

Gynaecomastia in Adults Guideline

Introduction

Gynaecomastia is defined as the benign enlargement of male breast tissue, resulting from a proliferation of the glandular component of the breast. Firm subareolar gland and ductal tissue will be palpable on examination, as opposed to breast enlargement caused by excess adipose tissue, which is referred to as pseudogynaecomastia.

Gynaecomastia is common, with an incidence of more than 30%. It can occur at any age and may be physiological or pathological. It results from relative oestrogen excess or relative testosterone deficiency resulting in a high oestrogen-to-testosterone ratio.

Physiological gynaecomastia occurs in the newborn period, during puberty, and with ageing and obesity. Gynaecomastia is more common in men aged over 50, owing to the general decline in testosterone levels and a tendency towards weight gain in later life. In overweight men, breast tissue is stimulated by excess oestrogen resulting from the conversion of testosterone to oestradiol by the enzyme aromatase found in adipose tissue.

Many medicines, environmental exposures, illnesses, and some genetic conditions increase the risk for gynaecomastia.

Pathological gynaecomastia

Any condition or medication associated with low levels of testosterone (whether true reduction or due to high SHBG levels), significant conversion of testosterone to oestrogen, or raised oestrogen levels can result in gynaecomastia.

Symptoms and signs

Being aware of the causes of gynaecomastia will assist with appropriate history-taking and examination. It is important to ascertain the duration and course of symptoms, and note any history of sexual dysfunction as well as medications and any recreational drugs, especially alcohol (as a risk factor for cirrhosis) and anabolic steroids.

Gynaecomastia is often asymptomatic, but can present with tenderness or nipple irritation. Ideally, breast examination should be carried out with the patient at 45 degrees. The breast disc sits behind the areola. It can be palpated using the flat of the fingers.

A general physical examination should also be undertaken to look for signs of hyperthyroidism, chronic liver disease and hypogonadism, and include measurement of BMI. Testicular examination should be done to assess size, because small testicles suggest hypogonadism, and to check for masses or abnormal consistency, suggestive of testicular cancer.

Gynaecomastia is usually bilateral and although about 10% of cases can involve just one breast, always consider the possibility of breast cancer in a unilateral presentation.

If an unusual mass, distorted nipple or areola, skin abnormality or axillary lymphadenopathy is found, the patient should be referred urgently to the breast cancer clinic.

Medicines Associated with Causing Gynaecomastia

Medicines frequently causing gynecomastia	
Antiandrogens	Bicalutamide, flutamide, finasteride, dutasteride
Antihypertensive	Spironolactone
Antiretroviral	Protease inhibitors (saquinavir, indinavir, nelfinavir, ritonavir, lopinavir), reverse transcriptase inhibitors (stavudine, zidovudine, lamivudine)
Environmental exposure	Phenothrin (antiparasitical)
Exogenous hormones	Oestrogens, prednisone (male teenagers)
Gastrointestinal medicines	H2 histamine receptor blockers (cimetidine)
Antipsychotic	Lurasidone, Olanzapine, Ziprasidone, Amisulpride, Paliperidone, Risperidone, Sulpiride, Haloperidol, Chlorpromazine, Zuclopenthixol, Flupenthixol
Medicines possibly causing gynecomastia	
Antifungal	Ketoconazole (prolonged oral use)
Antihypertensive	Calcium channel blockers (amlodipine, diltiazem, felodipine, nifedipine, verapamil)
Antiretroviral	Efavirenz
Chemotherapy medicines	Methotrexate, cyclophosphamide, carmustine, etoposide, cytarabine, melphalan, bleomycin, cisplatin, vincristine, procarbazine
Exogenous hormones	Androgens (athletes abuse)
Gastrointestinal medicines	Proton pump inhibitors (omeprazole)
Cardiovascular medicines	Phytoestrogens (soya-based products, high quantity)
Other	
Recreational Drugs	Marijuana, amphetamines, heroin, methadone

In medicine-induced gynaecomastia, the offending agent should be withdrawn, where possible. Where an underlying disorder has been identified, treating the condition should result in resolution of the gynaecomastia, especially if onset is recent.

Investigations

Further investigation will depend on history and examination findings. Blood tests are not necessary in men on medications associated with gynaecomastia.

If the underlying cause is not obvious, appropriate baseline blood tests would include liver function, thyroid function and renal function. Check prolactin level for men prescribed antipsychotic medication. If these are normal, consider a hormone blood screen, which might include testosterone, luteinising hormone (LH), follicle stimulating hormone (FSH), oestradiol, sex hormone binding globulin (SHBG) (to allow estimation of free testosterone levels), and prolactin if not already performed. **Referral to endocrinology is recommended in the event of any abnormality.**

If the history or examination is suggestive of testicular malignancy, check levels of β human chorionic gonadotrophin (β -hCG), α -fetoprotein, and lactate dehydrogenase. **Referral to urology is recommended if abnormal β -hCG or α -FP blood results or abnormal finding on testicular USS.**

Hormone test result	Possible diagnoses
All normal	Idiopathic gynaecomastia
Low testosterone with elevated LH	Primary hypogonadism; Klinefelter's syndrome
Low testosterone with normal LH	Pituitary/hypothalamic disease
Elevated testosterone with elevated oestradiol	Androgen exposure; testicular tumour
Elevated oestradiol with elevated SHBG	Oestrogen exposure; testicular/adrenal tumour
Elevated DHEA (dehydroepinandrosterone)	Adrenal tumour
Elevated β -hCG	Testicular/ectopic tumour
Elevated prolactin	Pituitary tumour; medicine-related cause

If there is testicular pain or a mass, testicular ultrasound is indicated and chest X-ray should be performed if lung cancer is suspected.

Management

If an unusual mass, distorted nipple or areola, skin abnormality or axillary lymphadenopathy is found, the patient should be referred urgently to the breast cancer clinic.

Men with pathological gynaecomastia should be considered for referral to the appropriate specialist.

The clinical course of gynaecomastia is proliferation of glandular tissue followed by fibrosis (thickening of tissue). If clinically the breast tissue feels fibrotic then treating the cause or stopping the implicated medicine may stop progression but is unlikely to reduce the excess breast tissue. It is not often possible to predict in which patients gynaecomastia will resolve and who will experience progression to the fibrotic stage.

If the underlying cause is still unclear after primary care investigations, the GP may wish to consider referring the patient to the breast clinic. A quarter of cases turn out to be idiopathic.

Elevated prolactin levels in men prescribed antipsychotic treatment should be discussed with the relevant mental health team. Management may include switching to another antipsychotic with a lower potential for prolactin elevation, continuing current treatment with monitoring or adding in adjunctive aripiprazole at a dose of 5-10mg daily. Prolactin levels should be re-checked 2-4 weeks after commencing adjunctive aripiprazole. Female patients with high prolactin levels may experience reduced fertility and other changes to their sexual function. If aripiprazole is started, they should be advised that these changes can reverse very quickly and that they should take necessary precautions with immediate effect to avoid unplanned pregnancy.

Medicine Treatment of Gynaecomastia

In patients with physiological gynaecomastia, reassurance can be given that most cases are transitory, however can take years to resolve.

Medical management is associated with a high success rate and avoids surgical intervention, but once fibrosis occurs it is largely ineffective. Tamoxifen (an oestrogen-receptor antagonist), although widely used for the treatment of gynaecomastia, is not licensed for this indication. However good response rates have been seen and it is therefore recommended by local clinicians.

Tamoxifen 20mg ALTERNATE days for 3 – 9 months is recommended. Treatment should be reviewed after 3 months and continued to 9 months if a response is seen. Treatment should be stopped at 9 months whether a response is seen or not.

Anastrozole 1mg daily for 3 months is recommended where the patient cannot tolerate tamoxifen or as a second line option if no response is seen with tamoxifen. Treatment should be stopped at 3 months whether a response is seen or not.

Ensure adequate calcium intake and vitamin D levels should be maintained above 50nmol/L. Patients can be advised to purchase vitamin D supplements and provided with the [Vitamin D Patient Information Leaflet](#).

Where response has been seen with treatment, a course can be repeated after 6 months. If further courses are requested, consider seeking specialist advice.

It is important to inform patients that tamoxifen and anastrozole are being used 'off-label'. The use of tamoxifen and anastrozole for this indication is classified as Amber 3.

Monitoring of Medicine Treatment

There are no suggested monitoring parameters specific to these medicines for this indication in male patients. The short term nature of usage would suggest that monitoring for any possible effects on bone density would be unnecessary.

When to Refer

Referral for male gynaecomastia falls under the 2 week wait process. Referral to the Breast Clinic for further assessment is indicated in those with:

- a clinical suspicion of malignancy
- no obvious physiological or medicine-related cause
- a unilateral lump
- persistent pain and swelling
- increased risk such as family history; Klinefelter's syndrome; androgen deficiency or oestrogen excess

Endocrinological abnormalities suspected

- Refer to the Nottingham Endocrine Service at Nottingham Treatment Centre.

Abnormal β -hCG or α -FP blood results or abnormal finding on testicular USS

- Refer to Urology

Surgery

As part of the Service Restriction Policy 2018, Gynaecomastia surgery is no longer commissioned in any circumstance. Clinicians are expected to direct patients to access these procedures privately if their shared decision is that there would be benefit to the patient.

References

Thiruchelvam P et al. Clinical Updates: Gynaecomastia. *BMJ* 2016; 354: i4833

Association of Breast Surgery Summary Statement: Investigation and Management of Gynaecomastia in Primary and Secondary Care. ABS Clinical Practice and Standards Committee. June 2019.