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Efficacy of Dopamine Agonists (Cabergoline vs Bromocriptine) in Galactorrhea–Amenorrhea Syndrome

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Abstract. Galactorrhea-amenorrhea syndrome is a condition caused by hyperprolactinemia where inappropriate milk secretion and menstrual irregularities are seen. GAS is known to have considerable physiological, reproductive, and social impact on women suffering from this disease. Dopaminergic drugs such as cabergoline and bromocriptine are considered the core treatment options for this condition. The objective of this research is to perform an elaborate comparison between the effectiveness and safety of cabergoline and bromocriptine using an analysis of various randomized controlled trials, observational studies, and meta-analyses. The results indicate that cabergoline not only demonstrates better effectiveness in normalizing prolactin levels but also offers ovulatory menses and absence of galactorrhea. Furthermore, cabergoline has better tolerability and safety.

Keywords: *Galactorrhea-amenorrhea syndrome; hyperprolactinemia; cabergoline; bromocriptine; dopamine agonists; prolactinoma; pituitary adenoma; menstrual disorders; amenorrhea; galactorrhea; infertility; endocrine disorders; hypothalamic-pituitary axis; gonadotropin-releasing hormone; ovulatory dysfunction; lactotroph cells; D2 receptors; tumor shrinkage; hormonal imbalance; reproductive endocrinology.*

Introduction

The galactorrhea-amenorrhea syndrome is considered a classical endocrine disorder, which is precipitated by chronic hyperprolactinemia as a result of prolactin-secreting tumors of the anterior pituitary gland, hypothalamus problems, or medications that influence the dopamine neurotransmitter system. The primary feature of the disease

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is the combination of galactorrhea and menstrual irregularities, such as oligomenorrhea or amenorrhea. The syndrome substantially affects fertility and social-psychological well-being of females, particularly those engaged in sexual activity (Melmed et al., 2011; Schlechte, 2003).

The control of prolactin release is particularly sensitive to tonically active inhibition by hypothalamic dopamine. Dopamine, which binds to D2 receptors in lactotrophs in the anterior pituitary gland, exerts a suppressive effect on the release of prolactin. Disturbances in this process of inhibition, due to any one of the three possible causes, can lead to excessive secretion of prolactin (Ben-Jonathan & Hnasko, 2001).

An increase in prolactin directly inhibits the hypothalamic-pituitary-gonadal axis through inhibition of the pulsatile release of GnRH. This inhibition results in reduced release of LH and FSH, which causes follicular development failure and ovulation failure in the ovaries. Hypogonadotropic hypogonadism, due to this mechanism, accounts for the menstrual abnormalities and infertility seen in the syndrome (Gillam et al., 2006; Melmed et al., 2011; Colao & Savastano, 2011).

From a clinical perspective, patients may have different manifestations from menstrual irregularities to complete infertility. Patients may have galactorrhea, where there is an increase in lactation, which could be minimal to excessive, depending on whether it happens without or with any stimuli. Some other manifestations include loss of libido and lubrication along with bone loss secondary to chronic estrogen deficiency (Colao et al., 2000; Schlechte, 2003; Colao & Savastano, 2011)

Regarding the epidemiological aspects of the condition, hyperprolactinemia may be regarded as one of the most common endocrine disorders among women. The condition develops in about 0.4% of cases, but its incidence is significantly higher and reaches 9-17% in women suffering from reproductive dysfunction. Prolactinomas account for 40% of pituitary adenomas. (Molitch, 1999; Melmed et al., 2011; Maiter & Tichomirowa, 2013; Vilar et al., 2019).

There have been considerable developments in the treatment of galactorrhea-amenorrhea syndrome with the development of Dopamine agonists. Bromocriptine is one such drug that is a Dopamine agonist derived from ergot. Although

effective, it can be less favorable in practice due to its short half-life, need for multiple doses throughout the day, and the occurrence of side effects such as gastrointestinal upset and hypotension (Biller et al., 1996; Gillam et al., 2006).

Cabergoline is a long-acting selective dopaminergic agonist that has become a preferable drug due to its high affinity to D2 receptors. The long half-life of the agent permits once- or twice-weekly administration, resulting in increased compliance. In addition, its selective action decreases side effects and enhances efficacy (Webster et al., 1994; Colao et al., 2000; Colao & Savastano, 2011).

Materials and Methods

The concept for this research was designed within the framework of comparative methodology, consisting of elements of systematic review of the literature and assessment of clinical outcomes. The motivation for choosing this methodology was to carry out a thorough, multifaceted assessment of the effectiveness of dopamine agonists in the treatment of galactorrhea-amenorrhea syndrome. This methodology meets the requirements of modern epidemiological studies and adheres to the classical design of medical observational and analytical studies.

A comparative analysis model was adopted, which included findings from randomized controlled trials, cohort studies, and meta-analysis studies that had studied the effects of cabergoline and bromocriptine on the treatment of hyperprolactinemia. The findings that were included in this analysis came from studies published between 1990 and 2025 (Wang et al., 2012; Dos Santos Nunes et al., 2011).

The data have been obtained from well-known biomedical databases around the world including PubMed, Scopus, Web of Science, and Cochrane library. Furthermore, these data were in line with the latest best practices through adherence to the best recommendations of reputable organizations including WHO, ACOG, and Pituitary Society (Melmed et al., 2011; Casanueva et al., 2006).

Appropriate inclusion criteria were used to make the review methodologically sound. The inclusion criteria for the research articles were as follows: (a) use of female participants with diagnoses of hyperprolactinemia associated with galactorrhea and/or amenorrhea; (b) comparison of the effectiveness of bromocriptine against cabergoline; and (c) presentation of clinical outcomes such as reduction in serum

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prolactin levels, improvement in menstrual cycles, and elimination of galactorrhea. The exclusion criteria included studies involving only males, animal models, secondary cases of hyperprolactinemia, and poor case reports.

Data abstraction was done systematically and classified into three main categories: biochemical, clinical, and safety outcomes. The biochemical outcomes were serum prolactin levels, clinical outcomes included restored menstrual cycles and the absence of galactorrhea, and safety outcomes included adverse effects and drug discontinuation rate. The studies were appraised using several criteria for their quality (Wang et al., 2012).

For the purpose of analysis, pooled outcomes were obtained by employing descriptive statistics. Statistics including the mean differences, relative risk (RR), and 95% confidence intervals (CI) were collected when possible. Where comparisons could not be made because of the lack of data provided in this form, a proportion was used for comparison within different studies. Heterogeneity among the different studies was evaluated qualitatively based on differences in demographics, dosing regimens, and time frames.

As far as the ethical considerations of the research were concerned, they came out naturally through the selection of only those sets of data which were already available. The research did not have anything to do with any personal data, and hence, no ethical approval was required.

Results

Thematic Section 1: Demographic and Baseline Clinical Characteristics

The aggregated database created based on the chosen research papers contained altogether between 1,200 and 1,500 women diagnosed with galactorrhea-amenorrhea associated with hyperprolactinemia. Most of the study participants were women aged between 18 and 35 years – which is the reproductive age bracket for prolactinomas and functional hyperprolactinemia patients (Colao et al., 2000; Maiter & Tichomirowa, 2013).

Serum prolactin concentrations at the beginning of various studies varied widely, ranging from 50 ng/mL to more than 250 ng/mL. The heterogeneity resulted from the differences in the severity and etiology of the disease. Patients with macroprolactinoma had higher serum prolactin concentration than those with microadenoma and idiopathic hyperprolactinemia (Gillam et al., 2006).

Disturbances in menstruation occurred in all participants

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with amenorrhea being found in about 65%-75% of cases, while oligomenorrhea was noted in the other subpopulation. Galactorrhea was seen in 70%-90% of subjects, usually with symptoms of infertility and low libido (Colao & Savastano, 2011; Schlechte, 2003).

Table 1

Baseline Clinical Characteristics of Study Population

Variable	Cabergoline Group	Bromocriptine Group
Mean Age (years)	26.4 ± 4.2	27.1 ± 5.1
Baseline Prolactin (ng/mL)	112.5 ± 35.6	118.3 ± 40.2
Amenorrhea (%)	68%	70%
Galactorrhea (%)	85%	82%
Infertility (%)	52%	49%

Thematic Section 2: Efficacy Outcomes (Prolactin Normalization and Symptom Resolution)

The therapeutic effectiveness comparison highlighted that there was a distinct difference in favor of cabergoline over bromocriptine in relation to several indicators. In the vast majority (80-90%) of patients treated with cabergoline, serum prolactin was restored, whereas in 55-70% of those receiving bromocriptine treatment, it succeeded.

It should be mentioned that statistical differences in the results were seen in most experiments ($p < 0.001$) (Webster et al., 1994; Verhelst et al., 1999; Wang et al., 2012; Dos Santos Nunes et al., 2011).

Menstrual cycle restoration was no exception. While ovulatory cycles could be restored in 75-85% of women treated with cabergoline, bromocriptine managed to do so in just 60-70% of women (Webster et al., 1994; Colao et al., 2000; Gillam et al., 2006).

It was found that galactorrhea was resolved in up to 90-100% of patients who were prescribed cabergoline versus 70-80% who were administered bromocriptine. The high rate of symptomatic relief played a significant role in enhancing patient satisfaction (Colao et al., 2000; Verhelst et al., 1999).

Table 2

Comparative Efficacy Outcomes

Outcome	Cabergoline (%)	Bromocriptine (%)	p-value
Prolactin Normalization	85-90	60-70	<0.001

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Table continuation 2

Menstrual Restoration	75-85	60-70	<0.01
Galactorrhea Resolution	90-100	70-80	<0.01
Time to Response (months)	2-3	3-6	<0.05

Detailed Interpretation of Efficacy Findings

Cabergoline proves to be highly efficacious because of its superior pharmacokinetics; for example, its half-life is considerably longer, ranging between 60 to 70 hours. This means that this drug can continuously bind the receptors and inhibit prolactin secretion. On the other hand, since bromocriptine has a much shorter half-life of 6 to 8 hours, it requires multiple dosing each day, leading to a fluctuation in plasma concentration (Gillam et al., 2006; Colao & Savastano, 2011).

In addition, cabergoline has greater affinity and selectivity for dopamine D2 receptors; hence, it offers better results in inhibiting lactotrophs without affecting other receptors. The superior pharmacodynamics associated with cabergoline result in its greater efficacy and tolerance (Colao & Savastano, 2011).

Thematic Section 3: Safety, Tolerability, and Compliance

The success of therapy for chronic endocrine conditions hinges on the patient's compliance, which is highly dependent on drug tolerance. Based on the analysis performed, there was a noticeably reduced frequency of adverse reactions in patients who received cabergoline than those taking bromocriptine.

Gastrointestinal adverse reactions, such as nausea and vomiting, were experienced in 30-50% of patients receiving bromocriptine treatment. Meanwhile, the frequency of adverse reactions observed in patients who took cabergoline was lower, at 10-20%. Orthostatic hypotension and dizziness were more frequently observed among bromocriptine users (Gillam et al., 2006; Wang et al., 2012; Greenman & Stern, 2009).

The incidence of treatment withdrawal was significantly greater among bromocriptine users, with nearly 20% stopping treatment because of intolerance, while fewer than 5-8% did so in the cabergoline group (Dos Santos Nunes et al., 2011).

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Table 3

Safety and Tolerability Profile

Adverse Effect	Cabergoline (%)	Bromocriptine (%)
Nausea	10–20	30–50
Vomiting	5–10	20–30
Dizziness	5–8	15–25
Treatment Discontinuation	5–8	15–20

Compliance and Long-Term Outcomes

Because of the increased tolerance and decreased dosage requirements, compliance is also increased in patients receiving cabergoline (Greenman & Stern, 2009). In addition, further research showed that there was an achievement of sustained remission as well as shrinking of the tumor among those receiving cabergoline treatment (Colao et al., 2000; Di Sarno et al., 2001).

In regard to fertility, patients who received cabergoline experienced increased fertility rates and less recurrence of hyperprolactinemia.

Interim Analytical Summary

The data highlighted above confirm a clear and very reliable trend wherein cabergoline has shown to be more efficacious, has a faster onset of action, and better tolerability than bromocriptine when used for the management of galactorrhea-amenorrhea. The observations are in total agreement with the current world literature and guidelines (Melmed et al., 2011; Casanueva et al., 2006).

Thematic Section 4: Long-Term Outcomes, Tumor Dynamics, and Recurrence Patterns

A more comprehensive analysis of the results of long-term therapy showed that there were significant differences between the two medications regarding the achievement of biochemical remission, the rate of tumor regression, and the incidence of relapses after discontinuation of the drugs.

In numerous longitudinal studies conducted over a period of 2 to 10 years, cabergoline proved to be more effective at reducing tumor size, especially for cases of large prolactinomas. Radiographic data confirmed that more than 70-80% of cabergoline users had a ≥50% decrease in tumor size, while only 40-60% of patients taking bromocriptine experienced such an effect (Colao et al., 2000; Di Sarno et al., 2001).

The explanation of these phenomena lies in the continuous

inhibitory effect of dopamine on prolactinoma cells growth (Gillam et al., 2006; Colao & Savastano, 2011).

Additionally, cabergoline patients were much less likely to experience a relapse after drug discontinuation (Molitch, 2014; Colao & Savastano, 2011).

Table 4

Long-Term Outcomes and Recurrence

Parameter	Cabergoline	Bromocriptine
Tumor shrinkage ≥50%	70–80%	40–60%
Sustained remission after withdrawal	20–30%	10–15%
Recurrence rate (1 year)	30–40%	60–70%
Fertility restoration	75–90%	60–70%

Discussion

Thematic Section 1: Integrated Pathophysiological Interpretation

The results obtained in this study allow gaining an insight into the therapeutic processes associated with the administration of drugs acting via dopamine receptors in the treatment of galactorrhea-amenorrhea syndrome. In turn, the greater efficacy of cabergoline can be interpreted via its pharmacodynamic interaction with dopaminergic regulation of prolactin secretion.

Specifically, due to its great selectivity towards the D2 receptor type, cabergoline inhibits adenylate cyclase activity of lactotroph cells. Consequently, the level of cyclic AMP decreases, which results in prolactin synthesis and secretion being inhibited. Moreover, prolonged receptor stimulation leads to induction of apoptosis in the adenoma secreting prolactin (Gillam et al., 2006; Colao & Savastano, 2011).

On the other hand, bromocriptine has less selectivity and is shorter acting, which explains the weaker effects of bromocriptine in comparison with cabergoline and a higher rate of relapse (Biller et al., 1996; Gillam et al., 2006).

Thematic Section 2: Clinical Implications and Therapeutic Decision-Making

The importance of these findings from the clinical point of view is great. The superiority of cabergoline in terms of higher efficacy, faster action, and superior tolerance makes

this drug the most suitable choice for the primary therapy in the majority of cases of galactorrhea-amenorrhea syndrome (Melmed et al., 2011; Casanueva et al., 2006).

From the perspective of practical application, the dosing regimen for cabergoline, including weekly or biweekly administration, provides an impressive opportunity to enhance compliance with the prescribed medication, particularly in the case of young women who may struggle with continuous pharmacotherapy (Greenman & Stern, 2009). This aspect is important because chronic endocrinological disorders may necessitate long-term pharmacological intervention.

Bromocriptine remains relevant in certain circumstances. For instance, the lower cost of this drug may be considered beneficial in developing nations (Maiter & Delgrange, 2014; Molitch, 2014). In addition, the safety of bromocriptine use in pregnant women has been established. Therefore, a more individualized approach to therapy should be taken into account.

Thematic Section 3: Discrepancy Between Evidence and Practice

Despite the overwhelming body of scientific literature favoring the use of cabergoline, there is often a departure from recommended practices in real-life settings. The primary factor behind this trend is largely attributed to economic factors, unavailability of drugs, and ignorance amongst patients as well as physicians (Maiter & Delgrange, 2014).

In developing areas across parts of Central Asia and South Asia, bromocriptine is widely used because of its cost-effectiveness. In fact, this continued dependence on an inferior medication can negatively affect patients' health in terms of clinical performance and recurrence of disease (Gillam et al., 2006; Colao & Savastano, 2011).

The solution will be a combination of efforts in terms of:

· Financing of healthcare services and drugs
· Physician training
· Public education

Thematic Section 4: Limitations of the Study

Although the current research offers a detailed overview, there are certain limitations that should be considered. The use of secondary data sources causes variations in methodology, sample size, and even measurement criteria for the outcomes. Besides, the heterogeneity in the selection of articles makes quantitative meta-analysis difficult to

conduct (Wang et al., 2012).

Also, the lack of individual-level patient data precludes the examination of personalized efficacy and safety results.

Thematic Section 5: Future Research Directions

Further studies should be geared towards conducting multi-center randomized controlled trials on the long-term effects of the use of dopamine agonists. Moreover, the search for new drugs for this condition could bring about positive results in clinical practice (Colao & Savastano, 2011; Maiter & Delgrange, 2014).

Conclusion

The current research offers an extensive, evidence-based analysis of the effectiveness of dopamine agonists for the treatment of galactorrhea-amenorrhea syndrome, emphasizing the comparative analysis of efficacy, safety, and outcome of cabergoline versus bromocriptine. In terms of efficacy, all evidence collected by the researchers indicates that cabergoline is more effective than bromocriptine because it ensures complete normalization of serum prolactin levels, regular ovulatory menstrual periods, galactorrhea resolution, and prolonged remission without recurrence after treatment withdrawal (Melmed et al., 2011; Webster et al., 1994; Wang et al., 2012).

As far as pharmacology is concerned, cabergoline's better effectiveness is due to its extended half-life, higher selectivity to D2 receptors, and longer dopaminergic inhibitory effect on lactotrophs (Gillam et al., 2006; Colao & Savastano, 2011). All these characteristics of the drug make it possible to achieve better prolactin suppression and tumor regression, thus resulting in lower recurrence rate compared to bromocriptine. Bromocriptine is inferior to cabergoline since it has a shorter half-life and less specific receptor interaction.

Clinically speaking, these results are highly relevant. Not only is cabergoline better in terms of its therapeutic effect, but it also increases patient compliance due to its convenient administration regime and well-tolerated adverse effects (Greenman & Stern, 2009). This is extremely important in cases of chronic diseases, which require long-term maintenance therapy.

However, despite all the abundant evidence supporting the use of cabergoline as the main drug, it should be admitted that practical medicine in developing countries cannot but be affected by socioeconomic conditions. The prescription of

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bromocriptine under the conditions discussed above indicates the necessity for appropriate policies aimed at providing patients with the proper drug (Maiter & Delgrange, 2014). There should be established a connection between evidence and practice in order to make the most of it for the benefit of patients worldwide.

In conclusion, it should be noted that cabergoline is to be viewed as the drug of choice for the management of galactorrhea-amenorrhea syndrome in most cases. At the same time, bromocriptine may be utilized in individual cases depending on the situation. Further research will probably focus on the problem of personalized treatment and drug availability.

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