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DRUG-INDUCED GYNECOMASTIA: AN OVERVIEW

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ABSTRACT

Gynecomastia is a benign growth of tissue in the male breast. This is caused by an imbalance of the Estrogen, and Androgen hormones in the breast tissue. Drugs are responsible for approximately 20% of gynecomastia instances in men. The most frequently implicated drug classes were antiretrovirals (23.5%), diuretics (15.5%), proton pump inhibitors (11.9%), HMG-CoA reductase inhibitors (9.1%), neuroleptics and related drugs (6.5%), calcium channel blockers (6.3%), and 5-alpha reductase inhibitors (4%). A drug, Selective Estrogen Receptor Modulator, and Aromatase Inhibitor can be used to treat gynecomastia. Asymptomatic gynecomastia is a relatively common finding on physical examination, and careful history-taking and physical examination are usually sufficient to identify pubertal gynecomastia, drug-induced causes, or an underlying pathologic process. Correct diagnosis and treatment can be helpful in avoiding emotional distress and physical discomfort related to gynecomastia in young adults.

KEYWORDS: Gynecomastia, Breast enlargement, Estrogen, Androgen.

1. INTRODUCTION

Gynecomastia is defined histologically as a benign proliferation of the glandular tissue of the male breast and clinically by the presence of a rubbery or firm mass extending concentrically from the nipple.[1] Gynecomastia can usually be detected when the size of the glandular tissue exceeds 0.5 cm in diameter. True gynecomastia is mainly characterized by ductal epithelial hyperplasia and an increase in stromal and periductal connective tissues. Generally, it is asymptomatic, not noted by the patients, and the prevalence increases with aging and obesity. Gynecomastia is the most prevalent breast change in men. Pubertal gynecomastia affects up

to 70% of all males. It is self-limiting in up to two-thirds of cases, but it can be treated to reduce the emotional and physical discomfort.[2-4] Gynecomastia, which can be physiological, arises when the estrogen-to-testosterone ratio in males is altered, resulting in glandular breast tissue development.[5] Drugs are thought to be responsible for 10 to 25% of all cases of gynecomastia observed in referral medical facilities. However, these reports have a number of flaws, including poor evidence quality.[6] The implication is that these medications were responsible for its appearance or progression, which was induced by a change in the sex hormone status. Because palpable breast tissue (PBT) is so common, usually bilateral, and almost always asymptomatic, the administration of a drug and the concurrent detection of gynecomastia may be purely coincidental; alternatively, if pain/tenderness (mastodynia) is present, the breast enlargement represents an independent (unique) syndrome, the etiology of which may or may not be related to a specific drug. This is especially true if the action is unilateral.[7] In evaluating a candidate for breast augmentation, a comprehensive physical examination, and medical history are essential tools. Gynecomastia is frequently self-resolving.

Table 1: Drugs causing gynecomastia with known mechanism.[8]

Drugs	Mechanism
Cimetidine	Androgen receptor antagonism
Cytotoxic agents (alkylating agents, vincristine, nitrosoureas, methotrexate)	Primary hypogonadism due to Leydig cell damage
Flutamide	Androgen receptor antagonism
Hormones • Androgens • Estrogens • Human chorionic gonadotropin	Aromatization to estrogens Direct stimulation of the breast Stimulation of testicular Leydig cell estrogen secretion.
Ketoconazole, metronidazole	Inhibition of testosterone synthesis
Marijuana	Androgen receptor antagonism
Phenothiazines	Elevated serum prolactin
Spironolactone	Androgen receptor antagonism; at high doses, interference with testosterone biosynthesis.

2. Drugs causing gynaecomastia with unknown mechanism[8]

1. Amiodarone
2. Calcium channel blockers (Diltiazem, Verapamil, Nifedipine)
3. Central nervous system(Amphetamine, Diltiazem, Verapamil, Nefidipine)
4. Isoniazed
5. D-penicillamine

6. Theophylline

Table 2: Strength of evidence for drugs associated with gynecomastia.[9]

Strength of evidence	Quality of evidence
Good	A systematic review of randomized controlled trials, or Randomized placebo-controlled trials, or Prospective cohort studies with or without concurrent controls plus a good pathophysiological explanation
Fair	Retrospective studies, or Case-control studies, or Case series with good pathophysiological explanation

Drugs with good quality of evidence for association with gynecomastia

1. **Spironolactone:** 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.[10]

2. **Cimetidine:** Cimetidine blocks the androgen receptors in the breast leading to decreased androgen action causing the growth of breast tissue because of 'unopposed' estrogen action. Another possible mechanism includes decreased 2-hydroxylation of estrogen leading to elevated serum estrogen levels.[11]

3. **Ketoconazole:** Ketoconazole, in conventional doses transiently blocks testosterone synthesis and adrenal response to corticotrophin when studied in healthy volunteers. Higher therapeutic dose of 800-1200 mg/day causes a marked and much more prolonged blockade which is still transient.[12] Ketoconazole also selectively displaces 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.[13]

4. **Growth hormone:** 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.[14]

5. **Gonadotropins:** hCG or LH stimulation of the Leydig cells increases the aromatase activity, thus leading to a higher conversion of testosterone to estrogen.[15]

6. **Anti-androgen therapies:** 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 analogues (goserelin, leuprorelin) and combined androgen deprivation, both with incidences of 13% each.[16]

7. **5α-Reductase inhibitors:** 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.[10]

Drugs with fair quality of evidence for association with gynecomastia

1. **Risperidone:** All traditional first-generation antipsychotics 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 antipsychotics such as aripiprazole, clozapine, olanzapine, quetiapine, and ziprasidone.[17]

2. **Calcium channel blockers (Verapamil and nifedipine):** 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 CCBs including verapamil and nifedipine.[18-19]

3. **Omeprazole:** Omeprazole at high concentrations has some properties of inhibiting the estradiol catalytic enzyme, cytochrome P450 in the liver. This can lead to inhibition of estradiol metabolism possibly causing elevated estrogen/androgen ratio leading to breast tissue growth.[20]

4. **HIV drugs:** A direct mammographic effect of anti-retroviral drugs mimicking the action of estrogen on breast tissue has been proposed. Cytokine perturbations occurring with immune restoration resulting in altered breast tissue estrogen availability have also been suggested to cause gynecomastia.[21]

5. **Alkylating agents:** gynecomastia has also been described secondary to chemotherapy for testicular cancer and malignancies including multiple myeloma, Hodgkin's and non-Hodgkin's lymphomas.[22]

6. **Anabolic steroids:** anabolic-androgenic steroids (AAS) users displayed more frequent gynecomastia (25 out of 88) as compared with non-users (2 of 68). 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.[23]

Assessment and Treatment of gynecomastia

A history and physical examination may reveal a likely drug cause of gynecomastia. Further workup may be required to identify nondrug causes as described in a recent review.

1. Discontinuation of the offending drug
2. Weight loss in the over-weight male with pseudo gynecomastia
3. Testosterone treatment for primary hypogonadism
4. Selective estrogen-receptor modulator tamoxifen Aromatase inhibitor anastrozole
5. Surgical subcutaneous mastectomy, ultrasound-assisted liposuction and suction-assisted lipectomy for cosmetic improvement for Tanner stage III and above and if gynecomastia is present for > 1 year.[24]

The physician should first stop any offending drug-causing gynecomastia. Assuming the offending medication cannot be discontinued, there are several treatment options available. If a specific cause of gynecomastia can be identified and treated during the painful proliferative phase, regression of breast enlargement may occur. This regression most often occurs with discontinuation of an offending drug or after initiation of testosterone treatment for primary hypogonadism. If the gynecomastia is drug-induced, decreased tenderness and softening of the glandular tissue will usually be apparent in 1 month after discontinuation of the drug. However, if the gynecomastia has been present for > 1 year, it is unlikely to regress substantially, either spontaneously or with medical therapy, because fibrotic tissue is usually present. In such circumstances, surgical subcutaneous mastectomy, ultrasound-assisted liposuction and suction-assisted lipectomy are the best options for cosmetic improvement.[25-26] Although not approved for the treatment of gynecomastia, the selective estrogen-receptor modulator tamoxifen, administered orally at a dose of 20 mg daily for up to 3 months, has been shown to be effective in randomized and nonrandomized trials, resulting in partial regression of gynecomastia in ~ 80% of patients and complete regression in about 60%.[27-29] In patients in whom tamoxifen is effective, one usually experiences a decrease in pain and tenderness in 1 month. In a retrospective analysis of a series of patients with idiopathic gynecomastia, 78% of patients treated with tamoxifen had complete resolution of

gynecomastia, as compared with only 40% of patients receiving danazol.[30] It has also been suggested that therapy with tamoxifen may prevent the development of gynecomastia in men receiving monotherapy with high doses of bicalutamide for prostate cancer. In a randomized, double-blind, controlled trial pof patients who received tamoxifen at a dose of 20 mg daily, but it occurred in 51% of those who received anastrozole at a dose of 1 mg daily and in 73% of those who received placebo, over a period of 48 weeks.[31-32]

DISCUSSION

Gynecomastia is the most common breast alteration in males occurring more frequently during infancy, puberty, and old age. Prevalence rates, as suggested by Johnson et al., are 60–90 % in newborns, 50–60 % in adolescents, and 70 % in men between 50 and 69 years.[6] The most frequently implicated drug classes were antiretrovirals (23.5%), diuretics (15.5%), proton pump inhibitors (11.9%), HMG-CoA reductase inhibitors (9.1%), neuroleptics and related drugs (6.5%), calcium channel blockers (6.3%), and 5-alpha reductase inhibitors (4%).[33] Nuttall examined 306 Air Force personnel and showed that 36% suffered from gynecomastia. Its overall prevalence is about 32% in hospital patients.[3] It can be as high as 64% in adolescent boys and 40% in autopsy studies.[34] Niewoehner et al. reported a prevalence of 80% in males with a BMI of 25kg/m2 or greater.[35] It is probable that many of these statistics will have included cases of pseudo-gynaecomastia. Many males may notice breast enlargement but do not report it. Asymptomatic gynecomastia is a relatively common finding on physical examination, and careful history-taking and physical examination are usually sufficient to identify pubertal gynecomastia, drug-induced causes, or an underlying pathologic process.[24]

In most situations, patients perceive it as a problem, often associated with tenderness and/or a cosmetic concern affecting self-esteem Therefore, every effort should be made to diagnose and treat gynecomastia.

CONCLUSION

Gynaecomastia is a common, harmless disorder, mostly it is due to an imbalance of Estrogen and Androgen in breast tissue. Hence it is accompanied with major systemic hormonal disorder. It is crucial to diagnose and treat drug-induced gynecomastia that have been documented. Gynecomastia can be treated by substituting a medicine, if it is drug induced. Selective oestrogen receptor modulators (Tamoxifen or Raloxifene) and aromatase inhibitors (Anastrozole and Androgens, etc) can also be used to treat gynecomastia. Correct diagnosis

and treatment can be helpful in avoiding emotional distress and physical discomfort related to gynecomastia in young adults.

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