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Consensus statement

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Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society international Consensus Statement

In the format provided by the authors and unedited

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Supplementary Information

Supplementary Table 1. Epidemiology of Prolactinomas.

Study	Country	Study population	Pituitary adenoma prevalence per 100,000	Prolactinomas, %	Estimated prolactinoma prevalence per 100,000
Daly, 2006	Belgium (Liege)	71,972	94	66	63
Fontana, 2009	Switzerland	54,607	81	56	45
Fernandez, 2010	UK (Banbury)	81,149	78	57	44
Raappana, 2010	Finland	722,000	49	51	25
Gruppetta, 2013	Malta	417,600	76	46	35
Agustsson, 2015	Iceland	321,857	115	47	54
Day, 2016	Argentina	150,000	67	58	39
Totals		**1,819,185**	**73**	**50**	**37**

Calculated based on data from Chanson, P. & Maiter, D. The epidemiology, diagnosis and treatment of prolactinomas: The old and the new. *Best Pract Res Clin Endocrinol Metab* **33**, 101290 (2019).

Supplementary Table 2: Remission Rates Following Withdrawal of Dopamine Agonist Therapy.

Study	N	Withdrawn		Tumor size, %		Mean DA duration, mo		Reason for withdrawal		Persistent remission, %			PRL normal, mo	
		n	%	Micro	Macro	Micro	Macro	PRL normal	Tumor reduction	Micro	Macro	All	Micro	Macro
Colao, 2007	354	194	55	59	41	43	42	Yes	>50%	66	47	58	47	44
Kharlip 2009	194	42	22	74	26	43	56	Yes	“substantial”	48	45	48	15	16
Huda, 2010	NA	40	–	100	0	108		Yes	no	23	–	23	58	
Barber, 2011	NA	60	–	75	25	49	90	Yes	“substantial”	36	7	28	12	12
Anagnostics, 2012	79	26	33	77	23		79	Yes	>50%	60	50	58		49
Sala, 2016	NA	74	–	76	24	66	79	Yes	“substantial”	55	50	54	12	12
Dogansen, 2016	NA	67	–	34	66		77	Yes	>50%	65	36	46		109
Watanabe, 2017	NA	11	–	0	100		54	Yes	no	–	73	73		12
Ji, 2017	433	89	21	34	66	24	31	Yes	no	43	42	43	26	25
Teixeira, 2017	142	50	35	82	18		118	Yes	no	78	44	72	NA	NA
Kim, 2021	655	44	7	77	23	31	36	Yes	yes	79	60	75	23	27
Total		**697**		**62**	**38**					**57**	**44**	**52**		

DA, dopamine agonist; Micro, microadenoma; Macro, macroadenoma; mo, month; NA, not available; PRL, prolactin. – denotes not applicable.
Calculated based on data from Chanson, P. & Maiter, D. in *The Pituitary, Fifth Edition* (ed. Melmed, S.) 495–544 (Elsevier, 2022).

Supplementary Table 3: Outcomes of Recent Surgical Series for Prolactinomas.

All series*											
		Sex, %		**Tumor size, %**		**Remission, %**			**Recurrence, %**		
Study	**N**	**Male**	**Female**	**Micro**	**Macro**	**Micro**	**Macro**	**All**	**Micro**	**Macro**	**All**
Hamilton, 2005	79	38	62	32	68	72	30	43	NA	NA	NA
Kreutzer, 2008	212	37	63	26	74	84	35	48	7	29	19
Dehdashti, 2008[1]	25	NA	NA	48	52	100	77	88	NA	NA	NA
Gondim, 2010[2]	41	NA	NA	17	83	100	82	85	NA	NA	NA
Raverot, 2010	94	66	34	46	54	93	39	64	10	15	12
Sinha, 2011	172	NA	NA	9	91	88	44	48	9	14	13
Babey, 2011	34	12	88	71	29	92	100	94	0	20	6
Qu, 2011	87	100	0	21	79	83	45	53	13	23	20
Hofstetter, 2011[3]	35	37	63	37	63	92	57	71	NA	NA	NA
Maric, 2012[4]	61	21	79	64	36	100	73	90	NA	NA	NA
Primeau, 2012	63	29	71	43	57	63	33	46	24	50	34
Tamasauskas, 2012	32	0	100	100	0	59	–	59	–	NA	NA
Ikeda, 2013	138	0	100	15	85	86	74	75	NA	NA	NA
Loyo-Varela, 2013	510	23	77	78	22	82	9	66	NA	NA	NA
Paluzzi, 2014	53	NA	NA	21	79	91	45	55	NA	NA	NA
Yan, 2015	99	0	100	69	31	81	52	72	NA	NA	NA
Akin, 2016	142	46	54	13	87	74	41	46	NA	NA	8
Andereggen, 2017	71	0	100	58	42	66	60	63	NA	NA	25
Han, 2018	52	27	73	6	94	100	59	62	0	21	19
Liu, 2018	31	100	0	0	100	–	6	6	–	NA	NA
Yi, 2018	63	0	100	49	51	90	69	79	NA	NA	12
Micko, 2019	60	17	83	100	0	82	–	82	18	–	18
Mattogno, 2021	194	42	58	40	60	67	39	50	NA	NA	NA
Park, 2021	96	23	77	21	79	65	43	48	31	52	46
Baussart, 2021	114	9	91	100	0	91	–	91	4	–	4
Total 2005-2015	*1735*	*29*	*71*	*47*	*53*	*83*	*44*	*62*	*10*	*23*	*17*
Total 2016-2021	*823*	*28*	*72*	*44*	*56*	*79*	*44*	*60*	*10*	*32*	*16*
Total 2005-2021	**2594**	**29**	**71**	**46**	**54**	**82**	**44**	**61**	**10**	**25**	**16**
Gillam, 2006 (50 studies, 1980-2005)	**4363**			**49**	**51**	**75**	**34**	**54**			

Series with remission rates based on Knosp grade

Study	n	Sex, %		Knosp grade, %					Remission rate by Knosp grade, %					
		Male	Female	0	1	2	3	4	0	1	2	3	4	All
Zielinksi, 2020	48	8	92	40	40	8	6	6	95		20			79
Giese, 2021	162	30	70	36	44	8	5	7	81	75	38	25	9	67
Abou-Al-Shaar, 2022	78	59	41	17	13	18	22	31	84			59	42	65
Force, 2022	60	27	73	65	15	5	7	8	81	67	67	33	0	71

*Calculated based on data from Chanson, P. & Maiter, D. in *The Pituitary, Fourth Edition* (ed. Melmed, S.) 467–514 (Elsevier, 2017) [12 publications, 2005-2015] and Chanson, P. & Maiter, D. in *The Pituitary, Fifth Edition* (ed. Melmed, S.) 495–544 (Elsevier, 2022) [9 publications, 2016-2021], and an additional 4 publications, as indicated.

Macro, macroadenoma; micro, microadenoma; NA, not available. – denotes not applicable.

Supplementary Box 1: Background

Epidemiology

Prevalence of symptomatic prolactinomas varies from 25 to 63 cases per 100,000 persons.[5] Incidence is estimated at 2 to 8.2 new cases per 100,000, with 80-90% occurring in females. Small, subclinical microadenomas are encountered in 10% of autopsies.[6]

In women, prolactinomas are usually diagnosed between the ages of 25 and 40 years; nearly all (90%) are microadenomas.[7] Prolactinomas in pre-adolescent and postmenopausal women are rare.[8,9] In men, prolactinomas are usually macroadenomas, typically identified after the age of 40. After the 5th decade, incidence is the same in both sexes.

Molecular Pathogenetic Mechanisms

Although hormonal factors, including estrogen, promote prolactinoma growth,[10] molecular mechanisms that underlie tumorigenesis are the subject of current research. PTTG1 (securin), the ErbB family,[11] and heparin-binding secretory transforming protein[12] initiate experimental prolactinoma tumorigenesis. Over-expressed PTTG results in prolactinoma genomic instability, DNA damage response initiation, and senescence.[13,14]

A rare gain-of-function *PRLR* Asn492Ile mutation has been associated with increased prolactinoma Akt signaling and proliferation.[15] Prolactinomas also may very rarely be associated with *SDHx*, *PRKAR1A*, and *MAX* germline mutations.[16]

Although mutations in *DRD2* encoding the D2 receptor (D2R) have not been identified,[17] reduced D2R expression was shown in prolactinomas resistant to DA.[18] Nerve growth factor (NGF) increases lactotroph differentiation and proliferation, and sensitivity in DA-resistant prolactinomas was restored by NGF treatment.[19,20] High KBTBD6/7 levels in DA-resistant prolactinomas may promote D2R degradation.[21] Impaired D2R response to DA therapy was shown with reduced levels of filamin A, required for D2R function, and response was rescued with filamin A.[22]

Supplementary Box 2: Clinical Presentation

Hyperprolactinemia and Hypogonadism

As female patients usually seek early medical attention for menstrual disorders or galactorrhea, they are typically younger at prolactinoma diagnosis, and present with lower PRL levels, smaller adenoma size, and a higher percentage of microadenomas compared with males. The proliferative potential of prolactinomas is higher in males;[23] 70% of giant prolactinomas are observed in males,[24] and they show a more aggressive disease presentation.

Other presenting features include hyperandrogenism in females and anemia or reduced muscle mass in males.[25] Reduced bone mineral density, vertebral fractures, depression, anxiety, and reduced quality of life may also occur.[25,26]

Other Pituitary Hormone Deficiencies Before and After Treatment

Effect of Dopamine Agonist Therapy

Prospective evaluation of 12 patients receiving cabergoline and assessed prior to treatment showed GH/TSH/ACTH deficiencies in 83%, 36%, and 17% patients, respectively; recovery after 3 years of treatment was noted for TSH in 25% of patients, along with adenoma shrinkage.[27] Rates of both deficiency and recovery are highly variable. One study of 57 patients receiving DA therapy followed for 52 weeks found pretreatment abnormal ACTH stimulation tests in 36% (macro>microadenomas) at baseline; of these, 67% recovered after DA therapy, which was predicted by lower baseline PRL level.[28]

Effect of Surgery

Prevalence of baseline ACTH/TSH deficiency reported in surgical series should be interpreted with caution as some series included patients previously treated with DA therapy.[29-31] Among those with giant prolactinomas (≥40 mm), the prevalence of GH/TSH/ACTH deficiencies was 26-41%, 23-26%, and 25.6-30.4%, respectively.[32,33] Postoperative recovery of TSH/ACTH axes was seen in 35.3% and 22.2%, respectively, in one study.[34] New postoperative TSH/ACTH deficiencies in non-giant prolactinomas are uncommon, reported in ≤5% patients, although data are generally published by centers with experienced pituitary surgeons.[31,34-36]

Effect of Radiation Therapy

The risk of new GH/TSH/ACTH deficiencies as a result of stereotactic radiation therapy was 6%, 15%, and 11%, respectively, at a median follow-up of 60 months (range, 4-266 months) in one large retrospective cohort study,[37] but a review of 11 studies showed pituitary insufficiencies occurred in 5-42% of patients.[38] Risk factors for new anterior hypopituitarism have not been identified.[37] As new pituitary hormone deficiencies could occur >20 years after radiation exposure, long-term follow-up is required.

Supplementary Box 3: Initial Assessment

Causes of Hyperprolactinemia

During pregnancy, maternal PRL levels are elevated above non-pregnant reference ranges by 6 weeks, and levels rise up to 300 ng/mL in anticipation of lactation, while increased lactotroph size and number lead to an enlarged pituitary gland,[39] all of which are likely mediated by estrogens. PRL secretory pulses are enhanced soon after sleep onset, especially with non-REM sleep.[40]

A very rare heterozygous mutation in the *PRLR gene* (His188Arg) results in partial PRL insensitivity with hyperprolactinemia, oligomenorrhea, and sometimes infertility.[41] Germline inactivating *PRLR* variants were reported in a woman with hyperprolactinemia and postpartum agalactia.[42]

Biochemical Evaluation

Macroprolactinemia

PEG precipitation is an inexpensive method that correlates well with gel chromatography.[43] As patients with both macroprolactinemia and increased levels of monomeric PRL may be misclassified, reporting of monomeric PRL instead of percent total PRL has been suggested.[44] Limitations of the PEG method[45] include interference in some PRL assays[46] and very high levels of gamma globulin resulting in false-positive results for macroprolactin.[47]

Supplementary Box 4: Imaging

Novel Imaging Strategies

Functional imaging using radioligands that target the D2R dopamine receptor may predict future response to medical therapy,[48] while ^{11}C-methionine, ^{18}F-fluorodeoxyglucose, and ^{18}F-DOPA, with PET/CT coregistered with MRI (PET/MR^{CR}) or PET/MR, allows precise localization of microadenomas and subsequent successful surgery.[49,50] Similarly, sites of residual tumor following primary therapy for resistant prolactinoma can be pinpointed to inform further decision-making.[51,52]

Supplementary Box 5: Complications

Hypogonadism

Decreased libido, menstrual dysfunction, galactorrhea, infertility, hirsutism, erectile dysfunction, and premature osteoporosis are specific indications to treat prolactinoma, regardless of tumor size.[53,54]

Hypogonadal premenopausal women with prolactinoma treated with DA who do not have return of menses or do not desire fertility may receive replacement therapy with oral contraceptives or other forms of sex hormones. Subsequently, patients need to be observed for increases in PRL levels or mass enlargement.[53] No substantial risk for adenoma size increase was documented following treatment with estrogen/progesterone replacement for two years in women with prolactinoma.[55] However, there was a small risk for pituitary adenomas, including in those with documented hyperprolactinemia, in a more recent case-control study of patients identified as current or past users of oral contraceptives.[56] Oral contraceptives/sex hormone replacement may be used instead of DA in hypogonadal premenopausal women with microadenomas without pregnancy desire, although no controlled head-to-head trials are available and periodic evaluation of PRL levels is recommended.[57] In asymptomatic postmenopausal women with microprolactinoma, given the physiological state of hypogonadism and the lack of fertility concerns, medical treatment with DA is not required, whereas those with macroprolactinomas should be maintained on DA to prevent adenoma enlargement.[58] Management of estrogen replacement in postmenopausal women should follow recommendations and guidelines for the general population.

Resolution of testosterone deficiency is fully achieved in approximately 75% of men who achieve normoprolactinemia on long-term DA treatment.[59-61] Treatment for hypogonadism may be required in others. As validated clinical trials are lacking, the schedule of androgen therapy in men with prolactinoma remains empirical. Aggressiveness, hypersexuality, increased hematocrit, or prostate enlargement may occur as side effects following androgen treatment and require proper dose adjustment.[62]

Bone Disease

Eighty percent of male patients with prolactinoma have osteopenia or osteoporosis on lumbar dual-energy x-ray absorptiometry (DXA), whereas only a minority show a low bone mineral density (BMD) at the femoral neck, suggesting that trabecular bone may be affected earlier than cortical bone.[63] Twenty-two percent of premenopausal women with prolactinoma show reduced DXA Z-scores, particularly at the lumbar spine.[64] Lumbar BMD is significantly lower in amenorrheic than in eumenorrheic women with prolactinoma, and DA therapy suppressing PRL excess generally leads to increased BMD.

In two cross-sectional studies, the prevalence of radiologic vertebral fractures (VFs) was high in both females and males with prolactinoma. In a study of 78 women with prolactinoma and 156 controls, radiologic VFs were found in 32.6% of women with prolactinomas compared with 12.8% of control women of comparable age, and prevalence of VFs was higher in postmenopausal women with prolactinoma than in

premenopausal patients and postmenopausal controls.[65] In the second study, radiological VFs were found in 37.5% of 32 male patients with prolactinoma; this rate was 5-fold higher than what was observed in 64 age-matched controls.[66]

Improvement of BMD is linked more to recovery from hypogonadism than to normalization of PRL levels, confirming the dependence of these bone changes on gonadal steroids.

Supplementary Box 6: Treatment

Dopamine Agonists

Cabergoline normalizes PRL levels and reduces adenoma size in 90% and 71% of patients with microprolactinomas, respectively, and in 83% and 71% of patients with macroprolactinomas, respectively.[67] Bromocriptine normalizes PRL levels and reduces adenoma size in 68% and 62% of patients, respectively.[68]

Side Effects

An association between high-dose cabergoline treatment and cardiac valvulopathy was reported in patients with Parkinson's disease.[69,70] A meta-analysis in 2018 showed that cabergoline treatment in patients with prolactinomas was associated with a moderate risk of tricuspid valve alterations, although this was not clinically significant.[71] Other reports are more reassuring about the true clinical risk of low-dose cabergoline used in the majority of prolactinoma patients.[72-74] The British Society of Echocardiography, the British Heart Valve Society, and the Society for Endocrinology jointly published recommendations on valvular disease screening stating:[75]

- All patients should undergo echocardiography before commencing DA therapy;
- Patients treated with ≤2.0 mg/week of cabergoline should undergo surveillance echocardiography at 5 years;
- Patients treated with >2 mg/week of cabergoline should undergo annual echocardiography;
- Patients treated with ≤2.0 mg/week of cabergoline who develop clinical signs or symptoms potentially suggestive of valvular abnormalities should undergo annual echocardiography if treatment is continued; and
- Decisions regarding discontinuation of DA therapy should only be made after review of serial imaging by a cardiologist experienced in analyzing drug-induced valvulopathy or carcinoid heart disease.

Treatment Withdrawal

A meta-analysis that included 19 studies and 743 patients showed a global remission rate of 21% (95% CI, 14-30%; I^2=81%) after withdrawal of any DA.[76] Slightly more favorable results were observed in patients with microprolactinoma (21%) than macroprolactinoma (16%), and in those treated for at least 2 years (34%) compared to patients treated for a shorter period of time (16%). The remission rate was also higher after use of cabergoline (35%) than after bromocriptine (20%). A similar remission rate of 35% was reported in another meta-analysis of 11 studies of cabergoline withdrawal.[77]

Surgery

With short-term follow-up (≤3 months), no significant difference was seen between surgery and DA treatment for microprolactinoma.[78] At ≥12 months, higher remission rates were seen with DA treatment (96%) than surgery (86%), but patients treated with surgery without subsequent DA therapy achieved a higher remission rate at final follow-up than did those treated with DA followed by withdrawal (78% versus 44%).

Similar results for microprolactinoma were demonstrated in two other meta-analyses.[79,80]

A meta-analysis showed that 38% of patients with medically resistant prolactinomas or intolerance to DA achieved remission with subsequent surgery without the need for further treatment, and 62% achieved remission with multimodal treatment.[81] Complication rates of surgery are low: 0% mortality, 2% permanent diabetes insipidus, and 3% CSF leaks if performed by expert pituitary surgeons.[80]

Of note, the long-term remission rate after withdrawal of DA therapy was only 34%, versus 67% after surgery.[80] In another meta-analysis, long-term remission was achieved in 88% of patients treated with surgery and in 52% treated with DA therapy.[79]

Radiation Therapy

In a meta-analysis of studies using Gamma Knife radiosurgery (median marginal dose, 19-31 Gy) for mostly large and invasive prolactinomas, reported rates of PRL normalization were 15% and 50% after follow-up periods between 13 and 45 months, respectively;[82] using a weighted random effects model to calculate pooled outcome estimates, remission of hyperprolactinemia was 35% (95% CI, 17-53%; I^2=91%, $p<0.001$).[82] A review summarizing data from 11 studies observed tumor control in 85-100%.[38] Late radiation toxicities, specifically new-onset hypopituitarism, optic neuropathy, cranial nerve palsy, and second brain tumors, should be considered when using this management approach.[83]

Supplementary Box 7: Special Situations

Mixed GH-PRL Pituitary Adenomas

In patients with acromegaly, PRL co-secretion is most commonly seen with adenomas composed of somatotrophs and lactotrophs. Approximately 8-10% of GH-secreting adenomas are composed of an aggregation of monomorphous mammosomatotroph cells, with both GH and PRL secreted from a single cell.[84] These mammosomatotroph tumors tend to result in a higher degree of hyperprolactinemia and may have a better long-term prognosis.

Mixed GH-PRL secretion may also occur in patients with acidophilic stem cell adenoma.[85] These adenomas may behave more aggressively than pure lactotroph adenomas and have lower surgical cure rates.

Acromegaly develops in approximately 4% of cases in large, retrospective series of patients with prolactinoma managed with DA therapy.[86,87]

Pregnancy and Fertility

Surgery, DA therapy, and hormone therapy for ovulation induction have made pregnancy possible for women harboring prolactinomas. However, caution is warranted, as use of DA therapy can lead to fetal exposure, and tumor size can increase after discontinuation of DA therapy during pregnancy. Adenomas enlarge in 2.5% of patients with microprolactinomas, 18% of patients with treatment-naïve macroprolactinomas, and 4.7% of those with prior surgical or radiotherapy treatment.[88] Bromocriptine has been the drug of choice for women desiring pregnancy mainly due to its shorter half-life as compared to cabergoline[89] and has been safely used in more than 6,000 pregnancies.[88,90] However, cabergoline use is nowadays preferred by most expert centers[91] as it has been reported in more than 1,000 pregnancies and, overall, data on its use during pregnancy do not point to greater risk of preterm delivery or fetal malformations.[88] Nevertheless, in a Brazilian multicenter retrospective observational study including 233 pregnancies in 194 women, 43.6% presenting with microadenomas and 56.4% with macroadenomas, the miscarriage rate was higher in the small subgroup of patients with cabergoline maintenance after pregnancy confirmation (38% versus 7.5%).[92]

For microprolactinomas and intrasellar macroprolactinomas, DA should be withdrawn as soon as pregnancy is confirmed. For expansive/invasive macroprolactinomas, DA maintenance should be individualized, especially with regard to the need for tumor shrinkage.[93] MRI without gadolinium is indicated if symptoms of tumor mass effects occur during pregnancy. Surgery, either before or during pregnancy, is indicated when DA treatment fails to alleviate tumor mass effect.[93] Breastfeeding is usually allowed. As adenoma volume and PRL levels typically decrease after pregnancy, remission of hyperprolactinemia may be seen.[94] PRL levels and adenoma size should be re-evaluated before re-initiating treatment. Women harboring prolactinomas and who desire pregnancy or who are already pregnant should preferably be followed in Pituitary Tumor Centers of Excellence.[95]

Workshop participants discussed results of the EFEMERIS pharmaco-epidemiological database study,[96] which showed an increased risk of pregnancy loss and preterm birth with DA use during pregnancy. Caveats included that most women

in the exposed group (64%) were treated with bromocriptine and other DAs, including quinagolide, lisuride, ropinirole, and piribedil, but not cabergoline, which is now commonly used. Furthermore, not all study subjects were being treated for prolactinoma; medical history and treatment compliance is lacking. Conversely, a review of the literature for the European Society of Endocrinology Clinical Practice Guidelines[91] showed normal rates of miscarriage, preterm delivery, and congenital malformations with the use of cabergoline in prolactinoma.

Prolactinomas in Children and Adolescents

Prolactinomas are relatively rare in childhood and adolescence. Incidence of pituitary adenomas in individuals aged 10-19 years is 0.5 and 3 cases per 100,000 in males and females, respectively, with approximately 50% representing prolactinomas.[97] Females are more likely to present with microprolactinoma and hypogonadotrophic hypogonadism; males have a greater incidence of macroadenomas and may present with a higher prevalence of neuro-ophthalmologic signs.[98]

Patients with Underlying Psychiatric Disorders

In patients with microadenoma, serial monitoring of mass size without introduction of DA therapy may be appropriate, along with consideration of estrogen or testosterone replacement to manage hypogonadal symptoms.[99] DA therapy may contribute to exacerbation of underlying psychiatric illness. In a cohort study of 18 patients with psychiatric illness prescribed DA for macroprolactinoma, psychotic relapse occurred in those with more severe psychiatric disease who were either not on a DA or an antipsychotic treatment at the time of relapse.[100]

Transgender Individuals

An estimated 0.5% to 1% of adults experience gender incongruence with their sex assigned at birth, and many transgender women and transfeminine individuals seek medical care to affirm gender identity and promote physical feminization.[101] Current recommendations suggest target estradiol levels of 100-200 pg/mL, and testosterone levels suppressed to <50 ng/dL,[102] which is typically achieved with the addition of anti-androgen treatment in surgically naive women.[103]

Hyperprolactinemia associated with cyproterone acetate is dose dependent, with smaller increases observed with 10-mg doses despite similar efficacy in testosterone lowering.[104,105] Hyperprolactinemia is uncommon in transwomen treated with spironolactone or gonadotrophin-releasing hormone.[106,107] Effects are typically reversible with drug cessation following gender-affirming surgery.[108]

In a pharmaco-epidemiological database study of 2555 transwomen, the incidence of prolactinoma was four times greater than expected in a comparative cisgender female population and more than 20 times higher than expected for a cisgender male population.[109] However, the reference population represented all patients with DA-treated hyperprolactinemia and was not limited to those with prolactinoma. Furthermore, when inclusion was limited to transwomen with prolactinoma-associated symptoms at time of diagnosis, the incidence between transwomen and the general female population was largely comparable.

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