Treatment of hyperprolactinemia: a systematic review and meta-analysis

Appendix

Contents

Supplemental Table 1: Baseline characteristics of the included comparative studies

Author, Year	**Sample Size**	**Study Design**	**Description of Patients**	**Age** (yrs +/-SD unless noted otherwise)	**Intervention**	**Duration of Intervention** (months)
Asano, 2001[1]	13	Retrospective cohort	Men with pure prolactinomas	37.3	8 men underwent transsphenoidal surgery followed by bromocriptine administration; 5 received bromocriptine or terguride alone	NR
Bahceci, 2010[2]	239	Retrospective cohort	Infertile patients with otherwise asymptomatic hyperprolactinemia	32.0	122 treated with cabergoline (1mg/wk in two divide doses) and 117 treated with bromocriptine (5mg/day) during controlled ovarian hyperstimulation	NR
Brue, 1992 [3]	27	Retrospective cohort	Hyperprolactinemic bromocriptine resistant patients	29	Patients were treated with dopamine agonist CV205-502 alone (doses between 0.15 to 0.525mg daily) or with surgery	NR
Candrina, 1987 [4]	21	Prospective cohort	Patients with macroprolactinomas undergoing surgery	44+/-8	13 patients were operated by transsphenoidal approach, 8 patients combined TSS with TCS or only TCS. After intervention 6 patients were immediately given DA, the other 15 were only given DA if evidence of relapse.	NR
Colao, 1995 [5]	34	Prospective cohort	Patients with prolactinomas	Range: 18-54	10 patients received BRC-SRO daily, dose of 5-20 mg for 1-24 months; 8 patients received BRC-LAR monthly, dose of 50-100 mg for 6-24 months; 16 patients received CV 205-502 daily, dose of 0.075-0.6 mg for 6-12 months	NR
De Rosa, 1998 [6]	17	Retrospective cohort	Men with macroprolactinoma	Range: 22-38	Cabergoline at 0.5mg once weekly for 15 days, then 0.5mg twice weekly, then titrated by PRL level versus Bromocriptine at 1.25mg twice daily for 1 week. then to 2.5mg twice daily for 3 weeks, then titrated by PRL level	6
Di Sarno, 2001 [7]	207	Retrospective cohort	Consecutive de novo patients with hyperprolactinemia	29	Micro- 64 patients- Cabergoline 0.25mg once weekly x 1 week, twice weekly x 1 week, then 0.5 mg twice weekly, then titrated based on PRL level; Macro-56 patients- Cabergoline 0.5mg weekly x 1 week, then twice weekly, then titrated based on PRL level. 87 patients- Bromocriptine 2.5 mg q.P.M. x 2 weeks then to 5 mg after lunch and 2.5 mg q.P.M., then titrated based on PRL level	24
Di Somma, 1998 [8]	20	Prospective cohort	Consecutive hyperprolactinemic men	36.7	Group 1 (6 patients) treated with bromocriptine dose 2.5 to 10mg 2 to 3 times daily; group 2 (7 patients) treated with quinagolide dose 0.075 to 0.3mg 1 or 2 times daily; group 3 (7 patients) dose 0.5 to 1.5mg once or twice a week	18
Hildebrandt, 1992[9]	36	Retrospective cohort	Patients with immunohistochemically proven PRL secreting micro or macroadenomas	33+/-15	Group A: 14 patients-single dose of a long-acting bromocriptine followed by chronic oral dopamine agonist therapy; group B: 12 patients underwent surgical excision first and if hyperprolactinemia persisted then were started on oral dopamine therapy. Group C; 10 patients received DA and then surgery (additional DA after surgery if needed)	1-6
Hirahara, 1998[10]	48	Randomized controlled trial	Hyperprolactinemic women with history of	Range: 20-40	24 with occult hyperprolactinemia and 24 with hyperprolactinemia were randomly assigned to bromocriptine	12

			recurrent spontaneous abortion not associated with other etiologies		(2.5mg to 5mg/day until the end of 9th week of gestation) vs. no treatment	
Homburg, 1990[11]	22	Randomized controlled trial	Women with persistent hyperprolactinemia (microprolactinoma or macroprolactinoma)	33	Patients were randomized to either Bromocriptine (2.5mg/day up to 10mg/day) or CV-205-502 (0.075mg/day up to 0.15mg/day).	6
Jeffcoate, 1996[12]	10	Retrospective cohort	Women with confirmed microprolactinoma	29.1	Intermittent treatment with DA, 60 received DA, 10 did not	NR
Lappohn, 1992[13]	24	Randomized controlled trial	Women with hyperprolactinemia	35	CV 205-502 0.025 mg/d then increased to 0.075 mg at bedtime vs. bromocriptine 1.25 mg/d, then increased to 2.5 mg twice daily	6
Mahmood, 2010[14]	100	Prospective cohort	Hyperprolactinemic women	28.1	50 women received cabergoline at 0.5 mg/week vs. 50 women who received bromocriptine up to a maximum of 2.5 mg twice daily	8
Mattei, 1991[15]	176	Retrospective cohort	Hyperprolactinemic women treated medically, pregnancy or “just waiting”	NR	107 women (46 with normal sella and 61 with prolactinoma) were treated with dopamine agonist (bromocriptine, metergoline, lisuride, dihydroergocristine, dihydroergocryptine and cabergoline)	Normal sella-12.6 months; Prolactinoma-11 months
Motazedian, 2010[16]	183	Randomized controlled trial	Hyperprolactinemic infertile women undergoing ovulation induction for intrauterine insemination	28.9	94 women received bromocriptine 2.5 mg twice daily vs. 89 women given cabergoline 0.25 mg twice weekly	NR
Pascal-Vigneron, 1995[17]	120	Randomized controlled trial	Hyperprolactinemic women with amenorrhea at 21 French centers	32	Cabergoline 0.5-1mg twice weekly vs. bromocriptine 2.5-5mg twice daily	6
Perrin, 1991[18]	40	Retrospective cohort	Patients with prolactinomas and elevated prolactin levels	33.8	20 patients with bromocriptine preoperatively 2.5 to 7.5 mg daily dose then transsphenoidal resection; 20 patients resection alone	BCT: Micro 15 months; Macro 5 months
Pinzone, 2000[19]	46	Retrospective cohort	Men with prolactinomas	49 micro; 46 macro	Bromocriptine, quinagolide, and/or cabergoline were administered as medical therapy.	NR
Rush, 1991[20]	20	Retrospective cohort	Hyperprolactinemic patients PRL >200ng/ml, tumor size >2cm	Range: 21-64	Treated by transsphenoidal surgery and RDT with or without DA treatment	NA (Surgery)
Samaan, 1986[21]	190	Retrospective cohort	Women with hyperprolactinemia and evidence of pituitary tumor	Range: 17-39	Bromocriptine vs Surgery; 88 patients underwent transsphenoidal excision, 102 were given 5 to 7.5 mg bromocriptine daily	36-60
Sartorio, 1990[22]	29	Prospective cohort	Hyperprolactinemic women with microprolactinoma	Range: 18-43	Treated with dopaminergic agents; 10 received 20-30 mg/d dihydroergocryptine, 8 7.5-10 mg/d bromocriptine and 11 were given 500 ug/ once a week cabergoline.	12

Shih, 1983[23]	30	Prospective cohort	Women with primary/secondary amenorrhea, galactorrhea, infertility who were found to be hyperprolactinemic	Range: 17-42	3 macros 1 micro treated with surgery; others with bromocriptine 2.5 for 3 days, 5 x 3d, then 7.5 daily	NR
Sluijmer, 1992[24]	59	Prospective cohort	Women with idiopathic hyperprolactinemia with menstrual irregularities and or infertility	26.5	Group 1 (10) patients who opted for no treatment, group 2 (33) treated at one time with bromocriptine (dose range 2.5 to 7.5mg BID), group 3 (16) Patients who were treated continuously with bromocriptine throughout the study (dose 2.5mg to 7.5mg BID)	Median: 78 Range: 6-190
Torres, 2006[25]	32	Retrospective cohort	Patients with macroprolactinomas	35+/-17.2	Patients were treated with dopamine agonist (type and dose not specified) alone, or with surgery alone	86.4
Touraine, 2001[26]	246	Retrospective cohort	Hyperprolactinemic women, not due to drug intake, hypothyroidism or chronic renal failure	29+/-0.6	191 patients were treated with bromocriptine. 32 underwent surgery and 23 received no treatment.	NR
van der Heijden, 1991[27]	41	Randomized controlled trial	Hyperprolactinemic patients- PRL exceeding 1500mU/l persistently	Range: 18-47	CV 205-502 0.025 mg q.H.S. x 3 days, then 0.05 mg x 3 days, then 0.075 mg q.H.S. always with AM placebo vs. bromocriptine 1.25 mg q.H.S. with q.A.M. placebo x 3 days, then bromocriptine 1.25 mg twice daily x 3 days, then 2.5 mg twice daily	6
Verhelst, 1991[28]	12	Randomized controlled trial	Hyperprolactinemic patients	Range: 19-56	Patients randomly assigned to receive bromocriptine starting dose 1.25mg increased weekly up to 5mg/day then to a max of 20mg/day or Quinagolide starting dose 0.025mg/day and increased weekly to 0.1mg/day maintenance and then increased monthly to obtain normalized PRL levels	6
Webster, 1994[29]	459	Randomized controlled trial	Hyperprolactinemic women with amenorrhea	31	Cabergoline 0.5 to 1.0 mg twice weekly vs. bromocriptine 2.5 to 5.0 mg twice daily	6

TSS - Transsphenoidal surgery; TCS – Transcranial surgery; DA – Dopamine agonist; RDT – Radiotherapy

Supplemental Table 2: Quality of the observational comparative studies

Author, Year	% of patients lost to followup	Length of follow-up (months)	Cohorts are similar at baseline?	Cohorts are representative of clinical practice?	Outcome assessment blinded?	Analysis adjusted for confounders?	Funding
Asano, 2001[1]	NR	42.48 (surgery) 22.44 (no-surgery)	No	Yes	No	NR	NR
Bahceci, 2010[2]	NR	NR	Yes	Yes	No	NR	NR
Brue, 1992[3]	0	96+/-48	Yes	No	No	NR	NR
Candrina, 1987[4]	NR	46+/-6	No	Yes	No	NR	NR
Colao, 1995[5]	NR	NR	Yes	Yes	No	NR	NR
De Rosa, 1998[6]	NR	6	Yes	Yes	No	NR	NR
Di Sarno, 2001[7]	NR	24	Yes	Yes	No	NR	NR
Di Somma, 1998[8]	NR	18	No	Yes	No	Yes	NR
Frey, 2009 [8]	NR	116.5	Yes	Yes	No	NR	NR
Hildebrandt, 1992[9]	0	12	No	Yes	No	No	Part-for-profit
Jeffcoate, 1996[12]	0	61.2+/-45.6	Yes	Yes	No	NR	Not-for-profit
Mahmood, 2010[14]	NR	2	Yes	Yes	No	NR	NR
Mattei, 1991[15]	0	44.9	Unclear	Yes	No	NR	NR
Perrin, 1991[18]	NR	NR	Yes	Yes	No	NR	NR
Pinzone, 2000[19]	NR	50.4	Unclear	Yes	No	NR	NR
Rush, 1991[20]	10	24-144	No	Yes	No	NR	NR
Samaan, 1986[21]	NR	42	Unclear	Yes	No	NR	Not-for-profit
Sartorio, 1990[22]	NR	12	Unclear	Yes	No	NR	For-profit
Shih, 1983[23]	0	10 (1-19)	Unclear	Yes	No	NR	NR
Sluijmer, 1992[24]	0	78 (6-190)	Unclear	Yes	No	NR	NR
Torres, 2006[25]	0	86.4+/-62.4	Unclear	Yes	No	NR	NR
Touraine, 2001[26]	NR	99.9+/-3.6	Unclear	Yes	No	NR	NR

Supplemental Table 3: Quality of the included observational dopamine withdrawal studies

Author, Year	% patients lost to followup	Length of follow-up (months)	Cohorts representative of clinical practice?	Outcome assessment blinded?	Analysis adjusted for confounders?	Funding
Biswas, 2005[30]	NR	84	Yes	No	Yes	NR
Cannavo, 1999[31]	NR	12	Yes	No	NR	NR
Ciccarelli, 1997[32]	4	1 to 82	Yes	No	NR	NR
Colao, 2003[33]	NR	24	Yes	No	Yes	Part-for-profit
Corenblum, 1988[34]	NR	NR	Yes	No	NR	NR
Di Sarno, 2000[35]	NR	12	Yes	No	NR	Not-for-profit
Eversmann, 1979[36]	NR	NR	Yes	No	NR	NR
Hancock, 1985[37]	0	19-88	Yes	No	NR	NR
Johnston, 1983[38]	NR	NR	Yes	No	NR	For-profit
Kharlip, 2009[39]	0	1-48	Yes	No	Yes	Not-for-profit
Liuzzi, 1985[40]	NR	21	Yes	No	NR	Not-for-profit
Mattei, 1984[41]	0	7 to 9	Yes	No	NR	Not-for-profit
Moriondo, 1985[42]	NR	24.8	Yes	No	NR	Not-for-profit
Muratori, 1997[43]	19	24	Yes	No	NR	Not-for-profit
Passos, 2002[44]	NR	NR	Yes	No	Yes	NR
Tartagni, 1995[45]	NR	NR	Yes	No	NR	NR
Touraine, 2001[26]	NR	99.9+/-3.6	Yes	No	NR	NR
van't Verlaat, 1991[46]	NR	12	Yes	No	NR	NR
Winkelmann, 1985[47]	NR	21.5	Yes	No	NR	NR
Wu, 2008[48]	NR	18	No	No	NR	NR
Zarate, 1983[49]	0	48	Yes	NR	No	NR

Supplemental Table 4: Quality of the randomized trials

Author, Year	% of patients lost to follow-up	Length of follow-up (months)	Blinding			Allocation Concealment	Funding
			P	CG	OA		
Hirahara, 1998[10]	4	12	NR	NR	NR	Yes	NR
Homburg, 1990[11]	10	6	Y	Y	NR	Yes	For-profit
Lappohn, 1992[13]	17	6	Y	NR	NR	Yes	NR
Motazedian, 2010[16]	NR	NR	NR	NR	NR	Yes	Not-for-profit
Pascal-Vigneron, 1995[17]	20	6	Y	Y	NR	NR	NR
van der Heijden, 1991[27]	NR	NR	Y	Y	NR	NR	NR
Verhelst, 1991[28]	NR	6	Y	Y	NR	No	NR
Webster, 1994[29]	2	6	Y	Y	NR	Yes	For-profit

P: Patients CG: Caregiver OA: Outcome assessor

Summary of uncontrolled studies of dopamine agonists (Supplemental Tables 5A-E)

Supplemental Table 5A: Bromocriptine studies

Study	Main findings
Al-Suleiman, 1989[50]	Symptomatic tumoral and non tumoral hyperprolactinemic women who presented with infertility. Most had resolution of galactorrhea, amenorrhea and infertility after treatment
Bergh, 1978[51]	Hyperprolactinemic women with secondary amenorrhea had reduction of PRL after treatment with restoration of ovulation
Brue, 1992[52]	After 6-24 months of follow up of patients with macroprolactinomas, tumor size and PRL levels were significantly reduced
Cannavo, 1992[53]	After 12 months of follow up of patients with microprolactinomas, tumor size was significantly reduced in most patients
Chattopadhyay, 2005[54]	After 31 months of follow up, men with macro and giant prolactinomas had significant reduction in PRL level, tumor size, restoration of libido and potency and improvement in visual field defects
Corenblum, 1983[55]	After 5-9 years of follow up of women with hyperprolactinemia, tumor size, PRL levels and hypogonadal symptoms were significantly reduced
Corenblum, 1988[34]	After 5 years of follow up of women with hyperprolactinemia, tumor size, PRL levels and hypogonadal symptoms were significantly reduced
Espinos, 1994[56]	After 6 months of follow up of patients with microprolactinomas, PRL levels were significantly reduced in most patients
Essais, 2002[57]	After 6 months of follow up of patients with macroprolactinomas, tumor size and PRL levels were significantly reduced in most patients
Falsetti, 1988[58]	Non tumoral hyperprolactinemia (per CT scan) treated with bromocriptine. PRL declined but many cases turned out to harbor microprolactinomas after extended follow up.
Fletes Rabago, 1991[59]	After 12 months of follow up of patients with hyperprolactinemia who received vaginal bromocriptine, PRL levels were significantly reduced
Greenspan, 1989[60]	Hyperprolactinemic patients who had reversal of hypogonadism by bromocriptine had improvement in bone mass
Haase, 1993[61]	After 36 months of follow up of patients with macroprolactinomas, tumor size and PRL levels were significantly reduced in most patients
Holtkamp, 1988[62]	Women with progressive metastatic breast cancer and hyperprolactinemia who are resistant to chemotherapy. Bromocriptine reduced PRL levels but did not improve sensitivity to chemotherapy
Jamrozik, 1996[63]	After 3.3 years of follow up of patients with macroprolactinomas, tumor size and PRL levels were significantly reduced in most patients
Lengyel, 1993[64]	After 12 months of follow up of patients with macroprolactinomas, tumor size and PRL levels were significantly reduced in most patients
Lin, 1992[65]	After 3-7 months of follow up of infertile women with hyperprolactinemia, 80% became pregnant
Moberg, 1991[66]	Post menopausal women with hyperprolactinemia. Most cases turned out to be due to macroadenomas. PRL level significantly decreased
Maraschini, 1991[67]	After 19 months of follow up of patients with micro and macro prolactinomas, PRL levels and tumor size were significantly reduced in most patients with clinical improvement in other symptoms
Merola, 1992[68]	After 9 months of follow up of patients with tumoral and non tumoral hyperprolactinemia, tumor size and PRL levels were significantly reduced in most patients

Molitch, 1985[69]	After 6-12 months of follow up of patients macroprolactinomas, tumor size and PRL levels were significantly reduced and improvement in visual field defects was noted
Mornex, 1978[70]	Most women with hyperprolactinemia amenorrhea and galactorrhea regained fertility
Moro, 1991[71]	After 6 months of follow up of patients with hyperprolactinemia, PRL levels were significantly reduced and most patients had clinical improvement
Paoletti, 1994[72]	After 6 months of follow up of patients with prolactinomas, tumor size decreased in most patients
Rasmussen, 1990[73]	After 5-13 years of follow up, a third of women with tumoral hyperprolactinemia had progression of tumor size although the overall course was benign for almost all patients
Schettini, 1990[74]	After 48 weeks of follow up of patients with tumoral and non tumoral hyperprolactinemia, tumor size and PRL levels were significantly reduced in most patients
Skrabanek, 1980[75]	Most symptomatic hyperprolactinemic patients had resolution of infertility and related symptoms
Spark, 1982[76]	After 27 months of follow up of patients with pituitary adenomas (majority had hyperprolactinemia, some had previous surgery or radiotherapy), tumor size, visual field defects and pituitary function improved in most patients
Thorner, 1978[77]	Most patients with hyperprolactinemia had improved PRL level and gonadal functions
Tsagarakis, 1995[78]	After 6 months of follow up of patients with prolactin and GH producing adenomas, PRL levels were significantly reduced in most patients
van 't Verlaat, 1986[79]	After 2.4 years of follow up of patients with macroprolactinomas, tumor size and PRL levels were significantly reduced. Endocrinopathies (hypogonadism, hypothyroidism and hypocorticism) also improved
Walsh, 1997[80]	Men (70% macro, 15% micro, 15% no mass) had significant reduction in PRL level, tumor size, and restoration of sexual function
Wass, 1982[81]	After 3-22 months of follow up of patients with large pituitary adenomas (majority had hyperprolactinemia), tumor size, visual field defects and pituitary function improved in most patients
Weingrill, 1992[82]	After 12 months of follow up of patients with hyperprolactinemia, PRL levels were significantly reduced and infertility resolved in most patients
Wu, 2006[48]	After 37.5 months of follow up of patients with giant invasive macroprolactinomas, tumor size and PRL levels were significantly reduced
Yang, 2011[83]	After 44 months of followup, 86% of patients with invasive prolactinoma receiving bromocriptine were clinically controlled, while 14% required surgical debulking
Zarate, 1983[49]	After 2 years of follow up of women with prolactinomas , PRL levels were significantly reduced

Supplemental Table 5B: Cabergoline studies

Study	Outcome
Bhansali, 2010[84]	After 6 months of followup, men undergoing rapid escalation of cabergoline over 3 weeks experienced improvement in symptoms (93%) and normalization of PRL levels in 93%, and reduction in tumor size by 50% (73%)
Biller, 1996[85]	After 48 weeks of followup, cabergoline was found to be highly effective for lowering prolactin, including in patients who had failed to achieve normal levels on bromocriptine
Bolko, 2003[86]	After 6 months of cabergoline treatment, the drug was found to have a high efficacy and a very good tolerability in the treatment of patients with pituitary adenomas
Byuykbayrak, 2010[87]	After 6 months of followup in hyperprolactinemic patients, varying doses of short-term maintenance therapy (8 weeks) after an initial 8 weeks of cabergoline 0.5 mg twice per week were found to be no different
Cho, 2009[88]	After 19 months of follow-up, men with invasive giant prolactinoma given cabergoline treatment for 3 months exhibited a mean decrease in serum PRL of 98% and mean reduction in tumor size of 85+/-4%, at 12 months reduction in tumor size was 97+/-1%
Ciccarelli, 1989[89]	After 6-12 months of followup, cabergoline was found to have a well-tolerated long lasting activity in treating hyperprolactinemic patients
Ciccarelli, 1997[32]	After 1-82 months of treatment with cabergoline, it was found that long term treatment with this medication is effective and well-tolerated in patients with tumorous or idiopathic hyperprolactinemia
Colao, 1997[90]	After 12-24 months of cabergoline therapy, cabergoline was found to be an effective first line pharmacological treatment for macroprolactinoma
Colao, 2000[91]	Treatment with cabergoline for 1-3 years was found to increase the prevalence of macroprolactinoma shrinkage at standard doses, more so in naïve patients, than in intolerant, resistant and responsive patients
Colao, 2004[92]	After 24 months of cabergoline treatment, an increase in prostate size was noticed, along with an increase in testosterone and DHT until normal levels were reached
Colao, 2004[93]	After 24 months of cabergoline treatment, prolactin levels normalization was achieved in the majority of men, along with the restoration of testosterone, GH and ACTH in approximately 60% of cases
Corsello, 2003[94]	After followup of 13-68 months, cabergoline was found to be highly effective in reducing prolactin levels and causing tumor shrinkage in patients with giant aggressive prolactinomas
De Bellis, 2008[95]	After 3 years of followup, the presence of anti pituitary antibodies (APA) in some patients with idiopathic hyperprolactinemia suggests a possible occurrence of autoimmune hypophysitis at potential/subclinical stage. Early and prolonged cabergoline therapy could interrupt the progression of to an overt clinical stage of the disease
De Rosa, 2006[96]	After 24 months of cabergoline treatment, gonadal function was restored in 66.7% of men with hyperprolactinemia
Delgrange, 1996[97]	After 5-134 weeks of treatment, cabergoline was associated with improved compliance, tolerability and efficacy. It was also found to be useful in patients who are intolerant or resistant to bromocriptine
Ferrari, 1992[98]	After 3-52 months of followup, cabergoline was found to be safe, efficacious, and very simple to use
Ferrari, 1997[99]	After 3 months to 8 years of followup, cabergoline was found to be an effective and well-tolerated treatment for macroprolactinoma patients
Muratori, 1997[43]	After 21 months of followup, cabergoline was found to be effective in inhibiting hormonal secretion and controlling tumor growth in pathological conditions like tumorous prolactin and GH hypersecretion
Ono, 2008[100]	After one year of treatment with cabergoline, it was found that individualized high-doses of it can normalize

	hyperprolactinemia and hypogonadism in nearly all prolactinomas irrespective of tumor size or preceding treatments
Ono, 2010[101]	After 8 years of follow-up after initiation of cabergoline in hyperprolactinemic infertile women with micro- or macroprolactinoma, hyperprolactinemia and ovulatory cycle was recovered in 100% of patients, 94% became pregnant
Pontikides, 2000[102]	12 months of cabergoline treatment, resulted in tumor shrinkage and normalization of PRL levels in all subjects
Raverot, 2009[103]	After 12 months of followup in patients with newly diagnosed macroprolactinoma treated with cabergoline, 18% (5/28) of patients had chiasmal herniation on MRI; of these, 60% (3/5) experienced visual field worsening
Shimon, 2007[104]	After followup of 1-50 months, cabergoline therapy was found to be effective and safe in men with giant prolactinomas
Stalldecker, 2010[105]	90 women with hyperprolactinemia achieved 103 pregnancies after cabergoline treatment for 1 to 120 months with doses ranging from 0.125 to 5 mg/week
Walia, 2011[106]	After 6 months of followup, men with macroprolactinoma who were given cabergoline for six months, exhibited a decrease in PRL levels and improvement in seminal volume, sperm count and motility.
Webster, 1993[107]	After approximately 49 weeks of followup, cabergoline was found to be highly effective in suppressing prolactin secretion and restoring gonadal function

Supplemental Table 5C: Quinagolide (CV 205-502) studies

Study	Outcome
Colao, 1996[108]	Following 6-24 months of CV 205-502 use, it was found that prolonged periods of use of this drug, were successful in normalizing hyperprolactinemia and in restoring gonadal function, with excellent tolerability
Duranteau, 1991[109]	Following 6 months of treatment with CV 205-502, the drug was found to be more potent than bromocriptine in reducing prolactin levels in some bromocriptine-resistant prolactinomas
Kvistborg, 1993[110]	After followup of up to 36 months, CV 205-502 was found to be efficacious and mostly well-tolerated, in treating patients with macroprolactinomas. It was also found to be easier to use than bromocriptine
Merola, 1994[111]	After 6-12 months of CV 205-502 treatment, prolactin levels normalized in most patients and induced tumor shrinkage in macroprolactinomas, all that with very few side effects, making it a useful alternative to ergot dopamine agonists
Morange, 1996[112]	After 6 months-3 years of followup, long term control of hyperprolactinemia by quinagolide was obtained in 39% of patients previously resistant to bromocriptine, and 75% of women resumed normal gonadal function
Newman, 1989[113]	Following 2 years of CV 205-502 treatment, the drug was found to be useful in the treatment of hyperprolactinemia
Nickelsen, 1993[114]	Following 6-12 months of treatment, quinagolide did not affect hormonal systems other than prolactin
Rasmussen, 1988[115]	After 6 months of CV 205-502 once a day treatment, the drug was found to be effective in decreasing serum prolactin levels and in restoring ovulatory function in hyperprolactinemic women, with few mild side effects
Rohmer, 2000[116]	After 1-48 months of followup, quinagolide had an anti-tumoral effect in 30% of study population (selected from ergot dopamine agonist resistant patients). Normalization of plasma prolactin was obtained in 44% of cases
Shoham, 1991[117]	After 3-24 months of followup, CV 205-502 in one daily dose, was found to be effective, safe, tolerable and a valuable alternative to the dopamine agonists
van der Heijden, 1989[118]	After 12-52 weeks of followup, it was concluded that CV 205-502 had good prolactin lowering effects in hyperprolactinemic women. It was also well-tolerated
van der Lely, 1991[119]	After 52 weeks of followup, CV 205-502 was found to effectively suppress prolactin secretion and shrink tumor size in the majority of prolactinoma patients
Van't Verlaat, 1990[79]	After a followup of 2-18 months (mean: 11), CV 205-502 in a once daily dose was found to be an effective and safe alternative in the long term treatment of macroprolactinomas
Vance, 1990[120]	After 24 weeks of CV 205-502 treatment, the drug was found to reverse hyperprolactinemia and to promote reduction in tumor size with reversal of visual abnormalities and restoration of gonadal function in most patients
Vilar, 1994[121]	After 1-24 months of quinagolide (CV 205-502) therapy, after reviewing past literature, it was concluded that, prolactin can be normalized in 16-20% of patients with bromocriptine resistance (dose dependent) and in 58% of patient with bromocriptine intolerance, using quinagolide CV 205-502. Half of all patients received this drug did experience side effects, and around 7% were quinagolide intolerant

Supplemental Table 5D: Bromocriptine short release vs long release

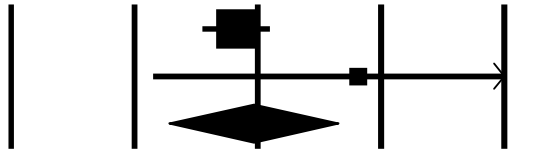
Study	Outcome
Merola, 1992[68]	After 9 months of followup, Parlodel SRO, a slow acting form of bromocriptine, was found to be very effective in the management of hyperprolactinemic syndromes
Moro, 1991[71]	After followup of 7 months, long acting bromocriptine forms, were shown to be as efficacious as short acting forms, in lowering plasma prolactin, while being more convenient and better tolerated
Weingrill, 1992[82]	After one year of followup, Parlodel SRO –a long acting oral bromocriptine- was found to be effective, tolerable and active for a long duration of time, making it an excellent alternative for the treatment of hyperprolactinemia

Supplemental Table 5E: Other dopamine agonist studies

Study	Outcome
Freda, 2000[122]	After 9-64 months of followup (mean: 27.4), pergolide was found to be effective, safe and generally well tolerated in long term treatment of macroprolactinomas
Jaspers, 1994[123]	After 6 months of followup, roxindol, a non-ergot dopamine agonist, was found to have a marked and prolonged prolactin-lowering activity that it may prove suitable for treatment of prolactinoma patients
Orrego, 2000[124]	Following 12 months of pergolide treatment, the drug was found to be safe, effective, and usually well tolerated, that it can be used as primary therapy for treatment of macroprolactinomas in men and women. Unlike bromocriptine, this dopamine agonists can be administered once daily
Sibal, 2002[125]	After a mean followup period of 4.2 years, it was determined that treating macroprolactinoma with dopamine agonists (bromocriptine, pergolide and cabergoline), had resulted in recovery of gonadotroph, thyrotroph and corticotroph function in 62, 44 and 67% of cases
Verde, 1980[126]	Following 2-25 months of Lisuride treatment, it was found that this dopamine agonist can control prolactin levels and in responsive individuals influence tumor size

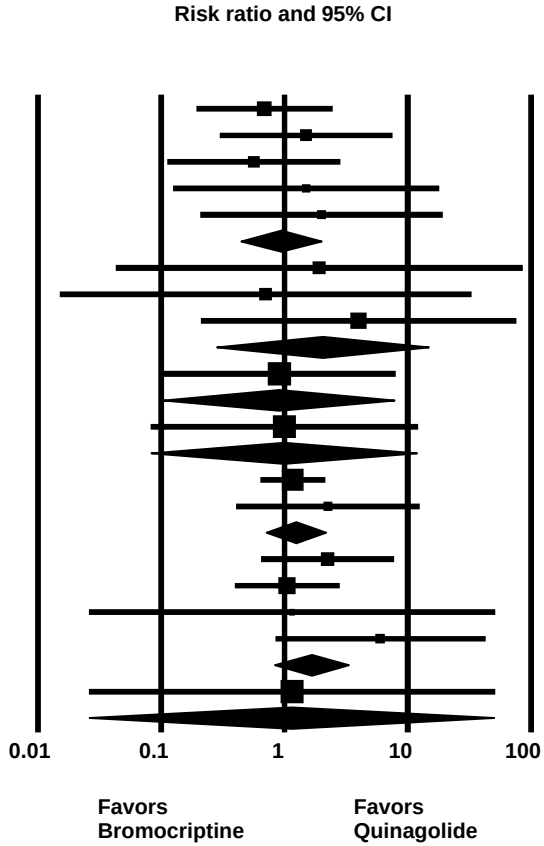
Supplemental Figure 1A: Bromocriptine vs. Quinagolide
Prolactin Level (ng/mL)

Study name	Difference in means	Lower limit	Upper limit	Bromo	CV
Lappohn	-35.07	-88.45	18.31	12	12
Colao	163.30	-168.08	494.68	10	16
PRL level	**-6.07**	**-143.43**	**131.30**	**22**	**28**



Supplemental Figure 1B: Bromocriptine vs. Quinagolide
Clinical Outcomes

Outcome	Study name	Risk ratio	Lower limit	Upper limit	Bromo	CV
	van der Heijden	0.69	0.20	2.41	3 / 12	4 / 11
	Lappohn	1.50	0.30	7.43	3 / 12	2 / 12
	Colao	0.56	0.11	2.79	2 / 13	3 / 11
	Verhelst	1.50	0.13	17.67	1 / 4	1 / 6
	Homburg	2.00	0.21	18.98	2 / 11	1 / 11
		0.95	**0.45**	**2.00**	**11 / 52**	**11 / 51**
	van der Heijden	1.91	0.04	83.79	1 / 6	1 / 11
	Colao	0.70	0.02	32.45	1 / 14	1 / 10
	Homburg	4.00	0.21	74.84	2 / 8	1 / 8
Galactorrhea, I^2=0%		**2.05**	**0.28**	**14.88**	**3 / 27**	**2 / 28**
	Colao	0.91	0.11	7.84	2 / 11	1 / 5
Decreased libido		**0.91**	**0.11**	**7.84**	**2 / 11**	**1 / 5**
	Colao	1.00	0.08	11.93	1 / 5	1 / 5
Erectile dysfunction		**1.00**	**0.08**	**11.93**	**1 / 5**	**1 / 5**
	van der Heijden	1.17	0.65	2.10	5 / 6	5 / 7
	Homburg	2.25	0.41	12.28	3 / 4	1 / 3
Female infertility		**1.25**	**0.72**	**2.19**	**8 / 10**	**6 / 10**
	van der Heijden	2.24	0.66	7.62	7 / 24	3 / 23
	Verhelst	1.05	0.40	2.75	3 / 5	4 / 7
	Di Somma	1.15	0.03	50.38	1 / 7	1 / 8
	Homburg	6.00	0.86	41.96	6 / 11	1 / 11
PRL level increased. I^2=0%		**1.67**	**0.84**	**3.35**	**17 / 47**	**9 / 49**
	Di Somma	1.15	0.03	50.38	1 / 7	1 / 8
Low testosterone level		**1.15**	**0.03**	**50.38**	**1 / 7**	**1 / 8**
Amenorrhea/ oligomenorrhea, I^2=0%						

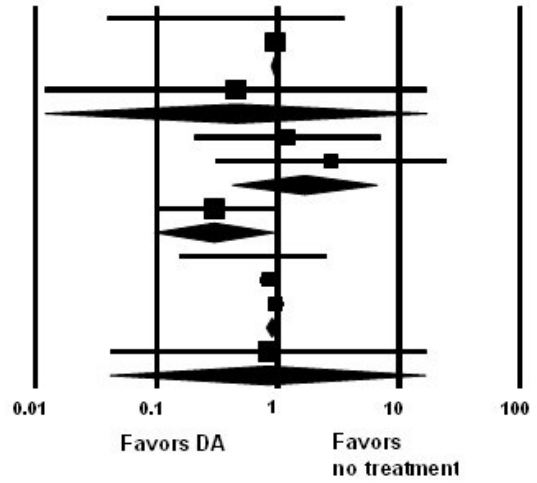


Supplemental Figure 2A: Dopamine Agonists vs. No Treatment
Prolactin Level (ng/mL)

Study name	Difference in means	Lower limit	Upper limit	Sample size: DA	Sample size: No treatment
Touraine	-53.90	-95.96	-11.84	191	23
Jeffcoate	-28.90	-81.10	23.30	23	10
PRL level	**-44.06**	**-76.81**	**-11.31**	**214**	**33**

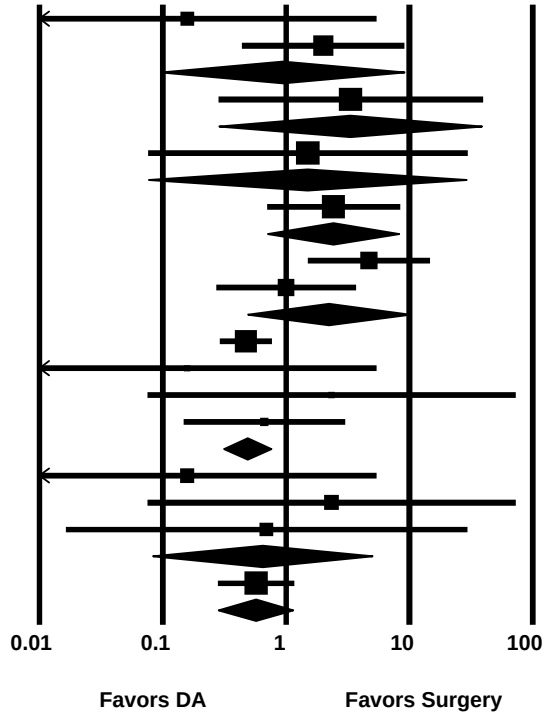
Supplemental Figure 2B: Dopamine Agonists vs. No Treatment
Clinical Outcomes

Outcome	Study name	Risk ratio	Lower limit	Upper limit	Events / Total: DA	Events / Total: No treatment
	Sluiimer	0.38	0.04	3.52	1 / 12	2 / 9
	Mattei	0.95	0.89	1.01	91 / 97	36 / 36
Amenorrhea/oligomenorrhea		**0.95**	**0.89**	**1.01**	**92 / 109**	**38 / 45**
	Sluiimer	0.45	0.01	17.03	1 / 6	1 / 3
Galactorrhea		**0.45**	**0.01**	**17.03**	**1 / 6**	**1 / 3**
	Sluiimer	1.20	0.20	7.05	4 / 10	1 / 3
	Hirahara	2.75	0.31	24.52	3 / 24	1 / 22
Infertility		**1.67**	**0.42**	**6.60**	**7 / 34**	**2 / 25**
	Hirahara	0.30	0.10	0.94	3 / 21	10 / 21
Miscarriages		**0.30**	**0.10**	**0.94**	**3 / 21**	**10 / 21**
	Sluiimer	0.63	0.16	2.51	3 / 16	3 / 10
	Mattei-Idiopathic	0.84	0.72	0.97	38 / 46	21 / 21
	Mattei-Prolactinoma	0.96	0.83	1.11	55 / 61	16 / 17
PRL Level		**0.90**	**0.81**	**0.99**	**96 / 123**	**40 / 48**
	Mattei	0.83	0.04	16.66	2 / 107	0 / 17
Tumor increase		**0.83**	**0.04**	**16.66**	**2 / 107**	**0 / 17**



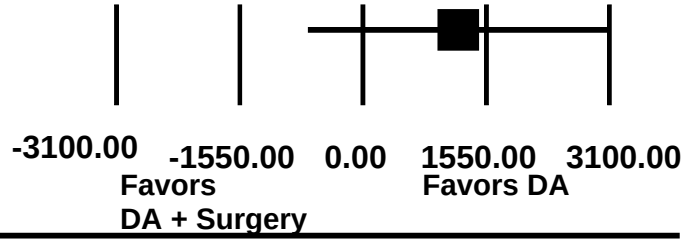
Supplemental Figure 3: Dopamine Agonists vs. Surgery
Clinical Outcomes

Outcome	Study name	Risk ratio	Lower limit	Upper limit	Events / Total DA	Events / Total Surgery
	Shih-Microprolactinoma	0.16	0.00	5.34	1 / 10	1 / 2
	Shih-Macroprolactinoma	2.00	0.45	8.94	1 / 1	1 / 3
Amenorrhea/oligomenorrhea		0.95	0.10	9.15	2 / 11	2 / 5
	Torres	3.33	0.29	38.75	2 / 2	0 / 1
Cranial nerve dysfunction		**3.33**	**0.29**	**38.75**	**2 / 2**	**0 / 1**
	Torres	1.50	0.08	29.15	1 / 7	0 / 3
Galactorrhea		**1.50**	**0.08**	**29.15**	**1 / 7**	**0 / 3**
	Torres	2.42	0.71	8.26	9 / 13	2 / 7
Headaches		**2.42**	**0.71**	**8.26**	**9 / 13**	**2 / 7**
	Samaan-Microprolactinoma	4.69	1.53	14.41	22 / 50	3 / 32
	Samaan-Macroprolactinoma	1.00	0.28	3.61	2 / 6	7 / 21
Female infertility		**2.24**	**0.49**	**10.17**	**24 / 56**	**10 / 53**
	Torres	0.47	0.30	0.75	11 / 25	7 / 7
	Shih-Microprolactinoma	0.16	0.00	5.34	1 / 10	1 / 2
	Shih-Macroprolactinoma	2.33	0.08	71.44	1 / 2	1 / 4
	Brue	0.67	0.15	2.98	2 / 6	2 /
PRL level increased, I2=0%		**0.49**	**0.32**	**0.76**	**14 / 42**	**16 / 16**
	Shih-Microprolactinoma	0.16	0.00	5.34	1 / 10	1 / 2
	Shih-Macroprolactinoma	2.33	0.08	71.44	1 / 2	1 / 4
	Brue	0.69	0.02	28.89	1 / 7	1 / 5
Increase in tumor size		**0.65**	**0.08**	**5.04**	**2 / 18**	**2 / 10**
	Torres	0.57	0.28	1.15	5 / 10	3 / 3
Visual field defects		**0.57**	**0.28**	**1.15**	**5 / 10**	**3 / 3**



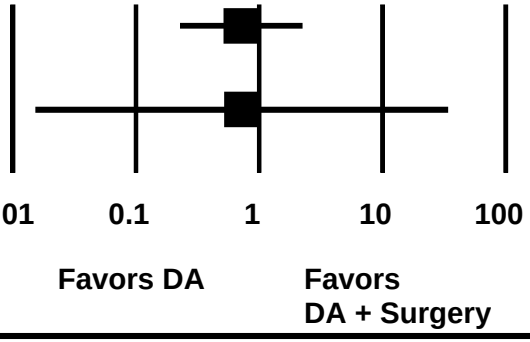
Supplemental Figure 4A: Dopamine Agonists vs. Dopamine Agonists + Surgery
Prolactin level (ng/mL)

Study name	Statistics for each study			Sample size		Difference in means and 95% CI
	Difference in means	Lower limit	Upper limit	DA	DA + Surgery	
Asano	1197.30	-677.86	3072.46	5	8	



Supplemental Figure 4B: Dopamine Agonists vs. Dopamine Agonists + Surgery
Clinical Outcomes

Outcome	Study name	Risk ratio	Lower limit	Upper limit	DA	DA + Surgery	Risk ratio and 95% CI
PRL levels increased	Hildebrandt	0.71	0.23	2.20	4 / 14	4 / 10	
Tumor size increased	Hildebrandt	0.72	0.02	33.64	1 / 15	1 / 11	

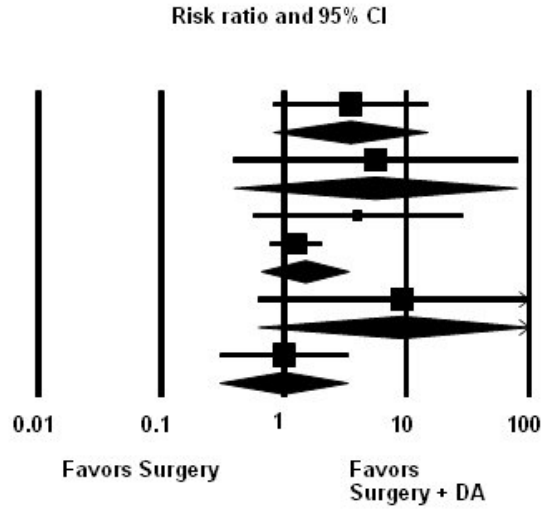


Supplemental Figure 5A: Surgery vs. Surgery + Dopamine Agonists
Prolactin level (ng/mL)

Study name	Statistics for each study			Sample size	
	Difference in means	Lower limit	Upper limit	Surgery	Surgery + DA
Rush	-2.37	-1569.01	1564.27	8	12
Candrina	-1580.00	-4201.57	1041.57	15	6
PRL level	**-426.67**	**-1797.74**	**944.41**	**23**	**18**

Supplemental Figure 5B: Surgery vs. Surgery + Dopamine Agonist
Clinical Outcomes

Outcome	Study name	Risk ratio	Lower limit	Upper limit	Surgery	Surgery + DA
	Perrin	3.50	0.83	14.83	7 / 20	2 / 20
Endocrine dysfunction		**3.50**	**0.83**	**14.83**	**7 / 20**	**2 / 20**
	Candrina	5.60	0.39	79.70	3 / 4	0 / 3
Amenorrhea/oligomenorrhea		**5.60**	**0.39**	**79.70**	**3 / 4**	**0 / 3**
	Perrin-Microprolactinoma	4.00	0.56	28.40	4 / 8	1 / 8
	Perrin-Macroprolactinoma	1.25	0.78	2.01	10 / 12	8 / 12
PRL level increased		**1.49**	**0.66**	**3.38**	**14 / 20**	**9 / 20**
	Candrina	9.19	0.62	135.95	10 / 15	0 / 6
Tumor size increased		**9.19**	**0.62**	**135.95**	**10 / 15**	**0 / 6**
	Candrina	1.00	0.30	3.32	4 / 8	2 / 4
Visual Field defects		**1.00**	**0.30**	**3.32**	**4 / 8**	**2 / 4**



Subgroup analyses (Supplemental Tables 6A-D)

Supplemental Table 6A: Bromocriptine vs. Cabergoline

Outcome/subgroup	# of Studies	RR (95% CI)	I^2	$P_{interaction}$
PRL level increased				
Macro	2	2.89 (1.54 to 5.41)	NA	0.71
Micro	2	3.49 (1.62 to 7.51)	NA	
Men	2	1.69 (0.6 to 7.90)	NA	0.37
Women	2	4.05 (1.29 to 12.68)	NA	
Amenorrhea/oligomenorrhea				
Macro	1	4.83 (0.95 to 24.55)	NA	0.22
Micro	2	0.68 (0.04 to 10.05)	NA	
Galactorrhea				
Men	1	0.69 (0.02 to 28.89)	NA	0.73
Women	1	1.80 (0.04 to 89.09)	NA	
Decreased libido				
Macro	1	0.28 (0.04 to 2.24)	NA	0.91
Micro	1	0.37 (0.01 to 15.25)	NA	
Increased tumor size				
Macro	1	0.512 (0.01 to 24.04)	NA	0.97
Micro	1	0.47 (0.01 to 19.04)	NA	

Supplemental Table 6B: Bromocriptine vs. CV 205-502

Outcome/subgroup	# of Studies	RR (95% CI)	I^2	$P_{interaction}$
PRL Levels				
Men	1	1.15 (0.03 to 50.38)	NA	0.64
Women	2	2.96 (1.05 to 8.35)	NA	
Amenorrhea/oligomenorrhea				
Macro	1	0.56 (0.11 to 2.79)	NA	0.72
Micro	2	0.81 (0.26 to 2.47)	NA	
Galactorrhea				
Macro	1	0.70 (0.02 to 32.45)	NA	0.72
Micro	1	1.91 (0.04 to 83.79)	NA	

Supplemental Table 6C: DA vs. Surgery

Outcome/subgroup	# of Studies	RR (95% CI)	I^2	$P_{interaction}$
PRL level increased				
Macro	2	0.49 (0.31 to 0.77)	NA	0.14
Micro	1	0.16 (0.00 to 5.34)	NA	
Amenorrhea/oligomenorrhea				
Macro	1	2.00 (.045 to 8.94)	NA	0.36
Micro	1	0.16 (0.00 to 5.34)	NA	
Increased tumor size				
Macro	1	2.33 (0.08 to 71.44)	NA	0.28
Micro	1	0.16 (0.001 to 5.34)	NA	

Supplemental Table 6D: Withdrawal from DA

Outcome/subgroup	# of Studies	RR (95% CI)	I^2	$P_{interaction}$
PRL level increased				
Macro	4	0.60 (0.41 to 0.76)	40.1	0.74
Micro	5	0.64 (0.47to 0.78)	63.7	
Amenorrhea/oligomenorrhea				
Macro	4	0.41 (0.1 to 0.82)	82.3	0.75
Micro	6	0.33 (0.1 to 0.67)	86.0	
Increased tumor size				
Macro	4	0.1 (0.04 to 0.24)	59.4	0.49
Micro	3	0.03 (0.01 to 0.09)	0%	
Galactorrhea				
Macro	4	0.20 (0.05 to 0.56)	75.4	0.90
Micro	5	0.23 (0.06 to 057)	78.2	
Decreased sexual potency and libido				
Macro	3	0.19 (0.09 to 0.36)	83.4	0.63
Micro	1	0.23 (0.08 to 0.52)	NA	

Summary of uncontrolled studies of radiotherapy, surgery, combinations of treatment, and pregnancy (Supplemental Tables 7A-F)

Supplemental Table 7A: Radiotherapy studies

Study	Main findings
Jezkova, 2009[127]	80% of patients with prolactinoma who failed DA treatment achieved normoprolactinemia in 96 months (mean) with gamma knife irradiation with halt in growth in 97% of patients.
Pan, 2000[128]	Nearly all patients with prolactinomas treated with gamma knife radiosurgery as a primary treatment achieved tumor control while clinical cure was achieved in over 50% of cases with associated clinical improvement followed for 33.2 months mean with higher doses associated with better clinical outcomes.
Pouratian, 2006[129]	26% of patients with medically and surgically refractory prolactinomas treated with gamma knife radiosurgery achieved clinical remission with low complication rates.
Sun, 2010[130]	In patients with prolactin-secreting adenomas, normalization of PRL occurred in 5/7 (71%) after fractionated radiotherapy, and 0/1 (0%) of patients after stereotactic radiosurgery.
Tsagarkis, 1991[131]	In women with prolactinomas, 50% had normalization of PRL, 28% had reduction in PRL after treatment megavoltage radiotherapy with 8 years follow-up
Yoon, 1998[132]	46% of patients with prolactinomas had normalization of hormonal levels after 1 year of stereotactic radiosurgery compared with 2 years in conventional radiation therapy with similar complication rates.
Zhang, 2000[133]	In patients with hypersecreting pituitary adenomas followed for average 31.6 months, gamma knife radiosurgery as a primary treatment may be safe and effective.
Zierhut,1995[134]	In patients with prolactinomas that were inoperable or had unsuccessful drug treatment who were treated with radiotherapy, all patients achieved persistent reduction of the prolactin level and 27% had normalization of PRL levels with mean follow-up of 6.5 years.

Supplemental Table 7B: Combination of radiotherapy and dopamine agonists studies

Study	Main findings
Kelly, 1978 [135]	Women with hyperprolactinemia and infertility were treated with pituitary implanted radiotherapy with mean follow-up of 27 months, with nearly 75% achieving fertility alone or in combination with bromocriptine.
Littley, 1991[136]	External radiotherapy is effective in reducing serum prolactin levels in patients with pituitary macroadenomas, especially in prolactin-producing tumors with observation of up to 154 months.
Rudoler, 1996[137]	Patients with macroprolactinomas received external beam radiotherapy for residual or recurrent disease after surgery alone or in conjunction with bromocriptine with follow-up for 140 months showed 10 and 15 year freedom from recurrence rates of 95% and 71% respectively with improvement in visual symptoms and prolactin levels in >80% of patients with complications of new or worsening endocrinopathies in 50% of patients.
Tanaka, 2010[138]	After 12 months of followup, 100% of patients with prolactinoma refractory to dopamine agonists who underwent stereotactic radiosurgery achieved tumor control, 77% had a reduction in size > 2mm. Dopamine agonist therapy was continued after radiosurgery until PRL normalized then was discontinued. 18% of patients had biochemical remission at 34 months after radiosurgery.

Supplemental Table 7C: Surgery studies

Study	Outcome
Amar, 2002[139]	After 6-18 years of followup, it was concluded that prolactin levels lower than 10ng/ml on post-op-day 1 predict a long term chemical cure in patients with pituitary adenoma, after undergoing transsphenoidal surgery
Babey, 2011[140]	After 33.5 months of followup, 90% of patients experiences improvement in signs and symptoms, 94% of patients had postoperative PRL levels that returned to normal in patients with small prolactinomas who underwent transsphenoidal surgery
Barbarino, 1982[141]	After 8-24 months of followup, it was found that total selective removal of the microadenoma acutely decreases the prolactin concentration, but a functional inhibition of the normal lactotrope can persist for a period of few months following surgery in some patients
Charpentier, 1985[142]	After average followup of 4.4 years, selective surgical adenomectomy was found to be the only treatment able to achieve a definitive cure with a low iatrogenic risk, in patients with prolactinomas
Dusick, 2008[143]	After at least 3 months of followup, it was found that, following transsphenoidal surgery on pituitary adenoma hyperprolactinemia resolution occurred in 67% of patients
Fatemi, 2008[144]	After 8 years of followup, it was concluded that after transsphenoidal adenomectomy, new unplanned hypopituitarism occurred in approximately 5% of patients, whereas improved hormonal function occurred in 50% of patients, and that new hypopituitarism occurs most commonly in patients with tumors larger than 20 mm in size
Feigenbaum, 1996[145]	After 9 years of followup, it was concluded that, women undergoing transsphenoidal surgery for prolactin-secreting adenoma form a heterogenous patient population and that the best long term results would be achieved in the pure prolactinoma group, for which this surgery is safe and effective
Gokalp, 2000[146]	After 1-10 years of followup, it was concluded that transsphenoidal microsurgery is a safe and efficient approach and can be recommended as an alternative to medical treatment, or for patients who are intolerant or resistant to dopamine agonists
Guidatti, 1987[147]	After 11 years of followup, it was determined that, transcranial surgery was preferred over transsphenoidal in debulking large adenomas. It was also determined, that post-operative radiotherapy was of value in invasive adenomas and in cases in which tumor removal was not radical
Hamilton, 2005[148]	After surgically intervening on 79 prolactinoma patients that are either resistant or intolerant to medical therapy, it was concluded that transsphenoidal surgery often provides a suitable option for treating that category of patients.
Hirohata, 1991[149]	After a mean followup period of 60 months, pregnancy was found to have no effect on prolactin level, in patients with normal post-operative hormone levels
Laws, 1985[150]	After 37 months of followup, 31% of patients receiving secondary transsphenoidal surgery for prolactinoma were deemed successful but with higher complication rates postoperatively
Maira, 1989[151]	After an average followup of 3.4 years, it was found that a slightly elevated postsurgical prolactin level does not imply that tumoral tissue is still present
Massoud, 1996[152]	After 10-20 years of followup, it was concluded that most of the patients who received transsphenoidal surgery for their microprolactinoma were asymptomatic. Furthermore, those who have had late relapse of hyperprolactinemia, it was found their hyperprolactinemia was mild, non symptomatic and functional
Nakagawa, 2001[153]	Following transsphenoidal surgery on 13 patients with prolactinomas, the result was normalization of prolactin levels post-op in 9 patients, with preservation of normal pituitary function
Pandey, 2005[154]	After a followup period ranging from 3 months, up to 10 years, it was concluded that the transsphenoidal approach is an effective and safe surgical modality for pituitary macroadenomas

Qu, 2011[155]	After 45 months of followup, men with prolactinoma undergoing transsphenoidal surgery, 52.9% of patients achieved initial remission (83.3% of microadenomas; 44.9% of macroadenomas). The long-term remission rate was 42.5% while relapse of hyperprolactinemia occurred in 19.6% of cured patients. The 5-year recurrence-free survival was 78.2%
Rawe, 1980[156]	After 18 months of followup, it was concluded that transsphenoidal microsurgical removal of prolactinomas is a highly effective approach, leading to significant normalization of preoperative prolactin levels, resumption of menses and the recovery of fertility in patients with microadenomas
Saitoh, 1986[157]	Following the surgical intervention on 98 patients with prolactinomas, it was found the post-operative course was closely related to tumor size and the preoperative levels of prolactin. Prolactin levels returned to normal in 37, 33% in patients with microadenomas, and expansive macroadenomas in that order. Furthermore, 35% of premenopausal women resumed normal menopause
Santoro, 2007[158]	After 56 months of followup, it was concluded that transsphenoidal surgery is an effective treatment for secreting pituitary tumors. Long term endocrinologic followup was recommended due to possibility of tumor recurrence
Scamoni, 1991[159]	After a followup period ranging from 18-120 months, transsphenoidal microsurgery was deemed the therapy of first choice for microadenoma and mesoadenoma treatment, especially with the presence of bromocriptine intolerance
Shen, 2000[160]	Following endoscopic endonasal transsphenoidal surgery on 18 patients with prolactinomas and subsequent 2-26 month followup, complete resolution was achieved in 78% of patients, 1 patient with recurrent microprolactinoma required second operation, all without complications related to the surgical approach
Sinha, 2011[105]	After 39 months of followup in patients with prolactinoma undergoing surgery either transsphenoidally or transcranially, hormonal remission was achieved in 44% (83% microadenomas, 48% macroadenomas, and 16% of giant adenomas). The overall mortality was 1.7%, all who had giant invasive tumors.
Soule, 1996[161]	After 38 months of followup of 34 patients, who underwent pituitary surgery for micro and macroprolactinomas, the cure rate in a tertiary referral centre, was relatively low compared to the results achieved in the past when surgery was used as a primary therapeutic modality
Webster, 1992[162]	After a mean followup period of 51 months, it was concluded that in carefully selected patients, partial hypophysectomy is an acceptable alternative to medical treatment for prolactinoma
Wolfsberger, 2003[163]	After 2-13 years of following up 11 men who received transsphenoidal surgery for pituitary microprolactinoma, it was concluded that microadenomas in men are potentially curable by transsphenoidal adenomectomy alone with low complication and recurrence rates in the hands of an experienced surgeon
Zhang, 2008[164]	After 13 months of followup, transsphenoidal surgery was found to be a safe and effective treatment for pituitary microadenoma, and that in order to obtain better effects; it must be ordered as first-line treatment for patients with locally non-invasive prolactin secreting microadenoma

Supplemental Table 7D: Combination of surgery and dopamine agonists studies

Study	Main findings
Jamjoom, 1995[165]	In large prolactin-secreting adenomas is high, only 27% of patients were normoprolactinemic after surgery; the rest required additional postoperative treatment with surgery and dopamine agonist therapy achieving overall normalization rates of 71% over a 10 year period.
Saeki, 1998[166]	Patients with giant prolactinomas with poor initial response to bromocriptine alone were treated with continued bromocriptine achieving normalization in 60% of cases while the remaining 40% required surgery
Thompson, 2002[167]	Patients with microprolactinoma who underwent transsphenoidal surgery were followed for 15-21 years with initial normalization in all patients. 18.2% experienced recurrent hyperprolactinemia at a mean interval of 5.3 years but was permanent in only 5% of patients.
Thomson, 1994[168]	Women with microprolactinoma who underwent transsphenoidal surgery were followed for 10 years had recurrence in 12% of patients.
Touraine, 2001[26]	Hyperprolactinemic women with menstrual disorders were followed for 100 months treated with bromocriptine with disappearance of adenoma in 45% and nearly all stabilization of tumor size in 40%; surgery which led to disappearance of adenoma in almost all cases but failed to provide a definitive cure.

Supplemental Table 7E: Combination of surgery and radiation therapy studies

Study	Main findings
Oruckaptan, 2000[169]	Patients with pituitary adenomas treated surgically with or without postoperative radiotherapy with mean follow-up time 40.5 months. Surgery alone achieved tumor control in 79.6% of patients and in 78.12% of those who received radiotherapy after surgery. Topical application of bromocriptine into the sellar cavity after tumor removal seems to provide superior results.
Rush, 1997[170]	After a median followup of 8 years, 97% of patients with pituitary macroadenomas receiving combination surgery and postoperative radiotherapy had regression or stabilization of the adenoma, while 84% with visual impairment improved

Supplemental Table 7F: Pregnancy studies

Study	Outcome
Badawy, 1997[171]	After a followup period of 1-14 years, it was concluded that it is safe for patients with prolactinomas to achieve pregnancy following bromocriptine treatment. It was also suggested that pregnancy might lead to a slight decrease in the size of prolactinomas, increase in size, no change, and in some cases complete resolution.
Berinder, 2007[172]	After examining the records of 271 women with primary hyperprolactinemia, it was concluded that parity was reduced compared to normal controls. However, there were no increased risks of adverse pregnancy or delivery outcomes once a woman with treated hyperprolactinemia became pregnant.
Ciccarelli, 1997[32]	After a followup period of 1-82 months (mean: 28.3) it was found that prolactin level in pregnant hyperprolactinemic women were within the normal limits, apart from one case (out of nine) which had a higher prolactin level towards the third trimester. All pregnancies had normal courses and outcomes.
Colao, 2008[173]	After a followup period of 12 years, it was concluded that fetal exposure to cabergoline through early pregnancy does not induce any increase in the risk of miscarriage of fetal malformation.
Cristiani, 1985[174]	After following up on 17 bromocriptine-induced pregnancies in hyperprolactinemic patients, it was observed that plasma prolactin levels were elevated during the entire pregnancy without the progressive rise, as in normal pregnancies. Pregnancies were all uneventful, with only one patient complaining of headache.
Crosignani, 1989[175]	After followup of about 6 months, it was concluded that pregnancy itself normalizes plasma prolactin in 17% of hyperprolactinemic women.
Crosignani, 1992[176]	After 6-18 months of followup of hyperprolactinemic women, it was suggested that prolactin levels can be normalized during pregnancy, and that pregnancy is quite safe for these patients.
Godo, 1989[177]	After following up on 50 hyperprolactinemic women, it was found that pregnancy did not increase the risk of pregnancy, delivery and nursing complications.
Holmgren, 1986[178]	After following up on 35 prolactinoma women, through 41 pregnancies, it was concluded that women with hyperprolactinemia, irrespective of sella pathology, should be treated with bromocriptine for at least one year before pregnancy is recommended.
Jeffcoate, 1996[179]	After followup period of 2.8+/-2.7 years, it was concluded that hyperprolactinemia will be self-limiting in up to one-third of women, and that pregnancy may be one factor which triggers a return to normal function.
Karunakaran, 2001[180]	After followup of 1-19 years, it was concluded that women with hyperprolactinemia who pass through menopause or through pregnancy have a significant chance of normalizing their prolactin levels.
Kelly, 1979[181]	After following up on 27 women through 41 pregnancies, it was found that tumor enlargement as shown by diminished visual acuity, visual field defects, severe headaches, diabetes insipidus and radiological changes occurred only in 3 of 14 patients who had not had pituitary implantation with 90 yttrium.
Kupersmith, 1994[182]	After following up on 65 hyperprolactinemic women, during 111 pregnancies, it was concluded that the risk of developing visual loss during single or multiple pregnancies in patient with microadenoma was small. Six of eight pregnant women with macroadenomas, however, developed visual field loss during pregnancy,
Mattei, 1991[15]	After a followup of 6-180 months (mean: 44.9), it was concluded pregnancy had a beneficial, yet unexplained effect on prolactin in women with pathologic hyperprolactinemia.
Ono, 2010[101]	After 8 years of follow-up after initiation of cabergoline in hyperprolactinemic infertile women with micro- or macroprolactinoma, hyperprolactinemia and ovulatory cycle was recovered in 100% of patients, 94% became pregnant with

	95 pregnancies (93 achieved while still on cabergoline). Of the 93, 86 resulted in 93 single live births, one stillbirth, and two abortions with 7 ongoing at the conclusion of the study. All babies were born healthy without malformations.
Rasmussen, 1985[183]	After followup of 58 hyperprolactinemic women for 13-108 months, it was concluded that bromocriptine induction of ovulation and pregnancy followed by lactation in these women, did not worsen their condition but rather a considerable number of them had a decrease in prolactin hypersecretion and even experienced the return of spontaneous uterine bleedings.
Rossi, 1995[184]	After examining the outcome of 103 pregnancies in 64 women with constant hyperprolactinemia, it was found 66% of all pregnancies ended in delivery, 17% in miscarriages, 10% in tubal pregnancy and 7% in induced abortion. The only significant effect of hyperprolactinemia was determined to be an increased risk of tubal pregnancy
Stalldecker, 2010[105]	90 women with hyperprolactinemia achieved 103 pregnancies after cabergoline treatment for 1 to 120 months with doses ranging from 0.125 to 5 mg/week with no significant complications during pregnancy. 7.2% had spontaneous abortions, preterm deliveries occurred in 8.8%, and neonatal abnormalities were seen in 3.6%.
Woodhouse, 1985[185]	After following up 14 previously infertile patients with hyperprolactinemia, it was concluded that fertility can be restored using bromocriptine even in patients with a large prolactin secreting tumor.
Zarate, 1979[186]	After 6-14 months of post pregnancy followup, it was concluded that patients with microadenomas can be allowed to become pregnant on bromocriptine alone, provided they are carefully supervised during pregnancy.

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Search Strategy:

Prolactinoma Agonists

EMBASE/MEDLINE
1. prolactin/bl, se or hyperprolactinemia/ or hyperprolactin*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2. exp Adenoma/
3. pituitary neoplasms/ or prolactinoma/
4. 3 or prolactinoma*.mp. or microprolactinoma*.mp. or macroprolactinoma*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
5. 2 or macroadenoma*.mp. or microadenoma*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
6. 1 and hypersecreting*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7. 1 and 5
8. 4 or 6 or 7
9. ((lactotroph or prl or prolactin) adj (producing or secreting)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
10. 8 or 9
11. exp Dopamine Agonists/
12. ((dopaminergic or dopamine) adj3 (stimulating or agonist*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
13. (abeorphine or acetergamine or adrogolide or aletnamol or amantadine or apocodeine or apomorphine or aripiprazole or bifeprunox or bromocriptine or cabergoline or carmoxirole or ciladopa or dihydrexidine).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
14. (dihydroergocryptine or disulergine or docarpamine or dopamine or dopexamine or dronabinol or epinine).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
15. (fenoldopam or glutamyldopa or ibopamine or indatraline or isomolpan or lisuride or mergocriptine or mesulergine or minaprine or moxiraprine or naxagolide or nolomirole or orotirelin or pardoprunox or pergolide or piribedil or pramipexole or preclamol).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
16. (propylnorapomorphine or quinagolide or quinelorane or quinpirole or roxindole or sibenadet or sumanirole or talixpexole or terguride or vanoxerine).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
17. or/11-16
18. 10 and 17
19. ..l/ 18 hu=y
20. 1 and hyperprolactinemia/dt, su, rt, th
21. 17 and 20
22. ..l/ 21 hu=y
23. 19 or 22
24. exp clinical trials as topic/
25. 23 and (exp cohort studies/ or exp case-control studies/ or cohort*.mp. or observation*.mp. or prospective studies/ or retrospective studies/)
26. 23 and 24
27. limit 23 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or practice guideline or randomized controlled trial)
28. 23 and follow-up studies/ and comparative studies/
29. 25 or 26 or 27 or 28
30. 29 and (outcome*.mp. or treatment outcome/ or follow-up studies/) [mp=title, original title, abstract, name of substance word, subject heading word]
31. (postoperative complications/ or exp radiotherapy/ae) and 29
32. 29 and ae.fs.
33. exp infertility, male/ or exp infertility, female/ or amenorrhea/ or exp headaches/ or exp cranial nerve disorders/ or gynecomastia/ or exp vision disorders/
34. exp Sexual Dysfunction, Physiological/ or exp Sexual Behavior/ or exp Erectile Dysfunction/
35. exp heart valve diseases/ or exp fractures, bone/ or exp bone diseases, metabolic/ or exp menstruation/
36. exp Withholding Treatment/
37. exp pituitary neoplasms/pa
38. or/33-37
39. exp quality of life/

40. (volume or size or growth or enlarge* or withdraw*).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
41. 29 and 38
42. 29 and (39 or 40)
43. 42 or 32 or 30 or 41 or 31
44. from 43 keep 1-540
45. restor*.mp. or recovery of function/ or neoplasm recurrence, local/ or normaliz*.mp. or normalis*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
46. 29 and 45
47. 46 not 44

WOS/SCOPUS
# 6 468 #5 OR #1
Databases=SCI-EXPANDED Timespan=1993-2009
# 5 311 #4 AND #3 AND #2
Databases=SCI-EXPANDED Timespan=1993-2009
# 4 >100,000 TS=(trial* or cohort* or random* or meta-analysis or metaanalys* or compar* or outcome*)
Databases=SCI-EXPANDED Timespan=1993-2009
# 3 4,433 TS=(prolactinoma* or hyperprolactin* or macroprolactin* or microprolactin* OR ((PRL or prolactin*) SAME (adenoma* or tumor* or tumour* or microadenoma* or macroadenoma*)))
Databases=SCI-EXPANDED Timespan=1993-2009
# 2 74,897 TS=(dihydroergocryptine or disulergine or docarpamine or dopamine or dopexamine or dronabinol or epinine or fenoldopam or glutamyldopa or ibopamine or indatraline or isomolpan or lisuride or mergocriptine or mesulergine or minaprine or moxiraprine or naxagolide or nolomirole or orotirelin or pardoprunox or pergolide or piribedil or pramipexole or preclamol or propylnorapomorphine or quinagolide or quinelorane or quinpirole or roxindole or sibenadet or sumanirole or talixpexole or terguride or vanoxerine)
Databases=SCI-EXPANDED Timespan=1993-2009
# 1 369 Topic=(prolactinoma* or hyperprolactin* or macroprolactin* or microprolactin* OR ((PRL or prolactin*) SAME (adenoma* or tumor* or tumour* or microadenoma* or macroadenoma*))) AND Topic=(((dopamine or dopaminergic) SAME (stimulat* or agonist*)) or (abeorphine or acetergamine or adrogolide or aletnamol or amantadine or apocodeine or apomorphine or aripiprazole or bifeprunox or bromocriptine or cabergoline or carmoxirole or ciladopa or dihydrexidine)) AND Topic=(trial* or cohort* or random* or meta-analysis or metaanalys* or compar* or outcome*)
Databases=SCI-EXPANDED Timespan=1993-2009

Prolactinoma - Natural History

1. hyperprolactinemia/ or prolactin/bl, se or hyperprolactin*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2. 1 and ((prolactinom* or microprolatinom* or macroprolactinom*).mp. or exp adenoma/ or microadenoma*.mp. or macroadenoma*.mp. or exp pituitary neoplasms/) [mp=title, original title, abstract, name of substance word, subject heading word]
3. ..l/ 2 hu=y
4. exp clinical trials as topic/ or registries/ or interventional study/
5. longitudinal studies/ or case-control studies/ or exp cohort studies/ or observation*.mp. or prospective*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
6. follow-up studies/ or series.mp. or longterm*.mp. or baseline*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7. limit 3 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or practice guideline or randomized controlled trial)
8. 3 and (4 or 5 or 6)
9. 7 or 8
10. exp adenoma/th, rt, su or exp pituitary neoplasms/th, su, rt or prolactinoma/th, rt, su or hyperprolactinemia/rt, th, su
11. exp radiotherapy/
12. exp Hypophysectomy/
13. exp Pituitary Gland/rt, th, de, su [Radiotherapy, Therapy, Drug Effects, Surgery]
14. 9 and (10 or 11 or 12 or 13)
15. 9 and (treatment outcomes/ or prognosis/ or disease progression/ or natural history/ or recurr*.mp. or treatment withdrawal.mp. or withdraw*.mp.) [mp=title, original title, abstract, name of substance word, subject heading word]
16. ((clinical or natural) adj2 (progress* or course* or history)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

17. (watchful* or monitor* or wait* or observ* or untreat* or nonoperat* or nontreat*).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
18. 9 and (16 or 17)
19. (volume or size or growth or enlarge* or withdraw*).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
20. exp Hypogonadism/
21. infertility/ or exp infertility, male/ or exp infertility, female/
22. exp Sexual Dysfunction, Physiological/
23. Galactorrhea/
24. exp bone diseases, metabolic/ or exp fractures, bone/ or exp heart valve diseases/
25. Amenorrhea/
26. Gynecomastia/
27. exp headaches/ or exp cranial nerve disorders/ or osteopenia.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
28. exp Vision Disorders/
29. exp quality of life/
30. or/20-29
31. 14 or 15 or 18
32. exp Hypogonadism/co, pc or (infertility/co, pc or exp infertility, male/co, pc or exp infertility, female/co, pc) or exp Sexual Dysfunction, Physiological/co, pc or Galactorrhea/co, pc or (exp bone diseases, metabolic/co, pc or exp fractures, bone/co, pc or exp heart valve diseases/co, pc) or Amenorrhea/co, pc
33. 9 and 32
34. Amenorrhea/co, pc or Gynecomastia/co, pc or (exp headaches/co, pc or exp cranial nerve disorders/co or osteopenia/co, pc) or exp Vision Disorders/co, pc or exp quality of life/ or treatment outcomes/
35. 9 and 34
36. 31 or 33 or 35
37. 36 and (untreat* or nontreat* or sham or control* or nonoperat* or nonsurg* or wait*).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
38. 36 and ((clinical or normal or natural) adj2 (course or progress* or history)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
39. 36 and placebo*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
40. 36 and watch*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
41. or/37-40
42. from 41 keep 1-140

SCOPUS
(TITLE-ABS-KEY(hyperprolactin* AND (hypersecret* OR prolactinom* OR macroprolactinom* OR microprolactin* OR adenoma* OR macroadenom* OR microadenoma*)) AND TITLE-ABS-KEY((untreat* OR "un-treated" OR "natural history" OR "normal course" OR progress*)))

WOS
Topic=(hyperprolactin* or prolactinoma* or macroprolactinoma* or microprolactinom* OR (prolactin secreting)) AND Topic=(((clinical or normal or natural) SAME (course or history or progress)) OR untreat* or "un-treat*")

COCHRANE
1 (hyperprolactin* or prolactinom* or microprolactin* or macroprolactin*).mp. [mp=title, short title, abstract, full text, keywords, caption text] 26 Advanced Display
2 ((clinical or normal or natural) adj2 (course or history or progress*)).mp. [mp=title, short title, abstract, full text, keywords, caption text] 580 Advanced Display
3 (untreat* or wait* or nontreat* or unoperat*).mp. [mp=title, short title, abstract, full text, keywords, caption text] 996 Advanced Display
4 1 and (2 or 3) 5 Advanced Display
5 1 and (arm*1 or control* or placebo* or sham).mp. [mp=title, short title, abstract, full text, keywords, caption text] 26
6 5 and (2 or 3) 5
7 4 or 6 5 Advanced Display