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META-ANALYSIS

Optimal timing of dopamine agonist withdrawal in patients with hyperprolactinemia: a systematic review and meta-analysis

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Abstract
Purpose Dopamine agonists (DAs) are recommended as first-line treatment for patients with hyperprolactinemia. Generally, it is accepted that patients with hyperprolactinemia do not need lifelong medication, but the optimal timing for DA withdrawal has not been determined. The aim of this systematic review and meta-analysis is to assess the impact of DA withdrawal on the clinical outcomes of patients with hyperprolactinemia, and to explore possible factors affecting successful DA withdrawal.
Methods The databases of PubMed, Cochrane and EMBASE were searched up to May 2016.
Results The proportion of patients with persisting normoprolactinemia after DA withdrawal reached 36.6% in a random effects model (95% CI, 29.4–44.2%; I-squared: 82.5%). Data of stratified analysis showed that the success rate of drug withdrawal was high in patients using cabergoline (CAB) as the only treatment (41.2%; 95% CI 32.3–50.4%) and those using CAB over 24 months (48.7%; 95% CI 38.9–58.5%), especially in patients with idiopathic hyperprolactinemia (73.2%; 95% CI 55.6–87.7%). In addition, patients who received a low maintenance dose of CAB, and had a significant reduction in tumor size (over 50%) before withdrawal, were more likely to achieve success (51.5 and 49.4%, respectively).
Conclusion The success rate of DA withdrawal has increased in recent years. Further, the success rate of CAB withdrawal was higher than that of bromocriptine, especially in patients with a duration of treatment longer than 24 months. Conclusively, the probability of success was higher in patients who received low-dose CAB maintenance treatment and those who achieved a significant reduction in tumor size before withdrawal.

Keywords Dopamine agonists · Withdrawal · Hyperprolactinemia · Prolactinoma · Cabergoline · Bromocriptine

Introduction

Dopamine agonists (DAs) are the first-line treatment for hyperprolactinemia, they can effectively reduce prolactin (PRL) level and tumor size [1–5]. Bromocriptine (BRC) and cabergoline (CAB) are the most commonly used DAs. However, after treatment, sudden stop of DA administration may run the risk of tumor re-growth and recurrence [6–8]. Therefore, the question of how to reasonably reduce the dose of DAs and achieve a complete withdrawal is a critical clinical issue of great significance.

The 2005 edition Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas [9] pointed out that a complete drug withdrawal in some patients was possible, and in patients with normalized PRL levels, and significant reduction in tumor volume, DA treatment should last more than 1 year. The end point of this guideline is to suggest the best timing of withdrawal in order to minimize recurrences.

Recently, the United States Endocrine Society emphasized the importance of "withdrawal standard" [1].

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According to the systematic review by Dekkers et al. [10] and other three supportive studies [11–13], patients should receive DA therapy for at least 2 years until their serum PRL levels got normalized and there was no residual tumor on magnetic resonance imaging (MRI). Obviously, the withdrawal standard of this guideline emphasizes the importance of prolonged DA treatment and tumor disappearance. In addition, the use of CAB prior to other DAs is also recommended, since CAB can help reduce the PRL level and tumor volume in a more efficient way.

The aim of this systematic review and meta-analysis is to discuss the optimal timing of DA withdrawal in hyperprolactinemia patients, by reviewing the past and the current studies to provide useful clues for decision making of DA withdrawal in clinical practice.

Subjects and methods

Search strategy

First search was performed in PubMed, Cochrane, and EMBASE databases. The references in the relevant papers were also examined. Unpublished results were not included in this analysis. The assessment of successful withdrawal was mainly based on PRL levels. Clinical symptoms and tumor size were regarded as auxiliary references.

Inclusion criteria

The validity of studies included in this review can be referred to the criteria in Table 1.

Methods

Whenever possible, each article was stratified by idiopathic hyperprolactinemia, microprolactinomas and macroprolactinomas, BRC, and CAB, respectively. If a subgroup of a cohort was withdrawn from DA treatment, data was extracted for this subgroup only.

These are two main units when measuring prolactin levels (mIU/l and ng/ml). All PRL levels in this meta-analysis were reported in nanograms per milliliter. It is impossible to acquire the conversion factors from all the assays. The conversion factor between them is 21.2 (as shown in http://prolactinemia.com/info/levels-units/). The tumor regression during DA treatment was determined by MRI and computed tomography (CT). Two independent reviewers (M.Y.X. and X.H.L.) were responsible for the study selection and data extraction. Any disagreement that occurred would be resolved by a group discussion and negotiation.

Table 1 Inclusion criteria

Kind of patients	All patients had hyperprolactinemia
	Dopamine agonists are limited to BRC and CAB. Cause of hyperprolactinemia are limited to idiopathic hyperprolactinemia, microprolactinomas and macroprolactinomas
	Treatment time was at least 2 years
	Patient's follow up period was at least 6 months
Study data	Rate of hyperprolactinemia recurrence in patients after DAs withdrawal must be reported or can be calculated
	Variables as type of dopamine agonist, and treatment duration had to be reported. Extra data like age, gender, mean PRL before treatment or before drug withdrawal, regression of tumor during treatment on MRI or CT, are also valuable, and the more detailed, the better
	There should be no duplication of cohort. In studies where partial duplication was present, the largest cohort was chosen

Statistical methods

The weighted average of the proportion of patients with persisting normoprolactinemia after DA withdrawal was the main outcome of this meta-analysis. We used Cohen's as the standardized mean difference calculation method. Since the original data did not conform to the normal distribution, all the statistical results were processed by double inverse sine statistical method. Multivariate regression analysis would be used to determine which of the independent variables are significant, and which are not. Sensitivity analysis would be conducted on low-quality studies. Heterogeneity degree was carried out for each meta-analysis using the I-squared statistic (I-squared $< 25\%$ and I-squared $> 50\%$ reflect small and large inconsistencies, respectively [14]).The Q statistic test would be used to assess the heterogeneity. And the Egger's test would be used to investigate whether there was a publication bias. A p-value < 0.05 was considered to be statistically significant. Based on the results of meta-analysis, several subgroup analyses were performed. Review Manager (version 5.3.5; the cochrane collaboration) and STATA (version 13.0; Stata Corporation, College Station, TX) were used for carrying out these statistical analyses.

Results

Search results

First search in PubMed, Cochrane, and EMBASE databases up to May 2016 retrieved a total of 795 articles by using following free terms: "dopamine agonist, withdrawl",

"Bromocriptine, withdrawal", "Cabergoline, withdrawl", and "hyperprolactinemia, withdrawal". Among them, 519 articles were excluded because of insufficient correlations with the theme. And an additional 198 papers were excluded based on the duplication. Moreover, another 49 articles were also excluded from further analysis due to the lack of specific experimental data, preliminary experimental results, or patient information. Also, two articles were excluded because they focused on the second time of drug withdrawal [15, 16]. Three more studies were eliminated for using different drugs: quinagolide, dihydroergocriptine, and lisuride [17–19]. One paper was added after check of ref. [20]. One paper mixed with patients with empty sella was also removed [21]. Finally, 24 potentially relevant papers [11, 12, 20, 22–42] were retrieved for full assessment (Fig. 1).

Study characteristics

Details of the 24 articles are summarized in Tables 2a, 2b and 2c. The time span ranged 37 years from 1979 to 2016, and the number of patients involved in each study varied from 2 to 221. The total number of patients in this meta-analysis was 1106. Stratified data was available for a total of 727 microprolactinoma patients and 306 macroprolactinoma patients. While a paper [32] engaged a total of 32 patients, the patients could not be separated concerning different etiologies. The proportion of patients with

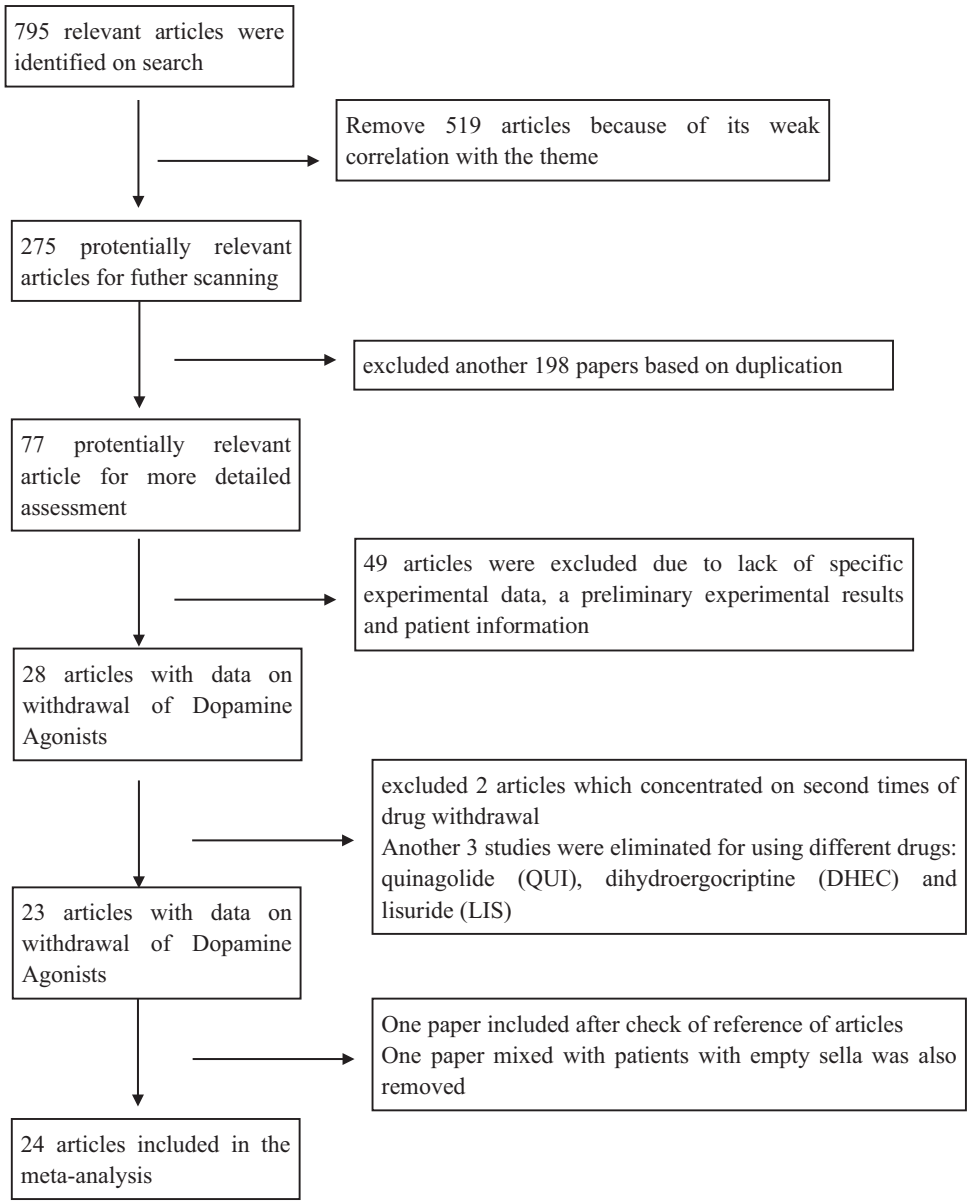

Fig. 1 Summary of study assessment and exclusion. The search in PubMed, Cochrane, and EMBASE databases yielded a total of 794 articles. After screening, 24 potentially relevant papers were retrieved for full assessment consequently

Table 2a Characteristics for included studies in patients with BRC

First author, year of publication	Cause of hyperprolactinemia	Low dose of CAB (Y or N)	DAs treatment	Mean dose (mg/week)	No. of patients	Mean age (year)	Male/female	Mean treatment duration (months)	Pretreatment	Mean PRL before treatment (ng/ml)	Normalization in therapy Y/N (dose)	Regression of tumor during treatment on MRI OR CT (Y or N)	Persisting normoprolactinemia	Mean follow-up in persisting normoprolactinemia (months)
Eversmann, 1979 [40]	Micro	NA	BRC	3.58	6	32.6	1/5	7.1	N	105.8	ND	NA	0	NA
Sobrinho, 1981 [42]	Macro	NA	BRC	7.5	2	31	0/2	6	N	3555	N	NA	0	NA
Zarate, 1983 [23]	Micro	NA	BRC	15–20	4	33.3	0/4	24	N	129.8	ND	N	2(50%)	24
	Macro	NA	BRC	15–20	10	28.2	0/10	24	N	262	ND	(2)	4(40%)	18.8
Coculescu, 1983 [39]	Micro	NA	BRC	7.5	2	36.5	0/2	8	N	(8)	ND	NA	0	NA
Maxson, 1984 [41]	Micro	NA	BRC	6	5	33.2	0/5	11	3OP	211	ND	ND	0	NA
Mattei, 1984 [34]	Idiopathic	NA	BRC	5–20	14	ND	0/14	10.6	N	80.6	(1)	NA	3(21.4%)	7
	Macro	NA	BRC	5–20	3	ND	0/3	18	N	77.3	(1)	N	0	ND
Moriondo, 1985 [29]	Micro	NA	BRC	8	32	29.9	0/32	12	8OP	106	ND	ND	4(12.5%)	24.8
Winkelmann, 1985 [20]	Micro ($n = 5$)	NA	BRC	ND	40	ND	19/21	62.4	28OP	ND	ND	(3)	Total 7(17.5%),	21.5
	Macro ($n = 35$)												Micro 4(80%), Macro 3(8.6%)	
Ho, 1985 [33]	Micro	NA	BRC	ND	7	27.4	0/7	63	N	120.8	ND	NA	4(57.1%)	28.8
van't Verlaat, 1991 [31]	Macro	NA	BRC	10.8	12	42.2	8/4	58.6	N	3113.2	Y(16.6–21.2)	(4)	1(8.3%)	12
Passos, 2002 [22]	Micro($n = 62$)	NA	BRC	6.9	131	32.1	30/101	60	7RT,38OP	894	Y	ND	Total 27(20.6%),	37
	Macro($n = 69$)												Micro 16(25.8%), Macro11(15.9%)	

BRC bromocriptine, *PRL* prolactin, *OP* surgery, *RT* radiotherapy, *NA* not applicable, *ND* no data, *Y* yes, *N* no

(1) back to normal or less than 50%, (2) no regression in tumor size in six patients, (3) tumor shrinkage in 4, (4) tumor volume reduction >50% in all patients, (8) the unit of prolactin level is unknown

Table 2b Characteristics for included studies in patients with CAB

First author,year of publication	Cause of hyperpro-lactinemia	Low dose of CAB (Y or N)	DAs treatment	Mean dose (mg/week)	No. of patients	Mean age (year)	Male/ female	Mean treatment duration (months)	Pretreatment	Mean PRL before treatment (ng/ml)	Normalization in therapy Y/N (dose)	Regression of tumor during treatment on MRI OR CT (Y or N)	Persisting normopro-lactinemia	Mean follow-up in persisting normoprolactinemia (months)
Ferrari, 1992 [32]	Micro/ macro	N	CAB	0.2–3.5	32	17–47	0/32	14	ND	105	ND	N	10 (31.25%)	12
Muratori,1997 [25]	Micro	N	CAB	0.93	25	25–48	0/25	12	3OP	124.8	Y	(5)	2(8%)	49
Cannavo, 1999 [24]	Micro	N	CAB	0.98	18	30.8	2/16	24	N	193.8	ND	(5)	4(22.2%)	12
	Macro	N	CAB	1.77	9	28.1	1/8	24	N	404.1	ND	(5)	1(11.1%)	1(11.1%)
Colao, 2007 [38]	Idiopathic	Y	CAB	0.5	27	27	0/27	39	N	95.9	NA	NA	20(74.1%)	57
	Micro	Y	CAB	1.2	115	32	12/ 103	43	N	222.4	NA	(4)	76(66.1%)	47
	Macro	Y	CAB	1.2	79	44	36/43	42	N	1261.8	NA	(4)	37(46.8%)	44
Kharlip, 2009 [12]	Micro	Y	CAB	ND	31	44	5/26	43	ND	73	Y(3.6)	(5)	15(48%)	15
	Macro	Y	CAB	ND	11	54	7/4	56	ND	310	Y(1.9)	(5)	5(45%)	16
Huda, 2010 [26]	Micro	Y	CAB	ND	25	41	0/25	108	ND	ND	ND	N	6(24%)	12
Buyukbayrak, 2010 [28]	Micro	Y	CAB	ND	128	31	0/128	2	ND	74.5	Y(2.5)	Y	51(39.9%)	6
Barber, 2011 [27]	Micro	N	CAB	ND	39	ND	3/36	49	ND	86.4	Y(13.11)	(6)	14(35.9%)	12
	Macro	N	CAB	ND	14	ND	6/8	90	ND	1332.4	Y(6.8)	(6)	1(7.2%)	12
Anagnostis, 2012 [11]	Micro	Y	CAB	ND	8	35.3	ND	79	ND	112	Y(12.2)	(4)	4(50%)	49
Sala, 2016 [37]	Micro	N	CAB	0.96 ± 0.41 (7)	56	41.4 ± 9.9	6/50	66 ± 39.6	N	113.5 ± 54.1	Y(7.3 ± 4.3)	(5)	31(55.3%)	12
	Macro	N	CAB	0.97 ± 0.37 (7)	18	70 ± 10.9	13/5	79.2 ± 30	N	258.9 ± 211.3	Y(13.4 ± 14.1)	(5)	9(50%)	12

CAB cabergoline, *PRL* prolactin, *OP* surgery, *RT* radiotherapy, *NA* not applicable, *ND* no data, *Y* yes, *N* no (4) Tumor volume reduction >50% in all patients, (5) tumor disappeared in most of cases, (6) tumor substantially narrowed in most of cases, (7) dose before withdrawal

Table 2c Characteristics for included studies with BRC and CAB being both used in patients

First author, year of publication	Cause of hyperpro-lactinemia	Low dose of CAB (Y or N)	DAs treatment	Mean dose (mg/week)	No. of patients	mean age (year)	Male/ female	Mean treatment duration (months)	Pre-treatment	Mean PRL before treatment (ng/ml)	Normalization in therapy Y/N (dose)	Regression of tumor during treatment on MRI OR CT (Y or N)	Persisting normopro-lactinemia	Mean follow-up in persisting normoprolactinemia (months)
Biswas, 2005 [30]	Micro	N	BRC($n = 22$) CAB($n = 67$)	BRC:2.5–10 CAB:0.5–3	89	32.7	5/84	37.2	N	100.9	NA	ND	23(26%)	43.2
Martin, 2013 [35]	Micro	NA	CAB/BRC	ND	47	ND	0/47	>48	N	ND	ND	NA	27(57.4%)	48
Dogansen, 2016 [36]	Micro ($n = 23$) Macro($n = 44$)	NA	BRC($n = 38$) CAB($n = 29$)	ND	67	34.3 ± 11.2	17/50	>24	N	14.9 ± 32.5	Y	(4)	Micro 15(65%) Macro 16(36%) BRC 15(39%) CAB 16(55%)	108.8 ± 55.1

CAB cabergoline, *BRC* bromocriptine, *PRL* prolactin, *OP* surgery, *RT* radiotherapy, *NA* no applicable, *ND* no data, *Y* yes, *N* no

(4) tumor volume reduction >50% in all patients

persisting normoprolactinemia after DA withdrawal ranged from 0 to 85% in different studies.

Risk of bias analysis

Publication bias exists, due to Egger's test (Fig. 2) showing $p = 0.006 < 0.05$. The clipping method (Fig. 3), was then used to evaluate the impact of the publication bias on the results. Our findings indicate that it has little effect, which proves the validity of the result. Sensitivity analysis (Fig. 4) shows that no study which was included had a large impact on the results. Due to the high test heterogeneity ($Q = 194.556$ on 34 degrees of freedom [$p = 0.000$]), the random-effects model (random: I–V heterogeneity) would handle the summary statistics.

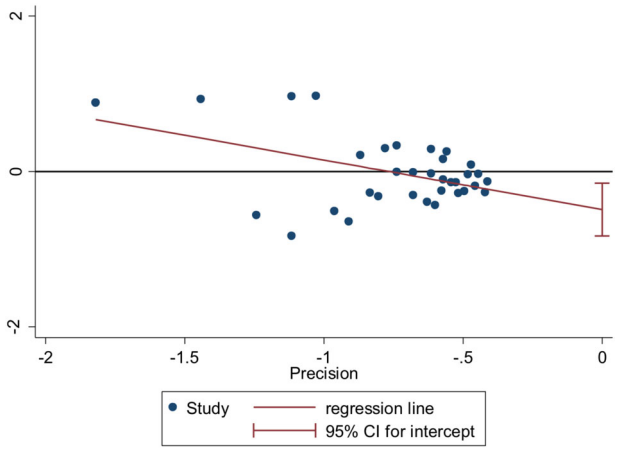

Fig. 2 The Egger's test. It was used to investigate whether there was a publication bias. Publication bias exists, due to Egger's test showing $p = 0.006 < 0.05$

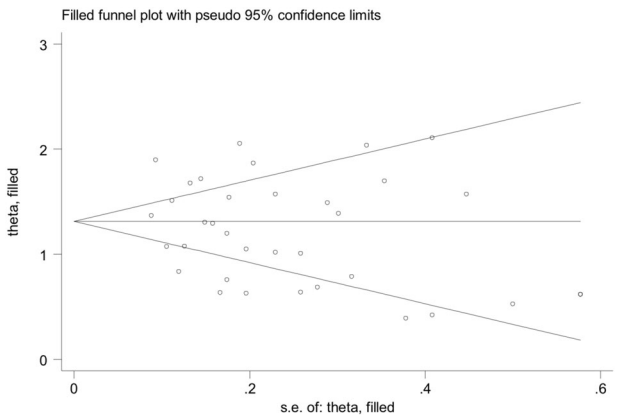

Fig. 3 The clipping method. It was used to evaluate the impact of the publication bias on the results. Our findings indicate that it has little effect, which proves the validity of the result

Meta-analysis

The primary aim of this meta-analysis was to explore the overall success rate of DA withdrawal. Surprisingly, the overall success rate after DA withdrawal reached 36.6% (95% CI 29.4–44.2%) (Fig. 5). The secondary aim was to investigate the favorable factors related to the high success rate of DA withdrawal, including the serum PRL concentration, treatment duration, cause of hyperprolactinemia, type, and dose of DAs, regression of tumor size, and follow-up period. These results are shown in Tables 3 and 4 (multivariate regression analysis)

Serum PRL concentrations

We analyzed differences in serum PRL concentrations between patients with PRL ≤ 200 µg/l and those with PRL >200 µg/l before treatment (36.5%; 95% CI 27.8–45.7 vs. 28.8%; 95% CI 16.4–43%), and between patients with PRL ≤10 µg/l and those with PRL >10 µg/l before drug withdrawal (36.6%; 95%CI 17.8–57.7 vs. 40.7%; 95% CI 27.9–54.2%).

Dosage of DAs

In this paper, a low maintenance dose of CAB was defined as 0.5 mg/week of CAB before withdrawal [11–13]. In patients with a low maintenance dose of CAB before withdrawal, the proportion of patients with normoprolactinemia was higher (51.5%; 95% CI 40–62.8%), compared with patients without low-dose CAB for maintenance therapy (21.5%; 95% CI 12.2–32.5%, $p = 0.007$). However, the success rate of drug withdrawal was not correlated with the dose of BRC treatment. Whether it was less than 7.5 mg or more than 7.5 mg, the results remained similar (17.5%; 95% CI 10.7–25.6 vs. 23.1%; 95% CI 9–41.3%).

Tumor size reduction

Tumor regression on CT or MRI during treatment is another important indicator. There were patients with tumor shrinkage (40.5%; 95% CI 31.4–49.9%), and patients without tumor shrinkage (22.1%; 95% CI 10.7–36.2%). A dramatic reduction in tumor size before withdrawal was generally associated with success of the treatment ($p = 0.032$). Further classification and calculation of cases with tumor volume reduction by more than 50% showed a 49.4% remission rate.

Types of DAs and treatment duration

The overall therapeutic outcome was better in patients using CAB as the only treatment (41.2%; 95% CI 32.3–50.4%)

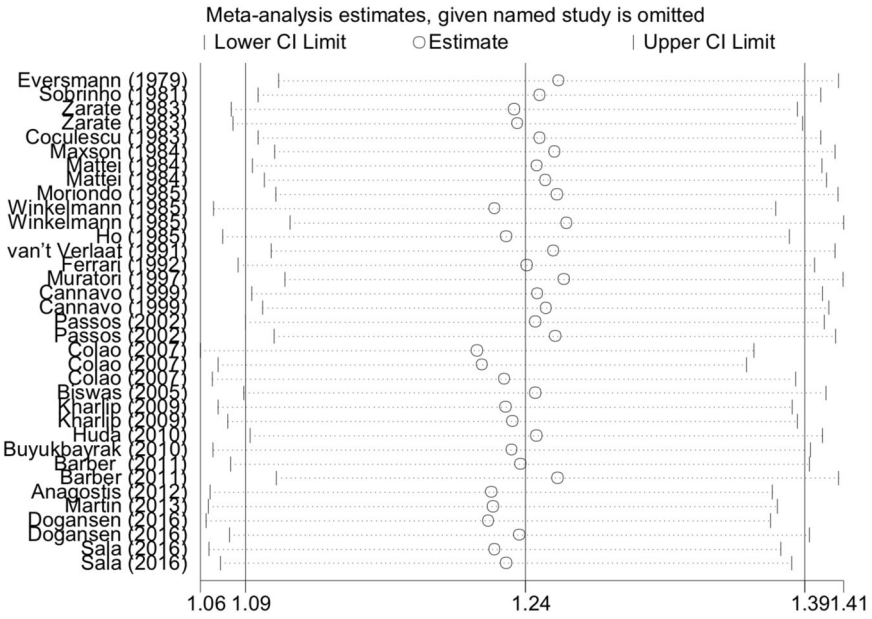

Fig. 4 Sensitivity analysis. Sensitivity analysis was conducted on low-quality studies. This analysis shows that no study which was included had a large impact on the results

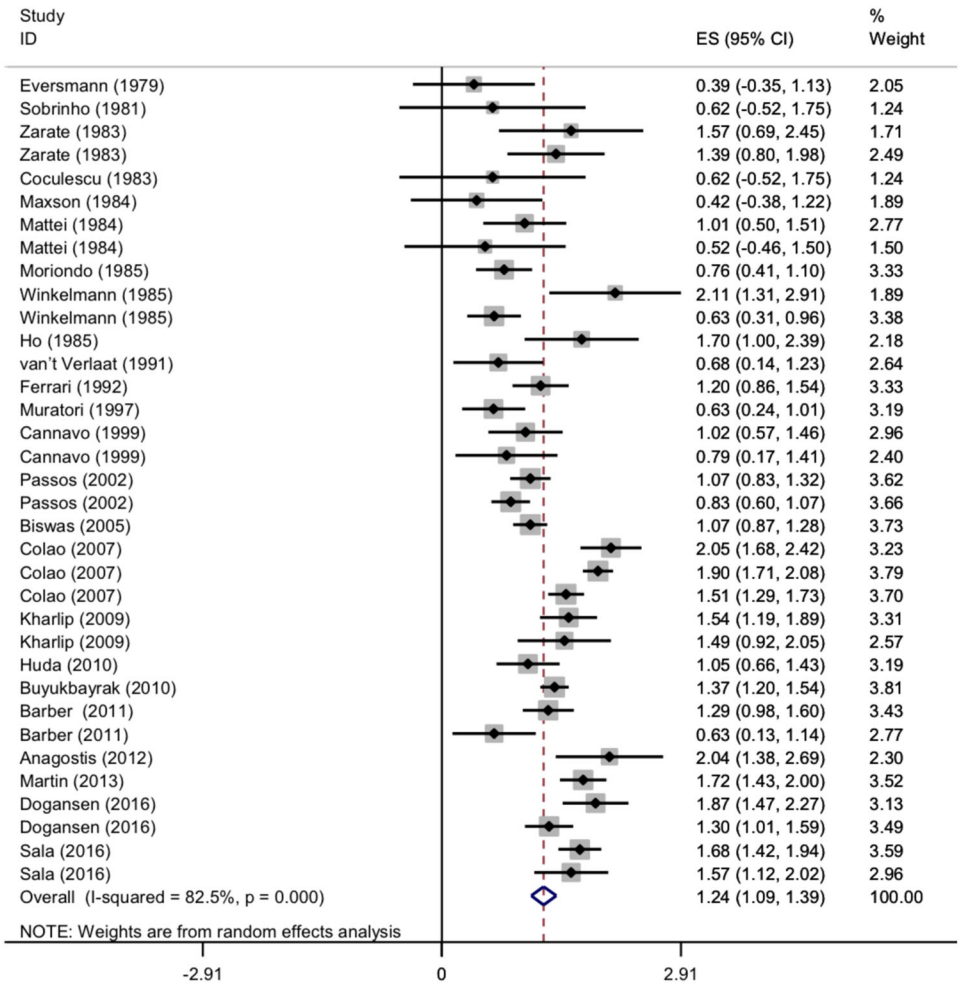

Fig. 5 Forest map. This forest map contains 24 articles included in this analysis. The proportion of patients with persisting normoprolactinemia after DA withdrawal reached 36.6% in a random effects model (95% CI, 29.4–44.2%; I-squared: 82.5%)

Table 3 Results of meta-analysis

	No. of study	No. of patients	I-squared	Random effects model (95% CI)
Over effect	24	1106	82.5%	36.6%(29.4–44.2%)
Treatment duration				
≤24 months	11	290	58.9%	20.8%(12.9–30%)
>24 months	13	816	81.6%	41.3%(32.1–50.8%)
≤24 months & BRC	7	78	18.3%	17.2%(8.9–27.5%)
≤24 months & CAB	4	212	72.4%	24.8%(13–38.8%)
>24 months & BRC	5	228	75.8%	27.3%(15.6–40.9%)
>24 months & CAB	7	452	75.4%	48.7%(38.9–58.5%)
Cause of hyperprolactinemia				
Idiopathic hyperprolactinemia	2	41	90.7%	48.7%(6.6–92.1%)
Micro	20	727	83.9%	37.3%(28–47%)
Macro	12	306	74.6%	25%(15.3–36.3%)
Idiopathic hyperprolactinemia & BRC	1	14		23.2%(6.1–47.1%)
Idiopathic hyperprolactinemia & CAB	1	27		73.2%(55.6–87.7%)
Micro & BRC	8	123	65.3%	25.9%(12.1–42.6%)
Micro & CAB	9	445	85.7%	40.8%(28.4–53.9%)
Macro & BRC	6	131	8.5%	15.1%(9.1–22.3%)
Macro & CAB	5	131	71.4%	33.5%(17.6–51.7%)
Dopamine agonists				
BRC	12	306	58.5%	22.4%(14.8–31%)
CAB	11	664	81.1%	41.2%(32.3–50.4%)
PRL before treatment				
PRL ≤ 200 μg/l	16	586	78.3%	36.5%(27.8–45.7%)
PRL > 200 μg/l	10	406	87.0%	28.8%(16.4–43%)
PRL before drug withdrawal				
PRL ≤ 10 ug/l	4	240	68.2%	36.6%(17.8—57.7%)
PRL > 10 ug/l	5	79	71.1%	40.7%(27.9 –54.2%)
Regression of tumor during treatment on MRI OR CT				
Tumor shrinkage	11	635	80.6%	40.5%(31.4–49.9%)
No tumor shrinkage	5	99	53.2%	22.1%(10.7–36.2%)
Further classification				
Tumor volume reduction > 50% in all patients	4	281	82.6%	49.4%(34–64.7%)
Dose of dopamine agonist				
Therapeutic doses of BRC ≤ 7.5 mg	5	146	15.2%	17.5%(10.7–25.6%)
Therapeutic doses of BRC > 7.5 mg	3	58	51.1%	23.1%(9–41.3%)
a low dose of CAB maintenance	5	424	79.1%	51.5%(40–62.8%)
not given a low dose of CAB maintenance	4	137	53.6%	21.5%(12.2-32.5%)
Follow-up period				
Follow-up period ≤ 12 months	8	365	65.5%	30.8%(22.4-39.8%)
12 months < Follow-up period ≤ 24 months	3	96	77.4%	41.4%(20.9-63.6%)
Follow-up period > 24 months	10	10	90.3%	41.3%(28.9-54.3%)
year of publication				
before 2000	13	221	50.3%	20.3%(13–28.7%)
after 2000	11	885	84.8%	43.1%(34.7-51.9%)

PRL prolactin, *BRC* bromocriptine, *CAB* cabergoline, micro microprolactinoma, *macro* macroprolactinoma

Table 4 Multivariate meta-regression analysis

	Coefficient	*p*	[95% Conf.	Interval]
Cause of hyperprolactinemia	0.3164469	0.067	−0.0296	0.662498
A low dose of CAB maintenance	0.5707492	0.007	0.226253	0.915246
Treatment time	0.3954675	0.037	0.034205	0.75673
Tumor shrinkage	0.7403209	0.032	0.090237	1.390405
Follow-up period	0.0095284	0.906	−0.17917	0.198225
_cons	−2.26855	0.023	−4.09746	−0.43964

than in patients treated only with BRC (22.4%; 95% CI 14.8–31%). It was found that the success rate of drug withdrawal was lower in patients using DAs for less than 24 months than in patients treated for more than 24 months (20.8%, 95% CI 12.9–30 vs. 41.3%, 95% CI 32.1–50.8%; $p = 0.037$). Based on this outcome, four subgroups were further designed: patients treated with BRC less than 24 months (17.2%; 95% CI 8.9–27.5%) and CAB less than 24 months (24.8%; 95% CI 13–38.8%); patients treated with BRC more than 24 months (27.3%; 95% CI 15.6–40.9%) and patients treated with CAB more than 24 months (48.7%; 95% CI 38.9–58.5%). Clearly, patients treated with CAB for more than 2 years have the best outcome.

Types of DAs and causes of hyperprolactinemia

Our results showed no significant difference in causes of hyperprolactinemia: idiopathic hyperprolactinemia (48.7%; 95% CI, 6.6–92.1%): microprolactinomas (37.3%; 95% CI, 28–47%), and macroprolactinomas (25%; 95% CI, 15.3–36.3%) ($p = 0.067$). These three causes of hyperprolactinemia were matched with two DAs into six subgroups: idiopathic with BRC (23.2%; 95% CI 6.1–47.1%); idiopathic with CAB (73.2%; 95% CI 55.6–87.7%); microprolactinomas with BRC (25.9%; 95% CI 12.1–42.6%); microprolactinomas with CAB (40.8%; 95% CI 28.4–53.9%); macroprolactinomas with BRC (15.1%; 95% CI 9.1–22.3%); and macroprolactinomas with CAB (33.5%; 95% CI 17.6–51.7%). These results indicate that idiopathic hyperprolactinemia, microprolactinoma, or macroprolactinoma had no significant impact on the success rate; but again, the fact that better results were achieved with CAB was confirmed.

Follow-up periods

The follow-up periods were classified into three groups: a follow-up period: follow-up period ≤12 months (30.8%; 95% CI 22.4–39.8%); 12 months < a follow-up period ≤ 24 months (41.4%; 95% CI 20.9–63.6%); and a follow-up period > 24 months (41.3%; 95% CI 28.9–54.3%). The success rate of persisting hyperprolactinemia after DA withdrawal was not related to the follow-up period ($p = 0.906$).

Year of publication

We analyzed differences in year of publication, paper published after 2000 get better success rate than those published before 2000 (43.1%; 95% CI 34.7–51.9% vs. 20.3%; 95% CI 13–28.7%).

Discussion

This meta-analysis showed that a normal PRL level could be successfully maintained after DA withdrawal in quite a proportion of patients. Compared with the success rate in meta-analysis by Dekkers et al. [10], the result of our analysis showed that the success rate of DA withdrawal has greatly increased. According to the analysis by Dekkers et al. the probability of treatment success was highest when CAB was used for at least 2 years. Our analysis found the same conclusion. Low-dose maintenance therapy with CAB and a significant reduction in tumor size were two independent factors affecting the success rate of DA withdrawal. We also found that the normoprolactinemia maintenance rate in patients who used CAB as the only treatment was increased compared with that reported by Hu et al. in 2015 [43]. In their study, the overall success rate of normoprolactinemia maintenance after CAB withdrawal was 35%. The greatly improved success rate of withdrawal was in relationship with the increased number of patients included, common use of CAB, longer durations of DA treatment, and patient selection according to several criteria.

The duration of DA treatment is critical in maintaining a normal PRL level, and treatment for more than 2 years is strongly recommended [1]. The guideline [1] formulated by the American Endocrine Society in 2011 also recommended that patients should be treated by DAs for at least 2 years with normalized serum PRL levels and with no residual tumor on MRI. However, the duration of treatment was not considered as a favorable contributive factor for successful DA withdrawal in the meta-analysis reported by Hu et al. [43]. In contrast, our meta-analysis showed that the length of treatment is still a factor affecting the successful withdrawal of DAs.

There are few studies considering whether significant reduction in tumor size is associated to success withdrawal. In the meta-analysis by Hu et al. [43], they divided the cases into two groups: tumor shrinkage (39%) and no tumor shrinkage (29%). Similarly, Colao et al. [13] observed that if the tumor was still visible, the recurrence rate was almost

twice as high as that in patients with no visible tumor [44], and the recurrence rate after DA withdrawal increased to 40% for microprolactinomas and 58% for macroprolactinomas. But if no tumor was visible, the recurrence rate after DA withdrawal decreased to 24% for microprolactinomas and 26% for macroprolactinomas. Based on these results, we further classified and calculated cases with tumor volume reduction by more than 50% and found that nearly half of the patients could stop using DAs without recurrence. These findings indicate that significant reduction in tumor size may be a contributive factor.

According to the results obtained from the present meta-analysis, more than half of the patients with low-dose CAB maintenance could safely stop using DAs. According to the guidelines of the American Endocrine Society [1], DAs should be tapered gradually before complete withdrawal. In line with other reports, Buyukbayrak et al. [28], Colao et al. [13], and Hu et al. [43] emphasized the importance of switching to maintenance treatment after PRL restored to normal levels. The remission rate reported in Colao et al.'s research was surprisingly high in patients with either microprolactinemia or macroprolactinemia (66.1% and 46.8%) after the CAB dosage was tapered to 0.5 mg/week. As a result, a gradual drug dose reduction is suggested. Nevertheless, the criteria for switching to maintenance treatment, the duration of maintenance treatment, and accurate dose adjustment needs to be further discussed and studied [28].

Limitations and strengths of this study

The main limitation of the present study is the high heterogeneity of the patients involved. Data derived from the articles included mostly are of average value. In each document, the extent of the tumor shrinkage before drug withdrawal was not absolutely accurate, devoid of mean values. These variables were given qualitative judgments with "no tumor shrinkage", and "tumor shrinkage" according to these original articles. In some articles, with a large number of cases, there were few patients with pregnancy, or undergoing surgery or radiotherapy, and these variables cannot be easily detached and might affect the statistical results. These issues highlight the inherent limitations in any meta-analysis based on observational data and the need for larger prospective studies in the future.

Conclusions

Although the results of each individual patient cannot be easily predicted, there are a few points that may help clinicians make sensible selection of patients in routine clinical practice: (1) the patient has used CAB for at least 2 years; (2) a low-maintenance dose of CAB has been used for at least 1 year; and (3) restoration of a normal serum PRL level and a significant reduction in tumor size have been achieved before drug withdrawal. The degree of tumor invasion may be associated with recurrence. In patients, whose PRL levels remain normal for at least 2 years and the tumor volume shrinks by more than 50% or even no tumor residue, the dose of DAs can be reduced step by step, knowing that low-dose medication can maintain the stability of PRL level and tumor size.

Both guidelines [1, 9] agree that CAB is preferred to BRC and a more-than-24-month treatment duration is conducive to withdrawal. However, our meta-analysis showed that the success rate of DA withdrawal has greatly increased in recent years. Compared with previously mentioned guidelines [1, 9] this article also addresses three other points to be considered in clinical practice: a low dose of CAB maintenance before withdrawal, a significant reduction in tumor size and the use of CAB in patients with idiopathic hyperprolactinemia, which may make sense in increasing the success rate.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References

1. S. Melmed, F.F. Casanueva, A.R. Hoffman, D.L. Kleinberg, V.M. Montori, J.A. Schlechte, J.A. Wass, Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J. Clin. Endocrinol. Metab. **96**(2), 273–288 (2011). https://doi.org/10.1210/jc.2010-1692
2. A. Colao, A. Di Sarno, E. Guerra, M. De Leo, A. Mentone, G. Lombardi, Drug insight: cabergoline and bromocriptine in the treatment of hyperprolactinemia in men and women. Nat. Clin. Pract. Endocrinol. Metab. **2**(4), 200–210 (2006). https://doi.org/10.1038/ncpendmet0160
3. Z.B. Wu, C.J. Yu, Z.P. Su, Q.C. Zhuge, J.S. Wu, W.M. Zheng, Bromocriptine treatment of invasive giant prolactinomas involving the cavernous sinus: results of a long-term follow up. J. Neurosurg. **104**(1), 54–61 (2006). https://doi.org/10.3171/jns.2006.104.1.54
4. A. Colao, A. di Sarno, R. Pivonello, C. di Somma, G. Lombardi, Dopamine receptor agonists for treating prolactinomas. Expert

Opin. Investig. Drugs **11**(6), 787–800 (2002). https://doi.org/10.1517/13543784.11.6.787
5. M.P. Gillam, M.E. Molitch, G. Lombardi, A. Colao, Advances in the treatment of prolactinomas. Endocr. Rev. **27**(5), 485–534 (2006). https://doi.org/10.1210/er.2005-9998
6. J.J. Orrego, W.F. Chandler, A.L. Barkan, Rapid re-expansion of a macroprolactinoma after early discontinuation of bromocriptine. Pituitary **3**(3), 189–192 (2000)
7. M.E. Molitch, Medical treatment of prolactinomas. Endocrinol. Metab. Clin. N. Am. **28**(1), 143–169 (1999)
8. M.O. Thorner, R.L. Perryman, A.D. Rogol, B.P. Conway, R.M. Macleod, I.S. Login, J.L. Morris, Rapid changes of prolactinoma volume after withdrawal and reinstitution of bromocriptine. J. Clin. Endocrinol. Metab. **53**(3), 480–483 (1981). https://doi.org/10.1210/jcem-53-3-480
9. F.F. Casanueva, M.E. Molitch, J.A. Schlechte, R. Abs, V. Bonert, M.D. Bronstein, T. Brue, P. Cappabianca, A. Colao, R. Fahlbusch, H. Fideleff, M. Hadani, P. Kelly, D. Kleinberg, E. Laws, J. Marek, M. Scanlon, L.G. Sobrinho, J.A. Wass, A. Giustina, Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin. Endocrinol. **65**(2), 265–273 (2006). https://doi.org/10.1111/j.1365-2265.2006.02562.x
10. O.M. Dekkers, J. Lagro, P. Burman, J.O. Jorgensen, J.A. Romijn, A.M. Pereira, Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. J. Clin. Endocrinol. Metab. **95**(1), 43–51 (2010). https://doi.org/10.1210/jc.2009-1238
11. P. Anagnostis, F. Adamidou, S.A. Polyzos, Z. Efstathiadou, E. Karathanassi, M. Kita, Long term follow-up of patients with prolactinomas and outcome of dopamine agonist withdrawal: a single center experience. Pituitary **15**(1), 25–29 (2012). https://doi.org/10.1007/s11102-011-0303-6
12. J. Kharlip, R. Salvatori, G. Yenokyan, G.S. Wand, Recurrence of hyperprolactinemia after withdrawal of long-term cabergoline therapy. J. Clin. Endocrinol. Metab. **94**(7), 2428–2436 (2009). https://doi.org/10.1210/jc.2008-2103
13. A. Colao, A. Di Sarno, P. Cappabianca, C. Di Somma, R. Pivonello, G. Lombardi, Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. N. Engl. J. Med. **349**(21), 2023–2033 (2003). https://doi.org/10.1056/NEJMoa022657
14. J.P. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses. BMJ **327**(7414), 557–560 (2003). https://doi.org/10.1136/bmj.327.7414.557
15. R. Kwancharoen, R.S. Auriemma, G. Yenokyan, G.S. Wand, A. Colao, R. Salvatori, Second attempt to withdraw cabergoline in prolactinomas: a pilot study. Pituitary **17**(5), 451–456 (2014). https://doi.org/10.1007/s11102-013-0525-x
16. L. Vilar, J.L. Albuquerque, P.S. Gadelha, F. Rangel Filho, A.M. Siqueira, M.M. da Fonseca, K.F. Viana, B.S. Gomes, R. Lyra, Second attempt of cabergoline withdrawal in patients with prolactinomas after a failed first attempt: is it worthwhile? Front. Endocrinol. **6**, 11 (2015). https://doi.org/10.3389/fendo.2015.00011
17. G. Faglia, A. Conti, M. Muratori, E. Togni, P. Travaglini, A. Zanotti, F. Mailland, Dihydroergocriptine in management of microprolactinomas. J. Clin. Endocrinol. Metab. **65**(4), 779–784 (1987). https://doi.org/10.1210/jcem-65-4-779
18. A. Liuzzi, D. Dallabonzana, G. Oppizzi, G.G. Verde, R. Cozzi, P. Chiodini, G. Luccarelli, Low doses of dopamine agonists in the long-term treatment of macroprolactinomas. N. Engl. J. Med. **313**(11), 656–659 (1985). https://doi.org/10.1056/nejm198509123131103
19. A. Di Sarno, M.L. Landi, P. Marzullo, C. Di Somma, R. Pivonello, G. Cerbone, G. Lombardi, A. Colao, The effect of quinagolide and cabergoline, two selective dopamine receptor type 2 agonists, in the treatment of prolactinomas. Clin. Endocrinol. **53**(1), 53–60 (2000)
20. W. Winkelmann, B. Allolio, U. Deuss, D. Heesen, D. Kaulen, in Persisting Normoprolactinemia After Withdrawal of Bromocriptine Long-term Therapy in Patients with Prolactinomas, (ed.), by R.M. Macleod, M.O. Thorner, U. Scapagnini. Basic and Clinical Correlates (Liviana Press, Padova, 1985), pp. 817–822
21. M. Giusti, E. Porcella, A. Carraro, M. Cuttica, S. Valenti, G. Giordano, A cross-over study with the two novel dopaminergic drugs cabergoline and quinagolide in hyperprolactinemic patients. J. Endocrinol. Investig. **17**(1), 51–57 (1994). https://doi.org/10.1007/bf03344963
22. V.Q. Passos, J.J. Souza, N.R. Musolino, M.D. Bronstein, Long-term follow-up of prolactinomas: normoprolactinemia after bromocriptine withdrawal. J. Clin. Endocrinol. Metab. **87**(8), 3578–3582 (2002). https://doi.org/10.1210/jcem.87.8.8722
23. A. Zarate, E.S. Canales, C. Cano, C.J. Pilonieta, Follow-up of patients with prolactinomas after discontinuation of long-term therapy with bromocriptine. Acta Endocrinol. **104**(2), 139–142 (1983)
24. S. Cannavo, L. Curto, S. Squadrito, B. Almoto, A. Vieni, F. Trimarchi, Cabergoline: a first-choice treatment in patients with previously untreated prolactin-secreting pituitary adenoma. J. Endocrinol. Investig. **22**(5), 354–359 (1999). https://doi.org/10.1007/bf03343573
25. M. Muratori, M. Arosio, G. Gambino, C. Romano, O. Biella, G. Faglia, Use of cabergoline in the long-term treatment of hyperprolactinemic and acromegalic patients. J. Endocrinol. Investig. **20**(9), 537–546 (1997). https://doi.org/10.1007/bf03348016
26. M.S. Huda, N.B. Athauda, M.M. Teh, P.V. Carroll, J.K. Powrie, Factors determining the remission of microprolactinomas after dopamine agonist withdrawal. Clin. Endocrinol. **72**(4), 507–511 (2010). https://doi.org/10.1111/j.1365-2265.2009.03657.x
27. T.M. Barber, J. Kenkre, C. Garnett, R.V. Scott, J.V. Byrne, J.A. Wass, Recurrence of hyperprolactinaemia following discontinuation of dopamine agonist therapy in patients with prolactinoma occurs commonly especially in macroprolactinoma. Clin. Endocrinol. **75**(6), 819–824 (2011). https://doi.org/10.1111/j.1365-2265.2011.04136.x
28. E.E. Buyukbayrak, A.Y. Karageyim Karsidag, B. Kars, O. Balcik, M. Pirimoglu, O. Unal, C. Turan, Effectiveness of short-term maintenance treatment with cabergoline in microadenoma-related and idiopathic hyperprolactinemia. Arch. Gynecol. Obstet. **282**(5), 561–566 (2010). https://doi.org/10.1007/s00404-010-1562-6
29. P. Moriondo, P. Travaglini, M. Nissim, A. Conti, G. Faglia, Bromocriptine treatment of microprolactinomas: evidence of stable prolactin decrease after drug withdrawal. J. Clin. Endocrinol. Metab. **60**(4), 764–772 (1985). https://doi.org/10.1210/jcem-60-4-764
30. M. Biswas, J. Smith, D. Jadon, P. McEwan, D.A. Rees, L.M. Evans, M.F. Scanlon, J.S. Davies, Long-term remission following withdrawal of dopamine agonist therapy in subjects with microprolactinomas. Clin. Endocrinol. **63**(1), 26–31 (2005). https://doi.org/10.1111/j.1365-2265.2005.02293.x
31. J.W. van't Verlaat, R.J. Croughs, Withdrawal of bromocriptine after long-term therapy for macroprolactinomas; effect on plasma prolactin and tumour size. Clin. Endocrinol. **34**(3), 175–178 (1991)
32. C. Ferrari, A. Paracchi, A.M. Mattei, S. de Vincentiis, A. D'Alberton, P. Crosignani, Cabergoline in the long-term therapy of hyperprolactinemic disorders. Acta. Endocrinol. **126**(6), 489–494 (1992)
33. K.Y. Ho, G.A. Smythe, P.J. Compton, L. Lazarus, Long-term bromocriptine therapy may restore the inhibitory control of prolactin release in some patients with pathological hyperprolactinemia. Aust. N. Z. J. Med. **15**(2), 213–219 (1985)

34. A.M. Mattei, C. Ferrari, G. Ragni, R. Benco, M.C. Picciotti, P. Rampini, R. Caldara, P.G. Crosignani, Serum prolactin and ovarian function after discontinuation of drug treatment for hyperprolactinaemia: a study with bromocriptine and metergoline. Br. J. Obstet. Gynaecol. **91**(3), 244–250 (1984)
35. M. Martin de Santa-Olalla y Llanes, V.M. Andia Melero, A. Jara Albarran, [Long-term evolution and outcomes of microprolactinoma with medical treatment]. Endocrinol. Nutr. **60**(9), 489–494 (2013). https://doi.org/10.1016/j.endonu.2013.03.007
36. S.C. Dogansen, O.S. Selcukbiricik, S. Tanrikulu, S. Yarman, Withdrawal of dopamine agonist therapy in prolactinomas: In which patients and when? Pituitary **19**(3), 303–310 (2016). https://doi.org/10.1007/s11102-016-0708-3
37. E. Sala, P. Bellaviti Buttoni, E. Malchiodi, E. Verrua, G. Carosi, E. Profka, G. Rodari, M. Filopanti, E. Ferrante, A. Spada, G. Mantovani, Recurrence of hyperprolactinemia following dopamine agonist withdrawal and possible predictive factors of recurrence in prolactinomas. J. Endocr. Investig. (2016). https://doi.org/10.1007/s40618-016-0483-z
38. A. Colao, A. Di Sarno, E. Guerra, R. Pivonello, P. Cappabianca, F. Caranci, A. Elefante, L.M. Cavallo, F. Briganti, S. Cirillo, G. Lombardi, Predictors of remission of hyperprolactinaemia after long-term withdrawal of cabergoline therapy. Clin. Endocrinol. **67**(3), 426–433 (2007). https://doi.org/10.1111/j.1365-2265.2007.02905.x
39. M. Coculescu, N. Simionescu, M. Oprescu, D. Alessandrescu, Bromocriptine treatment of pituitary adenomas. Evaluation of withdrawal effect. Endocrinologie **21**(3), 157–168 (1983)
40. T. Eversmann, R. Fahlbusch, H.K. Rjosk, K. von Werder, Persisting suppression of prolactin secretion after long-term treatment with bromocriptine in patients with prolactinomas. Acta. Endocrinol. **92**(3), 413–427 (1979)
41. W.S. Maxson, M. Dudzinski, S.H. Handwerger, C.B. Hammond, Hyperprolactinemic response after bromocriptine withdrawal in women with prolactin-secreting pituitary tumors. Fertil. Steril. **41**(2), 218–223 (1984)
42. L.G. Sobrinho, M.C. Nunes, C. Calhaz-Jorge, J.C. Mauricio, M.A. Santos, Effect of treatment with bromocriptine on the size and activity of prolactin producing pituitary tumours. Acta. Endocrinol. **96**(1), 24–29 (1981)
43. J. Hu, X. Zheng, W. Zhang, H. Yang, Current drug withdrawal strategy in prolactinoma patients treated with cabergoline: a systematic review and meta-analysis. Pituitary **18**(5), 745–751 (2015). https://doi.org/10.1007/s11102-014-0617-2
44. M.E. Molitch, Pituitary gland: can prolactinomas be cured medically? Nat. Rev. Endocrinol. **6**(4), 186–188 (2010). https://doi.org/10.1038/nrendo.2009.278