbidities linked to anabolic androgen use. We next determined the association between dosing and increasing exposure to anabolic androgens and the likelihood of having various comorbidities.

Results: Patients with HAE exposed to anabolic androgens had a 28% increase ($P = .04$) in non-HAE comorbidities when compared with their matched (nonexposed) controls. With each gram per month increase in exposure, a 12% increase in non-HAE comorbidities is observed ($P < .01$). The most commonly occurring non-HAE comorbidities were psychiatric, muscle cramps, obesity, and hyperlipidemia.

Conclusion: Our data suggest that long-term anabolic androgen use enhances the risk of developing comorbid health conditions, thus amplifying the cost of care. Our report provides additional support for the preferred use of newer, targeted therapies for the management of HAE.

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Introduction

Hereditary angioedema due to C1 inhibitor (C1INH) deficiency (HAE) is an autosomal dominant disease characterized by discrete episodes of nonpruritic, nonpitting angioedema that involve the extremities, genitourinary tract, abdomen, face, or oropharynx.¹

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The frequency and severity of angioedema attacks are highly variable between patients and even for an individual patient over time. Fifty percent of patients with HAE begin experiencing swelling at younger than 10 years, with some patients manifesting angioedema by 1 year of age. Although attacks can be precipitated by such triggers as trauma, emotion, and hormonal factors, many are unpredictable, thus heightening the stress and burden of disease. In a life time, almost 100% of patients with HAE experience extremity and abdominal attacks, and more than 50% of patients with HAE experience at least one laryngeal attack. Angioedema of the larynx in HAE is capable of closing the airway and resulting in death from asphyxiation. Historical surveys suggest a mortality rate in HAE because of laryngeal angioedema of approximately 30% or higher.^{1–3} The risk of mortality is notably enhanced for individuals without an established diagnosis of HAE, emphasizing the need for early detection of the condition.⁴ Abdominal attacks are a frequent cause of significant morbidity. The swelling can result in severe

abdominal pain with intractable nausea and vomiting, and third spacing of fluid can induce hypotension. Because of the dramatic presentation of some abdominal attacks, many patients with HAE have undergone unnecessary and inappropriate surgical interventions. Extremity attacks frequently prevent patients from attending school or work, thus significantly reducing their quality of life. Management strategies for these patients must take into account the significant morbidity and risk of mortality associated with HAE.

Management of HAE is divided into short-term treatment of an existing attack and prophylaxis to prevent future attacks.³ Effective on-demand treatment of angioedema attacks is essential to minimize the associated morbidity and mortality, in particular for attacks that involve the abdomen or larynx. Four drugs have been approved since 2009 for the acute treatment of HAE attacks.^{3,5} A recent international consensus article recommended that on-demand treatment be considered for any attack in all locations to reduce the morbidity and mortality of HAE.⁶ Prophylactic treatment of HAE can be either long term or short term.⁶ Short-term prophylactic therapy is meant to protect patients against the likelihood of experiencing acute attacks during a defined temporal window after a stimulus known to precipitate HAE attacks (such as extensive dental work, invasive medical procedures, or surgery). Long-term prophylactic treatment of HAE is meant to decrease the frequency or severity of HAE attacks.

Many patients can be managed with on-demand treatment of attacks; however, many other patients require long-term prophylaxis to reduce the number and severity of angioedema attacks. The decision regarding which patients with HAE should receive long-term prophylaxis must be individualized based on factors such as attack frequency, attack severity, location of attacks, access to acute care, comorbid conditions, and patient preference.⁷ The need for long-term prophylactic treatment may change in a given patient over time. Three different modalities for long-term prophylaxis have been used: 17 α -alkylated androgens, antifibrinolytics, and plasma-derived C1INH concentrates.^{3,5,6}

Orally administered 17 α -alkylated androgens decrease the frequency and severity of HAE attacks.^{8,9} The androgens used most commonly to treat HAE include danazol (Danocrine), stanozolol (Winstrol), oxandralone (Oxandrine), and methyltestosterone. Both the efficacy and the adverse effects of 17 α -alkylated androgens are dose related.¹⁰ If anabolic androgens are used, the dosage must be titrated to the lowest dose that provides effective control of attacks. The most common reported adverse effects from the 17 α -alkylated androgens include virilization in women along with menstrual irregularities, acne, changes in libido, changes in mood, increased aggression, abnormalities in the lipid profile, weight gain, and increased blood pressure. These drugs can also cause hepatotoxicity, including development of hepatic adenomas and hepatic carcinoma. The sequelae of androgens are expected to accrue over decades and may or may not reverse with discontinuation.

Treatment with an antifibrinolytic agent (ϵ -aminocaproic acid or tranexamic acid) provides somewhat effective and relatively safe long-term HAE prophylaxis but is generally less effective than androgens.¹¹ Common adverse effects of the antifibrinolytic drugs include nausea and diarrhea, vertigo, postural hypotension, fatigue, and muscle cramps or weakness with an increase in muscle enzymes concentrations. There is an additional enhanced risk of thrombosis from these drugs. Plasma-derived C1INH replacement is an effective and safe therapy for long-term HAE prophylaxis. In the United States this option became available with the approval of Cinryze in 2008.^{5,12} Administration of plasma-derived C1INH requires intravenous access.

Despite the emergence of targeted novel therapies for HAE, anabolic androgens continue to be used for disease management.

Because the treatments cited above are highly effective with few adverse effects, the most compelling argument for continued use of anabolic androgens has been cost. In this study, we use a comprehensive longitudinal health care database to examine potential risks that may be associated with anabolic androgen use for long-term prophylaxis related to the development of increased comorbidities. We targeted the timeframe before the emergence of on-demand short-term therapy or C1INH replacement. The more we understand the overall effect that anabolic androgen therapy has on patient health (and health care as a whole), the more accurate our comparative analysis will be in the future for the effect of novel therapies on disease outcomes and the cost of care. Findings from this study provide insights on the health and potential economic effect of anabolic androgen treatment for HAE, which will guide future management decisions and benefit patients under our care.

Methods

Study Participants

Participants were identified in 2 ways. First, patients with HAE (*International Classification of Diseases, Ninth Revision [ICD-9]* code 277.6) who also had compatible laboratory results (low C4, C1INH antigen, and functional C1INH levels) as of (or before) September 2008 were retrieved from the Kaiser Southern California (KPSC) database. We included patients with evidence of low C1INH function on a database of patients with HAE compiled by the Kaiser regional immunology laboratory. Unique medical records from these 2 identification methods were combined into a single HAE cohort. Patients with less than 5 years of combined Kaiser enrollment before September 2008 were excluded.

Included patients with HAE were subclassified into 2 groups based on the Kaiser medication record: (1) those who have never been dispensed an anabolic androgen during their continuous enrollment period and (2) those who had received dispensed anabolic androgen. Of note, manual medical record review of the nonexposed patients did not reveal any history of anabolic androgen dispensings by pharmacy record or physician-obtained history outside the continuous enrollment period.

A third group of participants were identified as non-HAE controls. We matched each patient with HAE to 5 individuals without HAE based on sex, ethnicity, age at the time of enrollment (± 2 years), age at study end (± 2 years), date of enrollment (± 1 years), census block median household income ($\leq \$45,000$, \$45,001–\$80,000, $> \$80,000$), and percentage who had achieved a high school degree (0%–50%, 51%–75%, 75%–100%). We also ensured that controls had never had anabolic androgens dispensed to them. Census block median household income and percentage of high school degree were surrogate measures for socioeconomic status.

Using these methods, we identified 105 individuals with an ICD-9 code 277.6 consistent with HAE and a low C4 or C1INH antigenic or functional level between 2001 and 2008. When only those individuals with at least 5 years of combined enrollment and coverage before September 1, 2008, were included, the number of included participants became 90. Manual medical record review of each of these 90 medical records yielded 50 patients with confirmed diagnoses of HAE with compatible laboratory values (of the 40 who were not included, most had low C4 levels because of other causes, such as autoimmune diseases and nephropathy; acquired angioedema due to deficiency of C1INH was also excluded). Of these 50 patients, 36 had at least 1 dispensing of anabolic androgens, and 14 were not androgen exposed.

Table 1
Demographics for Patients With Hereditary Angioedema and Their Matched Controls

Demographic	Androgen-exposed patients (n = 36)	Matched controls for androgen-exposed patients (n = 180)	Non-androgen-exposed patients (n = 14)	Matched controls for non-androgen exposed patients (n = 70)
Age at study beginning, mean (SD), y	30.4 (18.49)	30.7 (18.22)	11.1 (14.71)	11.3 (14.47)
Age at study end, mean (SD), y	48.7 (19.82)	48.4 (19.67)	25.3 (15.81)	25.3 (15.36)
Study period, mean (SD), y	18.4 (9.22)	17.6 (9.18)	14.1 (6.20)	14.0 (5.90)
Length of Kaiser membership, mean (SD), y	15.9 (8.55)	17.6 (9.18)	10.9 (4.64)	14.0 (5.90)
Patient sex, No. (%)				
Female	21 (58.3)	105 (58.3)	9 (64.3)	45 (64.3)
Male	15 (41.7)	75 (41.7)	5 (35.7)	25 (35.7)
Race/ethnicity, No. (%)				
White, non-Hispanic	18 (50)	90 (50)	3 (21.4)	15 (21.4)
Black, non-Hispanic	6 (16.7)	30 (16.7)	1 (7.1)	5 (7.1)
Hispanic	11 (30.6)	55 (30.6)	9 (64.3)	45 (64.3)
Asian, non-Hispanic	1 (2.8)	5 (2.8)	1 (7.1)	5 (7.1)
Census block income and educational level				
Adults with high school degree or above, No. (%)				
0%–50%	4 (11.1)	20 (11.1)	4 (28.6)	20 (28.6)
51%–75%	12 (33.3)	60 (33.3)	5 (35.7)	25 (35.7)
76%–100%	20 (55.6)	100 (55.6)	5 (35.7)	25 (35.7)
Median annual household income, No. (%)				
≤\$45,000	16 (44.4)	80 (44.4)	10 (71.4)	50 (71.4)
\$45,001–\$80,000	16 (44.4)	80 (44.4)	4 (28.6)	20 (28.6)
>\$80,000	4 (11.1)	20 (11.1)	0	0

Data Collection

The exposure of interest was use of anabolic androgens. We were able to identify whether patients had ever received a dispensing of anabolic androgens, what their total exposure (dose) was during their Kaiser enrollment period, and monthly mean dose. The primary outcome was number of non-HAE comorbidities (listed in eTable 1). In addition, demographic information, including sex, Kaiser membership start and end date, age at the time of enrollment, census block data, and race/ethnicity, was also collected. All data were obtained from manual medical record review or KPSC's electronic medical records, which include clinical databases on membership, laboratory tests, diagnoses, pharmacy, utilization, and mortality.

Statistical Analysis

Our primary outcome was to determine the number of comorbidities linked to anabolic androgen use. First, we compared the number of comorbidities (as of September 1, 2008, or the date of last enrollment, whichever came first) for the patients with HAE and anabolic androgen exposure vs their matched controls; the relative difference was assessed using an incidence rate ratio, which was derived as the incidence rate for the exposed divided by the incidence rate for the control. To account for the correlation among matched pairs, a generalized estimating equations (GEE) regression with Poisson distribution was conducted to estimate the incidence rate ratios. The identical analyses were performed between the patients with HAE without anabolic androgen exposure and their matched controls. We estimated the effect of HAE and anabolic androgens simultaneously by putting all 3 groups in 1 Poisson GEE model, adjusting for age.

Second, we analyzed the association between the anabolic androgen dose and the likelihood of having various comorbidities. Androgen exposure was measured as the total number of milligrams of danazol dispensed and the mean number of milligrams of danazol used per month (calculated as total danazol dispensed/[years of exposure × 12]). Because several different androgens may have been prescribed, we converted all anabolic androgen doses to danazol equivalents using the formulas in eTable 2. The association between the dose and the number of comorbidities was also estimated using Poisson GEE models.

Results

Table 1 provides the important demographic data for the HAE groups (androgen exposed and unexposed) and their matched controls. The mean (SD) age of the HAE exposed group at their inclusion into the study was 30.4 (18.5) years (mean [SD] age at the end of the study was 48.7 [19.8] years). The mean (SD) age of the HAE unexposed group at their time of inclusion was 11.1 (14.7) years (mean [SD] age at the end of the study was 25.3 [15.8] years). Patients with HAE exposed to anabolic androgens were 58.3% female (41.7% male), whereas the unexposed patients were 64.3% female (35.7% male). Anabolic androgen exposed patients with HAE tended to be white (50%), whereas Hispanics made up most of the nonexposed patients (64.3%).

The potential effect of anabolic androgen exposure in patients with HAE on the development of non-HAE-related comorbidities is given in Table 2. Androgen exposure in patients with HAE was correlated with a 28% ($P = .04$) increase in non-HAE comorbidities when compared with their matched (nonexposed) controls. This effect was not seen when nonexposed patients with HAE were compared with their nonexposed matched controls, suggesting that the largest contributor of non-HAE-related comorbidities in the androgen-exposed patients with HAE is attributable to the use of anabolic androgens for prophylaxis of HAE attacks. Because of a rather large age discrepancy between the androgen-exposed patients with HAE and the nonexposed patients with HAE, a direct comparison between these 2 groups could not be performed.

The dose dependency of the non-HAE comorbidities is given in Table 3 and eTable 3. With each gram-per-month (33.3-mg/d) increase in exposure, a 12% increase in comorbidities is observed

Table 2
Associations Among HAE, Androgen Exposure, and Number of Comorbidities

Variable	Incidence rate ratio (95% CI)	P value
Androgen-exposed patients with HAE vs matched controls (n = 216)	1.28 (1.01–1.60)	.04
Non-androgen-exposed patients with HAE vs matched controls (n = 84)	0.93 (0.51–1.67)	.79

Abbreviations: CI, confidence interval; HAE, hereditary angioedema.

Table 3

Association Between Androgen Dose and Number of Comorbidities in the 36 Androgen-Exposed Patients

Variable	Incidence rate ratio (95% CI)	P value
Anabolic androgen per month	1.12 (1.06–1.18)	<.01
Total anabolic androgen dose	1.0005 (1.0003–1.0007)	<.01

Abbreviation: CI, confidence interval.

($P < .01$). The most commonly associated comorbidities were psychiatric (anxiety/depression; $\Delta +12.8\%$ compared with matched controls), muscle cramps ($\Delta 7.8\%$), obesity ($\Delta 7.8\%$), and hyperlipidemia ($\Delta 6.2\%$).

Discussion

Advances in understanding the pathophysiology of HAE have led to the development of effective HAE treatments based on the mechanism of swelling. These new therapies are designed to replace C1INH, inhibit plasma kallikrein, or antagonize the β_2 -receptor. The specificity of these medications minimizes the potential for adverse effects (both short term and long term), which is an important consideration when treating patients with a life-long disease. Furthermore, these medications are more effective at preventing and treating HAE attacks than the medications used in the past.¹¹ Despite the improved safety and efficacy of these new therapeutic agents, the cost of these medications has been cited as a barrier to more widespread use in clinical practice.^{13,14} It has been argued that the low cost of attenuated androgens is a positive factor when considering pharmacologic management of HAE.

The adverse effects of anabolic androgens are well known and affect patient (as well as physician) enthusiasm for use of androgens in the treatment of HAE.¹⁰ We hypothesized that the use of androgen therapy may have additional effects on overall health, and thereby cost of care, through increasing the risk of development of comorbid conditions. Published literature on the economic effect of the development of comorbidities in the projected lifetime of an individual is noteworthy. For example, it has been reported that the mean annual US health care expenditure for people who were obese was \$5,148 compared with \$3,636 for those who were overweight and \$3,315 for people who were normal weight.¹⁵ Thus far, no true cost analysis studies have been performed to compare the use of older therapeutics with their newer counterparts. Our study brings to light that such an analysis would need to take into account the non-HAE-related comorbidities that develop as a result of using medications like anabolic androgens. As discussed below, consideration of these additional hidden costs challenge the one remaining cited advantage of androgen therapy—that they are cheap.

We found that increased exposure to anabolic androgens for HAE prophylaxis is associated, in a dose-dependent manner, with a higher incidence of several undesirable comorbidities. For each gram of anabolic androgen used per month (which translates to 33.3 mg/d), we observed a 12% increase in comorbid diagnoses. Using the KPSC database, we identified a cohort 50 patients with HAE with at least 5 years of combined enrollment before September 2008 (when the newer therapeutic options for HAE became available). These patients were subcategorized into anabolic androgen exposed and nonexposed groups. The advantage of conducting such an investigation using the KPSC database is that Kaiser is a closed health care system, which allows us to fully capture anabolic androgen dispensings and ICD-9 codes relevant to all comorbidities associated with androgen use. Thus, our findings represent the most complete analysis to date of the effects of anabolic androgen use long-term in patients with HAE.

Comparison of androgen-exposed patients with HAE to their matched controls revealed a statistically significant correlation between the use of androgens and a higher incidence of non-HAE-related comorbidities ($P = .04$) (Table 2). The largest increases in these comorbidity rates were found to be anxiety/depression, muscle cramping, obesity, and hyperlipidemia (eTable 1), although statistical significance was not found in these trends because of the small number of patients in the group. Each of these comorbid conditions has been associated with significant increases in health care cost. Mental health conditions (including anxiety/depression) account for 5.6% of the total cost of health care in the United States,¹⁶ placing it in the top 5 most costly conditions in 2002. In the United States, obesity is associated with increases in annual health care costs of 36% and medication costs of 77% compared with being of average weight.¹⁷ In a separate study, patients who were obese had annual medical spending that was a mean of \$1429 (42%) higher than patients of normal weight, representing about \$40 billion in increased medical spending overall.¹⁸ A 1% decrease in obesity/overweight rates of individuals aged 16 to 17 years could actually translate into a savings of \$586 million as a result of decreased lifetime medical costs.¹⁹ Closely tied to obesity is hyperlipidemia, which was a \$12.5 billion expenditure in 2002.²⁰ It is not surprising that evidence suggests treating patients with multiple comorbid chronic conditions costs up to 7 times as much as treating patients with a single chronic condition.^{15,16} Notably, the increase in these comorbidities associated with anabolic androgen use was observed in patients who were fairly young (Table 1). Thus, our data would suggest that any reduction in these comorbidities, by avoidance of anabolic androgens, would result in better long-term outcomes in patients with HAE. There was no difference for non-androgen-exposed patients with HAE with their matched control group, thus isolating the enhanced occurrence of comorbidities to anabolic androgen exposure. If this observation holds true in future studies, it would be tempting to speculate that the lack of lifetime exposure to anabolic androgens could reduce the risk of developing such conditions as obesity, anxiety and hyperlipidemia for the younger patients and consequently lower their burden of disease and potentially lifetime health care costs.

There are several limitations of the current study. In our cohort, the patients with HAE not exposed to anabolic androgens were much younger than those who were. Thus, the reduced frequency of comorbidities could be interpreted as more of a function of age than androgen exposure with simply a direct comparison. Recognizing this, we designed the study to use a matched control group (that included age) to compare to the androgen-exposed HAE patients, thus isolating the development of comorbidities to the androgen exposure. We additionally acknowledge the possibility that patients with HAE may have received more intensive medical care (because of their illness) than their matched controls and that certain diagnoses (hypertension, hypercholesterolemia, psychiatric conditions) may have been recognized as a consequence. Although it was not feasible to accurately quantify the frequency of physician visits among the patients with HAE and their matched controls, we used an inclusion criteria of at least 5 years of combined enrollment in the health plan as a means of broadening the time in which such a diagnosis would be captured in both the HAE and non-HAE group. The Kaiser health care system is also modeled to provide comprehensive care for all patients with an emphasis on disease prevention and early screening for risk factors, thus diminishing the likelihood that a discrepancy in care intensity would have affected our results.

The cost of treatment is a concern when designing management options for care of any disease. For patients with HAE who are facing the risk of debilitating, disfiguring, and life-threatening attacks, the current therapies have transformed the approach to care with the goal of normalizing their lives. It has been argued

that anabolic androgens should be considered because of their low cost in the management of HAE. This is despite the acknowledged risk of adverse effects and lower efficacy. Our current study's suggestion that an amplified risk of the development of comorbid conditions with the potential for attendant enhanced costs undermines this remaining argument. In addition to the risk of burdening a patient with another health condition, the development of a comorbid condition markedly escalates the overall cost of care. Given our findings, it can be argued that the long-term use of anabolic androgens in patients with HAE may result in not only inferior long-term outcomes but also a potential for enhanced lifetime cost burden resulting from the comorbid conditions. Future studies specifically designed to analyze the cost-benefit ratio of older vs newer therapeutic agents to prevent and treat HAE will be of great interest. Our study provides additional support for selecting the most effective targeted therapies for the management of patients with HAE.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2017.01.015>.

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eTable 1

Descriptive Statistics of Non-HAE Comorbidities for Patients With HAE and Their Matched Controls

Variable	Androgen-exposed patients (n = 36)	Matched controls for androgen-exposed patients (n = 180)	Non-androgen exposed patients (n = 14)	Matched controls for non-androgen-exposed patients (n = 70)
No. of non-HAE comorbidities, mean (SD)	2.1 (2.03)	1.9 (1.89)	0.9 (1.03)	1.0 (1.51)
With non-HAE comorbidities	25 (69.4)	126 (70)	8 (57.1)	29 (41.4)
Abnormal liver function test result	1 (2.8)	9 (5)	0	1 (1.4)
Benign and malignant liver tumors	0	0	0	0
Cancer	5 (13.9)	23 (12.8)	0	1 (1.4)
Obesity	8 (22.2)	26 (14.4)	5 (35.7)	11 (15.7)
Arterial hypertension	11 (30.6)	68 (37.8)	3 (21.4)	12 (17.1)
Menstrual and sexual function	5 (13.9)	30 (16.7)	0	8 (11.4)
Virilization	0	1 (0.6)	0	2 (2.9)
Anxiety/depression	14 (38.9)	47 (26.1)	1 (7.1)	10 (14.3)
Hyperlipidemia	11 (30.6)	44 (24.4)	1 (7.1)	7 (10)
Cardiac disease (MI, CAD, or CHF)	1 (2.8)	9 (5)	0	0
Diabetes	4 (11.1)	20 (11.1)	0	2 (2.9)
Stroke	1 (2.8)	11 (6.1)	1 (7.1)	1 (1.4)
Hematuria	0	1 (0.6)	0	0
Polycythemia	0	0	0	0
Insomnia	5 (13.9)	18 (10)	1 (7.1)	4 (5.7)
Headaches	2 (5.6)	11 (6.1)	0	2 (2.9)
Migraines	0	0	0	0
Muscle cramps	6 (16.7)	16 (8.9)	0	5 (7.1)
Flushing	0	0	0	0
Acne	1 (2.8)	6 (3.3)	0	3 (4.3)
Agitation	1 (2.8)	2 (1.1)	0	1 (1.4)

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; HAE, hereditary angioedema; MI, myocardial infarction.

Data are presented as number (percentage) of study participants unless otherwise indicated.

eTable 2

Anabolic Androgen Conversions

Androgen	Equivalent Dose, mg	Formula for Conversion
Danazol	200	Dose (mg) $\times$ 1
Stanozolol	2	Dose (mg) $\times$ 100
Oxandrolone	5	Dose (mg) $\times$ 40
Methyltestosterone	10	Dose (mg) $\times$ 20

eTable 3

Descriptive Statistics of Cumulative Androgen Exposure

Variable	No comorbidities (n = 11)	With comorbidities (n = 25)
Length androgen exposure, mean (SD), y	5.0 (3.85)	6.6 (5.80)
Total androgen exposure, mean (SD), d	886.7 (996.23)	1249.8 (1725.34)
Total dose of danazol taken, mean (SD), g	221.9 (186.37)	380.5 (642.79)
Dose of danazol used per month, mean (SD), g	3.4 (1.65)	3.6 (3.03)