

Drug-induced gynecomastia in children and adolescents

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ABSTRACT

QUESTION I frequently see adolescent boys in my practice with transient gynecomastia. My management includes reassuring the boys and their families; however, I also understand that specific medication, alcohol, and drugs can cause gynecomastia. How common is this phenomenon, and what medications can induce gynecomastia?

ANSWER While gynecomastia is a physiologic phenomenon in most newborns and adolescents, it is important to consider pathologic conditions and medications that can cause breast enlargement. Antibiotics, antiulcer drugs, growth hormones, and chemotherapy have been reported to induce gynecomastia. Adolescents who use anabolic steroids, or who abuse alcohol, marijuana, heroin, or amphetamines, should be alerted to the fact that gynecomastia might develop. Treatment of drug-induced gynecomastia includes discontinuation of the offending drug. Very rarely is surgical intervention required.

RÉSUMÉ

QUESTION Dans ma pratique, je vois souvent des adolescents ayant une gynécomastie transitoire. Ma prise en charge comporte de rassurer ces garçons et leurs parents. Par ailleurs, je comprends aussi que certains médicaments, l'alcool et certaines drogues peuvent causer une gynécomastie. Dans quelle mesure ce phénomène est-il commun et quels sont les médicaments qui peuvent déclencher une gynécomastie?

RÉPONSE La gynécomastie est un phénomène physiologique chez la plupart des nouveau-nés et des adolescents. Il importe par contre de tenir compte des problèmes pathologiques et des médicaments qui peuvent causer le grossissement des seins. On a signalé que des antibiotiques, des médicaments contre les ulcères, les hormones de croissance et la chimiothérapie pouvaient provoquer une gynécomastie. Il faut avertir les adolescents qui utilisent des stéroïdes anabolisants ou qui consomment de manière abusive de l'alcool, de la marijuana, de l'héroïne ou des amphétamines qu'une gynécomastie pourrait se développer. Le traitement d'une gynécomastie provoquée par une drogue comprend l'abandon de la substance en cause. Il est très rare qu'une intervention chirurgicale soit indiquée.

Gynecomastia, the development of abnormally large mammary glands in males resulting in breast enlargement, occurs frequently in newborn and adolescent boys. Clinically, the enlargement of the breast glandular tissue exceeds 0.5 cm.¹ The phenomenon was reported as early as in the days of Tutankhamen.²

An estimated 60% to 90% of infants have transient gynecomastia, and up to half of boys at puberty might experience the condition. Gynecomastia of the newborn usually occurs during the first week of life, owing to a surge of maternal hormones released during delivery.³ The process usually resolves spontaneously but can persist up to 6 months of age.¹ Adolescent gynecomastia is usually seen during the early stages of puberty, likely as a result of low testosterone in relation to estradiol levels. These conditions are regarded as normal development for boys, and treatment mostly includes reassurance and education of the adolescent and his family.⁴ The condition will usually regress after 18 months and very uncommonly will persist until after the age of 17.⁵ In some cases, however, it can interfere with normal daily activities and be associated with marked breast pain or tenderness.

Estrogenic and androgenic effects

The mechanisms inducing gynecomastia are not always clear. An imbalance between estrogenic and androgenic effects on the breast is likely to play a key role in the stimulation of the phenomenon. Excessive local production of estrogen due to increased aromatase activity, decreased estrogen degradation, or changes in androgen or estrogen receptors might all play a role.⁶

With the substantial increase in the incidence of obesity among children in the Western world, physicians should evaluate the possibility that adolescent breast tissue growth is "pseudogynecomastia." Obesity can cause prominent breasts, and no investigation is warranted in such cases.

Drugs and gynecomastia

Drug-induced gynecomastia is common and might account for a quarter of all cases, including those among children.⁷ The drugs that can cause gynecomastia are listed in **Table 1**.⁶ Although the mechanisms by which many medications induce gynecomastia are not yet understood, some mechanisms are clear. Direct action of estrogens or estrogen-like substances, enhancement of testicular

Table 1. Drugs that can cause gynecomastia

DRUG	MECHANISM
Amiodarone	Unknown
Calcium channel blockers (diltiazem, verapamil, nifedipine)	Unknown
Central nervous system agents (amphetamines, diazepam, methyl dopa, phenytoin, reserpine, tricyclic antidepressants)	Unknown
Cimetidine	Androgen receptor antagonist
Cytotoxic agents (alkylating agents, vincristine, nitrosoureas, methotrexate)	Primary hypogonadism due to Leydig cell damage
Flutamide	Androgen receptor antagonist
Hormones	
• Androgens	Aromatization to estrogens; other mechanisms?
• Estrogens	Direct stimulation of the breast
• Human chorionic gonadotropin	Stimulation of testicular Leydig cell estrogen secretion
Isoniazid	Isoniazid
Ketoconazole, metronidazole	Inhibition of testosterone synthesis
Marijuana	Androgen receptor antagonist
D-penicillamine	Unknown
Phenothiazines	Elevated serum prolactin
Spironolactone	Androgen receptor antagonist; at high doses, interference with testosterone biosynthesis
Theophylline	Unknown

Bembo SA, Carlson HE. Gynecomastia: its features, and when and how to treat it. *Cleve Clin J Med* 2004;71:511-7.⁶ Reprinted with permission. Copyright 2004 Cleveland Clinic. All rights reserved.

production of estrogens, and inhibition of testosterone synthesis or action are among the identified mechanisms.³

Therapeutic doses of testosterone can be peripherally aromatized to estrogen, which might result in gynecomastia; but other mechanisms might be involved, as nonaromatizable androgens such as methyltestosterone or dihydrotestosterone can also cause gynecomastia.

Drug-induced gynecomastia is more common in adults than in children and adolescents,⁵ and can be caused by antiandrogen therapy for prostate cancer, antiretroviral drugs for HIV, and calcium antagonists for hypertension.

Several other drugs were reported to be associated with gynecomastia.¹ Antibiotics, including ketoconazole, metronidazole, and isoniazid; antiulcer drugs,

like cimetidine, ranitidine, omeprazole; and growth hormones have also been reported to cause the phenomenon. Children going through chemotherapy courses, especially with methotrexate and alkylating agents, might also experience gynecomastia.⁸ One report detailed the cases of an adolescent and a neonate who were treated for gastroesophageal reflux and diagnosed with metoclopramide-induced gynecomastia.⁹

Adolescents who use anabolic steroids, or who abuse alcohol, marijuana, heroin, or amphetamines, should be alerted to the fact that gynecomastia could develop.¹⁰

Orally administered medications are not the only medications that can cause gynecomastia. A study published in the *New England Journal of Medicine* suggested that repeated topical use of products containing lavender oil or tea tree oil might also cause prepubertal gynecomastia.¹¹

Although in most adolescents gynecomastia is a physiological phenomenon, it is important to bear in mind pathologic conditions and medications that can cause breast enlargement. Treatment of drug-induced gynecomastia includes discontinuation of the offending drug. Very rarely is surgical intervention indicated. 🌿

Competing interests

None declared

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