Recurrence of Hyperprolactinemia after Withdrawal of Dopamine Agonists: Systematic Review and Meta-Analysis

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Context: Dopamine agonists are the treatment of choice for prolactinomas and symptomatic idiopathic hyperprolactinemia. However, the optimal treatment strategy and treatment duration is not clear in all details.

Objective: The aim of the study was to assess the effect of dopamine agonist withdrawal in patients with idiopathic hyperprolactinemia and prolactinomas.

Data Sources: PubMed, the Cochrane Library, the Web of Science, and EMBASE were searched electronically. No restriction was made with respect to language.

Study Selection: Studies reporting the proportion of normoprolactinemic patients after withdrawal of dopamine agonist or studies in which this proportion could be calculated were eligible. Both observational studies and clinical trials were eligible. Nineteen studies were included in the meta-analysis, with a total of 743 patients.

Data Extraction: Data extraction was performed by two reviewers independently.

Data Synthesis: The pooled proportion of patients with persisting normoprolactinemia after dopamine agonist withdrawal was 21% in a random effects model [95% confidence interval (CI), 14–30%; I^2 81%). Stratified analysis showed higher proportions of treatment success in idiopathic hyperprolactinemia (32%; 95% CI, 5–80%), compared with both microprolactinomas (21%; 95% CI, 10–37%), and macroprolactinomas (16%; 95% CI, 6–36%). In a random effects meta-regression adjusting for cause of hyperprolactinemia, a longer treatment duration was associated with treatment success ($P = 0.015$), whereas the use of cabergoline showed a trend of effect ($P = 0.07$).

Conclusions: This meta-analysis showed that hyperprolactinemia will recur after dopamine agonist withdrawal in a considerable proportion of patients. The probability of treatment success was highest when cabergoline was used for at least 2 yr. **(*J Clin Endocrinol Metab* 95: 43–51, 2010)**

Dopamine agonists are the treatment of choice for prolactinomas and symptomatic idiopathic hyperprolactinemia. Whether dopamine agonist treatment should be lifelong has been a subject of debate (1). Since the introduction of dopamine agonists more than 30 yr ago, several studies have assessed the effect of dopamine agonist withdrawal on the recurrence of hyperprolactinemia. The debate has shifted from whether a dopamine agonist can be stopped to the determination of the optimal timing for withdrawal (2). However, the optimal treatment strat-

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Abbreviations: CI, Confidence interval; CT, computed tomography; MRI, magnetic resonance imaging.

egy is not clear in all details, resulting in different treatment policies (3). A recent study (4, 5) indicated that a subgroup of hyperprolactinemic patients with a high likelihood of achieving remission can be identified on clinical criteria. In 2006 the Pituitary Society published consensus guidelines (6) that summarized these controversies.

To assess the effect of dopamine agonist withdrawal in patients with idiopathic hyperprolactinemia and prolactinomas in more detail, we performed a systematic review of the literature. The primary aim was to estimate the pooled proportion of patients with persistent normoprolactinemia after withdrawal of dopamine agonists in a meta-analysis. The second aim was to determine factors influencing the success of treatment outcome in a sensitivity analysis.

Materials and Methods

Eligibility criteria

The main outcome of the present analysis was the proportion of patients with persisting normoprolactinemia after withdrawal of dopamine agonist treatment in idiopathic hyperprolactinemia and prolactinomas. Studies reporting the proportion of normoprolactinemic patients after withdrawal of dopamine agonist or studies in which this proportion could be calculated were eligible for inclusion in this meta-analysis. The assessment of recurrence of hyperprolactinemia was based only on prolactin levels, irrespective of clinical symptoms. Both observational studies and clinical trials were eligible. There were no restrictions with respect to the sort of dopamine agonist.

Studies were eligible for inclusion in this review if they fulfilled the following criteria:

1. The normal reference values of prolactin had to be reported.

2. Duration of dopamine agonist treatment was at least 3 months, and during the treatment period normoprolactinemia had to be attained.

3. Follow-up period for patients with persisting normoprolactinemia after treatment withdrawal was at least 6 months.

4. The maximum proportion of pretreatment with radiotherapy in patients assessed for the effect of dopamine agonist withdrawal was set at 20%. The reason for this constraint is that the effect of radiotherapy on hyperprolactinemia can be delayed for many years. Therefore, radiotherapy is a confounder in the assessment of the effect of dopamine agonist withdrawal.

5. Variables as age, sex, type of dopamine agonist, and treatment duration had to be reported. If only a subgroup of a larger cohort was withdrawn from dopamine agonist treatment, these parameters were extracted for this subgroup only. If, however, these parameters were not reported for the subgroup separately, the parameters of the total cohort were extracted as a proxy for the subgroup. The latter condition was only permitted if the minimum percentage of patients in the study cohort who attained normoprolactinemia during treatment and subsequently stopped treatment was at least 75% of the total study group. In this way, the variables of the total cohort should be a reliable estimate of the variables of those who attained normoprolactinemia during treatment and subsequently stopped treatment.

6. There should be no (partial) duplication of cohorts. If, nonetheless, partial duplication was present, the largest cohort was included.

If the entire cohort did not fulfill the eligibility criteria, the included cohort was restricted to eligible patients. However, this was only possible in case the study provided data and outcomes on individual patients or if data and outcomes were shown according to subgroups; i.e., if possible, the cohort was restricted to patients without radiotherapy, nonpregnant during follow-up, and with a normalized prolactin before withdrawal of the medication.

Search strategy

We searched the PubMed, the Cochrane Library, the Web of Science, and EMBASE databases for publications in any language examining the effect of withdrawal of dopamine agonists on the recurrence of hyperprolactinemia. The search was restricted by date of publication from 1970 onward because dopamine agonists were not available for the treatment of hyperprolactinemia before 1970. For details of the search strategy, see the Appendix (published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

Searches were performed in July 2008. In addition, the references of relevant articles were checked for additional articles. Abstracts of meetings and unpublished results were not included in the analysis. There was no restriction with respect to language.

Data review and data analysis

Initial selection of studies by title and abstract was carried out by one reviewer (J.L.). These studies were retrieved for full assessment. This assessment and subsequent data extraction were performed by two independent reviewers (J.L. and O.M.D.). Disagreements were resolved by consensus. Whenever possible, the study cohort was stratified by cause of hyperprolactinemia: idiopathic hyperprolactinemia and hyperprolactinemia caused by micro- and macroprolactinomas, respectively. The provided reference ranges of the individual studies were used to determine the presence of hyper and normoprolactinemia, despite the fact that in a few studies the authors defined remission as mild hyperprolactinemia without symptoms. All prolactin levels in the present meta-analysis were expressed as micrograms per liter. The conversion factor for prolactin levels from milliunits per liter to micrograms per liter used was 1:30 (5), because we were not able to acquire all conversion factors for the various assays. For assessment of recurrence of hyperprolactinemia, the unit used by the authors was used, not the converted levels. For studies reporting outcomes for several time intervals, the last point in time was chosen for data extraction. For determination of tumor regression during dopamine agonist treatment, results from magnetic resonance imaging (MRI) and computed tomography (CT) were taken into account, not from conventional x-rays. For all studies, the number of pregnant patients during follow-up was extracted from the article if possible.

The main outcome of the meta-analysis was the weighted average of the proportion of patients with persisting normoprolactinemia after withdrawal of dopamine agonist therapy. The individual studies were weighted according to the inverse of the squared SE. The I^2 test was used to check for quantitative heterogeneity (7). This measures the proportion of inconsistency between the studies that cannot be explained by chance alone.

We performed the analyses stratified by causes of hyperprolactinemia (idiopathic hyperprolactinemia, microprolactinomas and microprolactinomas), the type of dopamine agonist, and treatment duration (up to and including 24 months *vs.* more than 24 months). Random effects meta-regression was performed to study the influence of treatment duration and dopamine agonist preparation on persisting normoprolactinemia.

Statistical analyses were done in Comprehensive Meta-Analysis (version 2.0; Biostat, Englewood, NJ) and Stata (version 10.0; Stata Corporation, College Station, TX).

Results

Literature search (Fig. 1)

The initial search in the databases resulted in a total of 968 articles (543 in PubMed, 29 in Cochrane Library, 84 in Web of Science, and 312 in EMBASE). Of these 968 studies, 754 were unique without duplications. We excluded 685 papers based on title and abstract. A total of 69 potentially relevant papers were retrieved for full assessment. Of these studies, 31 were excluded from further analysis because the studies did not contain original data on withdrawal of dopamine agonists in hyperprolactinemia. We were unable to obtain one study (8).

In 40 studies, a detailed assessment with respect to the eligibility criteria was performed. Twenty studies were excluded from further analysis because these did not met one or more of the eligibility criteria (4, 9–28). Two studies partially described the same cohort (4, 5); from these, the study representing the extension was included (5). Consequently, a total of 19 studies were included in the present review (5, 29–46).

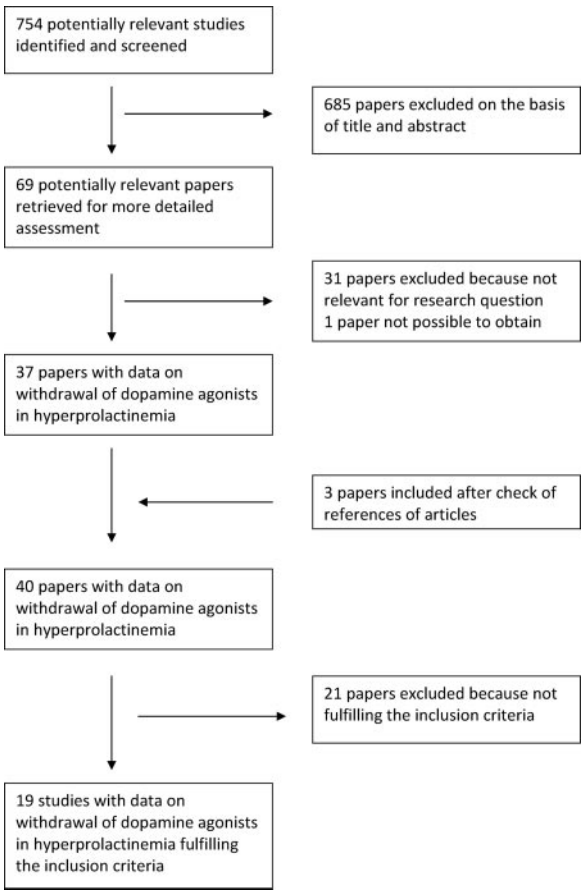

FIG. 1. Summary of study assessment and exclusion stages.

For some studies the following subgroups were not included: microprolactinomas treated with bromocriptine (38) and macroprolactinomas (31, 33, 36). Reasons for exclusions of these subgroups were the application of radiotherapy in a large proportion of the subgroup (31, 33, 36), and a duration of follow-up after withdrawal in the subgroup shorter than 3 months (38). In two studies, patients were assessed twice after treatment with two different dopamine agonists. To prevent multiplicity of patients in the meta-analysis from these two studies, only one of the assessed treatments was included. In one study with a crossover design, only the results for cabergoline, but not for treatment with quinagolide, were included because during treatment with quinagolide two patients were nonevaluable (35). In a second study, only the outcomes after the first treatment, *i.e.* quinagolide, were included (32). Of all included studies, three studies were retrieved after inspection of the references of relevant literature.

Study characteristics

Details of the 19 included studies are summarized in Table 1. Studies on persisting normoprolactinemia after withdrawal of dopamine agonists were published between 1979 and 2007. In nine studies, patients were treated according to a prespecified protocol (5, 30, 32, 34, 35, 37, 38, 40, 41). The number of included patients per study ranged from 2 to 221. The total number of patients included in this meta-analysis was 743. There were stratified data available for a total of 49 patients with idiopathic hyperprolactinemia, 353 with microprolactinomas, and 159 with macroprolactinomas. Idiopathic hyperprolactinemia was defined by authors as an unexplained hyperprolactinemia in the presence of normal CT or MRI (5, 35, 38). In none of these three studies was macroprolactinemia explicitly ruled out. In three studies with a total of 182 patients, the patients could not be separated with respect to different etiology. In two studies, a considerable proportion of patients were pregnant during follow-up: 43% (42) and 30% (29). In one study, the data for analysis could be restricted to nonpregnant patients (30). In a few other studies one (5, 34, 40) or two (41) patients became pregnant during follow-up.

Meta-analysis (Table 2)

The proportion of patients with persistent normoprolactinemia after withdrawal of dopamine agonists ranged

TABLE 1. Studies on persisting normoprolactinemia after withdrawal of dopamine agonist treatment in hyperprolactinemia

First author, year of publication (Ref.)	Cause of hyperprolactinemia	Treatment and mean dose (mg/d) [for CAB, mg/wk]	No. of patients	Mean age (yr)	Female sex (%)	Mean treatment duration (months)	Pretreatment	Mean PRL before treatment (μg/liter)	Regression of tumor during treatment on MRI or CT	Persisting normoprolactinemia, n (%)	Mean follow-up in persisting normoprolactinemia (months)
Colao, 2007 (5)	Idiopathic	CAB 0.5 mg	27	27	100	39	None	67.8	NA	20/27 (74.1%)	57[a]
	Micro	CAB 1.2 mg	115	32	89.6	43	None	157.2	At least 50% reduction in tumor volume	76/115 (66.1%)	47[a]
	Macro	CAB 1.2 mg	79	44	54.4	42	None	891.7	At least 50% reduction in tumor volume	37/79 (46.8%)	44[a]
Biswas, 2005 (29)	Micro	BRC (n = 22), range 2.5–10 mg; CAB (n = 67), range 0.5–3 mg	89	32.7	94.4	37.2	None	71.3[b]	ND	23/89 (26%)	43.2
Passos, 2002 (42)	Total (n =131), micro (n = 62), macro (n = 69)	BRC 6.9 mg	131	32.1	77.1	60	7/131 RT, 38/131 OP	894	ND	Total 27/131 (20.6%), micro 16/62 (25.8%), macro 11/69 (15.9%)	37
Di Sarno, 2000 (32)	Micro	QUI 0.121 mg	23	34.6	91.3	12	1/23 OP	155.6[b]	5/23 (22%) at least 80% reduction	0	
	Macro	QUI 0.257 mg	14	32.1	64.3	12	5/16 OP[c]	921.3[b]	4/16 (25%) at least 80% reduction	0	
Cannavo, 1999 (30)	Micro	CAB 0.98 mg	18[d]	30.8	87.0	24	None	193.8	11/23 (48%) total disappearance	4/18 (22.2%)	12
	Macro	CAB 1.77 mg	9[e]	28.1	90.9	24	None	404.1	4/11 (36%) total disappearance	1/9 (11.1%)	12
Muratori, 1997 (41)	Micro	CAB 0.93 mg	25[f]	Range 25–48	100	12	3/26 OP, 9/26 BRC, 9/26 DHEC	124.8	Lesion disappeared in 13/19 (68%)	2/25 (8%)	49
Giusti, 1994 (35)	Idiopathic 6, micro 5, empty sella 1	CAB 1.0 mg	11[g]	30.2	100	3	OP because of macroadenoma (n = 1) 10/12 BR	80.1	ND	0	NA
van't Verlaat, 1991 (44)	Macro	BRC 10.8 mg	12	42.2	33.3	58.6	None	2200[b]	Tumor volume reduction >50% in all patients	1/12 (8.3%)	12
Faglia, 1987 (34)	Micro	DHEC 30 mg	17[h]	Range 17–49	100	12	3/22 OP, 10/22 BRC	125	7/22 (32%) total disappearance	0	NA
Liuzzi, 1985 (37)	Macro	BRC (26), 8.4 mg; LIS (4), 0.4 mg	30	42.3	46.7	58.4	5/30 OP + RT, 7/30 OP	1869	In 25/30 (83%) reduction of tumor volume	1/30 (3.3%)	21
Ho, 1985 (36)	Micro	BRC ?	7	27.4	100	63	None	85.4[b]	NA	4/7 (57.1%)	28.8
Winkelmann, 1985 (45)	Micro 5, macro 35	BRC ?	40	ND	52.5	62.4	28/44 OP[i]	ND	Tumor shrinkage in 4/44[i]	Total 7/40 (17.5%) micro 4/5 (80%) macro 3/35 (8.6%)	21.5
Moriondo, 1985 (40)	Micro	BRC 8.0 mg	32	29.9	100	12	8/36 OP[i]	106	ND	4/32 (12.5%)	24.8
Mattei, 1984 (38)	Idiopathic	BRC range 5–20 mg[k]	14	ND	100	10.6	None	80.6	NA	3/14 (21.4%)	7.0
	Idiopathic	MET range 12–24 mg[l]	8	ND	100	12.9	None	57.1	NA	0	
	Micro	MET range 12–24 mg[l]	10	ND	100	11.5	None	88.9	No reduction tumor volume	2/10 (20%)	8.0
	Macro	BRC range 5–20 mg[k]	3	ND	100	18.0	None	77.3	No reduction tumor volume	0	

(*Continued*)

TABLE 1. Continued

First author, year of publication (Ref.)	Cause of hyperprolactinemia	Treatment and mean dose (mg/d) [for CAB, mg/wk]	No. of patients	Mean age (yr)	Female sex (%)	Mean treatment duration (months)	Pretreatment	Mean PRL before treatment (μg/liter)	Regression of tumor during treatment on MRI or CT	Persisting normoprolactinemia, n (%)	Mean follow-up in persisting normoprolactinemia (months)
Maxson, 1984 (39)	Micro	BRC 6.0 mg	5	33.2	100	11.0	3/5 OP	211.0	ND	0	NA
Zarate, 1983 (46)	Micro	BRC range 15–20 mg[m]	4	33.3	100	24	None	129.8	No regression	2/4 (50%)	24
	Macro	BRC range 15–20 mg[m]	10	28.2	100	24	None	262.0	4/10 regression; 6/10 no change	4/10 (40%)	18.8
Coculescu, 1983 (31)	Micro	BRC 7.5 mg	2	36.5	100	8.0	None	146.9[b]	NA	0	NA
Sobrinho, 1981 (43)	Macro[n]	BRC 7.5 mg	2	31.0	100	6	None	3555	NA	0	NA
Eversmann, 1979 (33)	Micro	BRC 3.58 mg	6	32.6[o]	83.3	7.1	None	74.8[b]	NA	0	NA

BRC, Bromocriptine; CAB, cabergoline; QUI, quinagolide; DHEC, dihydroergocriptine; LIS, lisuride; MET, metergoline; PRL, prolactin; OP, operation; RT, radiotherapy; NA, not applicable; ND, no data.

[a] Follow-up duration of those with persisting normoprolactinemia and those with recurrence of hyperprolactinemia.

[b] Conversion of mU/liter to μ g/liter by dividing through 30.

[c] Patient characteristics based on n = 16; 14 of 16 reached normoprolactinemia.

[d] Patient characteristics based on n = 23 all normoprolactinemic during treatment, but in five no follow-up because of pregnancy.

[e] Patient characteristics based on n = 11 all normoprolactinemic during treatment, but in one no follow-up because of pregnancy and one because CAB was not withdrawn.

[f] Patient characteristics based on n = 26; 25 of 26 reached normoprolactinemia.

[g] Patient characteristics based on n = 12; 11 of 12 reached normoprolactinemia.

[h] Patient characteristics based on n = 22; 17 of 22 reached normoprolactinemia.

[i] Patient characteristics based on n = 44; 40 of 44 reached normoprolactinemia.

[j] Patient characteristics based on n = 36; 32 of 36 reached normoprolactinemia.

[k] Range of BRC for idiopathic hyperprolactinemia, micro- and macroprolactinomas.

[l] Range of MET for idiopathic hyperprolactinemia and microprolactinomas.

[m] Range of BRC for micro- and macroprolactinomas.

[n] Macroprolactinomas with interruption of the sella turcica on x-ray or clinical evidence of extrasellar expansion of tumor.

[o] Data for age of n = 8; six of eight reached normoprolactinemia.

TABLE 2. Persisting normoprolactinemia after withdrawal of dopamine agonists

	No. of studies	Fixed effects model (95% CI)	I^2	Random effects model (95% CI)
Overall effect	19	35% (31–39)	81%	21% (14–30)
Dopamine agonist				
Cabergoline	4	54% (47–60)	85%	35% (19–56)
Bromocriptine	12	20% (16–26)	20%	20% (14–28)
Cause of hyperprolactinemia				
Idiopathic hyperprolactinemia	3	53% (36–70)	85%	32% (5–80)
Microprolactinoma	13	40% (34–46)	84%	21% (10–37)
Macroprolactinoma	8	37% (29–46)	68%	16% (7–36)
Treatment duration				
<24 months	12	16% (11–22)	0%	16% (11–22)
>24 months	7	40% (35–45)	91%	34% (19–52)
Prespecified protocol				
Yes	9	45% (39–51)	84%	18% (9–31)
No	10	23% (19–28)	11%	24% (18–30)

from 0 to 74%. This highest proportion of 74% was observed in a series with idiopathic hyperprolactinemia treated with cabergoline. The pooled proportion of patients with persisting normoprolactinemia after dopamine agonist withdrawal was 21% in a random effects model [95% confidence interval (CI), 14–30%; I^2 81%].

Sensitivity analysis (Table 2)

Restriction of the analysis to four studies using cabergoline as the only treatment showed a pooled proportion persisting normoprolactinemia of 35% (random effects model, 95% CI, 19–56%). In studies using bromocriptine, the proportion persisting normoprolactinemia was lower (20%; 95% CI, 16–26%). Stratified analysis according to cause of hyperprolactinemia showed higher proportions of treatment success in idiopathic hyperprolactinemia (32%; 95% CI, 5–80%) compared with both microprolactinomas (21%; 95% CI, 10–37%) and macroprolactinomas (16%; 95% CI, 6–36%). Higher proportions of persisting normoprolactinemia were shown in studies with treatment duration longer than 24 months (34%; 95% CI, 19–52%), compared with studies with shorter treatment duration (16%; 95% CI, 11–22%). Exclusion from the analysis of two studies that used radiotherapy in some patients (37, 42) showed persisting normoprolactinemia in 39% (95% CI, 34–44%). Studies in which 50% tumor reduction was achieved in all patients before stopping the dopamine agonist showed persisting normoprolactinemia in 55% (95% CI, 36–73%). Excluding two studies with a considerable proportion of pregnant patients during follow-up (29, 42) showed persisting normoprolactinemia in 20% (95% CI, 12–31%). In studies with a prespecified protocol, the treatment success was 18% (95% CI, 9–31%) using a random effects model (I^2 84%).

In a random effects meta-regression adjusting for cause of hyperprolactinemia, longer treatment duration was associated with higher proportion of persisting normoprolactinemia ($P = 0.015$), whereas the use of cabergoline showed a trend of effect ($P = 0.07$).

Exclusion of the study of Colao *et al.* (5) from the analysis decreased both the treatment success rates and the heterogeneity for idiopathic hyperprolactinemia (17%; I^2 0%), microprolactinomas (19%; I^2 39%), and macroprolactinomas (12%; I^2 31%). This decreasing heterogeneity showed that from a statistical point of view, the results from that particular study were outliers in relation to the results of the other studies.

Discussion

The present systematic review and meta-analysis was performed to estimate the pooled proportion of patients with persistent normoprolactinemia after withdrawal from dopamine agonists. The study showed that withdrawal was associated with persisting normoprolactinemia in only 21% of all patients. Success rates were higher in patients treated for idiopathic hyperprolactinemia, after treatment with cabergoline, and in patients with treatment duration of more than 2 yr.

Randomized controlled studies comparing different withdrawal strategies after successful treatment of hyperprolactinemia are lacking. In 2006, the Pituitary Society provided guidelines as practical clinical tools for the routine clinical care. These guidelines were mainly based on a landmark study by Colao *et al.* (4) that demonstrates that dopamine agonist treatment indeed can be successfully withdrawn in a considerable proportion of patients, provided that they fulfilled selected clinical criteria, such as significant tumor reduction on radiological imaging and a prolonged period of normoprolactinemia during treatment. The first study that tested the practical applicability of these 2006 Pituitary Society recommendations (6) was

recently published (47). In that study, the estimated 18-month risk of recurrence was 63% in a cohort of 46 selected normoprolactinemic patients previously treated with cabergoline for at least 2 yr. These data exemplify the clinical dilemma: apparently it is indeed possible in routine clinical practice to successfully withdraw selected patients from dopamine agonist treatment, but the likelihood of success is not easily predicted in individual patients.

In agreement, in the present systematic review, the main limitations were the heterogeneity of included patients and treatment regimes. These studies differed markedly with respect to the causes of hyperprolactinemia, the treatment before the start of the dopamine agonists, and the type and duration of dopamine agonist therapy. Despite these sources of heterogeneity, the proportion of patients with persisting normoprolactinemia after withdrawal of dopamine agonists was lower than 30% in the majority of studies. Only three studies reported a higher success rate (5, 36, 46), with a maximum of 74% in patients with idiopathic hyperprolactinemia (5).

It should be noted that the pooled proportion of treatment success is slightly overestimated in the current meta-analysis, because studies with success rates of zero are transformed to avoid zero cells for statistical purposes. Moreover, the pooled proportion is not an accurate reflection of treatment success in all patients with either hyperprolactinemia or prolactinomas, considering that most studies reported withdrawal for only a selected group of patients.

A sensitivity analysis showed that the study with the highest success rate may be viewed as an outlier from a statistical perspective. How does this particular study differ from the remaining ones? Of note, the duration of dopamine agonist treatment was not extremely long compared with other studies. However, the study from Colao *et al.* (5) differs with respect to two important aspects from all other included studies. First, before withdrawal, the dose was reduced to a minimum level and not abruptly stopped. Second, all patients fulfilling criteria for withdrawal (*i.e.* tumor regression of >50% on imaging and normoprolactinemia) continued treatment for another 12 months after fulfilling these criteria. In accordance, in another study with persistent normoprolactinemia in more than half of the microprolactinomas, dopamine agonist treatment was explicitly continued several years after normalization of prolactin levels (45). Because that study comprised only seven patients in whom the effect of withdrawal could be adequately assessed, the overall effect of that study for the current meta-analysis was small. A third aspect that could have contributed to the success rates in the study from Colao *et al.* (5) is the use of cabergoline, which is known to be the most potent of currently available dopamine agonists (48).

One limitation of the study from Colao *et al.* is that the included patients were clearly selected. From 381 newly diagnosed patients with hyperprolactinemia, 221 (58%) patients were included in the study (5). The patients who were not included can be supposed to have a less favorable outcome with respect to persistent normoprolactinemia after withdrawal of dopamine agonists. This is a limitation for the external validity of the study results (49). The prior probability of a newly diagnosed patient with a prolactinoma that the disease will be in remission after treatment with a dopamine agonist will therefore be lower than the proportions of treatment success reported in that study.

What are the clinical implications of the present meta-analysis? Our study demonstrates that treatment with cabergoline for more than 2 yr is associated with the best outcome. Although it seems reasonable first to reduce the cabergoline dose before withdrawal, this was only protocolized in one study (5). In addition, although observational studies have not reported clinical relevant cardiac valve disease after treatment with cabergoline for prolactinomas, the findings obtained with much higher cumulative doses of cabergoline in Parkinson patients underscore that unnecessary prolongation of treatment is undesirable (50–52). Finally, a withdrawal trial in individual patients is unlikely to negatively affect long-term outcome.

In conclusion, this meta-analysis showed that hyperprolactinemia will recur after dopamine agonist withdrawal in a considerable proportion of patients. The probability of treatment success is highest when cabergoline is used for at least 2 yr.

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