Drug-induced gynecomastia: A systematic review and meta-analysis of randomized clinical trials

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ANTIANDROGENS

Author/Year	Population	Intervention	Follow-up	Gynecomastia/ Painful gynecomastia
Cyproterone vs Flutamide				
Schröder 2004	Metastatic prostate cancer and favourable prognostic factors	Flutamide (250 mg t.i.d. p.o.) Cyproterone (100 mg t.i.d. p.o.)	8.6 yrs	Without pain 34 (22.5) 35 (23.0) Painful 65 (43.0) 11 (7.2)
Bicalutamide				
Iversen 2010	Localized (T1-2, N0/Nx) or locally advanced (T3-4, any N; or any T, N+) prostate cancer (all M0)	Bicalutamide 150 mg daily vs placebo three double-blind, placebo-controlled trials 8113 pts 4052+4061	9.7 yrs	Breast pain Gynaecomastia Bicalutamide 2766 (68.8) 2963 (73.7) Placebo 334 (8.3) 308 (7.6)
Shipley 2017	Prostate-cancer recurrence after radical prostatectomy (elevated PSA)	Radiation therapy Plus Bicalutamide 150 mg daily Vs Radiation therapy alone Plus placebo 258+258	24 months	Gynecomastia Bicalutamide Grade 1 42.4% Grade 2 23.6% Grade 3 3.7% Total 69.7% Placebo 8.8% 2.1% 0% 10.9%
Zanardi 2009	Phase I-II trial men with PSA > 4 ng/mL and negative biopsies	Nonrandomly assigned three-arm trial bicalutamide 50 mg/wk (n = 26) 100 mg/wk (n = 28) no treatment (n = 26)	6 months	Gynaecomastia Grade 2 6 (23%) 50 mg/wk 12 (43%) 100 mg/wk 0 (0%)
Flutamide				
Alberts 2006	Men with biopsy proven HGPIN	Flutamide 250 mg/d = 30 placebo = 30 randomized in a double-blind	1 yr	Slight/moderate Flutamide 11/4 Placebo 1/0
Narayan 1996	benign prostatic hyperplasia 372 patients	Flutamide 125 mg twice daily = 75 Flutamide 250 mg once daily = 69 Flutamide 250 mg twice daily = 74 Flutamide 250 mg three times daily = 75 Placebo = 74	24 weeks	Breast tenderness (42% to 52%) 38 36 31 32 4 gynecomastia (14% to 19%) 12 10 14 11 2

Zanoterone				
Berger 1995	Benign prostatic hyperplasia 463 patients	Zanoterone 100 mg. = 89 200 mg. = 92 400 mg. = 95 800 mg. = 94 Placebo = 93 double-blind randomized treatment	6 months	Breast pain 36 (40) 51 (55) 52 (55) 70 (74) 4 (4) Gynecomastia 16 (18) 16 (17) 19 (20) 32 (34) 1 (1)

5-ALPHA-REDUCTASE INHIBITORS

Author/Year	Population	Intervention	Follow-up	Gynecomastia Intervention/Control	Notes
Dutasteride					
Andriole 2010	REDUCE 50 to 75 years PSA 2.5-10.0 negative prostate biopsy	Dutasteride = 4105 Placebo = 4126	4 yrs	76 43	
Na 2012	253	Dutasteride 126 PBO 127	12 mo	1/126 0/127	
Roehrborn 2004	ARIA 3001 ARIA 3002 2802	Dutasteride PBO	1 yr 1397+1405 2 yr 1128+1123	1.1 vs 0.5% 1.6 vs 0.2%	
Finasteride					
McConnell 1998	3040	Finasteride = 1524 Placebo = 1516	2-4 yrs	1.8% 1.1%	
Thompson 2003	PCPT	Finasteride = 9423 Placebo = 9457	7 yrs	426 261	
Durasteride vs Finasteride					
Amory 2007	99 healthy men	Finasteride = 34 Dutasteride = 33 Placebo = 32 double-blinded, placebo-controlled trial	8/34 3/33 2/32	1 yr	D and F significantly (P < 0.001) suppressed serum DHT transiently increased serum T.
Nickel 2011	BPH patients = 1630	Dutasteride 813 Finasteride 817	48 wks	9/813 10/817	

SPIRONOLACTONE

Author/Year	Population	Intervention	Follow-up	Gynecomastia Intervention/Control
Bianchi 2006	Patients with chronic kidney disease	Spironolactone 25 mg/day randomized open-label study	1 yr	6/83 0/82
Charytan 2019	Hemodialysis patients	Spironolactone 12.5-50 mg/day placebo a double-blind, placebo-controlled	36 wks	3/76 2/51
Edelmann 2013	Chronic heart failure	Spironolactone 25 mg placebo	12 mo	9/213 0/209
Gao 2007	Congestive heart failure (CHF)	Spironolactone 20 mg placebo	6 mo	3/58 0/58
Ito 2014	ESRD undergoing peritoneal dialysis	Spironolactone control group	2 yrs	11/78 2/80
Kayrak 2010	Revascularized with percutaneous coronary intervention	Spironolactone 25 mg/day standard conventional therapy	6 mo	3/55 0/55
Matsumoto 2014	Oligoanuric hemodialysis patients	Spironolactone controls randomized, controlled, open-label trial	36 wks	16/157 0/152
Ni 2014	Dialysis patients with refractory hypertension	Spironolactone 25 mg/day placebo	12 wks	1/40 0/36
Pitt 1999	Severe heart failure left ventricular ejection fraction < 35%	Spironolactone 25 mg placebo	24 mo	61 of 614 men 9 of 604 men
Skvortsov 2013	Chronic heart failure (CHF) 25 - 75 mg	Group 1 - 19 patients receiving spironolactone in a 24 hour dose 25 - 75 mg, group 2 - control group - 30 patients	12 mo	Gynecomastia or pain in the region of mammary glands were fixed in 26,3% of patients in 12 months of treatment
Tofte 2020	Type 2 diabetes	Spironolactone 25 mg placebo 102 vs 107	2·51 years	Gynecomastisa 3/102 vs 0/107
Vatankulu 2013	Revascularized patients with acute ST elevation MI (STEMI)	Spironolactone 12.5 25 mg none	6 mo	0/50 4/54 0/56
Vizzardi 2015	Nonischemic dilated cardiomyopathy	Spironolactone 25 mg/day (up to 100 mg/day) placebo	6 mo	1/51 0/51
Zarraga 2012	Patients with implantable cardioverter-defibrillators (ICDs)	Spironolactone 25 mg placebo double-blind fashion	35 mo	4/44 0/46

ANTIPSYCHOTICS

Author/Year	Population	Intervention	Follow-up	Gynecomastia/galactorrhea Intervention/Control
Kelly 2006	Schizophrenia (males)	Risperidone (4 mg/day), quetiapine (400 mg/day) fluphenazine (12.5 mg/day) randomized double-blind	12-week	risperidone 1/9 males (11%) fluphenazine 0/8 quetiapine 0/6
Mc Evoy 2006	Schizophrenia with inadequate response to treatment	Clozapine (N=49) olanzapine (N=19) quetiapine (N=15) risperidone (N=16) randomly assigned to open-label treatment	3 mo	1/49 1/19 0/15 0/16
Mc Evoy 2007	Early psychotic illness	Olanzapine quetiapine risperidone randomized, double-blind	52-week	9/133 3/134 13/133
McEvoy 2014	Schizophrenia or schizoaffective disorder	Paliperidone Palmitate 39 to 234 mg Haloperidol Decanoate 25 to 200 mg Intramuscular monthly double-blind, randomized clinical trial	24 months	4 /147 (2.7%) 5/ 147 (3.4%)

Risk of Bias assessment

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other biases
Antiandrogens							
Cyproterone vs flutamide							
Schroder 2000-2004	?	?	?	?	?	L	L
Bicalutamide vs placebo							
Iversen 2010 Bicalutamide	L	L	L	L	L	L	L
Shipley 2017 Bicalutamide	?	?	?	?	H	L	L
Zanardi 2009 Bicalutamide	?	H	H	H	L	L	L
Flutamide vs placebo							
Alberts 2006 Flutamide	L	L	L	?	?	L	L
Narayan 1996 Flutamide	?	?	?	?	?	L	L
Zanoterone vs placebo							
Berger 1995 Zanoterone	?	?	?	L	L	L	L
5-alpha-reductase							
Dutasteride							
Andriole 2010	?	?	L	?	L	L	L
Na 2012	L	?	?	?	L	L	L
Roehrborn 2002	?	?	?	?	?	L	L
Finasteride							
McConnell 1998	?	L	?	?	?	L	L
Thompson 2004	L	?	?	?	L	L	L
Dutasteride vs finasteride							
Amory 2007	L	L	L	?	L	L	L
Nickel 2011	?	?	?	?	L	L	L
Spironolactone							
Bianchi 2006	L	H	H	H	?	L	?
Charytan 2019	L	L	L	?	L	L	?
Edelmann 2013	L	L	L	L	L	L	?
Gao 2007	?	?	?	L	L	L	?
Ito 2014	?	H	H	L	?	L	?
Kayrak 2010	?	H	H	H	?	L	?
Matsumoto 2014	?	H	H	H	H	L	?
Ni 2014	?	?	?	?	?	L	?
Pitt 1999	?	?	?	L	?	L	L
Skvortsov 2013	?	H	H	H	?	L	?
Tofte 2020	L	L	L	L	?	L	?
Vatankulu 2013	?	H	H	L	?	L	?
Vizzardi 2015	?	?	?	?	?	L	?
Zarraga 2012	L	L	L	L	L	L	L
Antipsychotics							
Kelly 2006	?	?	?	?	H	L	L
Mc Evoy 2006	?	?	?	?	L	L	L
Mc Evoy 2007	?	?	L	?	L	L	L
Mc Evoy 2014	?	?	L	L	L	L	L