EXPERT OPINION

Drug-induced gynecomastia: an evidence-based review

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Introduction: Drugs are estimated to cause about 10 – 25% of all cases of gynecomastia. Over the course of several decades, multiple medications have been implicated in the development of gynecomastia mostly in the form of case reports and case series. However, these reports suffer from a multitude of deficiencies, including poor quality of evidence.

Areas covered: Studies were selected for this review by performing an extensive electronic and hand-search using BIOSIS, EMBASE and Medline, from 1940 to present, for all reported drug associations of gynecomastia and their possible pathophysiology. Quality of evidence was assessed on a three-point scale: good, fair and poor, and each of the drugs reported to cause gynecomastia was assigned a level of strength. The pathophysiology of gynecomastia is also discussed in detail for each of the drugs found to have a good or fair evidence of association with gynecomastia.

Expert opinion: Most of the reported drug–gynecomastia associations were based on poor quality evidence. The drugs definitely associated with the onset of gynecomastia are spironolactone, cimetidine, ketoconazole, hGH, estrogens, hCG, anti-androgens, GnRH analogs and 5-α reductase inhibitors. Medications probably associated with gynecomastia include risperidone, verapamil, nifedipine, omeprazole, alkylating agents, HIV medications (efavirenz), anabolic steroids, alcohol and opioids.

Keywords: adverse drug reactions, breast enlargement, drugs, gynecomastia, side effects

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1. Introduction

Gynecomastia is a benign proliferation of male breast glandular tissue caused by an imbalance between the actions of estrogens relative to androgens at the level of breast tissue [1,2]. **Table 1** summarizes various medical causes of gynecomastia and **Figure 1** demonstrates various possible pathophysiological mechanisms leading to its development [1,2].

Drugs are estimated to cause about 10 – 25% of all cases of gynecomastia seen in referral medical centers [3]. Multiple medications have been implicated in the development of gynecomastia [4,5]. However, these reports suffer from a multitude of deficiencies including poor quality of evidence. Many of the drug associations have been based on anecdotal reports or small series, but not been subjected to rigorous cause–effect analysis, and many lack a plausible pathophysiological explanation. Gynecomastia is common, so just finding a temporal relationship alone is not sufficient to ascribe a true association. Unfortunately, a number of these associations have made their way into the published medical literature time and again without careful scrutiny leading to misinformation and confusion in the minds of both patients and providers. Therefore, the authors have attempted to carefully review the published literature for all the reported drug associations of gynecomastia and their possible pathophysiology.

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Article highlights.

- Gynecomastia is benign proliferation of glandular tissue of the breast in males.
- The reported prevalence of drug-induced gynecomastia varies from 10 to 25% of all cases of gynecomastia.
- Most of the reported drug–gynecomastia associations are based on poor quality of evidence.
- The drugs definitely associated with the onset of gynecomastia are spironolactone, cimetidine, ketoconazole, human growth hormone (hGH), estrogens, human chorionic gonadotropin (hCG), anti-androgens, gonadotropin-releasing hormone (GnRH) analogs and 5-α reductase inhibitors.
- The drugs probably associated with gynecomastia include risperidone, verapamil, nifedipine, omeprazole, alkylating agents, HIV medications (efavirenz), anabolic steroids, alcohol and opioids.
- A careful history should be taken to identify an underlying drug or over-the-counter product known to be associated with the development of gynecomastia and drug de-challenge should be considered whenever possible. Switching to other medications from the same class with lower association with gynecomastia may prevent re-emergence of gynecomastia.

This box summarizes key points contained in the article.

1.1 Methods

Studies were selected by performing an extensive electronic and hand-search using BIOSIS, EMBASE and Medline from 1940 to present with the help of a professional librarian. The key words used in different combinations were: gynecomastia, drugs and name/class of specific medications being reported to cause gynecomastia in the literature. Only English language reports were included.

1.2 Levels of evidence

The criteria for analysis of causality and association in adverse drug events (ADE) as described by Hill include the strength of association, consistency of results from different studies, specificity of association, temporal relationship, dose–response relationship, biologic plausibility, experimental demonstration and analogy [6]. Several other factors to consider while making such assessment are latency period for the ADE, exclusion of any other drugs or existing responsible conditions, improvement of condition on de-challenge and recurrence on re-challenge. De-challenge refers to withdrawal of the drug, and re-challenge indicates re-introduction of the suspected drug after resolution of the side effect on de-challenge.

Several grading scales are in use to determine the quality of an individual study, most prominent of which are the ones used by the United States Preventive Task Force guidelines (USPTF) and the GRADE Working Group [7,8]. However, these grading systems are developed primarily for determining the efficacy of a treatment or a screening tool. For the present article, the authors defined a three-point scale for evaluating the quality of evidence in order to determine the strength of association between the reported drug and gynecomastia as good (consistent high-quality evidence), fair (inconsistent or limited evidence) and poor (lack direct evidence) (**Table 2**) [7].

2. Drugs with good quality of evidence for association with gynecomastia

2.1 Spironolactone

Gynecomastia can develop as early as 1 month after initiating spironolactone. In a double-blind, randomized trial of 30 healthy men, gynecomastia occurred in 3 of 10 men receiving 100 mg/day, and 5 of 8 getting 200 mg/day of spironolactone as compared with none in 12 placebo patients [9]. In another prospective study, six of nine healthy young men developed gynecomastia after receiving 400 mg of spironolactone daily for 24 weeks [10]. Among 1663 heart failure patients randomized to receive either spironolactone 25 mg/day or placebo for 24 months, gynecomastia was noted in 10% in the treatment group versus 1% in the placebo arm [11].

Spironolactone acts as an anti-androgen by binding to the androgen receptors; lowers circulating testosterone by increasing its metabolic clearance and preventing a compensatory rise in testicular androgen synthesis; displaces estrogen from sex hormone-binding globulin (SHBG) and increases the peripheral conversion of testosterone to estrogen leading to elevated estradiol [12]. Estradiol levels decrease and testosterone increase significantly 3 – 6 months after stopping spironolactone [12].

2.2 Cimetidine

Spence and Celestin reported a 20% incidence of gynecomastia in a prospective study of 25 male duodenal ulcer patients treated with cimetidine 1.6 g/day [13]. Symptoms developed after 4 months of treatment and regressed within a month of stopping therapy. In another prospective cohort study involving 22 patients, cimetidine caused breast changes and erectile dysfunction in 60% of men which resolved completely in all cases when switched to ranitidine [14]. In the UK general practice database of over 80,000 men, the relative risk (RR) of gynecomastia among cimetidine users was 7.2 (95% confidence interval (CI 4.5 – 11.3) as compared with the non-users. Users with a daily dose ≥ 1000 mg had more than 40 times the risk of developing gynecomastia than the non-users. The period of highest risk was 7 – 12 months after starting cimetidine treatment [15].

Cimetidine blocks the androgen receptors in the breast leading to decreased androgen action causing the growth of breast tissue because of 'unopposed' estrogen action [16]. Another possible mechanism includes decreased 2-hydroxylation of estrogen leading to elevated serum estrogen levels [17]. There also are reports of cimetidine blocking testosterone biosynthesis and causing elevated prolactin levels in individual cases [18].

Table 1. Medical causes of gynecomastia.

Increased estrogen activity	
Increased estrogen production	Leydig or Sertoli cell tumors
	Eutopic or ectopic hCG-secreting tumors
	Adrenocortical tumors
Higher aromatization of androgen to estrogen	Aging
	Obesity
	Hyperthyroidism
	Liver disease
	Familial or sporadic aromatase excess syndrome
	Klinefelter's syndrome
	Testicular tumors
	Adrenal tumors
	Refeeding after starvation
Exogenous estrogen exposure	Topical estrogen creams
	Oral estrogen ingestion
Decreased androgen activity	
Primary gonadal failure	Trauma
	Chemotherapy
	Radiation
	Orchitis
	Klinefelter's syndrome
	Congenital anorchia
Secondary hypogonadism	Hypothalamic diseases
	Pituitary failure
	Kallmann's syndrome
Decreased androgen action	Androgen receptor defects
Miscellaneous diseases	Chronic renal failure
	Liver disease
	HIV
	Chronic illness

hCG: Human chorionic gonadotropin.

2.3 Ketoconazole

Ketoconazole was first reported by DeFelice *et al.* to cause bilateral mastalgia and gynecomastia in 3 of 40 patients who received therapy. Breast pain abated after several weeks despite continued therapy, although gynecomastia persisted [19]. In a prospective multicenter study involving 160 patients who received 400 – 2000 mg of ketoconazole once daily for non-meningeal or meningeal coccidiomycosis, 25 developed (21%) gynecomastia. It appeared as early as 1 month and as late as 32 months after initiation of therapy. Gynecomastia was dose related and increased at dose of more than 800 mg a day, but resolved after ketoconazole therapy was discontinued [20].

Ketoconazole, in conventional doses transiently blocks testosterone synthesis and adrenal response to corticotrophin when studied in healthy volunteers. Higher therapeutic doses of 800 – 1200 mg/day causes a marked and much more prolonged blockade which is still transient [21-23]. Ketoconazole also selectively displace dihydrotestosterone (DHT) and estradiol from serum-binding globulins. Suppression of testicular testosterone synthesis and displacement of estrogens from SHBG may decrease the androgen/estrogen ratio and contribute to the development of gynecomastia [24].

2.4 Growth hormone

In a systemic review of three randomized controlled trials, gynecomastia was reported in 6% of human growth hormone (hGH)-treated patients (n = 95) as compared with none in placebo controls (n = 63) [25]. Gynecomastia resolved within 3 months after hormone treatment was stopped [26]. Recombinant GH and insulin-like growth factor-1 (IGF-I) treatment lead to development of transient tender gynecomastia in four of nine undernourished frail elderly patients. Two were evaluated and found to have normal serum testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin levels [27]. Reduction in adipose tissue mass with GH therapy is associated with redistribution of adipose tissue from abdominal to peripheral areas [28,29]. In addition, GH and its downstream effector IGF-I have been shown to induce mammary gland hyperplasia in primates [30].

2.5 Gonadotropins

In a study of 60 men with hypogonadotrophic hypogonadism treated with FSH and human chorionic gonadotropin (hCG) for 6 months, 3 reported mild to moderate bilateral gynecomastia. It improved in one case after hCG dose reduction [31]. However, in another prospective study, 5 of 18 men treated with the same dose of hCG and FSH developed gynecomastia as compared with none of the 18 males receiving pulsatile gonadotropin-releasing hormone (GnRH) therapy. The investigators observed a significant increase in estradiol levels in the former group [32]. The gynecomastia reported with hCG therapy corresponds to physiological gynecomastia observed during the puberty. hCG or LH stimulation of the Leydig cells leads to an increase in the aromatase activity thus leading to higher conversion of testosterone to estrogen [33].

2.6 Anti-androgen therapies

Gynecomastia can be an embarrassing side effect for men receiving androgen deprivation therapy as seen in multiple prospective and cross-sectional studies [34-36]. Treatment with estrogen has the highest incidence of gynecomastia, at 40 – 80%, anti-androgens, including flutamide, bicalutamide and nilutamide, are next, with a 40 – 70% incidence, followed by GnRH analogs (goserelin, leuprorelin) and combined androgen deprivation, both with incidences of 13% each [37]. Gynecomastia usually starts within the first year of hormonal treatment and is initially reversible. It occurs secondary to the increase in estrogen-to-androgen ratio or blockade of the androgen receptor [35].

Anti-androgens block the binding of DHT to its cytosol receptors and subsequent translocation of the receptor into the nucleus. Bicalcutamide, a non-steroidal anti-androgen was shown to block central androgen receptors as well which results in an impaired negative feedback at the hypothalamic–pituitary level. This induces a rise in LH and testosterone and peripheral aromatization which leads to significant rise in estradiol levels [38].

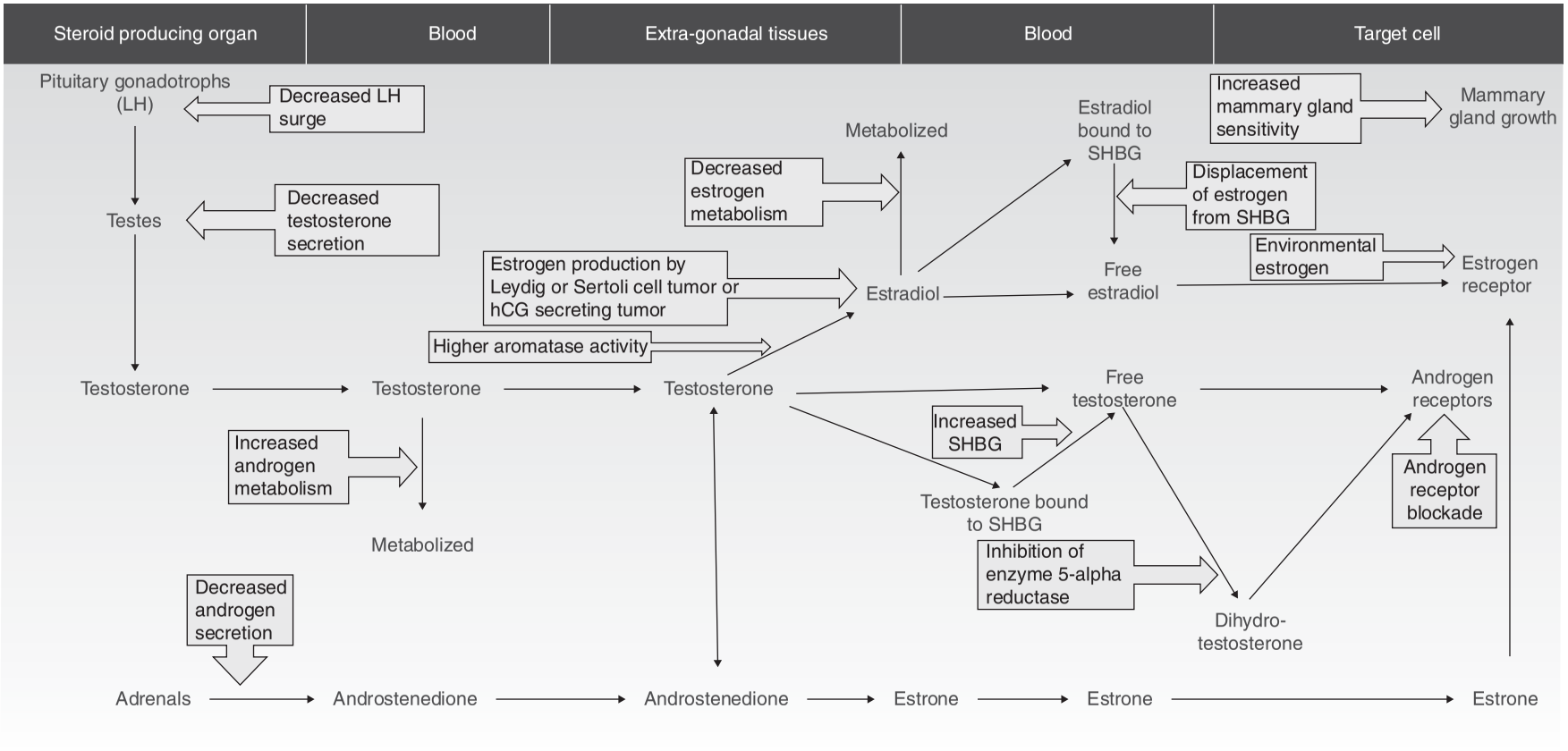

Figure 1. Pathophysiologic mechanisms of gynecomastia (pituitary LH stimulates testosterone secretion by the testes which binds to SHBG and a small amount circulates as the bioavailable fraction the free and albumin-bound components). This bioavailable testosterone then is converted to estradiol by aromatase enzyme in the extragonadal tissues. This enzyme complex also converts androstenedione of adrenal origin to estrone, which may be further converted to the more potent form of estrogen, estradiol through the activity of enzyme 17β-hydroxysteroid dehydrogenase. Some of the testosterone also is converted to the more potent metabolite dihydrotestosterone (DHT) through the action of 5α-reductase. The bioavailable testosterone, DHT, estradiol and estrone all enter target tissues and bind to their respective receptors. The pathways of estrogen and androgen production and action can be altered at multiple levels, resulting in gynecomastia from an enhanced estrogen effect or a diminished androgen effect at the target–tissue level.

Table 2. Classification of quality of evidence for strength of drug associations with gynecomastia.

Level of evidence	Quality of evidence
Good	Systematic review of randomized controlled trials, or Randomized placebo-controlled trial, or Prospective cohort studies with or without concurrent controls plus good pathophysiological explanation
Fair	Retrospective studies, or Case–control studies, or Case series with good pathophysiological explanation
Poor	Isolated case reports

2.7 5α-Reductase inhibitors

In an observational cohort study of 14,772 men on finasteride, gynecomastia or mastalgia occurred in 0.4%. The rate of gynecomastia was 0.26 per 1000 patient-months of finasteride therapy and it resolved on drug withdrawal in about half the men [39]. In a report submitted to the Food and Drug Administration (FDA), the range of onset of gynecomastia was 14 days to 2.5 years (median, 180 days) after the initiation of finasteride therapy [40]. Although most cases have been described with a regimen of 5 mg/day of oral finasteride, Ferrando *et al.* reported four patients who developed gynecomastia with 1 mg/day dose [41]. The rate of gynecomastia was 4.5% with finasteride as compared with 2.8% with placebo in a prostate cancer prevention trial involving 18,882 men [42]. In a 2-year open-label extension of three randomized controlled studies involving 4325 patients taking 0.5 mg dutasteride, the incidence of gynecomastia was low and relatively constant throughout the 4-year period (1.3% in year 1, 1.3% in year 2, 1.8% in year 3 and 0.7% in year 4) [43].

Finasteride and dutasteride inhibit 5α-reductase, which chemically reduces testosterone to DHT. As the conversion to DHT decreases, the metabolism of testosterone to estradiol and androstenediol increases via the liver, testes and peripheral blood (**Table 3**).

3. Drugs with fair quality of evidence for association with gynecomastia

3.1 Risperidone

In a retrospective pharmacovigilance study involving the FDA's Adverse Event Reporting System database, a total of 796 cases of hyperprolactinemia and 186 gynecomastia cases were reported to be associated with anti-psychotics. Of these adverse event reports, the majority (702 cases of hyperprolactinemia and 118 gynecomastia cases) were attributed to risperidone. Only risperidone had significantly higher adjusted reporting ratios for both hyperprolactinemia and gynecomastia [44].

All traditional first-generation anti-psychotics are known to cause mild to moderate hyperprolactinemia due to their dopamine D2 receptor blockade. Hyperprolactinemia frequently occurs with risperidone but is rare with other atypical anti-psychotics such as aripiprazole, clozapine, olanzapine, quetiapine, ziprasidone [45]. Serum prolactin levels are generally greater than 100 ng/ml in patients with prolactin-associated hypogonadism [46]. These levels are higher than most patients with drug-induced gynecomastia, which rarely exceed 100 ng/ml, the exceptions being with risperidone [47]. Although prolactin elevation can cause fullness in the breasts and mild galactorrhea in patients whose breasts have been stimulated by estrogens and progesterone, it does not lead to true gynecomastia directly [48]. However, hyperprolactinemia may reduce gonadotropin stimulation of the testes leading to a reduction in testosterone levels [49].

3.2 Calcium channel blockers (verapamil and nifedipine)

Various calcium channel blockers (CCB) have been implicated in gynecomastia. Thirty cases of CCB-associated gynecomastia were reported to the FDA [50], with 18 cases involving verapamil and 11 nifedipine. Resolution of symptoms occurred in those in whom discontinuation was attempted, although in two cases gynecomastia persisted despite stopping therapy. One patient experienced recurrence of symptoms on being re-challenged with nifedipine. Subsequently, the Australian Adverse Drug Reactions Advisory Committee also received reports of 12 cases (7 with verapamil and 1 with nifedipine) of gynecomastia associated with CCB [51]. Latency of onset ranged from 1 to 18 months. Although in most cases, other drugs were being taken as well, CCB were strongly implicated as the cause of the adverse reaction.

Verapamil may increase serum prolactin and suppress GnRH leading to decreased testosterone levels [52]. Another mechanism might be an increase in serum estradiol concentration by inhibition of cytochrome P450 3A activity. Satoh *et al*. demonstrated inhibition of 3- and 7-glucuronidation, 2-hydroxylation and 17-oxidation of estradiol with various CCB including verapamil and nifedipine [53-55].

3.3 Omeprazole

Although the risk of gynecomastia in the UK general practice analysis was not significantly increased with the use of omeprazole (RR 0.6; 95% CI 0.1 – 3.3) [56], 24 cases of gynecomastia associated with proton pump inhibitors (PPI) were identified in the Spanish pharmacovigilance database [57]. Omeprazole was used in 20 of the 24 reported cases, whereas lansoprazole and rabeprazole were used in 3 and 1 cases, respectively. The median time to onset was 91 days, ranging from 8 days to 4.8 years. Fourteen patients were also receiving other drugs at the time of adverse effect. In 11 of 15 cases, gynecomastia improved after PPI withdrawal. Whereas in five of six patients in whom the medication was not withdrawn, the condition continued [57]. Earlier, the World Health Organization's (WHO) international drug monitoring center reported 13 cases of gynecomastia with omeprazole

Table 3. Drugs with good quality of evidence for association with gynecomastia.

Name of medications	Range of onset	Dose related	De-challenge	Re-challenge	Prolactin levels	Sex hormones	Proposed pathophysiology
Spironolactone [9-11]	Variable	Yes	Yes	Yes	Normal	Low T, LH high E	Androgen receptor antagonist, increase androgen clearance, decrease testosterone production, displace estrogen from SHBG and increase testosterone to estrogen conversion
Cimetidine [13-15]	4 – 12 months	Yes	Yes	Yes	Normal	Mixed results, low T, high E	Androgen receptor antagonist, decreased testosterone biosynthesis and decreased estrogen metabolism
Ketoconazole [19,20]	1 – 32 months	Yes	Yes	Yes	Normal	Low T	Suppression of testicular testosterone synthesis, displacement of estrogens from SHBG
hGH [25-27]	1 week to 6 months	Unknown	Yes	No	Normal	Normal	Induce mammary gland hyperplasia, and redistribution of fat
Estrogens [34-37]	Variable	Possible	Yes	Yes	Normal	Low T, high E	Stimulate mammary gland growth
hCG [31,32]	Variable	Possible	Mixed response	No	Normal	High T, high E	Increased aromatase activity
Anti-androgens (flutamide, bicalcutamide, cyproterone acetate) [34-37]	3 – 5 months	Possible	Yes	Yes	Normal	High T, LH, high E	Androgen receptor blockers
GnRH analogs (goserelin, leuprorelin) [34-37]	Variable	Possible	Yes	Yes	Normal	Low T	Decrease testosterone production
5α-Reductase inhibitors (finasteride, dutasteride) [39-43]	2 weeks to 2.5 years	Possible	Yes	Yes	Normal	High E	Decrease conversion of testosterone to DHT leading to increased metabolism of testosterone to estradiol

DHT: Dihydrotestosterone; E: Estrogen; FSH: Follicle-stimulating hormone; hGH: Human growth hormone; LH: Luteinizing hormone; SHBG: Sex hormone-binding globulin; T: Testosterone.

therapy. The dose of omeprazole used was 20 mg daily for most patients. The mean time to onset was 2.9 months [58]. Santucci *et al.* re-challenged their patient who had earlier developed gynecomastia with 20 mg/day of omeprazole and had a successful resolution within 4 weeks of drug withdrawal. Six weeks after re-introducing the drug, the patient developed a second episode of painful gynecomastia [59].

Omeprazole at high concentrations has some properties of inhibiting the estradiol catalytic enzyme, cytochrome P450 in the liver [53]. This can lead to inhibition of estradiol metabolism possibly causing elevated estrogen/androgen ratio leading to breast tissue growth.

3.4 HIV drugs

Growing numbers of gynecomastia cases have been reported in AIDS patients who are taking anti-retroviral therapy. Such patients can also develop gynecomastia secondary to an underlying primary hypogonadism, increased aromatization of exogenous testosterone given to treat it and pseudogynecomastia from the fat redistribution syndrome. A longitudinal study found that the incidence of gynecomastia in HIV-infected male patients treated with highly active anti-retroviral therapy was 0.8/100 patient-years, with a prevalence of 2.8% in those treated for at least 2 years [60]. Gynecomastia was reported in five male patients who were receiving protease inhibitors associated with nucleoside reverse transcriptase inhibitors (NRTI, stavudine in four cases and zidovudine plus lamivudine in one case). Gynecomastia persisted in most cases despite change in anti-retroviral drugs [61]. Donovan *et al.* reported four cases of gynecomastia associated temporally with initiation of saquinavir treatment with subsequent resolution in those who stopped taking the drug. However, one of the patients was concomitantly taking ketoconazole and the other one was on risperidone and pimozide [62]. In a retrospective case–control study, efavirenz-containing regimen was strongly associated with the development of gynecomastia (odds ratio (OR) 20; $p < 0.001$) [63]. In a cross-sectional survey of 669 males treated with anti-retroviral therapy for at least 12 months, ultrasound-proven gynecomastia developed in 15 cases. A concurrent lipodystrophy was present in all cases. Efavirenz-based treatment apparently prompted gynecomastia in four patients, and worsened this sign in other four patients. Despite the therapeutic changes, no significant amelioration of gynecomastia was observed on follow-up [64]. Caso *et al.* reported three cases of pathologically confirmed gynecomastia without lipodystrophy syndrome in HIV-infected male patients treated with efavirenz. The drug was not withdrawn and gynecomastia persisted [65]. Qazi *et al.* noted in their series of 15 patients, that true gynecomastia could occur with the use of all currently available classes of anti-retroviral medications [66].

A direct mammotrophic effect of anti-retroviral drugs mimicking the action of estrogen on breast tissue has been proposed [67]. Cytokine perturbations occurring with immune restoration resulting in altered breast tissue estrogen availability has also been suggested to cause gynecomastia [66]. Anti-retroviral therapy can cause an improvement in the T-helper cell cytokine response [68], specifically an increased production of IL-2 which has been shown to increase the proliferation of human breast carcinoma cells *in vitro* [69]. In addition, IL-6 has been shown to increase aromatase activity in breast tissue, with a consequent increase in estrogen available to stimulate breast growth [70].

3.5 Alkylating agents

Gynecomastia is known to occur in patients with testicular cancer producing large amounts of hCG. This could be likely due to stimulatory effects of hCG on testicular estradiol secretion [71]. However, gynecomastia has also been described secondary to chemotherapy for testicular cancer [72-74] and malignancies including multiple myeloma [75,76], Hodgkin's [75,77] and non-Hodgkin's lymphomas [78]. Sixteen patients in complete remission after chemotherapy or radiotherapy for testicular cancer were reported to develop gynecomastia which appeared 2 – 9 months after the end of therapy and had a mean duration of 4.8 months [79]. These patients had statistically significant higher levels of estradiol, FSH and estrogen/testosterone ratio than the control group without gynecomastia that had received similar treatment. Both groups had low normal testosterone and normal levels of hCG, prolactin and progesterone. Sherins *et al.* reported moderate to severe gynecomastia in 9 of 13 pubertal boys who had been treated for Hodgkin's disease with mechlorethamine, vincristine, procarbazine and prednisone and survived at least 2 years. These boys had a 10-fold increase in mean serum FSH, a threefold increase in mean LH and reduced serum testosterone levels. However, gynecomastia was not associated with an increase in estradiol levels [77]. Among the commonly used anti-neoplastic agents, alkylating agents have been most commonly associated with primary testicular failure [80].

3.6 Anabolic steroids

Among a survey conducted in British gymnasia among 100 steroid abusers, subjective gynecomastia was reported in 34% [81]. The reported prevalence of gynecomastia in another such survey was 52%. Most commonly taken anabolic steroids were testosterone, nandrolone decanoate and methandrostenolone [82]. In another retrospective study involving 160 athletes, anabolic-androgenic steroids (AAS) users displayed more frequent gynecomastia (25 of 88) as compared with non-users (2 of 68) [83]. High doses of AAS suppress the hypothalamic–pituitary–gonadal (HPG) axis due to negative feedback which may take weeks or months and sometimes even longer to recover. Androstenedione, a major AAS used in the USA before being withdrawn from the market increased estradiol concentration in studies conducted in healthy men [84,85]. In a study on the effects of nandrolone, decanoate and testosterone in body builders for 6 months,

Table 4. Drugs with fair quality of evidence for association with gynecomastia.

Medications	Range of onset	Dose related	De-challenge	Re-challenge	Prolactin levels	Sex hormones	Proposed pathophysiology
Risperidone [44]	3 months to 3 years	Possible	Yes	Yes	10- to 20-fold elevation	Unknown	High prolactin may reduce gonadotropin stimulation of testes leading to a reduction in testosterone levels
Verapamil [50,51]	1 – 18 months	Unknown	Yes	No	Normal	Normal	Decreased estrogen metabolism
Nifedipine [50,51]	6 – 30 months	Unknown	Yes	Yes	Normal	Normal	Decreased estrogen metabolism
Omeprazole [56-59]	2.9 months	Possible	Yes	Yes	Normal	High E	Decreased estrogen metabolism
HIV medications (efavirenz) [60,63-66]	Variable	Unknown	Mixed response	No	Normal	T low or normal	Immune restoration resulting in altered breast tissue estrogen availability
Alkylating agents [77,80]	2 – 9 months	Unknown	Yes	Unknown	Normal	Low T, High FSH, LH, E	Decreased testosterone due to gonadotoxicity
Anabolic steroids [81-83]	1 month to 5 years	Possible	Yes	Unknown	Normal	Low T, High E	Decreased testosterone from suppression of HPG axis, and increased aromatization of some to estrogens
Alcohol [88]	10 days to years	Possible	Yes	No	Normal	Low T, High E	Reduced testosterone production, increased SHBG and increased estradiol levels
Opioids (heroin, methadone) [93,94]	Variable	Possible	Unknown	Unknown	Normal	Low LH, FSH, T	Decreased testosterone by suppression of HPG axis and direct reduction at the testicular level

E: Estrogen; FSH: Follicle-stimulating hormone; HPG: Hypothalamic–pituitary–gonadal; LH: Luteinizing hormone; SHBG: Sex hormone-binding globulin; T: Testosterone.

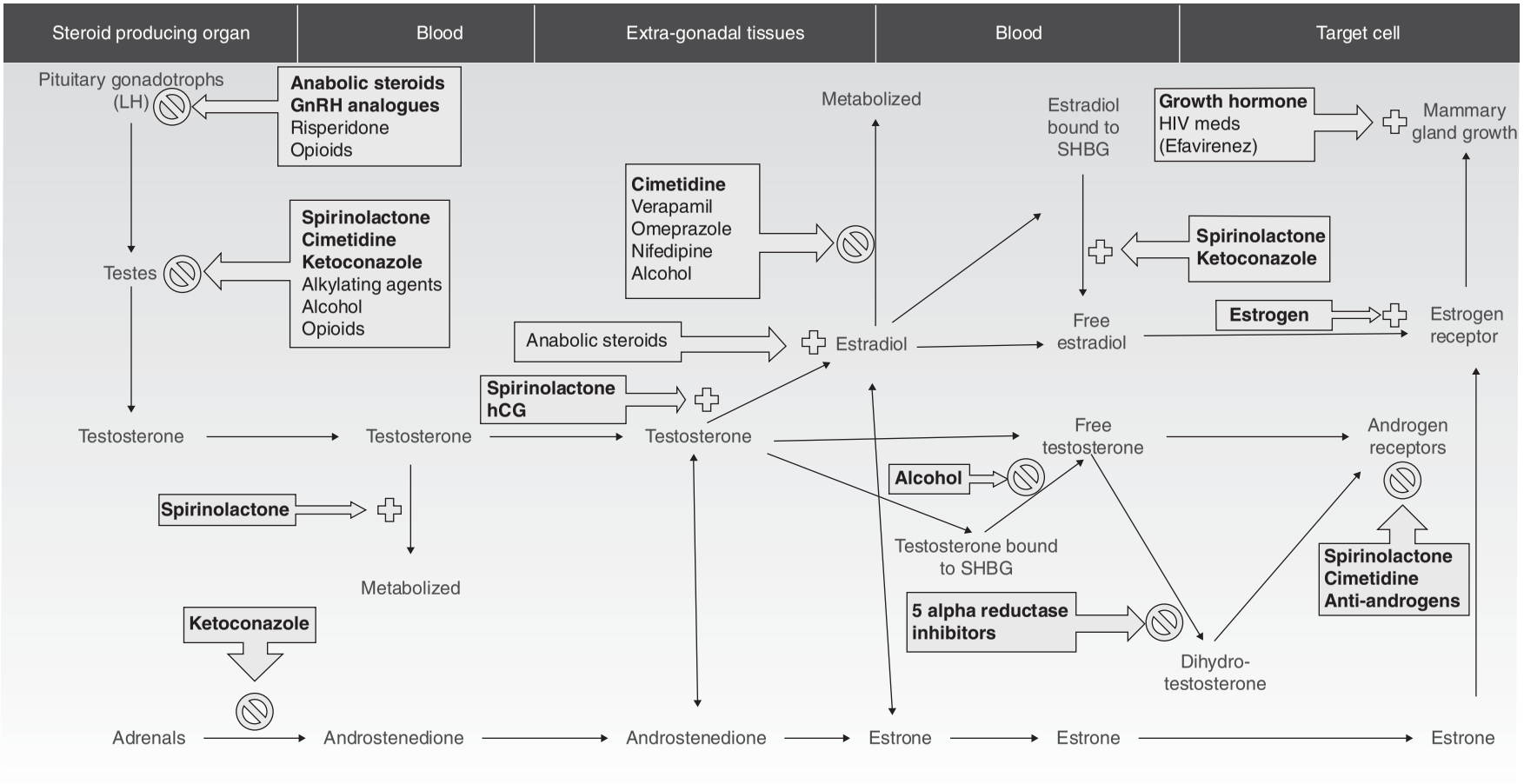

Figure 2. Evidence-based pathophysiologic mechanisms of drug-induced gynecomastia.

53, 77 and 87% reduction in serum testosterone, LH and FSH values, respectively were recorded. In addition, 45% of the subjects showed increase in serum estradiol, although not statistically significant as compared with the control estradiol levels [86]. Gynecomastia due to the use of aromatizable androgens can be easily explained by increased peripheral conversion of androgen to estrogens.

3.7 Alcohol

Alcoholic men may have symptoms of decreased sexual function. The presence of atrophic testes and gynecomastia usually implies chronic alcohol abuse. Both chronic and short-term intake of alcohol can cause direct testicular damage and impair function of the HPG axis, resulting in reduced testosterone production. The alcohol-induced increase in SHBG further leads to low free testosterone levels. Some men with alcoholic cirrhosis also have augmentation of serum estradiol levels. Together these changes lead to increased estrogen-to-testosterone ratio causing gynecomastia which may be reversible following alcohol withdrawal [87-89]. There are also reports in literature about the isolation and identification of variety of phytoestrogens in alcoholic beverages which may contribute to gynecomastia [90].

3.8 Opioids

Heroin and high-dose methadone (80 – 150 mg/day) use is associated with low plasma testosterone levels [91,92]. Gynecomastia was noted in a methadone clinic in Virginia among 8 of 12 men on methadone maintenance program for 4 – 11 years [93]. de la Rosa and Hennessey reported gynecomastia in a 47-year-old man with a history of heroin use undergoing methadone treatment (130 mg/day). Basal testosterone, LH and FSH were all below normal levels. The patient had a suboptimal increase in LH and FSH after administration of GnRH. The patient's symptoms regressed, and hormone levels improved after reduction in methadone dosage to 40 mg/day [94]. Methadone-induced suppression of testosterone levels is likely mediated by the inhibition of HPG axis as well as the direct reduction at the testicular level [95]. In the face of low testosterone levels, androstenedione from the adrenals is aromatized to estrone which is inter-converted to estradiol (**Table 4**) (**Figure 2**).

4. Drugs with poor quality of evidence for association with gynecomastia

Gynecomastia has also been associated with the use of numerous other medications. However, the quality of evidence is poor, primarily in the form of isolated case reports. Some of the reported patients had underlying medical condition which could explain the onset of gynecomastia, while others were concomitantly taking drugs known to cause gynecomastia. Most of these reports were just based on a temporal relationship with the offending drug. Resolution of gynecomastia after withdrawal of medication was not mentioned in few reports and re-challenge with the same drug was rarely attempted. The hormonal evaluation including the sex hormones and prolactin was also not determined in a number of these cases. Hence, their association with gynecomastia remains unproven. These drugs have been summarized in **Table 5**.

5. Expert opinion

Gynecomastia is a relatively common presenting complaint at the primary care and endocrine clinics. First and foremost palpable glandular tissue needs to be differentiated from pseudogynecomastia by careful physical examination using pincer movement with thumb and forefinger while the patient lying flat on his back with his hands clasped beneath his head. Once diagnosis of true gynecomastia is established, a thorough history and physical examination should be performed to identify any reversible causes including any drugs or herbal products. Most of the drug–gynecomastia associations reported in the literature are based on poor quality of evidence. The drugs definitely associated with the onset of gynecomastia are spironolactone, cimetidine, ketoconazole, hGH, estrogens, hCG, anti-androgens, GnRH analogs and 5-α reductase inhibitors. Medications probably associated with gynecomastia include risperidone, verapamil, nifedipine, omeprazole, alkylating agents, HIV medications (efavirenz), anabolic steroids, alcohol and opioids. Drug holiday should be considered whenever possible if the patient is found to be taking any of above-mentioned drugs.

In adults with symptomatic gynecomastia with no apparent cause, laboratory investigations should involve liver, renal and thyroid function tests and a limited hormonal work-up including testosterone, LH, hCG and estradiol levels as the yield of work-up is usually low. Breast imaging may be considered when signs and symptoms suggest breast cancer or presence of BRCA-2 mutation is suspected from the family history.

In adults with painful gynecomastia, a trial of the estrogen receptor blocker tamoxifen can be attempted at doses of 20 mg/day orally for up to 3 months. In patients who are likely to respond to tamoxifen, improvement is usually seen within a month. The overall response rate to tamoxifen has varied from 50 to 80% in the published literature. There are insufficient data at this time to recommend the use of raloxifene although it did show some encouraging results in small studies. The experience with aromatase inhibitors has been largely disappointing so far. It is important to note that none of the selective estrogen receptor modulators are approved by the FDA for the prevention or treatment of gynecomastia. Further studies with a better study design and adequate sample size are needed to conclusively establish the role of tamoxifen and raloxifen in the management of symptomatic gynecomastia. Having a placebo-treated control arm with adequate follow-up is essential in such trials to evaluate true efficacy of the medication studied as spontaneous regression of breast tissue is quite common.

Table 5. Drugs with poor quality of evidence for association with gynecomastia.

Class	Medications	Range of onset	Dose related	De-challenge	Re-challenge	Prolactin levels	Sex hormones	No. of cases reported
Anti-psychotics	First-generation neuroleptics (thioridazine, trifluperazine, prochlorperazine, perphenazine and sulpiride) [96-99]	3 – 5 months	Unknown	Yes	No	Mixed results, unknown in a number of reports	Mixed results, unknown in a number of reports	Few
	Atypical anti-psychotics (aripiprazole, clozapine, olanzapine, quetiapine, ziprasidone and haloperidol) [99,100]	Variable	Possible	Unknown	Unknown	Mild elevation	Unknown	Few
Anti-depressants	SSRI/SNRI (fluoxetine/paroxetine/ venlafaxine/duloxetine) [101-105]	3 months to 5 years	Unknown	Yes	No	Normal or mildly high	Normal or mild high E	Few
Benzodiazepines	Diazepam [106,107]	10 months	Possible	Yes	No	Unknown	Unknown	1
Anti-convulsants	Phenytoin [108,109]	2 – 10 years	Possible	2 of 6	No	Mild increase in 1 case	Normal	6
	Pregabalin [110]	4 – 10 weeks	Possible	Yes	No	Normal	Normal	2
	Gabapentin [111]	4 weeks	Unknown	No	No	Normal	Low T, LH, FSH	1
CCB	Diltiazem [50,51]	9 – 36 months	Unknown	Yes	No	Normal	Normal	Few
	Felodipine [50,51]	6 – 11 months	Unknown	Yes	No	Normal	Normal	Few
	Amlodipine [112,113]	3 – 6 months	Unknown	Yes	No	Normal	Normal	2
ACE inhibitors	Captopril, enalapril [114,115]	4 months	Unknown	Yes	No	Normal	Normal	2
Anti-arrhythmics	Amiodarone [116]	2 months	Unknown	Yes	Yes	Normal	Normal	1
	Digitalis [117-121]	Variable	Unknown	Yes	Yes	Normal	Low T, high E	Few
Anti-lipidemics	Statins [122-124]	2 – 6 months	Unknown	Yes	No	Normal	Normal	Few
	Fibrates [125]	1 year	Unknown	Yes	Yes	Normal	Normal	1
Anti-acids	Lansoprazole, rabeprazole [57]	1 month	Unknown	Yes	No	Unknown	Unknown	Few
	Rantidine [126]	8 days	Possible	Yes	Yes	Normal	Normal	1
Prokinetics	Metoclopramide [127]	3 weeks to 4 years	Unknown	Yes	No	Mildly elevated	Unknown	2
	Domperidone [128-130]	5 days to 9 months	Possible	Yes	No	Mildly elevated	Normal	3
Anti-TB	Isoniazid [131-134]	3 – 5 months	Unknown	Yes	Yes	Normal	Normal	Few
Antibiotics	Minocycline [135]	Unknown	Unknown	Yes	No	Normal	Normal	1
	Metronidazole [136]	1 month	Possible	Yes	Yes	Normal	Normal	1
HIV medications	NRTI (stavudine) [60,61,66]	2 months to 2 years	Unknown	Mixed response	No	Normal	T low or normal	Multiple
	Protease inhibitors (indinavir, saquinavir) [60,62,66]	Variable	Unknown	Mixed response	No	Normal	T low or normal	Multiple

ACE: Angiotensin-converting enzyme; CCB: Calcium channel blocker; E: Estrogen; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; NRTI: Nucleoside reverse transcriptase inhibitor; TB: Tuberculosis; SNRI: Serotonin/norepinephrine reuptake inhibitor; SSRI: Selective serotonin reuptake inhibitor; T: Testosterone.

Table 5. Drugs with poor quality of evidence for association with gynecomastia (continued).

Class	Medications	Range of onset	Dose related	De-challenge	Re-challenge	Prolactin levels	Sex hormones	No. of cases reported
Rheumatologic drugs	Methotrexate [136-141]	4 months to 2 years	Possible	Yes	Yes	Normal	Low T in 1 patient, elevated LH and FSH in 1 patient	Few
Chemotherapy agents	Thalidomide [142]	2 weeks	Unknown	No	No	Normal	Normal	3
	Cyclosporine [143]	6 – 10 months	Unknown	Yes	No	Elevated in 1 patient	Elevated LH and low T in 1 patient	2
Drugs of abuse	Marijuana [144-147]	Variable	Possible	No	No	Mixed results	Mixed results	Few
	Amphetamines [148]	2 – 8 months	Unknown	Yes	Yes	Not done	Not done	5
Miscellaneous	Theophylline [149]	Unknown	Unknown	Yes	No	Normal	Normal	1
	Clonidine [150]	4 weeks	Possible	Yes	No	Mildly elevated	Unknown	1
	Penicillamine [151]	7 months	Unknown	Yes	No	Normal	Normal	1
	Vitamin E [152]	Unknown	Possible	Yes	Yes	Unknown	Unknown	2
	Melatonin [153]	1.5 years	Unknown	Yes	No	Normal	Low T	1
	Diethylpropion [154]	1 – 3 months	Unknown	Yes	No	Not done	High LH, E	2
Plant products	Tribulus terrestris [155]	3 months	Unknown	Yes	No	Normal	Low T, FSH, LH	1
	Nettle (Urtica dioica) [156]	1 month	Possible	Yes	No	Normal	Normal	1
	Lavender and tree oil [157]	Variable	Possible	Yes	No	Normal	Normal	3
	Soy products [158]	Unknown	Possible	Yes	No	Normal	High E	1

ACE: Angiotensin-converting enzyme; CCB: Calcium channel blocker; E: Estrogen; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; NRTI: Nucleoside reverse transcriptase inhibitor; TB: Tuberculosis; SNRI: Serotonin/norepinephrine reuptake inhibitor; SSRI: Selective serotonin reuptake inhibitor; T: Testosterone.

In case of long-standing gynecomastia of more than 1 year in duration, medical therapy is usually futile, and surgical removal of breast glandular tissue can be offered to those who are symptomatic or bothered by their appearance.

Declaration of interest

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