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Clinical Research Article

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Predictors of the Response to Dopaminergic Therapy in Patients With Prolactinoma

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Abbreviations: AUC, area under the curve; CI, confidence interval; DA, dopamine agonist; IQR, interquartile range; MRI, magnetic resonance imaging; OR, odds ratio; ROC, receiver operating characteristic; SD, standard deviation.

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Abstract

Purpose: Withdrawal of dopamine agonist (DA) therapy in patients with prolactinoma who are controlled by a small dose of medication is recommended by several guidelines. So far, the likelihood of reaching withdrawal conditions based on baseline characteristics remains uncertain.

Methods: We retrospectively examined early clinical, radiological, or biochemical features that may predict the likelihood of reaching withdrawal conditions in prolactinoma patients. Data were obtained in a single academic medical center in the United States from patients seen between 2000 and 2018. Using multiple logistic regression, we compared patients who reached withdrawal conditions with those who did not.

Results: Of 213 patients, 78 (36.6%) reached withdrawal conditions after at least 2 years of DA treatment. Initial maximal tumor diameter was significantly smaller in those who reached withdrawal conditions than in those who did not. Percent prolactin change at the first check from initiation of DA therapy and parasellar invasiveness were predictors of reaching withdrawal conditions. With constant independent variables, there was a 7% increase in odds for reaching withdrawal conditions for every 1% decrease in percent prolactin change at first check after DA therapy start ($P = 0.0000$). Parasellar invasion decreased the odds of reaching withdrawal conditions by 84% ($P = 0.0000$).

Conclusions: DA remains a potential life-long treatment modality for most prolactinoma patients. Patients with parasellar invasiveness and low prolactin percent change from baseline to first prolactin check are more likely to require long-term treatment.

Key Words: prolactinoma, hyperprolactinemia, dopamine agonists

Prolactinomas account for about 40% of all pituitary tumors (1, 2). More common in women of child-bearing age, these tumors slowly increase in size until symptoms such as infertility, hypogonadism, and galactorrhea bring the patients to medical attention (3-9). Most commonly, patients are treated with dopamine agonist (DA) drugs (10). For the majority, this is a lifetime treatment (11-14). A question that patients often ask, at the time of diagnosis or early during treatment, is how long they will need DA therapy. Answering such a question would be of important value and would also help patients choose between DA and surgery (15).

The Endocrine Society guidelines note that DA withdrawal may be safely undertaken after 2 years in patients

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who have achieved normoprolactinemia with a significant tumor volume reduction (1). Guidelines of the Pituitary Society suggest that it is safe to consider discontinuing DA if a patient has normal prolactin levels after therapy with DA for at least 3 years and the tumor volume is markedly reduced (2). Although a recent small study of 69 patients suggested that male gender, a large tumor volume, prolonged time to prolactin normalization, and presence of a cystic, hemorrhagic, and/or necrotic component predict DA resistance (16), no clear criteria are available as a predictor for meeting conditions for future DA withdrawal attempts based upon early clinical, radiological, or biochemical features. To try to assess if such features exist, we have retrospectively reviewed the records of all prolactinoma patients seen by a single endocrinologist at an academic medical center over a period of 19 years, and determined which patients reached conditions that were deemed consistent with possible successful DA withdrawal.

Patients and Methods

Inclusion and exclusion criteria

Patients with prolactinomas completing a clinical visit with a single endocrinologist (R.S.) at the Johns Hopkins Hospital (Baltimore, Maryland, USA), regardless of referral origin, from January 2000 to April 2018, were retrospectively included in the cohort. Thereafter, patients were similarly retrospectively and/or prospectively assessed upon follow-up visits. According to the Endocrine and Pituitary societies, diagnosis of hyperprolactinemia is determined by a measurement of serum prolactin that is on a level above the upper limit of normal unless the patient is asymptomatic or has any discrepancy. All patients were asked to undergo a prolactin check within 2 months from starting DA therapy, although not all of them did in the recommended time frame. DA withdrawal conditions were assessed by the treating physician based upon a significant decrease in prolactin level and tumor size after 2 years of treatment, as described by societies' guidelines.

The exclusion criteria were: patients who had developed hyperprolactinemia before the year 2000; nonavailable data for both prolactin and adenoma size at the time of diagnosis and prolactin levels at the first clinical follow-up visit; follow-up <2 years; or pregnancy before 2 years of DA treatment. Otherwise, intention-to-treat analysis was maintained.

Data collection

A list of all prolactinoma patients was maintained by the treating endocrinologist during the above-mentioned period. During this period, patients whose prolactin was well-controlled (generally below 10 ng/mL) on 0.5 mg of cabergoline per week or 2.5 mg of bromocriptine per day or less, along with reduction in maximal tumor diameter were considered as having reached withdrawal conditions, and were proposed to attempt stopping DA therapy. Demographic characteristics such as age, sex, gender, race, ethnicity, and clinical and hormonal features were extracted from electronic medical records. All patients underwent magnetic resonance imaging (MRI) at the time of the first clinical visit for the classification of the tumor size. Maximal tumor diameter was extracted from radiologist's reading. Routine hormonal tests were analyzed to determine the presence of pituitary deficits. For every subsequent visit, data for every variable were collected if available and were calculated.

This study received Institutional Review Board approval. Given the retrospective nature of the study, informed consent was not needed.

Statistical analysis

Categorical variables were analyzed using frequencies and proportions and compared using χ^2 tests, with Fisher exact test used when at least one of the expected frequencies was less than 5. Continuous variables were expressed using mean ± standard deviation (SD) if values are symmetrical, or median and interquartile range (IQR) if the data is skewed with significantly distorting outliers and compared using the Student *t* test or the nonparametric Mann-Whitney test accordingly.

For further elaboration to the final model, and upon performing multiple logistic regression analysis, some continuous variables were converted for added comparison to categories based on published data as follows: advanced age (≥60 years), hypothyroidism (yes vs no), hypogonadism (yes vs no), parasellar extension (yes vs no), prolactin (≥ 20 ng/mL), size (macro vs micro), cystic (yes vs no).

Subject predictors with $P < 0.20$ in univariate analyses were included in a multiple logistic regression testing. Likelihood Ratio Test statistic compared nested models when needed. Beta regression coefficients and odds ratios (OR) were calculated with 95% confidence intervals (CI).

The discrimination power of the model was assessed by calculating the area under the receiver operating characteristic (ROC) curves (AUC). Variables with an AUC above 0.7 were considered useful, with the strongest near-perfect discrimination considered when AUC approaches 1.

The model that best predicts the event probabilities was cross validated using Akaike's Information Criterion. Agreement between predicted and observed outcome probabilities was again assessed by calibration via LOWESS of

observed versus predicted probabilities. Calibration of the final model reflecting the link between the predicted and the observed risk was evaluated by the Hosmer-Lemeshow goodness-of-fit test.

A left-sided P value < 0.05 was considered statistically significant for all analyses. Data were analyzed using the statistical software Stata version 15.1.

Results

Cohort

We identified 335 patients with at least one clinical visit with R.S. at Johns Hopkins Hospital between January 1, 2000, and April 30, 2018. Twenty patients who had no initial prolactin levels and/or initial MRI assessment upon referral were excluded. Another 10 patients undergoing surgery electively rather than initiating medical treatment, and 9 patients who became pregnant before completing 2 years of treatment were excluded. In addition, 83 patients who were not followed up for at least 2 years were also not included in the analysis. The final study cohort contained 213 patients. For the recommended first prolactin level check, the median time was 1.73 months (IQR, 1.05-5.7), with 111 patients completing the lab workup at 2 months (52%) and 43 (20%) other patients by 6 months.

Patients description

Demographic and treatment characteristics are shown in Table 1. The mean age at diagnosis was 36.8 (±15.1) years; slightly more than half (120/213, 56%) were women. Among the study cohort, 144/213 (68%) were white, of whom 6 were of Hispanic ethnicity; 37/213 (17%) were black, and 11/213 (5%) were Asian (Table 1). Although 36 patients were on psychotropic medications ranging from selective serotonin reuptake inhibitors to stimulants (amphetamines, methylphenidate, dextroamphetamine/amphetamine combination), only 1 patient was on antipsychotic medication (<1%). Among the female subjects, 27% (32/120) were on estrogen and/or progesterone therapy, with 25% (30/120) having a history of a prior pregnancy. Only 11 patients had a family history of pituitary disorders. Of all these demographic characteristics, none were significantly different between the 2 groups (reaching withdrawal vs not reaching withdrawal conditions).

The clinical characteristics at first visit are shown in Table 2. Most patients (91%) received cabergoline as their primary treatment with a mean dose of 0.85 mg/week (±0.35) (Table 2). No significant difference was noted between the 2 arms of the study (Table 2). This similarly applies to bromocriptine, with 19 individuals treated initially with a mean dosage of 25.74 mg/week (±14.33) (Table 2). Macroprolactinomas comprised 59% of tumors while microprolactinomas were 41% (Table 2). Pituitary deficits were hypogonadism in 43 (20%) and central hypothyroidism in 11 (5%) cases (Table 2). Fifteen patients were diagnosed with panhypopituitarism (Table 2). Symptoms were not different between the 2 groups (withdrawal vs non-withdrawal) (Table 2). Oligomenorrhea/amenorrhea was the most prevalent symptom, with 64 complaints in females, 40 in microprolactinomas and 23 in macroprolactinomas. Gynecomastia was present in 9 men (5 in micros and 4 in macros), while galactorrhea was reported by 48 females (33 in micros and 15 in macros). Headache was reported by 47 patients (29 men and 18 women, 9 microprolactinomas and 38 macroprolactinomas), and vision changes were reported by 24 patients (16 males and 8 females) all with macroprolactinomas. Forty-one patients, 37 males and 4 females, 16 micros and 25 macros, presented with decreased libido and sexual dysfunction.

Initial mean maximal tumor diameter in the entire cohort was 1.53 cm (±1.24) (Table 2). Diameter was significantly smaller in those who reached withdrawal conditions (1.27 ± 0.96 cm) versus those who did not (1.69 ± 1.36 cm) (t [198] = 2.38, P = 0.0182). However, no statistically significant difference was observed between micro- and macroprolactinomas. Cystic appearance was similarly

Table 1. Baseline Characteristics of Patients Included in the Study

Characteristics	Total	(N = 213)
Age (years), mean (SD)	36.74	(15)
Female sex, no. (%)	120	(56)
White racial background, no. (%) [a]	144	(68)
Hispanic ethnicity, no. (%) [a]	6	(3)
Smoker, no. (%) [b]	34	(16)
Excessive alcohol, no. (%) [c]	12	(6)
Psychotropic medications, no. (%) [d]	36	(17)
Antipsychotics, no. (%)	1	0
Oral contraceptive pills, no. (%) [e]	32	(27)
Pregnancy prior to DA initiation, no. (%) [e]	30	(25)
Positive family history of pituitary disorders, no. (%) [f]	10	(5)

Abbreviations: DA, dopamine agonist(s); SD, standard deviation.
[a] Race and ethnicity as reported by patients.
[b] Nicotine/tobacco dependence or a recent history of 1 pack-year. Does not include passive smoker.
[c] According to the ICD-10 definition of heavy alcohol usage &/or binge drink.
[d] Includes antidepressants, antipsychotics, anxiolytics, mood stabilizers, and stimulants.
[e] no. = 120 (female only).
[f] Includes only first-degree relatives. 4 have unknown history.

Table 2. Baseline Clinical and Tumoral Characteristics

Characteristics	Total	Non-Withdrawal	Withdrawal	*P* value
	(N = 213)	(n = 135)	(n = 78)	
Classification [a]				
Microprolactinoma, no. (%)	86 (41)	48 (37)	38 (49)	0.072
Macroprolactimoma, no. (%)	122 (59)	83 (63)	39 (51)	
Additional pituitary deficiencies [b]				
None, no. (%)	144 (68)	88 (65)	56 (72)	0.471
Hypogonadism, no. (%)	43 (20)	27 (20)	16 (21)	
Hypothyroidism, no. (%)	11 (5)	8 (6)	3 (4)	
Panhypopituitarism, no. (%)	15 (7)	12 (9)	3 (4)	
Symptoms upon presentation [c]				
Decreased libido, no. (%)	41 (19)	24 (18)	17 (22)	0.474
Galactorrhea, no. (%)	51 (24)	34 (25)	17 (22)	0.576
Gynecomastia, no. (%) [g]	9 (4)	3 (2)	6 (8)	0.077
Headache, no. (%)	47 (22)	30 (22)	17 (22)	0.942
Menstrual irregularities, no. (%) [b]	64 (53)	33 (46)	31 (63)	0.070
Vision changes, no. (%)	24 (11)	16 (12)	8 (10)	0.723
Initial tumor size (cm) – mean (SD) [f a]	1.53 (1.24)	1.69 (1.36)	1.27 (0.96)	0.018*
Cystic aspect, no. (%) [d]	46 (22)	30 (22)	16 (21)	0.749
Parasellar invasiveness, no. (%) [e]	80 (40)	62 (50)	18 (23)	0.000*
Bromocriptine, no. (%)	19 (9)	12 (9)	7 (9)	0.983
Cabergoline dosage (mg/wk) - mean (SD) [f]	0.85 (0.35)	0.87 (0.38)	0.82 (0.28)	0.316
Bromocriptine dosage (mg/wk) - mean (SD) [f]	25.74 (14.33)	28.44 (15.44)	19.25 (9.59)	0.240

Abbreviation: SD, standard deviation.

[a] Classification based on the initial tumor size recorded as the maximal diameter on MRI's radiological reading with micro < 1cm and macro ≥ 1cm.

[b] Deducted according to the clinical laboratory range.

[c] As reported by patients upon diagnostic presentation, all symptoms were assessed in review of systems.

[d] Includes both cystic and hemorrhagic aspect as reported by the radiologist.

[e] Denotes suprasellar extension and/or chiasmatic invasion based on MRI's radiological readings

All *P* values are $\chi 2$ test unless otherwise indicated with [f]: *t* test, [g]: Fisher exact, and *: statistically significant at $P < 0.05$.

[b] no. = 120 (female only).

divided between the 2 groups, with 46 total cystic/hemorrhagic tumors. Parasellar invasiveness comprising suprasellar extension and/or chiasmatic invasion was more frequent in patients who did not reach withdrawal conditions (62/135, 50%) than in those who did (18/78, 23%) $\chi^2 = 13.70$, $P = 00.000$.

Thirty-eight patients (18%) underwent surgery, of whom 58% (22/38) before 2 years of treatment divided into 33% (7/22) microprolactinomas and 67% (14/22) macroprolactinomas. From these 22 patients, 10 opted for surgery after only a short time of DA treatment. The other 12 patients had failed DA therapies due to side effects (3), lack of decrease in prolactin despite increase in DA dosage (6), or worsening of visual field (3). All are in the non-withdrawal treatment at an average of 1.93 years (±1.62) since initiation of medication. A total of 13 females became pregnant following at least 2 years of treatment, with 5 having more than one pregnancy. Eight of those never reached withdrawal conditions, whereas 5 patients remained off medications following delivery or end of pregnancy (Fisher exact = 1.000) at an average of 6.59 years (±4.86) since starting DA.

Primary outcome

The mean duration of all patient follow-up was 79.9 months (±47.6). Seventy-eight of the 213 (37%) patients reached withdrawal conditions. The mean age at withdrawal was 42.4 years (±16.1), the mean time to withdrawal from starting medication was 48.8 months (±33.6), and the mean duration of follow-up after drug withdrawal was of 44.8 months (±43.9). Time to reaching withdrawal conditions is shown in Fig. 1.

Among these 78 individuals, 22 (28%) patients elected not to stop their medication. Of the ones who withdrew, hyperprolactinemia recurred in 42/56 (75%). For all withdrawal condition patients, the mean lowest prolactin level during treatment was 4.03 ng/mL (±4.01), the mean lowest cabergoline maintenance dose was 0.46 mg/week (± 0.17), and the mean lowest measured maximal adenoma diameter

was 0.60 cm (±0.72). 23 patients had an MRI at the time of withdrawal, with a mean maximal diameter of 0.52 cm (±0.56) and a median of 0.35 cm (IQR, 0-0.7) with a mean decrease from diagnosis of 0.82 cm (±0.77).

Prolactin level at diagnostic visit and at first follow-up visit are shown in Table 3. The mean prolactin level at diagnosis was higher for non-withdrawal patients (1499.7 ± 3937.7 ng/mL) than for withdrawal patients (602.4 ± 1412.3 ng/mL) (t [204] = 1.90, P = 0.0584), while the median was 289 ng/mL (IQR, 98-1322) for non-withdrawal and 144.4 ng/mL (IQR, 71.5-466.2) for withdrawal (z = 2.30, P = 0.0213). We generally recommended a follow-up prolactin measurement within 2 months from DA therapy start, although not all patients followed the suggested recommendation. We then calculated the prolactin percent change as the difference between the first follow-up prolactin and the diagnostic prolactin divided by the diagnostic prolactin levels. At first check after starting DA therapy, a mean percent change of 81.65% (±20.63) was observed for all patients, with significantly lower decline in the non-withdrawal group (75.24% ± 22.69) than the withdraw group (91.79% ± 11.01, t [109] = –4.46, P = 0.000). Regardless of the time from diagnosis to the first follow-up measurement, prolactin percent change was statistically significantly different between the 2 groups. The mean ratio between initial prolactin and maximum adenoma diameter was not different between the 2 groups (t [187] = 1.36, P = 0.1760. Conversely, the mean maximum diameter divided by prolactin and multiplied by 1000 was higher in the withdrawal group (t [186] = –2.03, P = 0.0440).

Upon withdrawal, the median serum prolactin was 5.3 ng/mL (IQR, 2.2-9.2) with 13 patients having values higher than 10 ng/mL. The mean prolactin level for these 13 patients was 14.9 ng/mL (±3.5) and median 14.5 ng/mL (IQR, 13.3-16.2). Nine of these patients had a nonvisible adenoma on their MRI, 4 others had their lowest prolactin levels below 10 ng/mL in previous checks with a low dose DA. Three of these patients remained in remission.

In terms of recurrence, the 42 patients had a median follow-up time since DA withdrawal of 41.46 months (IQR, 18.27-78.47) with the last recurrence occurring after more than 14 years. The recurrence rate for patients completing medical withdrawal by 1 year was 9% (5/56), by 2 years was 31% (15/56), and reached 56% (26/56) by 5 years, with the remaining 12 patients occurring beyond 5 years since withdrawal. The mean prolactin at withdrawal was not different between the remission group (6.18 ± 7.65 ng/mL) and the recurring patients (6.51 ± 4.74) (t [54] = –0.19, P = 0.85). Similarly, the mean maximal tumor diameter was not different between remission at 0.58 cm (±0.82) and recurrence at 0.51cm (±0.64) (t [52] = 0.28, P = 0.7774).

Excluding patients reaching withdrawal conditions and not attempting medical withdrawal, 14 patients remained

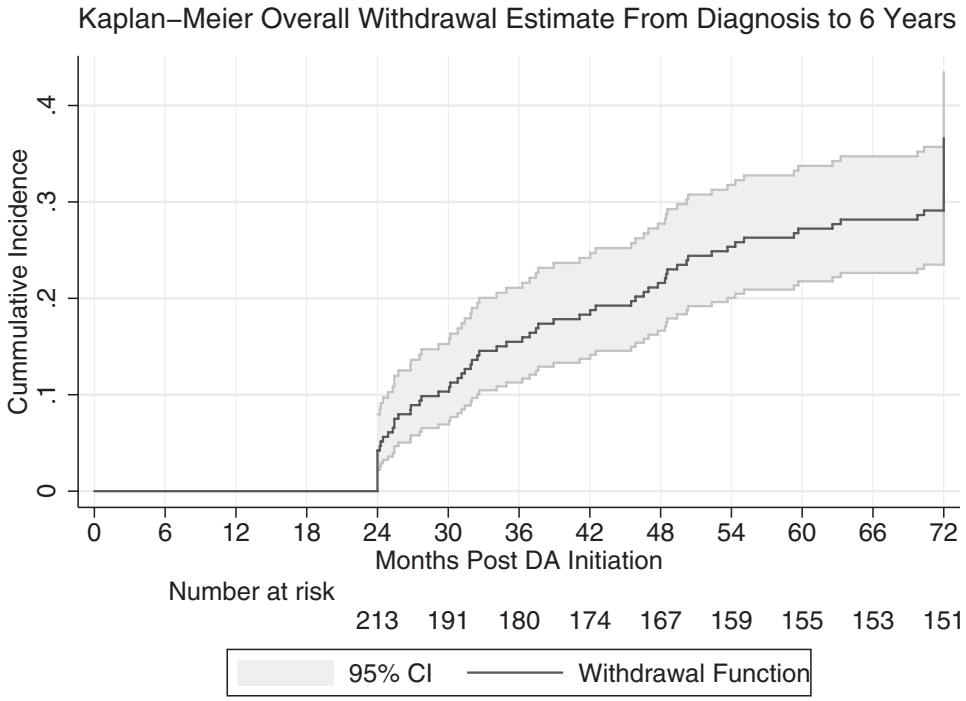

Figure 1. Time to reaching withdrawal conditions. Kaplan-Meier overall withdrawal estimate from diagnosis to 6 years. Data regarding withdrawal conditions were censored at 6 years. Starting with 213 patients, the cumulative incidence at 2 years is 4.23% (2.22%-7.96%). At 4 years, the expected cumulative incidence is 22.07% (17.07%-28.26%), reaching 29.11% (25.30%-35.71%) just before 6 years.

Table 3. Prolactin Level Trends at Diagnostic Visit and at First Follow-Up

Characteristics	Total	Non-Withdrawal	Withdrawal	*P* value
	(N = 213)	(n = 135)	(n = 78)	
Prolactin level at diagnosis, ng/mL				
Mean (SD)	1173.03 (3277.18)	1499.73 (3937.67)	602.39 (1412.30)	0.0584
Median (IQR) [b]	254.2 (89-980)	289 (98-1322)	144.4 (71.5-466.2)	0.0213*
Prolactin percent change, % [a]				
Mean (SD)	79.65 (26.76)	72.82 (30.48)	90.91 (12.86)	0.0000*
2 months	81.65 (20.63)	75.24 (22.69)	91.79 (11.01)	0.0000*
6 months	80.89 (25.14)	74.30 (28.60)	92.41 (10.16)	0.0000*
Median (IQR) [b]	90.14 (70.33-97.05)	83.73 (58.15-94.73)	95.86 (89.52-98.46)	0.0000*
Diagnostic prolactin to volume ratio				
Mean (SD)	501.46 (1041.19)	578.41 (1214.89)	364.53 (607.16)	0.1760*
Median (IQR) [b]	239.79 (137.22-526.67)	275 (145-581.54)	215.28 (120.63-360.76)	0.0433*
Diagnostic volume to prolactin ratio (×1000)				
Mean (SD)	5.51 (5.37)	4.90 (4.48)	6.54 (6.50)	0.0440*
Median (IQR) [b]	4.02 (1.83-6.96)	3.55 (1.71-6.79)	4.54 (2.63-7.69)	0.0585

Abbreviations: IQR, interquartile range; SD, standard deviation.

[a] This is the prolactin percent change from diagnosis to the following recommended prolactin level check divided by the diagnostic level. The recommended prolactin level check following diagnosis is 2 months, some patients presented later. The subcategories represent all values by that specific time point.

All *P* values are *t* tests unless otherwise indicated with [b]: Mann-Whitney test and *: statistically significant at $P < 0.05$

in full remission at a mean duration of 24 months. Keeping the same exclusion criteria, these patients who withdrew successfully had only one significantly different variable when compared with all other patients who either did not reach withdrawal or failed withdrawal: parasellar invasiveness was present in only 14% of patients who were successful (2/14) when compared with 43% (72/167) of all other patients (Fisher exact = 0.046). Of note, the mean percent prolactin change was 90.61% (±9.54) for the remission group and 77.75 (±28.02) for all others (t [174] = –1.64, $P = 0.1021$).

Predictors

With reaching withdrawal conditions as our primary outcome, we looked at unadjusted univariate odds ratios (OR) for every aforementioned characteristic. The initial prolactin level had a nonstatistically significant OR to reach withdrawal conditions (OR = 1.00; 95% CI, 0.99-1.00; $P = 0.069$). Importantly, looking at the percent change between diagnostic and first follow-up level, we found a 5% increase in withdrawal chance for every 1% increase percent drop (OR = 1.05; 95% CI, 1.03-1.08; $P = 0.000$). Calculating the adjusted predictions at a univariate level, we estimate that at a 70% prolactin percent drop, there is an expected 0.22 probability (±0.05) of withdrawing from DA medications, while at 90% the probability is 0.46 (±0.04) (Table 4). Maximal tumor diameter on the first MRI also had a statistically significant effect (OR = 0.72; 95% CI, 0.55-0.95; $P = 0.021$). For every 1 cm increase in the maximal diameter size, there was a 28% lower odds of achieving withdrawal conditions, without significant difference between micro- and macro-adenomas. In terms of parasellar invasiveness, if a tumor is diagnosed with a suprasellar extension or chiasmatic compression, there was a 69% lower odds of withdrawing from DA (OR = 0.31; 95% CI, 0.16-0.58; $P = 0.000$). No significant values were obtained for any other univariate analysis.

Following clinical and statistical decisions, the most appropriate model for our multivariate-adjusted withdrawal analysis contained percent prolactin change and parasellar invasiveness. With this model, the ORs for both percent change and parasellar invasiveness remained statistically significant. If the parasellar invasiveness is kept constant, there is a 7% increase in odds of reaching withdrawal conditions for every increase in 1% drop for prolactin values (OR = 1.07; 95% CI, 1.04-1.10; $P = 0.000$). Similarly, keeping prolactin percent change constant, if parasellar invasion is present there is an 84% decrease in odds of halting medications (OR = 0.16; 95% CI, 0.07-0.33; $P = 0.000$). Regardless of the model obtained, and adjusting for several demographic characteristics, no change in effect was observed. Confounding was assessed accordingly as initial prolactin levels and first follow-up prolactin are clinically related to the prolactin percent change. Additionally, the initial maximal diameter is clinically related to parasellar invasiveness. To reinforce our selection, the model's goodness-of-fit test was not statistically significant, confirming our *null* hypothesis of Hosmer-Lemeshow that what we observed is what is expected ($P = 0.4827$). Similarly, the area under the ROC curve for our multivariate analysis showed a value = 0.8105 with a smooth LOWESS for predicted probabilities and an expected sensitivity of 0.72 and

Table 4. Expected Withdrawal ProbabilityBased on Prolactin Percent Change

Prolactin Percent Change (%)	Adjusted Marginal Percent Probability (%)	Standard Error	*P* value
50	9.62	4.10	0.019
60	14.96	4.64	0.001
70	22.52	4.63	0.000
80	32.46	4.08	0.000
90	44.27	3.94	0.000
95	50.53	4.39	0.000
99	55.53	4.94	0.000

In the final multiple logistic regression model, the marginal predicted probability for reaching withdrawal conditions reaches only 9.62% (± 4.10) if the prolactin percent change from diagnosis to first prolactin check is 50%. While at 99% prolactin percent change, there is a 46% increase to 55.53% (±4.94) of reaching withdrawal conditions.

a specificity of 0.65. Given the Kaplan-Meier Withdrawal Estimate function (Fig. 1), the cumulative chance of withdrawal is only 12% (±0.04) at 2 years and reaches 53% (±0.06) by 4 years. It is not until 6 years that more than three-fourths of all expected withdrawal occurs, with a cumulative incidence of 78% (±0.05) (Fig. 1).

Discussion

In recent years, clinical research on prolactin-secreting pituitary tumors has revolved around determining the recurrence/remission rate after DA withdrawal (10-14, 17). Multiple articles, systematic reviews, and meta-analysis have tried to establish predictive factors that define the predictors of successful DA withdrawal after prolonged therapy (11-14, 18–20). The current recommendations revolve around the duration of treatment, the decrease in tumoral size, and the serum prolactin at withdrawal (1, 2). However, whether due to nonstatistical significance or simply unavailability of data, few studies have managed to establish the characteristics that may predict, at the time of initial diagnosis or shortly after DA therapy is started, which patients will eventually reach conditions that would allow considering DA withdrawal (16). Having predictive tools of the chance of eventually being able to stop therapy would help counseling patients. This is important, as DA are not completely free of side effects; for example, cabergoline is potentially able to cause valvular heart damage (21, 22). This adverse effect mostly occurs at doses higher than that needed for prolactinomas, but the possibility of a cumulative dose effect is not completely excluded (23); however, it is reassuring that a recent paper showed that in macroprolactinomas the dose of cabergoline needed to maintain normal prolactin levels reduces with time even in patients who require very high initial doses (24). Additionally, DA agents have recently been associated with troubling behavioral changes (25), and tissue scarring following long-term DA treatment may render a future surgery more challenging (26, 27). Finally, acknowledging the need for long-term medication from early in the treatment creates a trust factor for physicians and builds patients' expectations on the projected management.

Detecting early predictors of response to DA was the scope of this work. Our sample included a broad spectrum of age, race, and ethnicity, with variably distributed past medical and surgical history. Worthy to note, we observed only a slight female prevalence in the initial cohort (61%), possibly since some female patients at our institution are managed by their gynecologist (28). Additionally, a further reduction of female prevalence in the final cohort is due to the fact that we have excluded from the analysis patients who became pregnant before completing 2 years of treatment.

Here we found that medical treatment will, unfortunately, be a long-term need for the majority of our sample (63% did not reach withdrawal conditions and about three-quarters of those who reached withdrawal and decided to stop the medication eventually recurred). However, their early tumor responsiveness to DA therapy is an important predictor of the possibility of reaching withdrawal conditions. With initial prolactin proving to be a nonstatistically significant determinant of the chance of withdrawal, it is the initial change in prolactin level from the first assessment that could determine the probability to reach these conditions. In fact, there was a 5% increase in the chance of reaching withdrawal every 1% percent drop at the first follow-up prolactin assessment after DA therapy initiation. A patient with a 90% decrease in prolactin levels at the first check has double the probability to withdraw than someone with only a 70% decrease. Additionally, parasellar invasiveness negatively predicted the withdrawal probability. While no statistically significant difference was noted between micro and macroprolactinomas, suprasellar extension or chiasmatic invasion are associated with a lower chance of achieving withdrawal conditions. We attempted to create a score that could determine, based on a multitude of factors, the prospect of attaining the withdrawal conditions. However, this was unsuccessful, as few demographic characteristics showed significance.

Even though the use of cabergoline is usually preferred (14, 29), the choice of the initial medication (cabergoline or bromocriptine) and the dosage did not seem to affect the likelihood of reaching withdrawal conditions. Despite the lack of a specific written protocol, with a single physician managing all these patients, dosage was uniformly adjusted accordingly to prolactin levels and repeat MRIs. As long

as there was a decline in the prolactin value, the DA dose was not increased, with the goal of reaching normal levels without an attempt to force the prolactin to drop as low as possible. Whether a higher starting DA dose, or the attempt to reach the lowest possible prolactin level versus normalization, or early referral to surgery (with the goal of cure or debulking) would improve outcome is not known.

Interestingly, we found that the median ratio of maximum diameter to prolactin was higher in the withdrawal group. This may suggest that adenomas that are less efficient in secreting prolactin may be more likely to reach withdrawal conditions (30, 31).

It is important to note that not every patient reached withdrawal conditions at 2 years of treatment. With an average of 4 years for 50% of all withdrawal, one must inform patients of the likely long duration of DA treatment.

Our subanalysis showed that the rate of successful DA withdrawal reduces over time, with 29% of patients that had a recurrent hyperprolactinemia after 5 years since withdrawal. This fits with the results of the recent systematic reviews and meta-analyses (12, 14). However, an abnormal prolactin does not necessarily imply the need for restarting DA therapy, particularly if the patient is asymptomatic or is a postmenopausal woman (32). Regrettably, our database lacked information on menopausal status, and therefore we could not determine if reaching menopause had any effect on the outcome. However, we must note that 9% (11/120) of our female population were older than 50 years, and 9 patients (82%) reached withdrawal conditions, possibly suggesting a better outcome at older age.

Our study has several limitations. One is inherent to its retrospective nature. The second is the lack of a specific protocol, although this is mitigated by the fact that all patients were cared for by a single endocrinologist, who tried to apply uniform care to his patients. Additionally, the possibility of macroprolactinemia was not ruled out systematically, although patients in whom macroprolactinemia was suspected and demonstrated were not included in this series. Finally, loss to follow-up bias, perhaps present in this scenario, is a possible underestimation of attainment of withdrawal conditions. With successful treatment, patients might become asymptomatic and less reliant on medical treatment and clinical visit, leading to missed outcome reporting as the retention of these patients become harder.

Conclusion

Prolactinoma patients, upon diagnosis and shortly after initiation of DA treatment, can be given an idea of the likelihood of reaching DA therapy withdrawal conditions. In total, 37% of patients started on DA therapy reach withdrawal conditions, and in the majority (75%) of these patients, hyperprolactinemia recurs. An invasive tumor with a nonsignificant drop in prolactin early in the course of DA therapy has a low odds of reaching these conditions. Additionally, reaching withdrawal conditions may require several years of therapy. Finally, the majority of patients who are withdrawn have recurrent hyperprolactinemia. Using these predictors may help physicians counseling patients about the expected duration of DA therapy and about the possibility of choosing alternative means of treatment.

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Additional Information

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Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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