Scoping Review

A scoping review to understand the indications, effectiveness, and limitations of cabergoline in radiological and biochemical remission of prolactinomas

Rakesh Mishra, Subhas K. Konar[1], Adesh Shrivastava[2], Pradeep Chouksey[2], Sumit Raj[2], Amit Agrawal[2]

Department of Neurosurgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, [1]Department of Neurosurgery, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, Karnataka, [2]Department of Neurosurgery, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India

Abstract

Cabergoline has long been used in the medical management of prolactin-secreting pituitary adenomas. However, there is contradicting and inadequate evidence on the efficacy of cabergoline in achieving radiological and biochemical remission in prolactinoma. This article presents scoping review of evidence in cabergoline achieving radiological and biochemical remission in cases of prolactinoma. We have used a recommended scoping review methodology to map and summarize existing research evidence and identify knowledge gaps. The review process was conducted according to the PRISMA-ScR guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews). The selection of studies was based on the criteria defined. Essential information such as reference details, study characteristics, topics of interest, main findings, and the study author's conclusion are presented in text and tables. With the study selection process, eight publications were finally included—one systematic review and meta-analysis, one RCT, and six primary studies. Cabergoline is effective in achieving biochemical and radiological remission in cases of prolactinoma. We identified several knowledge gaps with the scoping review and directions for future studies. Future studies, including randomized studies, will help address challenging questions associated with the management of prolactinoma.

Keywords: Cabergoline, dopamine agonist, hyperprolactinemia, prolactin levels, prolactinoma

Introduction

Pituitary adenomas have a prevalence of 10% in persons with the non-pituitary disease found at autopsy.[1] Prolactinoma is one of the most common central nervous system (CNS) tumors arising from the adenohypophysis's hormone-secreting epithelial cells.[2] About 32–66% of pituitary adenomas in community-dwelling adults secrete prolactin.[3] World Health Organization (WHO) classification of intracranial tumors-2016 classifies prolactinomas as benign grade tumors I/II.[4]

A significant number of Prolactinomas occur most commonly in women in the age group of 20–50 years.[5] Prolactinomas are also common in MEN type I.[6] Apart from clinical features aiding in the diagnosis of prolactinomas, imaging also plays an important role. Magnetic resonance imaging (MRI) can display the size, consistency, vasculature, and lesion extent. It also helps determine the invasiveness concerning the presellar, retrosellar, and cavernous sinus extensions of the prolactinoma. Medical management is the first line of treatment for prolactinomas, followed by surgery, genetherapy, molecular therapeutics, chemotherapeutics, radiotherapy and physiotherapy, being used as adjunctive therapy.[5,7,8]

We chose to perform the scoping review, a relatively novel study design that provides a broad overview of the topic and

Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.ijem_338_21

Address for correspondence: Dr. Rakesh Mishra, Department of Neurosurgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi - 221 005, Uttar Pradesh, India.
E-mail: rakeshmishra_afmc@yahoo.co.in

Submitted: 29-Jul-2021 **Revised:** 22-Nov-2021
Accepted: 10-Dec-2021 **Published:** 17-Feb-2022

How to cite this article: Mishra R, Konar SK, Shrivastava A, Chouksey P, Raj S, Agrawal A. A scoping review to understand the indications, effectiveness, and limitations of cabergoline in radiological and biochemical remission of prolactinomas. Indian J Endocr Metab 2021;25:493-506.

determines the scope of coverage of existing literature.[9,10] While it is still unclear what additional, more specific issues might be presented and valuable addressed by a more thorough systematic review and meta-analysis, this review technique is particularly effective for analyzing the growing data relating to cabergoline therapy in achieving radiological and biochemical remission in prolactinoma. Several systematic reviews have been published on the topic of cabergoline and prolactinoma. To the best of our knowledge, there is no systematic review to address multiple questions related to the questions of interest in the present article. Also, the articles published regarding radiological and biochemical remission of prolactinoma with cabergoline are heterogeneous, making the conduction of a systematic review inappropriate. This is important as there are variations in the definition of biochemical and radiological transmission, recurrence, refractory drug prolactinoma, duration of therapy, and dose of cabergoline as currently described by diverse workers interested in it from diverse regions of the world. Therefore, scoping review is the perfect medium to present an overview of existing literature to identify the knowledge gap, and later systematic review can be proposed on particular questions arising from the current review and as more evidence is gathered.

Methods

Study design

We used PRISMA-ScR guidelines[11] and the strategies plotted by the Joanna Briggs Institute Methods Manual for scoping reviews.[12] We did a systematic literature search to identify the peer-reviewed studies on Cabergoline in the management of prolactinoma. Scoping review research question was "What is the clinical, biochemical and radiological response of Cabergoline in treatment of prolactinoma?"

Search strategy

A systematic literature search was conducted in Medline, PubMed, Google Scholar, and the Cochrane Library on September 2 2020 and updated in December 2020. We used the following MeSH words and Boolean strings:

Search strategy "Cabergoline response in prolactinoma "revealed 367 results

("cabergoline"[MeSH Terms] OR "cabergoline"[All Fields]) AND response [All Fields] AND ("prolactinoma"[MeSH Terms] OR "prolactinoma"[All Fields])

Search strategy "cabergoline and radiological response in prolactinoma "yielded 89 results

("cabergoline"[MeSH Terms] OR "cabergoline"[All Fields]) AND radiological [All Fields] AND response [All Fields] AND ("prolactinoma"[MeSH Terms] OR "prolactinoma"[All Fields])

Search strategy "cabergoline and biochemical response in prolactinoma" yielded 173 results

("cabergoline"[MeSH Terms] OR "cabergoline"[All Fields]) AND biochemical [All Fields] AND response [All Fields] AND ("prolactinoma"[MeSH Terms] OR "prolactinoma"[All Fields])

No time limit was applied in the search strategy. Two authors (RM and AA) did the unbiased literature search and approved the search strategy. We then reviewed the references of the studies to identify further studies. In addition, we did a non-systematic search in the Institute repository.

Inclusion and exclusion criteria

We included RCT, systematic reviews and primary research studies: qualitative and quantitative on using cabergoline to manage prolactinoma for all age groups. We collected data on Cabergoline dose, frequency, duration of therapy, medical complications, biochemical response, and radiological response. We excluded studies regarding diagnostics, genetics, anatomy, pathophysiology and consensus guidelines, book chapters, letters to the editor, conference abstracts, and case reports. Only publications in English were included.

Study selection, data extraction, and data synthesis

Two authors (RM and AA) did an unbiased and independent screening of the titles and abstracts of the articles. The full text was reviewed by the authors (RM and AA/SKK) for eligibility. One of the authors (RM) did the data extraction, whereas the other (SKK) verified the results for comprehensiveness and accuracy. Any disagreement in the search results, studies selection and data extraction, were resolved by mutual discussion. We neither assessed the risk of bias of the included studies, nor excluded any studies based on methodology quality as per guidelines of the scoping review.[11,13]

Results

Search results

Searching the database yielded 616 articles and 364 articles after removing duplicates. The full text of 27 articles was then reviewed as per the criteria mentioned. The reason for exclusion was predominantly genetic studies and studies on anatomy. Finally, a total of nine records were included, of which eight were primary studies and one was a review article. PRISMA Flow chart[14] for the screening of the selected studies is shown in Figure 1.

Study selection and data extraction

Table 1 lists the studies (n = 19) that were excluded along with the reason for exclusion [Table 1].[15-33] Finally, eight (n = 8) studies were included in this scoping review.[34-41] Characteristics of all the studies[34-41] are shown in Table 2. The included studies included a systematic review[36] and an RCT.[35] Table 3 shows the study methodology and the conclusions drawn from the included studies.

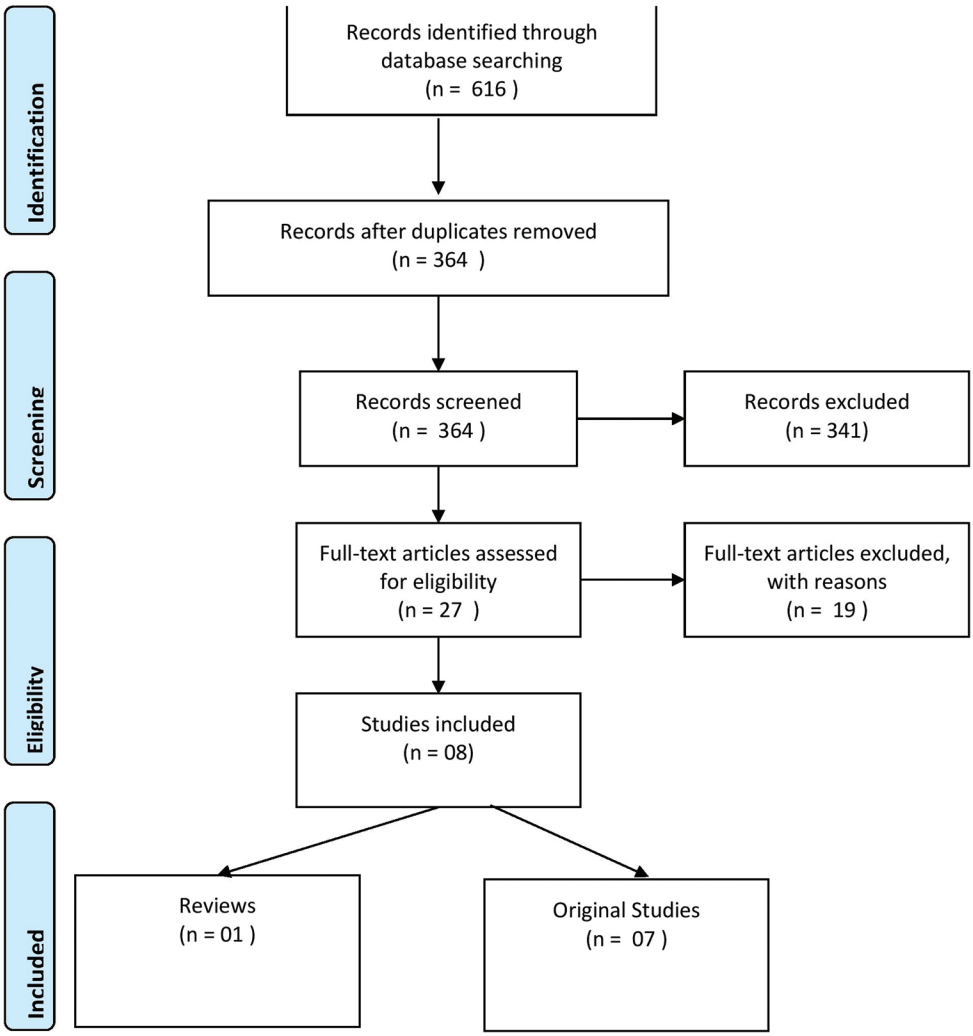

Figure 1: PRISMA flow chart showing a screening of studies, selection, final, and exclusion of the studies

Discussion

Many factors determine the medical management's efficacy including lesion size, prolactin levels, and tumor morphology. The clear evidence of the efficacy of cabergoline in achieving radiological and biochemical remission in prolactinoma is yet to be determined. Cabergoline fails to achieve radiological and biochemical transmission in several patients with prolactinoma. It is not clear as to which patients will have an adequate clinical, radiological, and biochemical response to prolactinoma. It is also not well established what predictors determine refractoriness of increased likelihood of recurrence with cabergoline therapy. There is a paucity of rigorous data and contemporary evidence that is mostly based on experience from case reports and small series. Therefore, with this scoping review, we attempt to identify existing knowledge gaps in the topic and understand the available evidence on the parameters predicting the efficacy of cabergoline in achieving radiological and biological remission in prolactinoma. The primary objective of this review was to collate and describe the efficacy and safety of cabergoline for treating patients with prolactinomas. The secondary objective was to present challenging situations, dopamine agonists resistance, radiological and biochemical failure.

Gender differences in prolactinoma

Women with prolactinoma present at 30 years, whereas men present after 50 years of age.[42] Eighty percent of men with prolactinoma have macroprolactinomas compared to women, where the ratio of micro to macroprolactinoma is 1:8.[42,43] In addition, men tend to have a more aggressive tumor, and the estrogen receptor pathway has some role to play in it.[43] In a recent series of hyperprolactinemia, 50% did not have any sellar mass.[21] The study by Cho *et al*.[34] showed that reduction in the size of the tumor was more significant when Cabergoline was given for more than 1 year compared to the shorter duration of the treatment. The prolactin levels decreased in studies for up to 95%, and a 60–100% reduction in the size of the tumor was seen with cabergoline therapy.[38-40] Further, in these patients, the Cabergoline de-escalation was possible in more than 95% of

Table 1: Excluded papers (*n*=19) read in full-text, and reason for exclusion

First author, year	Title	Reason for exclusion
Van Uum,[32] 2004	Massive reduction of tumor load and normalization of hyperprolactinemia after high-dose cabergoline in metastasized prolactinoma causing thoracic syringomyelia	Case report
Keil M.F.,[25] 2009	Advances in the Diagnosis, Treatment, and Molecular Genetics of Pituitary Adenomas in Childhood	No primary study or systematic review
Sano H,[30] 2009	Cabergoline Effectively Induced Remission of Prolactinoma in a 9-year-old Japanese Boy	Case report
Gibson C.D,[22] 2012	Randomized Pilot Study of Cabergoline, a Dopamine Receptor Agonist: Effects on Body Weight and Glucose Tolerance in Obese Adults	Treatment. Not within the scope
Raappana A,[29] 2012	Long-Term Health-Related Quality of Life of Surgically Treated Pituitary Adenoma Patients: A Descriptive Study	Treatment. Not within the scope
Bozkirli E,[18] 2013	Successful Management of a Giant Pituitary Lactosomatotroph Adenoma Only with Cabergoline	Case Report
Alsubaie S,[15] 2014	Cabergoline Treatment in Invasive Giant Prolactinoma	Case Report
Oki Y,[28] 2014	Medical Management of Functioning Pituitary Adenoma: An Update	No primary study or systematic review
Mohan N,[27] 2017	Cabergoline-induced fibrosis of prolactinomas: a neurosurgical perspective	Case Report
Zygourakis, C. C.,[33] 2017	Cost-Effectiveness Analysis of Surgical versus Medical Treatment of Prolactinomas	No primary study or systematic review
Han Y.L,[23] 2018	Retrospective analysis of 52 patients with prolactinomas following endoscopic endonasal transsphenoidal surgery	Treatment. Not within the scope
Ji L,[24] 2018	Management of prolactinoma: a survey of endocrinologists in China	Not within the scope
Binar M,[17] 2019	Cabergoline treatment in prolactinoma: Amelioration in obstructive and central sleep apneas	Not within the scope
Casulari L.A,[19] 2019	Giant cabergoline-resistant prolactinoma in a man who presented with a psychotic episode during treatment: a case report	Case reports
Eren E,[21] 2019	Clinical and Laboratory Characteristics of Hyperprolactinemia in Children and Adolescents: National Survey	Not within the scope
Michail M,[26] 2019	Clinical manifestations, evaluation and management of hyperprolactinemia in adolescent and young girls: a brief review	No primary study or systematic review
Astaf' eva L,[16] 2020	Decrease of Proliferative Potential and Vascular Density of Giant Prolactinoma in Patients Treated with Cabergoline	Pathophysiology/anatomy. Not within the scope
Soutiero P,[31] 2020	Dopamine agonist resistant prolactinomas: any alternative medical treatment?	No primary study or systematic review
Cho K.R,[20] 2013	Bromocriptine Therapy for the Treatment of Invasive Prolactinoma: The Single Institute Experience	Not within the scope

the patients.[38-40] However, prolactinomas perform differently with medical management in patients lesser than 20 years of age, where macroproactinemia requires multimodal therapy, including surgical intervention.[44]

Measurement of serum prolactin levels

One of the main challenges in dealing with prolactinomas is correct measurement and interpretation of serum prolactin levels and necessitates measurement in serially diluted samples.[21] Nevertheless, serum prolactin elevation could be due to stimulation of nipples, drugs, prolactinoma, and stalk effect due to any compressive sellar mass. As asymptomatic pituitary adenoma occurs in 10% of the general population, one out of 10 can have elevated prolactin levels without a prolactinoma.[1] Eighty percent cases of men with prolactinoma are macroprolactinomas as compared to women where ratio of micro to macroprolactinoma is 1:8.

Interpretation of raised serum prolactin levels

The consensus guideline states that elevated serum prolactin levels due to the stalk effect will not rise above 150 mcg/L.[45] It can reach up to 250 mcg/L in patients with macroadenoma with stalk effect and medications.[46] Kono *et al*.[47] described a 44-year-old patient diagnosed with prolactinoma based on clinical symptoms and neuroimaging and was treated with cabergoline. Prolactin levels and lesion size decreased with cabergoline therapy; however, they increased after 4 years of stopping the treatment. Later with surgical biopsy, the lesion was found to be a Langerhan cell histiocytosis mimicking gangliocytoma. Piloneita *et al*.[48] described three cases of cystic sellar lesions with increased prolactin levels treated with dopamine agonists. The prolactin levels normalized, but there was no control in the lesion size with the medical management. Tissue biopsy obtained with surgery showed cholesterol granuloma subsequently. Yano *et al*.[49] reported a 16-year-old girl with a large pituitary tumor and prolactin levels presenting with hydrocephalus and features of raised intracranial pressure. The patient was treated with cabergoline initially and showed normalization of prolactin levels, but not the tumor size. After 6 months, prolactin levels began to increase further and was refractory to the cabergoline therapy. Endoscopic trans-sphenoidal pituitary decompression then showed mixed pituitary gangliocytoma and prolactinoma. However, Fernandes *et al*.[50] described a 28-year-old patient with 7.6-cm-size prolactinoma, and 1,58,700 μU/mL (reference

Table 2: Characteristics of all included studies

Year	Reference details	Title	Study design	Standardized instruments	Inclusion criteria	Exclusion criteria	Study limitations discussed	Study population (*n*)	Country of origin
2009	Cho *et al.*[34]	Efficacy and Safety of Cabergoline as First Line Treatment for Invasive Giant Prolactinoma	Retrospective	Plasma prolactin levels and MRI	All Giant invasive prolactinoma	x	Yes, Retrospective, Non-controlled and small sample size	10	Korea
2012	Rastogi *et al.*[35]	Efficacy and safety of rapid escalation of cabergoline in comparison to conventional regimen for macroprolactinoma: A prospective, randomized trial	RCT	Di Chiro and Nelson formula for tumor volume and plasma prolactin levels	Yes (randomization)	X	X	42	India
2012	Wang *et al.*[36]	Treatment of hyperprolactinemia: a systematic review and meta-analysis	Systematic Review and Meta-analysis	PRISMA, Ottawa-Newcastle tool, Cochrane risl of bias tool, GRADE framework	Yes	Yes	Yes, imprecision, heterogeneity in the results, low quality of the studies included, high risk of publication and reporting bias	-	USA
2014	Lee *et al.*[37]	Early Prediction of Long-Term Response to Cabergoline in Patients with Macroprolactinomas	Retrospective	Di Chiro and Nelson formula for tumor volume and plasma prolactin levels	X	x	Yes, Retrospective, Single center, Non-randomized, Short follow-up and absence of standardized tools	44	Korea
2017	Paepegaey *et al.*[38]	Cabergoline Tapering Is Almost Always Successful in Patients With Macroprolactinomas	Retrospective	X	Yes	Yes	Yes, Retrospective design and prescription bias	260	France
2018	Gonzaga *et al.*[39]	Prolactinomas Resistant to Treatment With Dopamine Agonists: Long-Term Follow-Up of Six Cases	Retrospective	X	X	X	X	6	Brazil
2020	Almalki *et al.*[40]	Clinical Features, Therapeutic Trends, and Outcome of Giant Prolactinomas: A Single-Center Experience Over a 12-Year Period	Retrospective	X	Yes	X	Yes, retrospective and single center	33	Saudi Arabia
2020	Yang *et al.*	Clinical, Hormonal, and Neuroradiological Characteristics and Therapeutic Outcomes of Prolactinomas in Children and Adolescents at a Single Center	Retrospective	x	Yes	X	Yes, retrospective, single center, small sample size and limited follow-up	25	South Korea

Table 3: Main findings of studies included

Reference details year	Title	Authors	Design and Methods	Materials *n*: Number	Main results and primary authors' conclusion
2009	Efficacy and Safety of Cabergoline as First Line Treatment for Invasive Giant Prolactinoma	Cho *et al*.[34]	Retrospective study of patients from April 2003 to June 2007 with invasive giant prolactinomas: tumor diameter >40 mm, serum prolactin concentrations >1,000 ng/mL, and invasive extrasellar tumor growth	10	Cabergoline treatment for more than 12 months caused a greater reduction in tumor size compared to the treatment for less than 12 months (97±1% vs. 78±7%, P<0.05).
2012	Efficacy and safety of rapid escalation of cabergoline in comparison to conventional regimen for macroprolactinoma: A prospective, randomized trial	Rastogi *et al*.[35]	Randomized, prospective, interventional trial. Subjects and Methods:: Forty-two patients (male or female) with macroprolactinoma were randomized to conventional (group A) or rapid escalation (group B) of CAB dosing. In group B, CAB was started at a dose of 0.5 mg twice a week followed by a weekly hike of 1 mg/week, based on serum PRL and then monthly. The end point of the present study was a composite of normoprolactinemia and tumor shrinkage≥50% from baseline.	42	A weekly or a conventional 4 weekly escalation of CAB have a similar efficacy with regards to the achievement of normoprolactinemia and significant tumor shrinkage for macroprolactinoma.
2012	Treatment of hyperprolactinemia: a systematic review and meta-analysis	Wang *et al*.[36]	Systematic Review and Meta-analysis	-	Cabergoline was more effective than bromocriptine in reducing persistent hyperprolactinemia, amenorrhea/ oligomenorrhea, and galactorrhea.
2014	Early Prediction of Long-Term Response to Cabergoline in Patients with Macroprolactinomas	Lee *et al*.[37]	6-year retrospective study of patients with macroprolactinomas who were treated with CAB as a primary drug at Severance Hospital, Seoul, Korea between 2008 and 2013.	44	Determining cabergoline response using TVR and NP 3 months after treatment is useful for predicting later outcomes. However, further cabergoline administration should be considered for patients with TVR >25% at 3 months without NP, particularly those with huge prolactinomas, because a delayed response may be achieved.
2017	Cabergoline Tapering Is Almost Always Successful in Patients With Macroprolactinomas	Paepegaey *et al*.[38]	Retrospectively studied 260 patients. CAB was introduced at a mean dose of 0.83 6 0.52 mg/wk. When the PRL level had normalized, the patient's physician chose to either maintain the CAB dose (fixed-dose group) or to taper it (de-escalation group) until the minimal effective dose required to maintain a normal PRL level was established.	260	PRL normalized in 157 patients (60.8%) during CAB treatment. CAB de-escalation was attempted in 84 (53.5%) of these 157 patients and was successful in 77 (91.7%) cases. The mean CAB dose was reduced from 1.52 6 1.17 mg/wk to 0.56 6 0.44 mg/ wk at the last visit (P , 1 3 1024)
2018	Prolactinomas Resistant to Treatment With Dopamine Agonists: Long-Term Follow-Up of Six Cases	Gonzaga *et al*.[39]	Retrospective study design	6	Tumor regression occurred in all patients, ranging from 20 to 100%, but total disappearance of the adenoma with an empty sella occurred in one patient. The maximum weekly doses of cabergoline ranged from 3.0 to 4.5 mg.
2020	Clinical Features, Therapeutic Trends, and Outcome of Giant Prolactinomas:	Almalki *et al*.[40]	Retrospective Design	33	Prolactin levels decreased by as much as 95.4% after CAB treatment. Serum PRL concentrations completely normalized in 11 patients and

Contd...

Table 3: Contd...

Reference details year	Title	Authors	Design and Methods	Materials *n*: Number	Main results and primary authors' conclusion
	A Single-Center Experience Over a 12-Year Period				significantly reduced in 22 patients. The mean tumor volume at baseline was 42.87 cm3, whereas the mean post-treatment tumor volume was 3.42 cm^3 (no residual tumor in 2 patients, whereas in others, it ranged from 0.11 to 16.7 cm^3) at the last follow-up visit. The mean change in tumor volume was 88.84%. Tumor volume decreased by an average of 92% for men and 80.4% for women.
2020	Clinical, Hormonal, and Neuroradiological Characteristics and Therapeutic Outcomes of Prolactinomas in Children and Adolescents at a Single Center	Yang *et al*.[41]	This retrospective cohort study included 25 patients with prolactinomas diagnosed before 19 years of age, who presented at Samsung Medical Center during a 15-year period (March 2005-August 2019).	25	Male gender, the prolactin (PRL) level at diagnosis, and the presence of panhypopituitarism were positively correlated with maximum tumor diameter (r=0.443, P=0.026; r=0.710, P<0.001; and r=0.623, P=0.001, respectively)

range 58–254) prolactin levels treated with dopamine agonist for 10 years and reported 96.8% reduction in prolactin levels, an effective reduction in tumor size and clinical symptoms.

Therefore, it is pretty apparent about prolactinoma when the prolactin levels commensurate with the size of the lesion. When a lesion is much smaller, elevated prolactin levels could be due to the stalk effect. However, prolactin levels in multiples of thousands in large lesions are due to prolactinoma. Nevertheless, alternative diagnosis arises when the prolactin levels do not match the lesion's size. For example, when the lesion size is enormous but the levels are in thousand, the same cannot be explained either by the stalk effect or the diagnosis of prolactinoma.

There is growing evidence that measurement of serum prolactin per cm^3 of the tumor has better accuracy in the differential diagnosis of conditions leading to hyperprolactinemia.[51] Serum prolactin/volume of the tumor (PRL/V) may be better than the PRL level in achieving a differential diagnosis, and the optimal PRL/V ratio for differentiating prolactinomas from other types of hyperprolactinemia-causing pituitary adenomas was 54.00 μg/(1 × cm^3).[51] Six case series have shown that when macroprolactinoma is observed for 8 years without treatment, approximately 7% showed growth.[5,52-56] A significant increase in levels of serum prolactin indicates the growth of prolactinoma, though not always.[57] Imaging and hormone analysis should closely follow asymptomatic patients. It is improbable for the prolactinoma to grow significantly without a corresponding increase in the serum prolactin levels, though reports indicate such an occurrence.[58] Therefore, a microadenoma with demonstrable change in size should undergo therapy, despite stable serum prolactin levels as it may be one of the 7%, which will progress to become macroadenoma.[5]

Medical management of prolactinomas

The optimal treatment strategy and duration of therapy with dopamine agonists in patients with hyperprolactinemia and prolactinoma is not clear. Studies show that a significant proportion of patients recur after cabergoline withdrawal and the probability of treatment success is more when cabergoline is used for two years.[59] Persisting normoprolactinemia after dopamine agonist withdrawal was seen in 21% in a random-effects model [95% confidence interval (CI), 14–30%; I (2): 81%).[59] Stratified analysis showed higher proportions of treatment success in idiopathic hyperprolactinemia (32%; 95% CI, 5–80%), compared with both (21%; 95% CI, 10–37%), and macroprolactinomas (16%; 95% CI, 6–36%).[59] Though medication is the choice of management for these tumors, there is a subset of patients in which surgery may yield better results than protracted medical management.[60] These patients are intolerant, non-compliant, or non-responsive to the medical management and for various reasons.[60] Long-acting dopamine agonists (DAs) achieve stable normoprolactinemia in 80% and is considered the initial treatment of choice.[61] Reduction in tumor size is seen in 60% of patients receiving dopamine agonist.[62] However, the use of these agents is not immune to various side-effects, some severe enough to warrant discontinuation of medical therapy favoring surgical intervention. For example, cabergoline, a type of dopamine agonist, increases the risk of valvular heart disease and pituitary apoplexy after initiation of therapy.[63,64] Though surgery may seem to have a potential for single shot cure, 50–80% of resections result in only temporary improvement and about half of these eventually have a relapse.[65] The above observations support the practice of "medical-first" management strategy for prolactinomas with dopamine agonists like bromocriptine and cabergoline. The latter is often the preferred choice because of its ease of dosing and better patient compliance.[45,46,61,62,66,67] One of the major challenges to its use being the fact that

eventhough patients do achieve reasonable hormonal remission, they can still have a progressively increasing size of the prolactinoma.[61,67-71]

It is important to differentiate primary and secondary resistance of prolactinoma to dopamine agonists (DA).[31,67-72] Some patients who initially responded to bromocriptine but then developed some degree of resistance have benefited from a switch to cabergoline, and, therefore, they should not be regarded as genuinely DA-resistant.[70] Therefore, resistance to one DA but a response to another DA should not be mistaken for actual resistance. Secondary (or acquired) resistance to DAs is sporadic and is defined as initial remission followed by a resurgence in prolactin levels or tumor enlargement.[31,67-72] There are only six cases reported in the literature with true secondary DA resistance.[67,69,73-75] It is not clear if the mechanisms underlying secondary resistance is the same or different from primary resistance.[71,72]

The current scoping review suggests that Cabergoline is significantly effective in achieving clinical, radiological, and biochemical control in patients with Prolactinoma. The study by Cho *et al*.[34] showed that reduction in the size of the tumor was more significant when Cabergoline was given for more than 1 year compared to the shorter duration of the treatment. The prolactin levels decreased in studies up to 95%, and a 60–100% reduction in the size of the tumor was seen with cabergoline therapy.[38-40] Further, in these patients, the Cabergoline de-escalation was possible in more than 95% of the patients.[38-40]

Effectiveness of Cabergoline

Cabergoline is effective in achieving the radiological and biochemical control of prolactinoma.[15] Cabergoline at starting dose of 0.25 mg weekly gradually increased up to 1 mg for 8 months results in an 88% reduction of prolactin levels in a case of invasive giant prolactinoma.[76] One study has reported a reduction in tumor size of more than 50% at a cabergoline dose of 3 mg/week given for 18 months.[77] Cabergoline normalizes the prolactin levels and reduces the size of the tumor by reducing proliferative tendency as demonstrated by a reduction in Ki67 index, reduced expression of CD31, and CD34.[16] Bozkirli *et al*. demonstrated a reduction in the size of the tumor by 50% in follow-up MRI after 4 months, while the patient was on Cabergoline 2 mg weekly dose.[18] A study showed complete resolution of adenoma and normalization of prolactin levels with the use of cabergoline 1.5 mg/week for 7 months in a 9-year-old child, establishing safety and efficacy of cabergoline in the pediatric population as well.[30]

Contrary to these, Casulari *et al*.[19] reported a case wherein the prolactin levels remained high after 48 months of cabergoline therapy.[19] In addition, there was no significant reduction in the size of the adenoma after 41 months.[19] Summary of the case reports is in Table 4.

Table 4: Case reports on cabergoline treatment in prolactinoma

Authors_ Year	Country	Titleof the study	Study Design	Age (years)	Initial Prolactin levels (mIU/L)	Initial Perimetry	Dose of cabergoline (mg)	Frequency	Escalation of dose of cabergoline	Followup prolactin levels (months)	Follow-up prolactin levels (months)	Follow-up Perimetry (months)
Alsubaie *et al*., 2014[15]	Saudi Arabia	Cabergoline Treatment in Invasive Giant Prolactinoma	Case Report	52	125347	Bilateral Superior Quandrantonopia	0.25	twice weekly		9983 (5)	11635 (9)	Normal (5)
Dutta *et al*., 2012[76]	India	Rapid reduction with cystic transformation of invasive giant prolactinoma following short-term low-dose cabergoline	Case Report	60	33872.3	Bitemporal Hemianopia	0.25	once weekly	1 mg/week over 3 weeks	4085 (8)	255.31 (12)	Normal (3)
Rehmanian *et al*., 2013[77]	Iran	Giant prolactinoma: case report and review of literature	Case Report	29	255319	Right Temporal Hemianopia	1	twice weekly	3 mg/week after 3 months	4723.4 (3)	3510.63 (12)	Normal (18)
Bozkirli *et al*. 2013[18]	Turkey	Successful Management of a Giant Pituitary Lactosomatotroph Adenoma Only with Cabergoline	Case Report	46	>40000	Normal	2	weekly		174.49 (2)	1521.2 (18)	Normal (4)
Casulari *et al*., 2019[19]	Brazil	Giant cabergoline-resistant prolactinoma in a man who presented with a psychotic episode during treatment: a case report	Case Report	60	318978.7	Normal	1	weekly	3.5 mg/week after 8 months	36531.9 (2)	17872.3 (48)	Normal (4)
Sano *et al*., 2009[30]	Japan	Cabergoline Effectively Induced Remission of Prolactinoma in a 9-year-old Japanese Boy	Case Report	9	17268	Bitemporal Hemianopia	1.5	weekly	-	691.4 (1.15)	376.5 (4.37) 212.7 (7.6)	Normal (7.6)

Table 5: Responses as recorded in the included studies

Study	Selection criteria	Number of patients	Population	Mean age (years)	Baseline tumor diameter (cm)	Baseline tumor volume (cm^3)	Mean prl level	Average treatment duration	CAB Intial Dose
Almalki *et al.*, 2020[40]	Giant Invasive Prolactinoma	33	Adult	38.13	4.29	49.88	95615.03 nmol/L		0.25
Cho *et al.*, 2009[34]	Giant, prolactin >1000 ug/ml	10	Adult	37+-4	51	-	11,426 ng/mL	19 months	0.5
Gonzaga *et al.*, 2018[39]	Prolactinoma resistant to dopamine aagonists	6	Adult	36.5	-	-	3838 ng/ml	12 months	1
Lee *et al.*, 2014[37]	Macroprolactinomas treated with cabergoline	66	Adult	36.8		3.71	796.7 ng/dl	12 months	1
Paepegaey *et al.*, 2017[38]	Macroprolactinoma patients	260	Adult	32.7			680 ng/ml	9.96 month	0.5
Rastogi *et al.*, 2012[35]	Macroprolactinoma patients	42	Adult	-	-	-	1901 ng/ml	24 weeks	0.5
Yang *et al.*, 2020[41]	Prolactinoma patients <19 years	25	-	16.9	1.2		207 ng/ml	1.1 year	1.5

Study	Frequency	Escalation	De-escalation of Cabergoline	Follow-up period	Post-treatment mean diameter (cm)	Post *t*-treatment PRL	%PRL change	Post-treatment volume	% reduction in tumor	% PRL normalization	Significant decrease in PRL %
Almalki *et al.*, 2020[40]	weekly	yes	Yes, done when PRL levels normalized and reduction >50%	6.3 years	1.5	2503.5 nmol/L	94.3-98.3 after 5 months	3.4	92	33	66.67
Cho *et al.*, 2009[34]	weekly	yes	-	20.6 months		-	97 after 3 months	-	85+/-4	-	
Gonzaga *et al.*, 2018[39]	Weekly	Yes	-	180 months	-	621.35 ng/ml		-	90-100%	-	-
Lee *et al.*, 2014[37]	Weekly	Yes	Yes, with good response	16 months	-	-	81.8	-	74.7	-	-
Paepegaey *et al.*, 2017[38]	Weekly	Yes	Yes, 91.75 had successful de-escalation				95			71.6	
Rastogi *et al.*, 2012[35]	Weekly	Yes	-	24 weeks	-	172.8 ng/ml	72.7+/-26.2		92.3	82	-
Yang *et al.*, 2020[41]	Weekly	Yes	-	3 years	-	-	-	-	-	-	-

Some of the salient findings are enumerated in Table 5. Most patients significantly reduced serum prolactin levels after 6 months of cabergoline therapy, with normalization after a median duration of 9 months. In a study by Paepegaey *et al*., researchers reported that 71.7% of patients had normalized PRL levels after 9 months.[38] Most common causes reported for failure were resistance, CSF leaks, Intolerance and poor compliance.[38] Even in these patients >955 had a significant reduction in PRL level, improvement in clinical symptoms, and resolution of the tumor size.[38] In addition, they suggested that patients with resistance have higher PRL levels at diagnosis and take a longer time for normalization; however, there was no significant variation in the tumor size.[38] Failure rate for cabergoline discontinuation has been reported up to 36.8%.[38]

In a clinical trial, Colao *et al*.[78] prospectively studied the efficacy of cabergoline in a group of patients previously untreated, treated with bromocriptine and responsive, treated but intolerant, and treated but had resistance to bromocriptine therapy. After standard doses of cabergoline for 1–3 years, the researchers found that more tumor shrinkage occurred in the previously untreated group (92.3%) than previously treated and responsive patients (38.4%) and other groups.[78] This has important clinical implications as it suggests better efficacy of cabergoline when used as first-line therapy for prolactinomas. In addition, they also found a correlation between the tumor shrinkage size and the suppressed levels of PRL; many other studies fail to show this correlation.

Radiological changes with cabergoline therapy

Araujo *et al*.[79] reported an asynchronous relationship between PRL levels and tumor size after cabergoline treatment. The study found that 87% of patients had normalisation of PRL levels in the first 2 years of therapy, whereas only 62% had >50% reduced tumor size.[79] Fibrosis in the prolactinoma has been described after long-term therapy with bromocriptine and rarely with cabergoline therapy.[27,80] Mohan *et al*.[27] reported a case of prolactinoma, which developed fibrosis in the tumor after 6 months of cabergoline therapy. Additionally, the patient also developed moderately severe tricuspid valve regurgitation after 9 months of therapy with cabergoline.[27]

Surgical implications of fibrosis in prolactinoma are controversial. Some studies suggest that fibrosis makes the tumor hard and adherent to the nearby structures, thereby increasing complications and adverse outcomes; other studies point out that fibrosis leads to tumor shrinkage and better surgical outcomes.[81-83] Menucci *et al*.[80] found no significant difference in the complication rates and surgical outcome in the tumor with fibrosis and without. DA-induced fibrosis of the prolactinomas can be reversed by stopping DA therapy for months.[84] As fibrosed tumors have strong implications for neurosurgeons, it is imperative to identify them in preoperative imaging. The fibrous nature of the tumor is revealed by iso-hyperintense T2W and is-hypo-hyper on T1W MRI imaging.[85] Contrast enhance 3D-FIESTA MRI imaging modality as potential applications in identifying fibrous tumor is a prospect to be further explored in future studies.[86]

In most of the studies, cabergoline is well tolerated. No significant side-effects were noticed even when the dose of cabergoline was escalated.

Valvular Heart Diseases Associated with Cabergoline Therapy

An association between valvular heart disease and cabergoline therapy is found in patients with Parkinson's disease.[87] Very few case reports suggest an etiological role of low-dose cabergoline therapy in developing valvular heart disease.[88-90] Several pharmaco-epidemiological studies fail to show the relationship between the development of valvular heart disease and the dose of cabergoline therapy used to treat hyperprolactinemia.[88,91] Elenkova *et al*. suggested that clinically significant valvular lesions are not associated with long-term, low-dose cabergoline therapy, but subclinical lesions are present, and therefore, baseline 2D echo should be done in all patients and should be periodically followed up.[92]

Key Message

There is no significant correlation between baseline tumor characteristics on PRL levels and outcomes.[37] Initial tumor size and radiological predictors like parasellar invasiveness serves as indicators for responsiveness of DA therapy.[93] In addition, the presence of cystic and hemorrhagic/necrotic component and high contrast characteristics of tumor on MRI imaging indicates poor responsiveness for cabergoline therapy.[94] With this scoping review, we conclude that cabergoline is effective in the medical management of prolactinoma. It should be started at a low dosage of 0.25 mg twice weekly to 1 mg weekly and dose escalation can be done as preresponse over 3–4 weeks. Generally, good biochemical and radiological response is achieved in 6 months, some patients may require longer duration of therapy ranging for more than 12 months. Even after 12 months of continuous therapy, the patient should be put on the lowest dose maintenance therapy. Dose de-escalation can be done if prolactin levels are normalized or if there is >50% reduction in the size of the adenoma. However, maintenance therapy duration is unclear, and the patient should be followed up for long once the cabergoline is tapered or stopped. Serum prolactin levels should be assessed at the end of 3 months, 6 months, and after 12 months to assess the efficacy of cabergoline and perform dose adjustment. Studies have found that a maintenance dose of 1 mg/week is required to keep PRL levels normalized in patients in whom de-escalation of cabergoline dose is done.[38] A simple algorithm guiding the management of prolactinoma is presented in Figure 2, based on the current evidence available.

Strengths and Limitations

The current scoping review attempts to answer the challenging questions in the management of prolactinoma. How effective

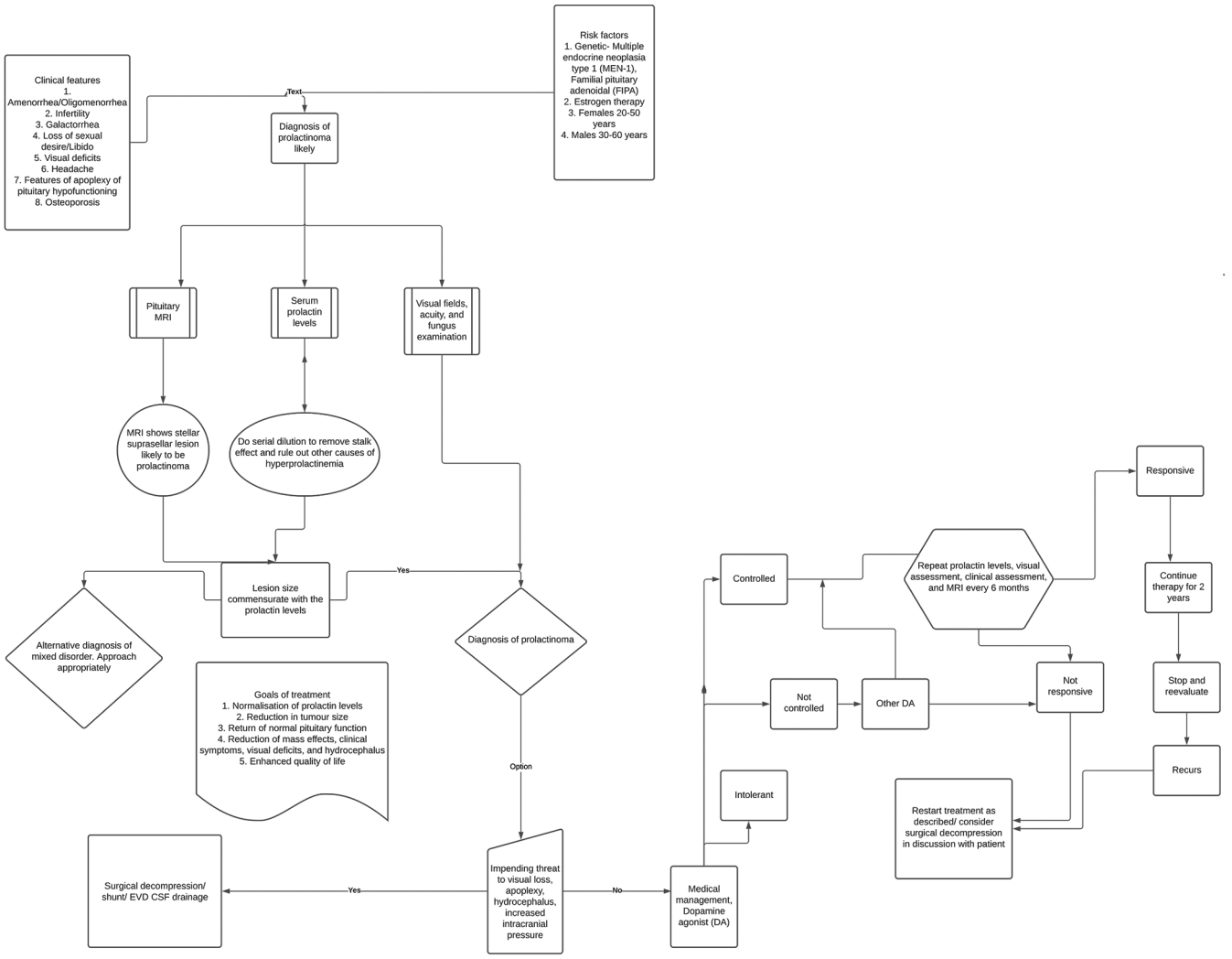

Figure 2: The algorithm on the practice model for management of prolactinoma

is cabergoline in radiological and biochemical remission in patients with prolactinoma? The main strength of this scoping review is its methodological approach. We used a systematic framework recommended in the PRISMA checklist for scoping reviews (PRISMA-ScR)[12,14] to investigate a broad research question. This methodology can fill the knowledge gap and help in designing systematic reviews in future.

Although we performed a systematic search for the studies, there is a scope that some of the relevant articles were left out.

Research gap and directions for future research

Though there is evidence on the measurement of prolactin in serially diluted serum samples and rise in levels due to stalk effect, the evidence is lacking on the relationship of serum prolactin levels with a diagnosis other than prolactinoma. It is not clear from the available literature about the minimum and maximum possible serum prolactin levels when the pathology is something other than prolactinoma or mixed with prolactinoma. It is also not clear how much responsive cabergoline is in achieving clinical, radiological, and biochemical remission in these patients because several reports described the resolution of symptoms, prolactin levels, and lesion size in these patients, only to recur later.

The role of gender on occurrence, natural history and response of prolactinoma to the cabergoline therapy is not well elucidated in the existing literature. In the systematic review and meta-analysis of 22 patients aged less than 20 years with prolactinoma, the authors found that macroprolactinoma (size > 20 mm) is more likely to require multimodality therapy, including surgical intervention.[44] These patients usually have larger tumors and prolactin levels, and are usually not responsive to cabergoline therapy. However, even giant prolactinomas are shown to be responsive to cabergoline therapy in adults.[15,40,50]

As per 2011 Endocrine society practical guideline and other studies, it has been found that persistent normoprolactinemia is more likely in idiopathic normoprolactinemia than micro or macroprolactnimeia due to prolactinoma.[59,95,96] Longer duration of therapy with cabergoline is more likely to have higher success. However, the heterogeneity of the patients in these studies reduces the strength of evidence, and 20–40%

of patients with prolactinoma may fail to achieve persistent normoprolactinemia,[59] raising the need for further studies to identify a subset of patients based on radiological parameters most likely to benefit with prolonged cabergoline therapy.

Therefore, future prospective studies focussing on age, gender, radiological parameters, and correlating the histobiochemical tumor profile with serial neuroimaging and duration of cabergoline therapy will help identify its efficacy in achieving radiological and biochemical remission.

Conclusions

Cabergoline is effective in achieving clinical, radiological, and biochemical remission in patients with prolactinoma. This remission is seen with more prolonged therapy than the shorter duration therapy. Significant reduction in the PRL levels and tumor size occurs after 6 months of cabergoline therapy with normalization after a median duration of 9–12 months. Patients should be kept on low-dose maintenance therapy and closely followed up for recurrence. Non-normalization or reduction in PRL levels after 12 months suggest resistance, and alternative treatment options should be sought. Cabergoline is effective in reducing the tumor size even in cases of dopamine agonist resistant prolactinoma cases. Future studies need to be conducted to determine how long a person needs to be on maintenance therapy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH. Pituitary magnetic resonance imaging in normal human volunteers: Occult adenomas in the general population. Ann Intern Med 1994;120:817-20.
2. Theodros D, Patel M, Ruzevick J, Lim M, Bettegowda C. Pituitary adenomas: Historical perspective, surgical management and future directions. CNS Oncol 2015;2015;4:411-29.
3. Molitch ME. Diagnosis and treatment of pituitary adenomas: A review. JAMA 2017;317:516-24.
4. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, *et al*. The 2016 World Health Organization classification of tumors of the central nervous system: A summary. Acta Neuropathol 2016;131:803-20.
5. Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the treatment of prolactinomas. Endocr Rev 2006;27:485-534.
6. de Laat JM, Dekkers OM, Pieterman CRC, Kluijfhout WP, Hermus AR, Pereira AM, *et al*. Long-term natural course of pituitary tumors in patients with MEN1: Results from the DutchMEN1 study group (DMSG). J Clin Endocrinol Metab 2015;100:3288-96.
7. Donoho DA, Laws ER Jr. The role of surgery in the management of prolactinomas. Neurosurg Clin N Am 2019;30:509-14.
8. Loeffler JS, Shih HA. Radiation therapy in the management of pituitary adenomas. J Clin Endocrinol Metab 2011;96:1992-2003.
9. Armstrong R, Hall BJ, Doyle J, Waters E. Cochrane update. 'Scoping the scope' of a cochrane review. J Public Health (Oxf) 2011;33:147-50.
10. Munn Z, Peters MD, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol 2018;18:143.
11. Tricco A, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, *et al*. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. Ann Intern Med 2018;169:467-73.
12. Peters MD, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil H. Chapter 11: Scoping Reviews (2020 version). In: JBI Manual for Evidence Synthesis. JBI; 2020. doi: 10.46658/JBIMES-20-12. Available from: https://synthesismanual.jbi.global.
13. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc 2015;13:141-6.
14. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:e1000097. doi: 10.1371/journal.pmed1000097.
15. Alsubaie S, Almalki MH. Cabergoline treatment in invasive giant prolactinoma. Clin Med Insights Case Rep 2014;7:49-51.
16. Astaf'eva L, Shishkina L, Kalinin P, Kadashev B, Melnichenko G, Tserkovnay D, *et al*. Decrease of proliferative potential and vascular density of giant prolactinoma in patients treated with cabergoline. Asian J Neurosurg 2020;15:385-90.
17. Binar M, Karakoc O, Haymana C, Arslan H. Cabergoline treatment in prolactinoma: Amelioration in obstructive and central sleep apneas. J Postgrad Med 2019;65:47-9.
18. Bozkirli E, Bakiner O, Ersozlu Bozkirli ED, Ertorer E, Bascil Tutuncu N, Guvener Demirag N. Successful management of a giant pituitary lactosomatotroph adenoma only with cabergoline. Case Rep Endocrinol 2013;2013. doi: 10.1155/2013/134241.
19. Casulari LA, de Castro LF, Kessler IM, Mendonça JL, de Fátima Magalhães Gonzaga M. Giant cabergoline-resistant prolactinoma in a man who presented with a psychotic episode during treatment: A case report. J Med Case Rep 2019;13:183.
20. Cho KR, Jo KI, Shin HJ. Bromocriptine therapy for the treatment of invasive prolactinoma: The single institute experience. Brain Tumor Res Treat 2013;1:71-7.
21. Eren E, Törel Ergür A, İşgüven ŞP, Çelebi Bitkin E, Berberoğlu M, Şıklar Z, *et al*. Clinical and laboratory characteristics of hyperprolactinemia in children and adolescents: National survey. J Clin Res Pediatr Endocrinol 2019;11:149-56.
22. Gibson CD, Karmally W, McMahon DJ, Wardlaw SL, Korner J. Randomized pilot study of cabergoline, a dopamine receptor agonist: Effects on body weight and glucose tolerance in obese adults. Diabetes Obes Metab 2012;14:335-40.
23. Han YL, Chen DM, Zhang C, Pan M, Yang XP, Wu YG. Retrospective analysis of 52 patients with prolactinomas following endoscopic endonasal transsphenoidal surgery. Medicine (Baltimore) 2018;97:e13198. doi: 10.1097/MD.0000000000013198.
24. Ji L, Yi N, Zhang Q, Zhang S, Liu X, Shi H, *et al*. Management of prolactinoma: A survey of endocrinologists in China. Endocr Connect 2018;7:1013-9.
25. Keil MF, Stratakis CA. Advances in the diagnosis, treatment, and molecular genetics of pituitary adenomas in childhood. US Endocrinol 2009;4:81-5.
26. Michail M, Ioannis K, Charoula M, Alexandra T, Eleftheria H. Clinical manifestations, evaluation and management of hyperprolactinemia in adolescent and young girls: A brief review. Acta Biomed 2019;90:149-57.
27. Mohan N, Chia YY, Goh GH, Ting E, Teo K, Yeo TT. Cabergoline-induced fibrosis of prolactinomas: A neurosurgical perspective. BMJ Case Rep 2017;2017. doi: 10.1136/bcr-2017-220971.
28. Oki Y. Medical management of functioning pituitary adenoma: An update. Neurol Med Chir (Tokyo) 2014;54:958-65.
29. Raappana A, Pirilä T, Ebeling T, Salmela P, Sintonen H, Koivukangas J. Long-term health-related quality of life of surgically treated pituitary adenoma patients: A descriptive study. ISRN Endocrinol 2012;2012. doi: 10.5402/2012/675310.
30. Sano H, Takigami M, Ogino T, Morioka K, Ito T, Sudo A, *et al*. Cabergoline effectively induced remission of prolactinoma in a 9-year-old Japanese boy. Clin Pediatr Endocrinol 2009;18:65-72.
31. Souteiro P, Karavitaki N. Dopamine agonist resistant prolactinomas: Any alternative medical treatment? Pituitary 2020;23:27-37.
32. van Uum SH, van Alfen N, Wesseling P, van Lindert E, Pieters GF,

Nooijen P, *et al*. Massive reduction of tumour load and normalisation of hyperprolactinaemia after high dose cabergoline in metastasised prolactinoma causing thoracic syringomyelia. J Neurol Neurosurg Psychiatry 2004;75:1489-91.
33. Zygourakis CC, Imber BS, Chen R, Han SJ, Blevins L, Molinaro A, *et al*. Cost-effectiveness analysis of surgical versus medical treatment of prolactinomas. J Neurol Surg B Skull Base 2017;78:125-31.
34. Cho EH, Lee SA, Chung JY, Koh EH, Cho YH, Kim JH, *et al*. Efficacy and safety of cabergoline as first line treatment for invasive giant prolactinoma. J Korean Med Sci 2009;24:874-8.
35. Rastogi A, Walia R, Dutta P, Bhansali A. Efficacy and safety of rapid escalation of cabergoline in comparison to conventional regimen for macroprolactinoma: A prospective, randomized trial. Indian J Endocrinol Metab 2012;16(Suppl 2):S294-6.
36. Wang AT, Mullan RJ, Lane MA, Hazem A, Prasad C, Gathaiya NW, *et al*. Treatment of hyperprolactinemia: A systematic review and meta-analysis. Syst Rev 2012;1:33.
37. Lee Y, Ku CR, Kim EH, Hong JW, Lee EJ, Kim SH. Early prediction of long-term response to cabergoline in patients with macroprolactinomas. Endocrinol Metab (Seoul) 2014;29:280-92.
38. Paepegaey AC, Salenave S, Kamenicky P, Maione L, Brailly-Tabard S, Young J, *et al*. Cabergoline tapering is almost always successful in patients with macroprolactinomas. J Endocr Soc 2017;1:221-30.
39. Gonzaga Mde Fde M, de Castro LF, Naves LA, Mendonça JL, Oton de Lima B, Kessler I, *et al*. Prolactinomas resistant to treatment with dopamine agonists: Long-term follow-up of six cases. Front Endocrinol (Lausanne) 2018;9. doi: 10.3389/fendo. 2018.00625.
40. Almalki MH, Aljohani N, Alzahrani S, Almohareb O, Ahmad MM, Alrashed AA, *et al*. Clinical features, therapeutic trends, and outcome of giant prolactinomas: A single-center experience over a 12-year period. Clin Med Insights Endocrinol Diabetes 2020;13. doi: 10.1177/1179551420926181.
41. Yang A, Cho SY, Park H, Kim MS, Kong DS, Shin HJ, *et al*. Clinical, hormonal, and neuroradiological characteristics and therapeutic outcomes of prolactinomas in children and adolescents at a single center. Front Endocrinol (Lausanne) 2020;11. doi: 10.3389/fendo. 2020.00527.
42. Fernandez A, Karavitaki N, Wass JAH. Prevalence of pituitary adenomas: A community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin Endocrinol 2010;72:377-82.
43. Wierinckx A, Delgrange E, Bertolino P, François P, Chanson P, Jouanneau E, *et al*. Sex-related differences in lactotroph tumor aggressiveness are associated with a specific gene-expression signature and genome instability. Front Endocrinol (Lausanne) 2018;9:706. doi: 10.3389/fendo. 2018.00706.
44. Arya VB, Aylwin SJB, Hulse T, Ajzensztejn M, Kalitsi J, Kalogirou N, *et al*. Prolactinoma in childhood and adolescence-Tumour size at presentation predicts management strategy: Single centre series and a systematic review and meta-analysis. Clin Endocrinol (Oxf) 2021;94:413-23.
45. Klibanski A. Clinical practice. Prolactinomas. N Engl J Med 2010;362:1219-26.
46. Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, *et al*. Guidelines of the pituitary society for the diagnosis and management of prolactinomas. Clin Endocrinol 2006;65:265-73.
47. Kono M, Inomoto C, Horiguchi T, Sugiyama I, Nakamura N, Saito R. Adult langerhans cell histiocytosis diagnosed by biopsy of the skull tumor generated after craniotomy. NMC Case Rep J 2021;8:101-5.
48. Pilonieta M, Martin M, Revuelta Barbero JM, Hardesty DA, Carrau RL, Otto BA, *et al*. Sellar cholesterol granuloma mimicking cystic sellar lesions: A report of three cases and literature review. World Neurosurg 2020;144:250-5.
49. Yano S, Hide T, Uekawa K, Honda Y, Mikami Y, Kuratsu JI. Mixed pituitary gangliocytoma and prolactinoma resistant to the cabergoline treatment. World Neurosurg 2016;95:620.e617-22.
50. Fernandes V, Santos MJ, Almeida R, Marques O. Ten-year follow-up of a giant prolactinoma. BMJ Case Rep 2015;2015. doi: 10.1136/bcr-2015-212221.
51. Huang Y, Ding C, Zhang F, Xiao D, Zhao L, Wang S. Role of prolactin/adenoma maximum diameter and prolactin/adenoma volume in the differential diagnosis of prolactinomas and other types of pituitary adenomas. Oncol Lett 2018;15:2010-6.
52. Koppelman MC, Jaffe MJ, Rieth KG, Caruso RC, Loriaux DL. Hyperprolactinemia, amenorrhea, and galactorrhea. A retrospective assessment of twenty-five cases. Ann Intern Med 1984;100:115-21.
53. March CM, Kletzky OA, Davajan V, Teal J, Weiss M, Apuzzo ML, *et al*. Longitudinal evaluation of patients with untreated prolactin-secreting pituitary adenomas. Am J Obstet Gynecol 1981;139:835-44.
54. Schlechte J, Dolan K, Sherman B, Chapler F, Luciano A. The natural history of untreated hyperprolactinemia: A prospective analysis. J Clin Endocrinol Metab 1989;68:412-8.
55. Sisam DA, Sheehan JP, Sheeler LR. The natural history of untreated microprolactinomas. Fertil Steril 1987;48:67-71.
56. Weiss MH, Teal J, Gott P, Wycoff R, Yadley R, Apuzzo ML, *et al*. Natural history of microprolactinomas: Six-year follow-up. Neurosurgery 1983;12:180-3.
57. Sisam DA, Sheehan JP, Schumacher OP. Lack of demonstrable tumor growth in progressive hyperprolactinemia. Am J Med 1986;80:279-80.
58. Höfle G, Gasser R, Mohsenipour I, Finkenstedt G. Surgery combined with dopamine agonists versus dopamine agonists alone in long-term treatment of macroprolactinoma: A retrospective study. Exp Clin Endocrinol Diabetes 1998;106:211-6.
59. Dekkers OM, Lagro J, Burman P, Jørgensen JO, Romijn JA, Pereira AM. Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: Systematic review and meta-analysis. J Clin Endocrinol Metab 2010;95:43-51.
60. Sinha S, Sharma BS, Mahapatra AK. Microsurgical management of prolactinomas-clinical and hormonal outcome in a series of 172 cases. Neurol India 2011;59:532-6.
61. Webster J, Piscitelli G, Polli A, Ferrari CI, Ismail I, Scanlon MF. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group. N Engl J Med 1994;331:904-9.
62. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, *et al*. Diagnosis and treatment of hyperprolactinemia: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:273-88.
63. Zamanipoor Najafabadi AH, Zandbergen IM, de Vries F, Broersen LH, van den Akker-van Marle ME, Pereira AM, *et al*. Surgery as a viable alternative first-line treatment for prolactinoma patients. A systematic review and meta-analysis. J Clin Endocrinol Metab 2020;105:e32-41.
64. Ghadirian H, Shirani M, Ghazi-Mirsaeed S, Mohebi S, Alimohamadi M. Pituitary apoplexy during treatment of prolactinoma with cabergoline. Asian J Neurosurg 2018;13:93-5.
65. Nakhleh A, Shehadeh N, Hochberg I, Zloczower M, Zolotov S, Taher R, *et al*. Management of cystic prolactinomas: A review. Pituitary 2018;21:425-30.
66. Ono M, Miki N, Kawamata T, Makino R, Amano K, Seki T, *et al*. Prospective study of high-dose cabergoline treatment of prolactinomas in 150 patients. J Clin Endocrinol Metab 2008;93:4721-27.
67. Breidahl HD, Topliss DJ, Pike JW. Failure of bromocriptine to maintain reduction in size of a macroprolactinoma. Br Med J (Clin Res Ed) 1983;287:451-2.
68. Vroonen L, Jaffrain-Rea ML, Petrossians P, Tamagno G, Chanson P, Vilar L, Borson-Chazot F, *et al*. Prolactinomas resistant to standard doses of cabergoline: A multicenter study of 92 patients. Eur J Endocrinol 2012;167:651-62.
69. Behan LA, Draman MS, Moran C, King T, Crowley RK, O'Sullivan EP, *et al*. Secondary resistance to cabergoline therapy in a macroprolactinoma: A case report and literature review. Pituitary 2011;14:362-6.
70. Delgrange E, Crabbé J, Donckier J. Late development of resistance to bromocriptine in a patient with macroprolactinoma. Horm Res 1998;49:250-3.
71. Colao A, Di Sarno A, Sarnacchiaro F, Ferone D, Di Renzo G, Merola B, *et al*. Prolactinomas resistant to standard dopamine agonists respond to chronic cabergoline treatment. J Clin Endocrinol Metab 1997;82:876-83.
72. Maiter D. Management of dopamine agonist-resistant prolactinoma. Neuroendocrinology 2019;109:42-50.
73. Alberiche Ruano M, Boronat Cortés M, Ojeda Pino A, Rodriguez Perez C, Gracía Nuñez M, Marrero Arencibia D, *et al*. Acquired resistance to cabergoline: Progression from initially responsive micro to

macroprolactinoma. Pituitary 2010;13:380-2.
74. McCall D, Hunter SJ, Cooke RS, Herron B, Sheridan B, Atkinson AB. Unusual late development of dopamine agonist resistance in two women with hyperprolactinaemia associated with transition from micro to macroadenoma. Clin Endocrinol (Oxf) 2007;66:149-50.
75. Sbardella E, Farah G, Fathelrahman A, Cudlip S, Ansorge O, Karavitaki N, *et al*. A macroprolactinoma becoming resistant to cabergoline and developing atypical pathology. Endocrinol Diabetes Metab Case Rep 2016;2016. doi: 10.1530/EDM-16-0038.
76. Dutta D, Ghosh S, Mukhopadhyay S, Chowdhury S. Rapid reduction with cystic transformation of invasive giant prolactinoma following short term low dose cabergoline. Indian J Endocrinol Metab 2012;16:1048-51.
77. Rahmanian M, Meybodi HA, Larijani B, Mohajeri-Tehrani MR. Giant prolactinoma: Case report and review of literature. J Diabetes Metab Disord 2013;12:3.
78. Colao A, Di Sarno A, Landi ML, Scavuzzo F, Cappabianca P, Pivonello R, *et al*. Macroprolactinoma shrinkage during cabergoline treatment is greater in naive patients than in patients pretreated with other dopamine agonists: A prospective study in 110 patients. J Clin Endocrinol Metab 2000;85:2247-52.
79. Araújo C, Marques O, Almeida R, Santos MJ. Macroprolactinomas: Longitudinal assessment of biochemical and imaging therapeutic responses. Endocrine 2018;62:470-6.
80. Menucci M, Quiñones-Hinojosa A, Burger P, Salvatori R. Effect of dopaminergic drug treatment on surgical findings in prolactinomas. Pituitary 2011;14:68-74.
81. Giovanelli M, Losa M, Mortini P, Acerno S, Giugni E. Surgical results in microadenomas. Acta Neurochir Suppl 1996;65:11-2.
82. Arita K, Kurisu K, Tominaga A, Kawamoto H, Iida K, Mizoue T, *et al*. Trans-sellar color Doppler ultrasonography during transsphenoidal surgery. Neurosurgery 1998;42:81-5; discussion 86.
83. Sughrue ME, Chang EF, Tyrell JB, Kunwar S, Wilson CB, Blevins LS Jr. Pre-operative dopamine agonist therapy improves post-operative tumor control following prolactinoma resection. Pituitary 2009;12:158-64.
84. Faglia G, Moriondo P, Travaglini P, Giovanelli MA. Influence of previous bromocriptine therapy on surgery for microprolactinoma. Lancet 1983;1:133-4.
85. Naganuma H, Satoh E, Nukui H. Technical considerations of transsphenoidal removal of fibrous pituitary adenomas and evaluation of collagen content and subtype in the adenomas. Neurol Med Chir (Tokyo) 2002;42:202-12; discussion 213.
86. Yamamoto J, Kakeda S, Shimajiri S, Takahashi M, Watanabe K, Kai Y, *et al*. Tumor consistency of pituitary macroadenomas: Predictive analysis on the basis of imaging features with contrast-enhanced 3D FIESTA at 3T. AJNR Am J Neuroradiol 2014;35:297-303.
87. Valassi E, Klibanski A, Biller BM. Potential cardiac valve effects of dopamine agonists in hyperprolactinemia. J Clin Endocrinol Metab 2010;95:1025-33.
88. Kars M, Delgado V, Holman ER, Feelders RA, Smit JW, Romijn JA, *et al*. Aortic valve calcification and mild tricuspid regurgitation but no clinical heart disease after 8 years of dopamine agonist therapy for prolactinoma. J Clin Endocrinol Metab 2008;93:3348-56.
89. Colao A, Galderisi M, Di Sarno A, Pardo M, Gaccione M, D'Andrea M, *et al*. Increased prevalence of tricuspid regurgitation in patients with prolactinomas chronically treated with cabergoline. J Clin Endocrinol Metab 2008;93:3777-84.
90. Cawood TJ, Bridgman P, Hunter L, Cole D. Low-dose cabergoline causing valvular heart disease in a patient treated for prolactinoma. Intern Med J 2009;39:266-7.
91. Lafeber M, Stades AM, Valk GD, Cramer MJ, Teding van Berkhout F, Zelissen PM. Absence of major fibrotic adverse events in hyperprolactinemic patients treated with cabergoline. Eur J Endocrinol 2010;162:667-75.
92. Elenkova A, Shabani R, Kalinov K, Zacharieva S. Increased prevalence of subclinical cardiac valve fibrosis in patients with prolactinomas on long-term bromocriptine and cabergoline treatment. Eur J Endocrinol 2012;167:17-25.
93. Hage C, Salvatori R. Predictors of the response to dopaminergic therapy in patients with prolactinoma. J Clin Endocrinol Metab 2020;105:dgaa652. doi: 10.1210/clinem/dgaa652.
94. Vermeulen E, D'Haens J, Stadnik T, Unuane D, Barbe K, Van Velthoven V, *et al*. Predictors of dopamine agonist resistance in prolactinoma patients. BMC Endocr Disord 2020;20:68.
95. Pereira AM. Update on the withdrawal of dopamine agonists in patients with hyperprolactinemia. Curr Opin Endocrinol Diabetes Obes 2011;18:264-8.
96. Hu J, Zheng X, Zhang W, Yang H. Current drug withdrawal strategy in prolactinoma patients treated with cabergoline: A systematic review and meta-analysis. Pituitary 2015;18:745-51.