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Review

Critical appraisal of androgen use in hereditary angioedema A systematic review

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ABSTRACT

Objective: To provide an objective basis for evaluating the risk-benefit ratio of long-term androgen use in patients with hereditary angioedema (HAE).**Data Sources:** PubMed was searched with no time limitations using the keywords *hereditary angioedema* or *angio-oedema* combined with *danazol*, *stanazolol*, and *androgen*.**Study Selection:** Qualifying articles were English-language reports of androgen use in patients with HAE, with relevant safety and/or efficacy information. Reports were categorized according to level of evidence (LOE).**Results:** The search process identified 153 citations, 63 of which contained relevant information; 2 additional publications were identified while other citations were being reviewed. Fifteen LOE 2 studies and multiple LOE 4 reports provided efficacy data, confirming a high level of prophylactic efficacy for androgen therapy in HAE, with occasional reports of poor prophylactic response. Common adverse events include weight gain, menstrual irregularities, virilization, headaches, myalgias or cramps, mood changes, and elevations in creatine phosphokinase level, liver function test results, and serum lipid level. The risk of adverse events is often correlated with dose and/or treatment duration. Rare cases of hepatic adenomas and hepatocellular carcinoma associated with long-term androgen use often had no preceding changes in liver function test results.**Conclusion:** Androgen therapy may be effective for most patients with HAE; however, potential risks and adverse effects must be carefully considered and discussed with patients when considering options for long-term HAE prophylaxis.

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Introduction

Hereditary angioedema (HAE) is a rare genetic disorder characterized by episodes of localized subcutaneous or mucosal edema, which can be painful, debilitating, or even fatal in the case of laryngeal swelling.^{1,2} Variants of HAE have been established based on the particular biochemical deficit; type I HAE is characterized by a quantitative deficiency in circulating levels of C1 inhibitor (C1-INH) protein, and type II is characterized by dysfunctional C1-INH protein with normal or high circulating levels.^{2,3} Lack of sufficient C1-INH activity allows for unchecked activity of the natriopeptide bradykinin, which has potent vasodilatory effects.⁴ A third type of

HAE with normal C1-INH levels and function has been more recently described.^{5,6} Hereditary angioedema can impose significant burdens on patient quality of life (QOL), work and school productivity, social functioning, finances, and emotional health.^{7–10}

Some patients with HAE benefit from long-term prophylaxis to reduce the frequency and severity of attacks. Short-term prophylaxis can prevent angioedema episodes in patients undergoing a stressor or procedure (eg, dental surgery) that is likely to precipitate an attack. Until recently, attenuated androgens (danazol, stanazolol, and oxandrolone) were the only effective prophylactic options available in the United States.^{2,11} With the emergence of newer therapies for the prophylaxis and treatment of HAE, the role of androgen therapy should be carefully considered in this population, especially given the chronic nature of HAE and the need for long-term treatment in patients receiving long-term prophylaxis. The purpose of this review is to systematically analyze the published literature regarding the long-term efficacy and safety of androgen treatment in patients with HAE and thereby provide data for physicians evaluating the risk-benefit ratio of long-term androgen therapy. Although most data pertain to danazol use,

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Table 1
Studies Included in the Literature Review

Study	Study design	Androgen	Dose	No. of patients	Duration of treatment
Level of Evidence: II					
Birjmohun et al, ¹² 2008					
Study 1	Placebo-controlled, crossover study	Danazol	200 mg/d or placebo	15	4 wk (each treatment)
Study 2	Cross-sectional comparison, patients treated with danazol vs matched healthy controls	Danazol	Mean daily dose, 170 mg	17	≥2 y
Gelfand et al, ¹³ 1976	Double-blind, randomized, crossover study (short-term prophylaxis)	Danazol	600 mg/d or placebo	9	Up to 28 d (46 danazol courses)
Sheffer et al, ¹⁴ 1997	Double-blind, placebo-controlled, crossover study	Methyltestosterone	10 mg sublingual	4	10–13.5 mo
Agostoni et al, ¹⁵ 1980 ¹⁵	Retrospective case series	Stanozolol, danazol	Danazol: 600 mg/d first month, followed by 5 days on/5 days off Stanozolol: 4–12 mg/d	14	Danazol: <1 y, n = 3; 1–2 y, n = 8; >2 y, n = 1 Stanozolol: <1 y, n = 6
Füst et al, ¹⁶ 2011	Prospective (?) follow-up of 2 different cohorts	Danazol	Mean initial dose, 128–136 mg/d	German cohort: 45 Hungarian cohort: 39	≥6 y
Hosea et al, ¹⁷ 1980	Prospective, open-label study	Danazol	Initiated at 600 mg/d	69	1–6 y
Ott et al, ¹⁸ 2007	Prospective, open-label pilot study	Tibolone	Initiated at 2.5 mg/d, titrated to a maximum of 7.5 mg/d	8 Women	Up to 30 wk
Perricone et al, ¹⁹ 2000	Prospective, open-label study	Danazol	400–600 mg/d	2 Women	Not reported
Rosen and Beyler, ²⁰ 1980	Prospective, open-label study	Danazol	Initiated at 600 mg/d for first few patients, with subsequent patients started at lower dosages (1 at 400 mg/d, 5 at 300 mg/d, 10 at 200 mg/d, 2 at 100 mg/d, 1 inadvertently at 50 mg/d); dosages titrated based on patient response	28	For all patients, cumulative total of 408 months
Rothbach et al, ²¹ 1979 ²¹	Prospective, open-label study (also described as 4 cases)	Danazol	Initiated at 400 mg/d for 2 mo; reduced by 100 mg/d every 2 mo to find minimum effective dose	4	Range, 13–17 mo; cumulative, 60 mo
Santaella and Martinó, ²² 2004 ²²	Prospective, open-label study	Danazol	Initiated at 600 mg/d, reduced to 400 mg/d after 4 wk, then individually titrated	32 (17 treated with danazol)	Range, 3 mo–10 y
Sheffer et al, ²³ 1979	Prospective, open-label study	Oxymetholone	Initiated at 5 mg/d; if symptoms controlled 2–3 mo, switched to 5 mg every other day; asymptomatic patients switched to 5 mg/every third day	16	Range, 3–16 mo
Sheffer et al, ²⁴ 1981	Prospective, open-label study	Stanozolol	Initiated at 2 mg/d and titrated to 0.5 to 6 mg/d	27	Mean duration, 21 wk at 0.5 mg/d, 24 wk at 1 mg/d, 32 wk at 2 mg/d, 4.5 wk at 4 mg/d, and 5 wk at 6 mg/d
Sheffer et al, ²⁵ 1987	Prospective, open-label study	Stanozolol	Initiated at 2 mg/d and titrated	37	Mean and range not reported; total of 1298 wk daily therapy, 2677 wk every other day therapy, and 1814 wk of extended interval (ie, every 3–5 d) therapy
Solé et al, ²⁶ 1992	Prospective, open-label study	Danazol	Not reported	10	Range, 2–6 mo
Zanicheli et al, ²⁷ 2011	Prospective, open-label study	Stanozolol or danazol	Danazol: 50–200 mg/d Stanozolol: 2–4 mg/d	103	Not reported
Level of Evidence: III					
Szégedi et al, ²⁸ 2008	Prospective? but similar to case-control design	Danazol	33–200 mg/d; mean, 100 mg/d	77	Range, 20–288 mo; mean, 72 mo
Széplaki et al, ²⁹ 2005	Prospective? but similar to case-control design	Danazol	33–200 mg/d; mean, 100 mg/d	130	Range, 5–195 mo; mean, 45.1 mo
Cicardi et al, ³⁰ 1997	Case control	Stanozolol, danazol	Stanozolol: 1–2 mg/d Danazol: 50–200 mg/d	70	Median, 125.5 mo; range, 22–273 mo
Level of Evidence: IV					
Sloane et al, ³¹ 2007	Retrospective long-term follow-up (via questionnaire) of the 1987 study by Sheffer et al	Stanozolol	Usually ≤2 mg/d	21	Median, 29 y; range, 23–29 y
Lumry et al, ⁸ 2010	Web-based survey	Not specified	Not specified	226	≥ 18 y (otherwise not reported)

Andriole et al, ³² 1986	Retrospective case series	Danazol	For 10 patients who developed hematuria and danazol-induced hemorrhagic cystitis, danazol dose was 200 mg/d: 1 patient; 300 mg/d: 2 patients; 400 mg/d: 4 patients; 600 mg/d: 2 patients; 800 mg/d: 1 patient	69	For 10 patients who developed hematuria and danazol-induced hemorrhagic cystitis: <3 years: 4 patients; 3–4 years: 2 patients; >4 years: 4 patients
Bork et al, ³³ 2008	Retrospective case series	Danazol	100–200 mg/d to up to 600 mg/d at initiation of treatment	118	Mean, 11.0 y; range, 2 mo–30 y; 2 mo–10 y
Bork et al, ³⁴ 2003	Retrospective case series	Danazol	50–200 mg/d	32	Mean, 7.4 y
Bork et al, ³⁵ 1999 and Bork et al, ³⁶ 2002 ^a	Retrospective case series and case studies	Danazol	Bork et al, 1999: Not reported Bork et al, 2002: 600 mg/d	Bork et al, 1999: 41 Bork et al, 2002: 1	Bork et al, 1999: 11 patients treated for >10 y Bork et al, 2002: 17 y
Bork et al, ³⁷ 2009	Retrospective case series	Danazol	Patient 1: 200 mg/d Patient 2: 100 mg/d	2	Patient 1: 12 y Patient 2: 6 y
Cicardi et al, ³⁸ 1991	Retrospective case series	Stanozolol, danazol	Stanozolol: 1 mg/d (35%), 2 mg/d (55%), 3 mg/d (5%), 4 mg/d (5%) Danazol: 50 mg/d (19%), 100 mg/d (41%), 200 mg/d (22%), 300 mg/d (18%)	61	<1 year, n = 12; 1–5 y, n = 20; 5–10 y, n = 14; >10 y, n = 10
Cicardi et al, ³⁹ 1982	Retrospective case series	Stanozolol, danazol	Stanozolol: 2–6 mg/d, 5 days on/5 days off Danazol: 100–600 mg/d, 5 days on/5 days off	29	Not reported
Cicardi et al, ⁴⁰ 1983	Retrospective case series	Stanozolol, danazol	Stanozolol: 1 mg/d (8%), 2 mg/d (42%), 3 mg/d (33%), 4 mg/d (8%), 5 mg/d (8%); Danazol: 100 mg/d (11%), 150 mg/d (33%), 200 mg/d (22%), 300 mg/d (22%), 400 mg/d (11%); androgens given 5 days on/5 days off	13	Stanozolol: <2 y: n = 6; 2–3 years: n = 6 Danazol: <2 y: n = 4; 2–<3 y: n = 4; 3–4 y: n = 1
Cicardi and Zingale, ⁴¹ 2003	Retrospective case series	Stanozolol, Danazol	Danazol: 400–600 mg/d for 1 month, tapering to minimal effective dose	141	1–5 y: n = 65; 6–10 y: n = 34; 11–20 y: n = 32; 21–25 y: n = 10
Farkas et al, ⁴² 2010	Retrospective case series	Danazol	Median, 98.44 mg/d; mean, 108 mg/d; range, 33–200 mg/d, with occasional temporary escalation to 300–400 mg/d	92	Treated: median follow-up 5.03 y Untreated: median follow-up 5.05 y
Farkas et al, ⁴³ 1999	Retrospective case series	Danazol	600 mg/d; in 6 patients receiving long-term danazol prophylaxis, dose increased from 200 to 600 mg/d	12	Initiated 4 d preoperatively and continued for 4 d after surgery
Farkas et al, ⁴⁴ 1999	Retrospective case series	Danazol	100 mg every 2–3 d	4	Range, 2–6 y
Farkas et al, ⁴⁵ 2002	Retrospective case series	Danazol	Long-term prophylaxis: Initiated at 100–200 mg/d, then increased dosage interval to 2–3 d if possible after 6 months of clinical remission; short-term prophylaxis: 300 mg/d	21	Long-term prophylaxis: 2–11 y Short-term prophylaxis: 4 days before and 4 days after dental procedure
Hoogerbrugge et al, ⁴⁶ 1995	Retrospective case series	Danazol	300 mg/d	5	>5 y
Pedrosa et al, ⁴⁷ 2009	Retrospective case series	Androgens (mostly stanozolol)	Not reported	31	Not reported
Kreuz et al, ⁴⁸ 2009	Retrospective phase associated with a prospective, open-label study of C1 inhibitor concentrate	Danazol	≤ 200 mg/d, 5 patients; 201–400 mg/d, 9 patients; 401–500 mg/d, 6 patients; 601–1000 mg/d, 2 patients	22	Median, 11.25 y; range, 0.5–23.5 y
Zurlo and Frank, ⁴⁹ 1990	Retrospective case series	Danazol	600 mg/d, titrated to minimal effective dose (50–1600 mg/d)	60	Mean, 59.7 mo; range, 7–131 mo
Altman et al, ⁵⁰ 2006	Case study	Danazol	Danazol 50 mg/d, increased to 100 mg/d at 2 wk, for prophylaxis, with C1 esterase inhibitor treatment for acute exacerbations	1	6 wk (2 wk, 50 mg/d; 4 wk, 100 mg/d)
Crampon et al, ⁵¹ 1998	Case study	Danazol	400 mg/d	1	13 y
Helsing and Nielsen, ⁵² 2006	Case study	Danazol	400 mg/d	1	16 y
Thoufeeq et al, ⁵³ 2012	Case study	Danazol	200 mg/d	1	19 y
Level of Evidence: V Kalaria and Craig, ⁵⁴ 2013	Expert opinion (Internet survey) and review	Androgens	Not reported	66 Physicians surveyed; 886 patients taking androgens	Not reported

^aGrouped because the study by Bork et al published in 2002 adds an additional patient to the series and describes long-term outcomes of patients described in the study by Bork et al published in 1999.

publications on any androgen compound used for HAE therapy were included.

Methods

Search Strategy

The literature search was conducted using PubMed, with no time limitation and with results limited to English-language, human data. The keywords were searched: *hereditary angioedema* and *angio-oedema* combined with each of the following: *danazol*, *stanazolol*, *oxandrolone*, and *androgen*. Bibliographies of identified citations and review articles were also searched for relevant references.

Criteria for Inclusion

All articles selected for inclusion reported on androgen use for HAE and were published in the English language. Search results were first screened for potential relevance, and the abstract must have provided some indication that the article contained information relevant to the safety and/or efficacy of an androgen in a patient(s) with HAE.

Identified studies and reports were categorized according to level of evidence (LOE):

- Level 1: High-quality randomized clinical trial or prospective study
- Level 2: Lesser-quality randomized clinical trial, prospective comparative study, or retrospective study
- Level 3: Case-control study or retrospective comparative study
- Level 4: Case series and case-control studies
- Level 5: Expert opinion

Case reports were not included, except for those describing hepatic-related events, because of numerous similar case reports and the seriousness of such events.

Results

The PubMed searches identified 153 unique citations. Of these, 112 were excluded as review articles, not descriptive of androgen use in patients with HAE, not English language, non–hepatic-related case reports, or publications in obscure journals for which full-text articles could not be retrieved. Two additional citations were identified while reviewing other published literature for a total of 43 references. The publications included in this review are summarized in Table 1, sorted by LOE.

Efficacy

Efficacy findings from studies of long-term androgen prophylaxis in patients with HAE are summarized in eTable 1. Two studies compared the prophylactic efficacy of androgen therapy with placebo in patients with HAE (LOE II). One was a double-blind, randomized, crossover study in 9 patients (5 women and 4 men; 8 with HAE type I and 1 with type II HAE) with HAE attacks occurring at least once per month. Patients were treated with alternating courses of danazol, 200 mg, or placebo 3 times daily.¹² Each course of treatment was terminated when an attack occurred or after 28 days with no attack. Overall, the 9 patients completed 93 courses (46 danazol and 47 placebo courses). Attacks of HAE occurred in 93.6% of placebo courses vs 2.2% of danazol courses ($P < .001$).

A second randomized, double-blind, placebo-controlled study of similar design evaluated the efficacy of methyltestosterone sublingual tablets (10 mg/d) in 4 male patients (2 brothers with type I HAE and 2 unrelated patients with type II HAE) with at least monthly HAE attacks.¹³ Patients received methyltestosterone or placebo until an attack occurred or 3 months passed without an

attack, after which they would switch to the other regimen. The patients experienced significantly fewer HAE attacks while receiving methyltestosterone (4 attacks in 46 months) compared with placebo (19 episodes in 11.8 months; $P < .001$), and the attacks that occurred during methyltestosterone treatment were shorter and milder. No upper respiratory tract swelling developed during methyltestosterone therapy, whereas 4 such attacks occurred with placebo. Although these studies were small, they suggest that androgen therapy significantly reduces the frequency and severity of attacks in patients with HAE.

The long-term prophylactic effectiveness of androgen therapy for HAE has been evaluated in multiple prospective, open-label studies (LOE II).^{14–26} Danazol reduced the severity and frequency of HAE attacks^{15,16,19,20,26} and resulted in improvement of clinical symptoms.^{18,25} In some studies, nearly all patients were able to find an effective dose of danazol that completely prevented HAE attacks.^{16,19,20} The cumulative percentage of patients without HAE attacks increased with increasing dosage of danazol.¹⁶ Similar findings were observed with stanozolol.^{14,23,24,26} In one study, tibolone treatment reduced the frequency and severity of HAE attacks and resulted in a significant decrease in the number of ampules of C1-INH administered for acute control of HAE attacks ($P < .001$).¹⁷

The results of retrospective case series studies (LOE IV) were generally consistent with the results of prospective, open-label studies described above, confirming a high degree of prophylactic efficacy with androgen use. A long-term survey of 118 patients with type I or II HAE reported that 24% of patients became symptom free while taking danazol, but 14% of patients continued to experience 11 or more attacks per year despite danazol therapy.³³ Reasons for breakthrough attacks in patients taking danazol included intentional dose reduction in an effort to reduce to the minimal effective dose (418 attacks in 81 patients), interruption of danazol therapy (171 attacks in 41 patients), and provocation by infection (17 attacks, including 9 episodes of laryngeal edema, in 4 patients) or trauma (11 attacks in 2 patients).

Retrospective case series have reported the efficacy of danazol and stanozolol for short-term prophylaxis before dental procedures.^{43,45} In 12 adult patients, prophylactic danazol given at a dosage of 600 mg/d for 4 to 5 days before and after dental surgery was successful.⁴³ Two pediatric patients (aged 11 and 14 years) received danazol, 300 mg, day 4 days before and 4 days after dental extraction, with no exacerbation of HAE.⁴⁵

Safety and Tolerability

Common adverse events

On the basis of data from prospective studies, the most commonly reported adverse events associated with androgen therapy for HAE include weight gain, menstrual irregularities, virilization, headaches, myalgias or cramps, and mood changes (eg, depression and anxiety) (eTable 2).^{15,17,20,22–25} In general, more prolonged use and higher doses were associated with an increased risk of adverse events. Frequently reported laboratory abnormalities included elevations in creatine phosphokinase levels (primarily in males) and abnormal liver function test (LFT) results.^{23,25}

A case-control study compared patients with HAE treated with danazol and/or stanozolol (median duration, 125.5 months; range, 22–273 months) with age-matched, untreated patients with HAE.³⁰ This study included 5 patients treated with danazol only, 31 patients treated with danazol and stanozolol at different times, and 33 patients who had never received attenuated androgens or any other long-term prophylactic therapy. The most common adverse effects of androgens ($\geq 10\%$ incidence) were menstrual abnormalities (in 50% danazol-treated and 18% of stanozolol-treated premenopausal women), weight gain (28% with danazol and 17% with

stanozolol), arterial hypertension (25%), and acne (11.1%). Notably, development of hypertension was unrelated to dose or duration of therapy. No statistically significant differences were found between androgen-treated and untreated patients with regard to mean values of liver function, creatine kinase, total cholesterol, sodium, potassium, blood urea nitrogen, or plasma creatinine.

The most common adverse events associated with prophylactic androgen therapy in retrospective case series and questionnaires were generally consistent with those observed in the prospective, open-label studies and included weight gain, menstrual irregularities, virilization, headaches, myalgias or cramps, mood changes, and hypertension.^{8,31–33,39,41,48,49} The most common laboratory abnormalities were abnormal LFT results and changes in lipid profiles.

Weight gain is one of the most common adverse effects of androgen therapy,^{17,20,22,23,25,30,31,33,39,41,48,49} in some cases, quite marked.^{17,48,25} In a prospective follow-up of 69 patients with HAE receiving danazol (50–600 mg/d) for 1 to 6 years, weight gain averaged 2.3 to 4.5 kg, but occasional patients gained 13.6 to 18.1 kg.¹⁷ Weight gain appears to be dose related.³⁰

Menstrual changes are among the most common adverse effects among women receiving androgens,^{13,15,17,20,21,23–25,30,31,33,38,39,41,48,49,52} especially during the first few months of treatment.^{13,49} Many women cease menstruating after approximately 3 to 15 months of androgen therapy.^{13,22,49} Although menstrual changes appear to be dose related^{30,48} and often resolve with dose reduction,^{31,49} a prospective, open-label study in 27 patients with HAE (15 women) found that 60% of women developed menstrual abnormalities, and approximately 30% continued to have menstrual abnormalities at maintenance doses of stanozolol.²⁴

Virilization in women, especially acne and hirsutism, is a dose-dependent adverse effect of androgen therapy^{20,24,25,31,33,41,48–50,52} and appears to respond to dose reduction or discontinuation of treatment.^{20,49} Likewise, virilization of female fetuses carried by women using androgens during pregnancy is a concern; this phenomenon (mild, reversible virilization) has been reported in some but not all published cases of androgen exposure during pregnancy.^{38,50}

In a 9-year follow-up study of 69 danazol-treated patients with HAE, 13 (19%) developed hematuria, which was associated with hemorrhagic cystitis in 10 patients (14%).³² Analysis of the 10 patients with hemorrhagic cystitis revealed a nonspecific pattern of erythema, submucosal telangiectasia, and neovascularity. Bladder biopsy revealed numerous dilated submucosal vessels with hemorrhage, mucosal ulceration, and occasional inflammatory cells. The dose and duration of danazol therapy did not correlate with the severity of cystoscopic or pathologic findings. However, changes associated with hemorrhagic cystitis resolved after cessation of danazol therapy in 90% of patients. Other prospective, open-label²² and retrospective case series⁴⁹ have reported cases of hematuria with danazol treatment.

Changes in lipid profiles and atherogenic indexes

Results of several studies suggest that androgen treatment is associated with a decrease in high-density lipoprotein cholesterol (HDL-C) levels and possibly also with an increase in low-density lipoprotein cholesterol (LDL-C) levels,^{12,28,29,31,46} with or without a concomitant change in total cholesterol levels.^{30,33,12,28,29,31,46,49} There has been no consistent observation of elevated triglycerides with prophylactic androgen therapy in HAE.^{12,28,29,31,46}

A placebo-controlled, crossover study evaluated the safety of danazol (200 mg/d) during 4 weeks in 15 healthy male volunteers.¹² Danazol treatment was associated with a 23% decrease from baseline in HDL-C and a 21% decrease in apolipoprotein A-I (all $P \leq .001$ vs baseline and placebo), whereas other lipid parameters (eg, LDL-C

and triglycerides) did not change significantly. No changes were observed in flow-mediated dilation or parameters of coagulation, inflammation, or fibrinolysis after 4 weeks of danazol treatment.

The effect of androgen (danazol) therapy on serum lipid profiles in patients with HAE was most thoroughly studied by Széplaki et al²⁹ in Hungary. In this study, 37 danazol-treated patients (HAE-danazol group) were compared with 27 patients not taking danazol (HAE-control group) and with 66 age-matched and sex-matched healthy controls. The HAE-danazol group had significantly more severe disease than the HAE-control group. Danazol dosages ranged from 33 to 200 mg/d, with a mean dosage of 100 mg/d and a mean duration of treatment of 45.1 months (range, 23.4–84.9 months). Compared with HAE-control patients and healthy controls, HAE-danazol patients had significantly lower serum concentrations of HDL-C (20% lower than HAE-no danazol patients and 29% lower than healthy controls) and apolipoprotein A-I (18% lower than HAE-control patients and 22% lower than healthy controls) and significantly higher serum concentrations of LDL-C (25% higher than HAE-control patients and 22% higher than healthy controls) and apolipoprotein B-100 (18% higher than HAE-no danazol patients and 19% higher than healthy controls). Patients with HAE undergoing long-term danazol prophylaxis had an 11.6 times higher risk of abnormally low HDL-C levels and a 4.4 times higher risk of abnormally high LDL-C levels, whereas total cholesterol and triglyceride levels were unaffected. No significant differences in laboratory parameters were observed between HAE-control patients and healthy controls, suggesting that HAE alone does not account for differences in lipid metabolism.

A subsequent study by the same group compared the clinical presence of atherosclerosis in 32 patients with HAE receiving long-term danazol prophylaxis, 25 patients with HAE who had never received prolonged danazol prophylaxis, and 20 healthy volunteers.²⁸ Forty of the patients with HAE in this study were also included in the previously described study by Széplaki et al.²⁹ As expected given the overlap in patient populations, findings regarding lipids were similar between the 2 studies. Despite having an increased proatherogenic risk profile (elevated body mass index, level alanine aminotransferase level, decreased renal function reflected by increased creatinine levels, low HDL-C level, and high LDL-C level), HAE-danazol patients did not differ from HAE-control patients or healthy controls with respect to rates of atherosclerotic events, the presence of vascular disease, or carotid artery intima-media thickness. Analysis of the rate of atherosclerotic events was limited by the small number of such events.

Despite the observed increase in atherogenic indexes and risk factors associated with danazol treatment, there is thus far no published evidence of an increased risk of cardiovascular events or atherosclerotic complications based on measurement of carotid artery IMT.^{12,28,29} Long-term studies of large populations are often required to detect such treatment effects.

Hepatic changes

Small-to-moderate increases in liver enzymes are common with long-term androgen therapy and tend to normalize with a decrease in dose or with discontinuation of treatment.^{8,17,33,48,21–23,38,40,49} Most reports of increased hepatic enzymes have been with danazol. The long-term effects of stanozolol in HAE have generally been less well studied than danazol.

The clinical significance of changes in LFT results with androgen therapy is unclear. In a retrospective case series, 14 (30.4%) of 46 danazol-treated HAE patients had at least one occurrence of elevated hepatic enzyme levels during 5 years of follow-up, compared with 12 (21.6%) of 46 untreated HAE patients.⁴² However, changes in LFT results were not considered clinically important and did not correlate with the cumulative dose of danazol during the follow-up period. Review of abdominal

ultrasonographic findings for all 46 of the danazol-treated patients and for 38 of the control subjects revealed a number of lesions (ie, hepatomegaly, diffuse hepatic lesions, cholelithiasis, sludge, focal sparing, liver cyst, and hemangioma) in both danazol-treated and untreated patients, with no statistically significant differences in incidences between groups. Lesions occurred a mean of 5.97 years after initial ultrasonography. The results of this study question the clinical relevance of small changes in hepatic enzymes in danazol-treated patients. However, the study was not prospective, and its size may have been too small to detect rare malignant hepatic changes.

There have been reports of hepatic adenoma in patients treated with danazol for 16 to 20 years, even at low dosages (eg, 200 mg/d), which is of concern given the small risk of progression to malignant tumors (eTable 3).^{33,48,35,36,53} This literature review identified 9 reports of hepatic adenoma in patients with HAE receiving long-term danazol prophylaxis (no reports with other androgens). Five of these cases^{33,48} were reported with no details regarding dose or duration of treatment or patient characteristics, and it is unclear whether some or all may be redundant with prior publications. The remaining 4 cases were reported in both males and females taking daily danazol doses of 200 to 600 mg/d; in patients without a documented history of liver disease; and, at least in one case, in a patient with normal LFT results approximately 17 months before the presentation of hepatic adenoma.³⁶ A case of hepatocellular focal nodular hyperplasia despite normal levels of transaminases was also reported in a 32-year-old patient receiving danazol, 400 mg/d, for 16 years.⁵² Cases of liver angioma,⁴⁷ hepatic cyst,⁴⁷ and biliary hamartomas³³ have also been reported.

Three published cases of hepatocellular carcinoma (HCC) were identified in HAE patients treated with danazol, details of which were available for only 2 patients (eTable 3). The first patient described was a 34-year-old woman with type I HAE treated with danazol (400 mg/d) for 13 years.⁵¹ At the time that she presented with a mass, the patient did not have cirrhosis or viral hepatitis, levels of aminotransferases and alkaline phosphatases were normal, and the α -fetoprotein concentration was less than 5 μ g/L. The second case of HCC was in a 75-year-old man with type II HAE who had undergone 19 years of treatment with danazol (200 mg/d).⁵³ This patient was diagnosed as having HCC after he was found to have abnormal LFT results and liver nodules. He was initially diagnosed as having hepatic adenoma but refused biopsy and was diagnosed 8 months later as having advanced HCC.

It is difficult to draw conclusions about the risk for development of hepatic adenoma and HCC in patients with HAE receiving long-term danazol prophylaxis given the low numbers of reported cases with patient and treatment characteristics. However, one can conclude that these complications are likely rare, tend to develop only with more than 10 years of treatment, can occur even at relatively low doses of danazol (200 mg/d), and are not always preceded by a history of liver disease or abnormal LFT results. Thus, regular ultrasonography monitoring, as recommended by professional organizations,^{2,55} is necessary for early detection of nonmalignant and malignant hepatic changes.

Liver findings other than tumors have been reported with androgen therapy, including increased liver size,^{40,47} fatty infiltration of the liver or steatosis,^{31,40} steatohepatitis,⁴⁷ slight cholestasis,⁴⁰ small areas of hepatic intralobular necrosis,⁴⁰ consistent findings of scattered giant mitochondria and biliary pigments (not considered as specific for, or as indicative of, cell injury),⁴⁰ thickening of central hepatic veins with infiltration of eosinophils and histiocytes of undetermined significance,¹⁷ and portal hypertension.⁴⁷ Given the reported findings of similar abnormalities in untreated HAE patients,⁴² it must be considered that some such findings may be incidental and/or unrelated to danazol therapy.

Trends in Clinical Practice

Recent HAE expert consensus guidelines have shifted away from recommending routine use of danazol and other attenuated androgens in HAE, especially in select patient subgroups. The US Hereditary Angioedema Association Medical Advisory Board and the Hereditary Angioedema International Working Group recommend against using anabolic androgens for long-term prophylaxis in pregnant or breastfeeding women and in children who are still growing (generally <16 years of age).^{2,55} Androgen dose limits have been suggested to reduce long-term adverse effects: 200 mg/d or less of danazol^{55,56} and 2 mg/d or less of stanozolol.⁵⁵ On the basis of recommendations of the US Hereditary Angioedema Association Medical Advisory Board and/or the Hereditary Angioedema International Working Group, patients receiving long-term androgen prophylaxis should be monitored as follows: blood pressure, weight, signs of virilization, LFTs, α -fetoprotein, urinalysis, complete blood cell count, and lipid profile every 6 months and abdominal ultrasonography annually or every 6 months if the androgen dosage equivalent exceeds 200 mg/d of danazol.^{2,55}

Trends in HAE management behaviors suggest a decrease in androgen use in recent years. Sequential surveys of HAE-treating physicians in the United States (2009–2010 and 2013) found that the proportion of physicians who indicated a preference for danazol for long-term prophylaxis decreased from 56% in 2009–2010 to 23% in 2013.^{57,58}

Patient Considerations

Different treatment characteristics and adverse effect risks may have variable importance to individual patients. Recent consensus publications on HAE management recommend that decisions about long-term prophylaxis should be individualized with input from a well-informed patient, taking into account attack frequency and severity, the effect of attacks on QOL, comorbid conditions, access to emergency treatment, and prior patient experience and preferences.^{2,11,55,59} In particular, cost, adverse effects, and convenience may affect patient preferences. Medication cost may be a key concern for many patients, depending on the terms and coverage of their health insurance policies. Androgens are often the least expensive medication for long-term HAE prophylaxis, an important factor in regions with sparse health care resources. However, as with any long-term therapy, the long-term health costs of treatment effects should be considered.

Many common androgen adverse effects, such as weight gain, virilization in women, headache, myalgias, and mood changes, may affect patients' ability to function and QOL. A survey of 226 HAE patients receiving long-term prophylaxis with androgens suggested that long-term use of androgen therapy may be associated with reductions in QOL.⁸ Compared with HAE patients not receiving androgen therapy, patients receiving long-term androgen therapy reported significantly greater levels of depression ($P < .001$) and overall work impairment ($P = .003$). It should be considered that patients receiving long-term androgen prophylaxis likely had more severe disease than those patients not receiving long-term prophylaxis, and HAE disease severity itself may affect QOL.^{8,9}

Convenience is also a potentially important consideration for patients and relates to route and frequency of administration and monitoring requirements. Some patients may be opposed to injectable therapy and may prefer oral androgen therapy for long-term prophylaxis. The only currently available plasma-derived C1INH product approved for long-term prophylaxis is administered intravenously every 3 or 4 days.⁶⁰ Home-based self-administration of C1INH therapy is an option for some patients and may enhance the convenience of this treatment modality. The ongoing clinical development of additional long-term prophylactic

strategies for HAE, including subcutaneous C1INH, oral kallikrein inhibitors, and antikallikrein monoclonal antibodies, may improve the convenience of prophylactic therapy in the future.

Conclusions

Despite the lack of large, randomized, placebo-controlled trials, the efficacy of attenuated androgens in the long-term prophylaxis of type I and II HAE is well established and widely accepted. Other advantages of androgen use include convenience of oral dosing and low medication cost relative to other HAE therapies. The minimum effective androgen dose that controls HAE attacks is recommended to reduce the risk of short-term and long-term adverse effects. Common adverse effects of androgens, such as weight gain, virilization, headaches, and myalgias, may compromise patients' health and impair their functional ability and QOL. Long-term androgen therapy has been associated with changes in lipid profiles and atherogenic indexes and elevations in LFT results, the clinical significance of which remains unclear. Rare cases of hepatic adenomas and HCC have been reported, even with relatively low dosages (200 mg/d of danazol), and have not always been preceded by evidence of liver disease or abnormal LFT results, underscoring the need for regular monitoring. In keeping with current HAE consensus guidelines, disease management programs should be tailored individually, taking into consideration patient priorities and preferences, preexisting comorbid medical conditions, and the risk-benefit profiles of different treatment options.

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Supplementary Data

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eTable 1
Summary of Efficacy Findings From the Literature Review^a

Study	Androgen	No. treated	HAE symptoms	Attack frequency	Attack severity	Remission	Other
Double-blind, Placebo-Controlled, Crossover Studies							
Gelfand et al, 1976 ¹³	Danazol	9		HAE attacks occurred in 93.6% of placebo courses vs 2.2% of danazol courses ($P < .001$).			
Sheffer et al, ¹⁴ 1977	Methyltestosterone	4		4 Attacks during 46 mo of methyltestosterone treatment; 19 attacks during 11.8 mo of placebo exposure ($P < .001$).	Attacks during methyltestosterone treatment were milder and shorter duration		
Prospective, Open-label Studies							
Agostoni et al, ¹⁵ 1980	Stanozolol, danazol	Danzol: 8; stanozolol: 2; both: 4				All patients, except 1 man, reported complete remission of HAE symptoms with danazol With stanozolol, all patients reported complete remission, except for 1 woman who reported a reduction in frequency and severity of attacks and 1 man for whom stanozolol lost efficacy after 1 mo	
Füst et al, ¹⁶ 2011	Danazol	84		Significantly fewer subcutaneous, abdominal, and laryngeal attacks occurred in the first year of danazol treatment compared with the preceding year In a Hungarian cohort, there was a significant increase from year 1 to year 6 of treatment in the frequency of subcutaneous and abdominal but not laryngeal attack (statistically significant increase in abdominal attacks seen in females only); no changes in frequency of attacks seen during danazol treatment in a German cohort			
Hosea et al, ¹⁷ 1980	Danazol	69	Most patients reported complete symptom relief	All patients experienced a decrease in frequency of HAE attacks	All patients experienced a decrease in severity of HAE attacks	Most patients reported complete symptom relief The cumulative percentage of patients without HAE attacks increased with increasing danazol dosage	
Ott et al, ¹⁸ 2007	Tibolone	8		During 3 mo of treatment with tibolone vs 3 mo before treatment (control period), there was a significant ($P \leq .001$) decrease in frequency of attacks in all patients, with each patient experiencing a 60% to 100% decrease in attack frequency	During 3 mo of treatment with tibolone vs 3 mo before treatment (control period), there was a significant ($P \leq .001$) decrease in severity of attacks in all patients		During 3 mo of treatment with tibolone vs 3 mo before treatment (control period), there was a significant decrease in the No. of ampules of C1 esterase inhibitor administered for acute control of HAE attacks ($P < .001$)

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eTable 1 (continued)

Study	Androgen	No. treated	HAE symptoms	Attack frequency	Attack severity	Remission	Other
Perricone et al, ¹⁹ 2000	Danazol	2	Clinical symptoms of HAE improved				Ovarian ultrasonography normalized in both patients with danazol and no longer revealed the presence of cystic ovaries
Rosen and Beyler, ²⁰ 1980	Danazol	28		During 408 mo of danazol exposure, only 13 documented HAE episodes occurred; based on attack frequency before treatment, at least 508 HAE attacks would have been expected	Attacks were less severe than before treatment	399/408 mo (98%) were essentially symptom free, with the same pattern (98% of months symptom free) observed in adults and adolescents	
Rothbach et al, ²¹ 1979	Danazol	4		Danazol reduced frequency of HAE attacks	Danazol reduced severity of HAE attacks	All patients were able to find an effective dose that allowed no HAE attacks	
Santaella and Martín, ²² 2004	Danazol	17		Decrease in frequency of HAE attacks (during treatment, ranged from 1 every 2 mo to 1 per y)			
Sheffer et al, ²³ 1979	Oxymetholone	16		Oxymetholone reduced attack frequency The cumulative number of attacks relative to months of treatment was 1 attack per 108 mo at 5 mg/d, 7 attacks per 50 most at 5 mg every other day, and 5 attacks per 17 mo at 5 mg every third day		Oxymetholone, 5 mg/d, maintained 15 of the 16 patients attack free, and advancing 13 of these patients to 5 mg every other day was still effective, despite increase in attack rate in 7 patients (Sheffer et al, 1981)	
Sheffer et al, ²⁴ 1981	Stanozolol	27	All patients experienced improvement of clinical symptoms (edema/pain)	Reduced HAE attack frequency Mean pretreatment attack frequency was approximately 2–4 attacks per week At doses of 0.5 and 1.0 mg/d, attack rate was 0.14 and 0.12 attacks per week, respectively Higher doses associated with lower attack rates: weekly attack rate 0.07 at 2 mg/d, 0.06 at 4 mg/d, and 0.05 at 6 mg/d			
Sheffer et al, ²⁵ 1987	Stanozolol	37				17 Patients withdrawn from treatment after being symptom free for 3 mo	
Solé et al, ²⁶ 1992	Danazol	10					

Zanicheli et al, ²⁷ 2011	Stanozolol or danazol	Danazol: 37; stanozolol: 4	Median No. of attacks per year was not statistically significantly different between patients taking attenuated androgens vs tranexamic acid or no prophylaxis However, in patients taking androgens, the No. of attacks observed during the study period (7.6 per y for danazol, 7.9 per y for stanozolol) was significantly lower than the mean number of yearly attacks in the same patients before treatment ($P < .01$)		
Case-Control Study Cicardi et al, ³⁰ 1997	Stanozolol, Danazol	Danazol: 5; danazol and stanozolol: 31			All patients, except 2 receiving stanozolol and 6 receiving danazol remained nearly free of symptoms (≤ 2 minor attacks per year)
Retrospective Case Series Sloane et al, ³¹ 2007 ^b	Stanozolol	21		Stanozolol reduced HAE attack severity (follow-up of Sheffer et al, 1987)	
Bork et al, ³³ 2008	Danazol	118	Danazol reduced the mean number of attacks from 33.3 per year to 5.4 per year, an 83.8% reduction; reflecting reductions in skin swelling, abdominal attacks, and laryngeal edema 26 (22%) patients had ≤ 1 attack per year; 32 (27.1%) had 2–5 attacks per year; 15 (12.7%) had >5–10 attacks per year; 17 (14.4%) had >10 attacks per year Despite long-term treatment with danazol, 100 mg/d, 4 patients developed 1 episode, and 2 patients developed 2 episodes of laryngeal edema; all 6 of these patients developed skin swellings and abdominal pain attacks while taking danazol, but these symptoms occurred less frequently than before danazol therapy		28 Patients (23.7%) achieved complete remission Danazol was ineffective in 7 patients (6%) and was effective in 111 patients (94%) Seven patients discontinued because of lack of efficacy
Bork et al, ³⁴ 2003	Danazol	32			Complete remission of laryngeal edema in 26 patients (81.3%)
Bork et al, ³⁵ 1999 and Bork et al, ³⁶ 2002	Danazol	42	Efficacy described for 1 patient from Bork et al, 2002: sin swellings reduced from twice a week to 1–2 per year; abdominal attacks reduced from once a week to none		
Bork et al, ³⁷ 2009	Danazol	2 women			Both patients achieved complete remission

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eTable 1 (continued)

Study	Androgen	No. treated	HAE symptoms	Attack frequency	Attack severity	Remission	Other
Cicardi et al, ³⁸ 1991	Stanozolol Danazol	Stanozolol: 31; danazol: 20; both: 10				All patients, except 2 women, reported the complete disappearance of HAE symptoms	
Cicardi et al, ⁴⁰ 1983	Stanozolol Danazol	13				All patients were free of HAE symptoms and attacks while receiving treatment	
Cicardi and Zingale, ⁴¹ 2003	Stanozolol Danazol	141				At least 90% of patients achieved significant remission	
Farkas et al, ⁴³ 1999	Danazol	4 pediatric					Postoperative recovery after dental work uneventful in all 12 patients, with no occurrence of submucosal or subcutaneous edema
Farkas et al, ⁴⁴ 1999	Danazol	4 pediatric				Complete resolution of clinical signs and symptoms of HAE achieved	
Farkas et al, ⁴⁵ 2002	Danazol	8 pediatric			Danazol completely eliminated serious edematous attacks Doubling the daily dose for several days aborted prodromal symptoms or prevented progression from mild clinical symptoms to full-blown attacks		Danazol prevented complications of oral procedures
Zurlo and Frank, ⁴⁹ 1990	Danazol	60 women					1 Patient discontinued because of lack of efficacy

Abbreviation: HAE, hereditary angioedema.

^aOnly publications reporting efficacy data are listed here.

^bLong-term follow-up of the 1987 study by Sheffer et al.³¹ Note that, although assessment of the adverse events was retrospective or via questionnaire, some other measures (eg, laboratory tests liver ultrasonography) may have been prospectively studied.

eTable 2

Summary of AE Findings From the Literature Review (Long-term Prophylaxis Only)

Study	Drug	No. treated	Lipid changes	Weight gain	Virilization (female patients)	Menstrual changes	Headache	Muscle related	Hepatic	Other
Birjmohun et al, ¹² 2008	Danazol	32	X							Coagulation activation
Gelfand et al, ¹³ 1976	Danazol	9		X	No	X				Proliferative endometrium
Agostoni et al, ¹⁵ 1980	Stanozolol, danazol	Danazol: 8; stanozolol: 2; both: 4				N = 3				Sensation of thick saliva (danazol; n = 2); dyspepsia (danazol; n = 2)
Hosea et al, ¹⁷ 1980	Danazol	69		38%		16%	22%	Elevated CPK		Anxiety (16%), mild alopecia (17%), microscopic hematuria (13%), hemorrhagic cystitis (n = 3)
Ott et al, ¹⁸ 2007	Tibolone	8	No		No					
Perricone et al, ¹⁹ 2000	Danazol	2								No AEs reported
Rosen and Beyler, ²⁰ 1980	Danazol	28		5%	Acne, 5%	n = 1	10%			Hypertension (5%); muscle spasm (10%); muscle ache (5%)
Rothbach et al, ²¹ 1979	Danazol	4				All 3 women				Blood and urine analysis results normal; transient increase in LDL-C (n = 1)
Santaella and Martín, ²² 2004	Danazol	17		31%		33%	44%	18%	X	Microscopic hematuria (n = 1); increased liver function levels (n = 2)
Sheffer et al, ²³ 1979	Oxymetholone	16		44%		38%		Increased CPK, 7/8 male patients	X	Depression (13%); increased alkaline phosphatase (13%)
Sheffer et al, ²⁵ 1987	Stanozolol	37		41%	N = 1	N = 2		Increased CPK approximately 30%	X	19 Patients reported no AEs; increased ALT of approximately 25%
Solé et al, ²⁶ 1992	Danazol	10								None reported
Zanicheli et al, ²⁷ 2011	Stanozolol or danazol	Danazol: 37; stanozolol: 4								None reported
Szégedi et al, ²⁸ 2008	Danazol	32	X					X	X	No difference between danazol and no treatment in rates of atherosclerosis, intima-media thickness of common carotid arteries
Széplaki et al, ²⁹ 2005	Danazol		X							Danazol-treated patients: 11.6 times higher risk for decreased HDL-C and 4.4 times higher risk for increased LDL-C; no change in TC or TCL Arterial hypertension (25%)
Cicardi et al, ³⁰ 1997	Stanozolol, danazol	Danazol: 5; danazol and stanozolol: 31	X	Danazol: 8% Stanozolol: 17%		Danazol: 50%; Stanozolol: 18%				
Sloane et al, ³¹ 2007	Stanozolol	21	Decreased HDL-C, 24; increased TGL, 10	14%	Hirsutism, 33%; acne, 14%	14%			No	Postmenopausal bleeding (19%); mood changes (10%); abnormal liver ultrasonographic findings (3/8)
Lumry et al, ⁸ 2010	Not specified	226	Increased TC	70.8%	Hirsutism, 42.0%; acne, 40.3%; voice changes (13.7%)	36.7%			X	Mood changes (59.7%), agitation (59.7%), sleep changes/insomnia (45.6%), sexual AEs (37.2%), changes in attention span (26.1%), blood clots (2.7%), stunted growth (1.3%; all respondents were adults)
Andriole et al, ³² 1986	Danazol	69								Hematuria (19%); hemorrhagic cystitis (14%)
Bork et al, ³³ 2008	Danazol	118	X	42%	X	14%	14%	Myalgia, 13%	X	Depression (11%), acne (9%), MI (2 events, 1 patient), stroke (1 patient), DVT with embolus (1 patient), acute pancreatitis (1 patient), biliary hamartoma (1 patient); liver cell adenoma (3 patients)
Bork et al, ³⁴ 2003	Danazol	32								None reported

(continued on next page)

eTable 2 (continued)

Study	Drug	No. treated	Lipid changes	Weight gain	Virilization (female patients)	Menstrual changes	Headache	Muscle related	Hepatic	Other
Bork et al, ³⁵ 1999 and Bork et al, ³⁶ 2002	Danazol	42							X	Hepatocellular adenoma (3 patients);
Bork et al, ³⁷ 2009	Danazol	2 women								No AEs experienced by 1 patient; AEs not mentioned for second patient
Cicardi et al, ³⁸ 1991	Stanozolol, danazol	Stanozolol: 31; danazol: 20; both: 10		24%		80% of fertile women			X	Hepatic cell necrosis (1 patient); slight breast hypertrophy (1 patient); polyglobulia (2 patients)
Cicardi et al, ³⁹ 1982	Stanozolol, danazol	29		X		X				
Cicardi et al, ⁴⁰ 1983	Stanozolol, danazol	13							X	Overall, "negligible" AEs
Cicardi and Zingale, ⁴¹ 2003	Stanozolol, danazol	141		39%	Acne, 11%	53%				Polycythemia (5%); arterial hypertension (25%)
Farkas et al, ⁴² 2010	Danazol	46							No	No AE-related drug discontinuations
Farkas et al, ⁴⁴ 1999	Danazol	4 pediatric								No drug-related AEs
Farkas et al, ⁴⁵ 2002	Danazol	8 pediatric			1 patient					No drug-related AEs resulting in therapy discontinuation; delayed menarche in 1 patient; no hirsutism
Hoogerbrugge et al, ⁴⁶ 1995	Danazol	5	100%						X	Increased hepatic lipase activity
Pedrosa et al, ⁴⁷ 2009	Androgens ^a	31							X	All patients underwent abdominal ultrasonography; liver abnormalities in 29%
Kreuz et al, ⁴⁸ 2009	Danazol	22 ^b		55%	32%	55%	68%		X	Depression (77%), ↑transaminases (77%), indisposition (50%), hot flushes (36%), hypertension (23%), liver adenoma (9%)
Zurlo and Frank, ⁴⁹ 1990	Danazol	60 women	X	60%	Hirsutism, 12%	79%	30%	40%	X	Transaminase elevations (40%); elevated cholesterol (27%), low cholesterol (12%)
Altman et al, ⁵⁰ 2006	Danazol	1		X	Acne					Edema, irritability
Helsing and Nielsen, ⁵² 2006	Danazol	1	X	X	X	X			X	Arterial hypertension; hepatocellular focal nodular hyperplasia
Thoufeeq et al, ⁵³ 2012	Danazol	1							X	Hepatocellular carcinoma
Kalaria and Craig, ⁵⁴ 2013	Androgens	Survey (66 physicians; 886 patients)							X	Hepatocellular carcinoma (0.1%); other AEs not inquired about

Abbreviations: AE, adverse effect; ALT, alanine aminotransferase; CPK, creatine phosphokinase; DVT, deep vein thrombosis; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TGL, triglycerides; X, reported but no frequency specified.

^aMostly stanozolol; not otherwise specified.

^bPopulation composed of patients who were intolerant to or did not respond to danazol.

eTable 3Summary of Hepatic Tumors in Patients With HAE Treated With Androgen Therapy^a

Study	Age, y	Sex	HAE type	Androgen	Treatment dose	Treatment duration	Comments
Hepatocellular Carcinoma							
Crampon et al, ⁵¹ 1998	34	F	I	Danazol	400 mg/d	13 y	Noncirrhotic liver; no chronic viral hepatitis; normal aminotransferases
Thoufeeq et al, ⁵³ 2012	75	M	II	Danazol	200 mg/d	19 y	Initially diagnosed as having hepatic adenoma; refused biopsy; diagnosed 8 mo later as having advanced hepatocellular carcinoma
Kalaria and Craig, ⁵⁴ 2013							1 Case identified via survey; no further details provided
Hepatocellular Adenoma							
Bork et al, ³⁵ 1999	69	F	Not reported	Danazol	200 mg/d	20 y	No history of excessive alcohol ingestion, liver cirrhosis, or intake of sex hormones
Bork et al, ³⁵ 1999	29	F	Not reported	Danazol	200 mg/d	13 y	
Bork et al, ³⁵ 1999	39	M	Not reported	Danazol	400 mg/d, later 200 mg/d	16 y	
Bork et al, ³⁶ 2002	45	M	I	Danazol	600 mg/d	17 y	No history of liver disease; LFT results normal approximately 17 mo before presentation of hepatocellular adenoma
Bork et al, ³³ 2008							3 Cases of hepatic adenoma cited with no further details; unclear whether these cases duplicate others reported previously by this author
Kreuz et al, ⁴⁸ 2009							2 Cases of liver adenoma cited with no further details
Hepatocellular Focal Nodular Hyperplasia							
Helsing and Nielsen, ⁵² 2006	32	F	Not reported	Danazol	400 mg/d	Approximately 14 y	At 30 years of age, patient diagnosed as having polycystic ovarian syndrome and atrophic uterus; patients showed signs of virilization, with acne and hirsutism; high total cholesterol and LDL-C; patient under treatment for arterial hypertension; liver tumor diagnosed in the absence of elevated transaminases
Benign Biliary Hamartomas							
Bork et al, ³³ 2008	38	M	Not reported	Danazol	200 mg/d	>20 y	

Abbreviation: HAE, hereditary angioedema; LDL-C, low-density lipoprotein cholesterol; LFT, liver function test.

^aCases of liver angioma and hepatic cyst from Pedrosa et al not included here because of insufficient detail.