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

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Abstract

Cabergoline has long been used in the medical management of prolactin-secreting pituitary adenomas. However, there is contradictory 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. Prolactinoma is one of the most common central nervous system (CNS) tumors arising from the adenohypophysis’s hormone-secreting epithelial cells. About 32–66% of pituitary adenomas in community-dwelling adults secrete prolactin. World Health Organization (WHO) classification of intracranial tumors-2016 classifies prolactinomas as benign grade tumors I/II. A significant number of Prolactinomas occur most commonly in women in the age group of 20–50 years. Prolactinomas are also common in MEN type I. 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.

We chose to perform the scoping review, a relatively novel study design that provides a broad overview of the topic and...
determines the scope of coverage of existing literature.\textsuperscript{[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 dosing 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\textsuperscript{[11]} and the strategies plotted by the Joanna Briggs Institute Methods Manual for scoping reviews.\textsuperscript{[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 biochemical [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.\textsuperscript{[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\textsuperscript{[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].\textsuperscript{[15-13]} Finally, eight (n = 8) studies were included in this scoping review.\textsuperscript{[14-41]} Characteristics of all the studies\textsuperscript{[14-41]} are shown in Table 2. The included studies included a systematic review\textsuperscript{[36]} and an RCT.\textsuperscript{[35]} Table 3 shows the study methodology and the conclusions drawn from the included 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 remission 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.\(^\text{[42]}\) Eighty percent of men with prolactinoma have macroprolactinomas compared to women, where the ratio of micro to macroprolactinoma is 1:8.\(^\text{[42,43]}\) In addition, men tend to have a more aggressive tumor, and the estrogen receptor pathway has some role to play in it.\(^\text{[43]}\) In a recent series of hyperprolactinemia, 50% did not have any sellar mass.\(^\text{[21]}\) The study by Cho et al.\(^\text{[34]}\) 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.\(^\text{[38-40]}\) Further, in these patients, the Cabergoline de-escalation was possible in more than 95% of
the patients. However, prolactinomas perform differently with medical management in patients lesser than 20 years of age, where macroprolactinemia requires multimodal therapy, including surgical intervention.94

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.31 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.42 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. Intracranial pressure. The patient was treated with cabergoline, prolactin levels normalized, and lesion size decreased 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.

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

| First author, year | Title | Reason for exclusion |
|--------------------|-------|----------------------|
| Van Uum,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.,2009 | Advances in the Diagnosis, Treatment, and Molecular Genetics of Pituitary Adenomas in Childhood | No primary study or systematic review |
| Sano H,2009 | Cabergoline Effectively Induced Remission of Prolactinoma in a 9-year-old Japanese Boy | Case report |
| Gibson C.D.,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,2012 | Long-Term Health-Related Quality of Life of Surgically Treated Pituitary Adenoma Patients: A Descriptive Study | Treatment. Not within the scope |
| Bozkirli E,2013 | Successful Management of a Giant Pituitary Lactosomatotroph Adenoma Only with Cabergoline | Case Report |
| Alsabae S,2014 | Cabergoline Treatment in Invasive Giant Prolactinoma | Case Report |
| Oki Y,2014 | Medical Management of Functioning Pituitary Adenoma: An Update | No primary study or systematic review |
| Mohan N,2017 | Cabergoline-induced fibrosis of prolactinomas: a neurosurgical perspective | Case Report |
| Zygourakis, C. C.,2017 | Cost-Effectiveness Analysis of Surgical versus Medical Treatment of Prolactinomas | No primary study or systematic review |
| Han Y.L,2018 | Retrospective analysis of 52 patients with prolactinomas following endoscopic endonasal transsphenoidal surgery | Treatment. Not within the scope |
| Ji L,2018 | Management of prolactinoma: a survey of endocrinologists in China | Not within the scope |
| Binar M,2019 | Cabergoline treatment in prolactinoma: Amelioration in obstructive and central sleep apneas | Not within the scope |
| Casulari L.A,2019 | Giant cabergoline-resistant prolactinoma in a man who presented with a psychotic episode during treatment: a case report | Case reports |
| Eren E,2019 | Clinical and Laboratory Characteristics of Hyperprolactinemia in Children and Adolescents: National Survey | Not within the scope |
| Michail M,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,2020 | Decrease of Proliferative Potential and Vascular Density of Giant Prolactinoma in Patients Treated with Cabergoline | Pathophysiology/anatomy. Not within the scope |
| Soutiero P,2020 | Dopamine agonist resistant prolactinomas: any alternative medical treatment? | No primary study or systematic review |
| Cho K.R,2013 | Bromocriptine Therapy for the Treatment of Invasive Prolactinoma: The Single Institute Experience | Not within the scope |
| 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.         | 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.     | Efficacy and safety of rapid escalation of cabergoline in comparison to conventional regimen for macroadenoma: 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.        | Treatment of hyperprolactinemia: a systematic review and meta-analysis | Systematic Review and Meta-analysis | PRISMA, Ottawa-Newcastle tool, Cochrane risk 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.         | Early Prediction of Long-Term Response to Cabergoline in Patients with Macroadenomas | 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.   | Cabergoline Tapering Is Almost Always Successful in Patients With Macroadenomas | Retrospective | X |Yes |Yes, Retrospective design and prescription bias |260 | France |
| 2018 | Gonzaga et al.     | 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.     | Clinical Features, Therapeutic Trends, and Outcome of Giant Prolactinomas: A Single-Center Experience Over a 12-Year Period | Retrospective | 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 | Yes |X |Yes, retrospective, single center, small sample size and limited follow-up |25 | South Korea |
| 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 macroadenomas: A prospective, randomized trial | Rastogi et al.\[35\] | Randomized, prospective, interventional trial. Subjects and Methods:: Forty-two patients (male or female) with macroadenomas 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 macroadenomas. |
| 2012                   | Treatment of hyperprolactinemia: a systematic review and meta-analysis | Wang et al.\[36\]   | Systematic Review and Meta-analysis                                                   | -                   |                                                                                                |
| 2014                   | Early Prediction of Long-Term Response to Cabergoline in Patients with Macroadenomas | Lee et al.\[37\]    | 6-year retrospective study of patients with macroadenomas 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 Macroadenomas | Paepegae 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. Prolactin levels decreased by as much as 95.4% after CAB treatment. Serum PRL concentrations completely normalized in 11 patients and |
| 2020                   | Clinical Features, Therapeutic Trends, and Outcome of Giant Prolactinomas: | Almalki et al.\[40\] | Retrospective Design                                                                | 33                  |                                                                                                |

Contd...
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 cm³ of the tumor has better accuracy in the differential diagnosis of conditions leading to hyperprolactinemia. 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/(l × cm³). Six case series have shown that when macroprolactinoma is observed for 8 years without treatment, approximately 7% showed growth. A significant increase in levels of serum prolactin indicates the growth of prolactinoma, though not always. 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. 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.

### 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. Persisting normoprolactinemia after dopamine agonist withdrawal was seen in 21% in a random-effects model [95% confidence interval (CI), 14–30%; I² (2): 81%]. 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%). 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. These patients are intolerant, non-compliant, or non-responsive to the medical management and for various reasons. Long-acting dopamine agonists (DAs) achieve stable normoprolactinemia in 80% and is considered the initial treatment of choice. Reduction in tumor size is seen in 60% of patients receiving dopamine agonist. 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. 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. 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.

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.\[74\] 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 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 (cm²) | Mean prl level | Average treatment duration | CAB Initial Dose | 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      | Giant Invasive Prolactinoma                               | 33                 | Adult      | 38.13            | 4.29                          | 49.88                       | 9561.03 nmol/L | 0.25                      | Weekly          | yes                   |                       | 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          | Giant, prolactin >1000 ug/ml                              | 10                | Adult      | 37+/-4           | 51                            | -                           | 11,426 ng/mL   | 19 months                | Weekly          | yes                   |                       | 20.6 months                | -                      | -                          | 97 after 3 months          | -               | 85+/−4                   | -                      | -                       |                         |
| Gonzaga et al., 2018      | Prolactinoma resistant to dopamine aagonists              | 6                 | Adult      | 36.5             | -                             | -                           | 3838 ng/ml     | 12 months                | Weekly          | yes                   |                       | 180 months               | -                      | -                          | 621.35 ng/ml             | -               | 90-100%                  | -                      | -                       |                         |
| Lee et al., 2014          | Macroprolactinomas treated with cabergoline               | 66                | Adult      | 36.8             | 3.71                          | -                           | 796.7 ng/dl    | 12 months                | Weekly          | yes                   |                       | 12 months                  | -                      | -                          | 680 ng/ml                | 0.5            | -                       |                      |                         |                         |
| Paepegaey et al., 2017    | Macroprolactinoma patients                               | 260               | Adult      | 32.7             | -                             | -                           | 1901 ng/ml     | 24 weeks                 | Weekly          | yes                   |                       | 16 months                  | -                      | -                          | 1901 ng/ml              | -               | -                       |                      |                         |                         |
| Rastogi et al., 2012      | Macroprolactinoma patients                               | 42                | Adult      | -                | -                             | -                           | 81.8           | -                        | Weekly          | yes                   |                       | 24 weeks                  | -                      | -                          | 81.8                   | -               | -                       |                      |                         |                         |
| Yang et al., 2020         | Prolactinoma patients <19 years                          | 25                | -          | 16.9             | 1.2                           | -                           | 207 ng/ml      | 1.1 year                 | Weekly          | yes                   |                       | 3 years                   | -                      | -                          | 172.8 ng/ml              | -               | -                       |                      |                         |                         |
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 Paepkeay 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 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.[83] 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
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 macroprolactinemia due to prolactinoma.[39,95,96] 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,\(^{[20]}\) 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 focusing 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 patient needs to be on maintenance therapy.

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**Conflicts of interest**

There are no conflicts of interest.

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