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Cabergoline – Dopamine Receptor Agonist

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Abstract

Background: Cabergoline is a potent dopamine receptor agonist used primarily for the treatment of disorders related to dopamine dysregulation. It acts by stimulating dopamine receptors in various regions of the brain and has been approved for the management of hyperprolactinemia, Parkinson's disease, and restless legs syndrome. Its unique pharmacological profile and tolerability make it a valuable therapeutic option in the field of neurology and endocrinology.

Aim: The aim of this study was to investigate the efficacy and safety of cabergoline as a dopamine receptor agonist in the treatment of hyperprolactinemia, Parkinson's disease, and restless legs syndrome. The study also aimed to evaluate the impact of cabergoline on disease-specific symptoms and quality of life in patients with these conditions.

Materials and Methods: A systematic literature review was conducted, encompassing peer-reviewed studies, clinical trials, and meta-analyses from reputable databases. Key search terms included "Cabergoline," "dopamine receptor agonist," "hyperprolactinemia," "Parkinson's disease," and "restless legs syndrome." Studies involving adult patients and reporting relevant outcomes, including symptom improvement and adverse events, were considered for analysis.

Results: The analysis revealed that cabergoline effectively reduced prolactin levels in patients with hyperprolactinemia, leading to improvements in associated symptoms such as menstrual irregularities and galactorrhea. In Parkinson's disease, cabergoline demonstrated promising results in ameliorating motor symptoms, including rigidity, bradykinesia, and tremors. Additionally, studies investigating its role in restless legs syndrome showed a reduction in sensory and motor symptoms, leading to enhanced sleep quality. The drug's side effect profile was generally well-tolerated, with mild adverse events reported.

Conclusion: Cabergoline, as a dopamine receptor agonist, emerges as a valuable therapeutic option for hyperprolactinemia, Parkinson's disease, and restless legs syndrome. It effectively addresses specific symptoms associated with these conditions and shows potential for improving patients' quality of life. The drug's favorable tolerability further supports its use in clinical practice. However, careful monitoring and further research are necessary to fully elucidate its long-term safety and effectiveness. Cabergoline's role in the treatment landscape of dopamine-related disorders holds promise for future advancements in neurology and endocrinology.

Keywords: Cabergoline, Dopamine, Dilated Cardiomyopathy, Ergot Derivative, Peripartum Cardiomyopathy.

INTRODUCTION

Cabergoline, a dopamine receptor agonist, has used as one proposed potential drugs in the management of peripartum cardiomyopathy (PPCM)[1,2], Low incidence and potentially fatal form of left ventricular systolic failure. PPCM typically occurs in the early postnatal period (60–70% of cases) or late in pregnancy, affecting approximately 1 in every 15,000 live births globally [3]. Defined by the European Society of Cardiology in 2019, PPCM is an idiopathic cardiomyopathy characterized by a left ventricular ejection fraction (LVEF) of 45% or less, developing till the end of gestation or in the months after birth without any other known cause of heart failure [4].

The pathogenesis of PPCM remains poorly understood, but researchers propose a "two-hit" model involving autoimmune mechanisms and genetic predisposition (such as sarcomere gene mutations) leading to endothelial dysfunction and cardiomyocyte death through vasculo-hormonal pathways, including prolactin secretion, upregulation of endothelial miRNA-146a, and placental secretion of sFlt-1 [5]. The elusive nature of PPCM symptoms often results in misdiagnosis or delayed diagnosis, making it crucial to identify reliable diagnostic criteria, such as echocardiographic assessments, which may include reduced LVEF (below 45%), decreased fractional shortening (less than 30%), and a left ventricular end-diastolic dimension (LDD) greater than 2.7 cm/m2 [6].

Recent research has shed light on the role of prolactin in PPCM. Studies conducted over a decade ago by Hilfiker-Kleiner (2007) highlighted that oxidative stress during pregnancy triggers increased cathepsin D expression in cardiomyocytes, causing the breakdown of prolactin (PRL) into a 16-kDa fragment from its original 23-kDa protein form. This fragment possesses vasoconstrictor, antiangiogenic, and pro-inflammatory properties that may potentially contribute to myocardial damage [7].

In the quest to address PPCM, the use of prolactin inhibitors, particularly dopamine D2 receptor agonists, has emerged as a promising avenue. Currently, bromocriptine is the preferred medication for reducing prolactin synthesis in PPCM patients, but its use is associated with severe thrombotic side effects, such as myocardial infarction and ischemic stroke [8]. However, there is growing interest in the potential of cabergoline as an alternative treatment option, though its application in PPCM has been reported in only a limited number of cases [9]. Further investigations are warranted to comprehensively evaluate the efficacy and safety of cabergoline in managing PPCM and to explore its potential as a viable alternative to bromocriptine in the treatment of this challenging condition.

History:

Researchers for the Italian pharmaceutical business Farmitalia-Carlo Erba in Milan created cabergoline while researching semi-

synthetic ergot alkaloids, and a patent application was submitted in 1980. A scholarly abstract at the Society for Neuroscience meeting in 1991 served as the initial publication [10].

1993 Pharmacia purchased Farmitalia-Carlo Erba; in 2003, Pfizer acquired Pharmacia [11].

Dostinex, a cabergoline brand, was commercialized in The Netherlands in 1992.[12] The FDA gave the medication its blessing on December 23, 1996. After the US patent expired in late 2005, it became generic [12].

Pharmacology:

Pharmacokinetics:

The resorption of cabergoline from the GI tract after a single oral dose varies greatly and typically occurs between 0.5 and 4 hours. Its rate of absorption remains unaffected by food intake. The drug is only to be taken by mouth, human bioavailability has not been established. However, it was shown that the absolute bioavailability was 30% and 63%, respectively, in mice and rats. The liver quickly and thoroughly breaks down cabergoline, and the resulting metabolites are either completely inactive or less active than the parent substance. The elimination of cabergoline occurs primarily through bile excretion, with a minor portion being eliminated in the urine [13].

Individuals with Parkinson's disease exhibit an estimated human elimination half-life of 63 to 68 hours, while those with pituitary tumors have an estimated half-life of 79 to 115 hours, with a typical half-life of around 80 hours. The therapeutic impact on the management of hyperprolactinemia is usually sustained for at least 4 weeks after the end of treatment[13].

Pharmacodynamics:

Cabergoline is a dopamine receptor agonist that exerts its pharmacological effects through interactions with various receptors in the central nervous system. Its primary target is the dopamine D2 receptor, where it acts as a potent agonist, leading to inhibitory effects on prolactin secretion from lactotroph cells in the pituitary gland. By reducing prolactin levels, cabergoline effectively treats hyperprolactinemia and associated conditions[9].

Beyond its action on the D2 receptor, cabergoline also displays affinity for other receptors, including dopamine D3 and D4 receptors. Additionally, it binds to serotonin receptors such as 5-HT1A, 5-HT2A, 5-HT2B, and 5-HT2C, as well as adrenergic alfa 2 receptors. It exhibits moderate to low affinity for dopamine D1 and serotonin 5-HT7 receptors[9].

Cabergoline's binding to the mentioned receptors results in diverse effects. It functions as a partial or complete agonist on dopaminergic receptors such as (D2, D3, and D4 receptors), as well as serotonin 5-HT1A, 5-HT2A, and 5-HT2C receptors. These interactions contribute to its therapeutic benefits in conditions like hyperprolactinemia and Parkinson's disease See figure 1 .

Conversely, cabergoline acts as an antagonist on serotonin 5-HT7 receptors, and also on α2-adrenergic receptors,

specifically α2D-adrenergic receptors. This unique pharmacodynamic profile differentiates cabergoline from other dopamine receptor agonists and plays a crucial role in determining its therapeutic efficacy and potential side effects.

It is important to note that cabergoline's stimulation of 5-HT2B receptors has been associated with an increased risk of cardiac valvulopathy, a condition that affects heart valves. This aspect necessitates careful monitoring of patients receiving cabergoline treatment, particularly for prolonged durations[14].

Table:1 Activities of cabergoline at various sites:

Site	Affinity (K_i [nM])	Efficacy (E_{max} [%])	Action
D_1	214.0–32,000	?	?
D_{2S}	0.50–0.62	102	Full agonist
D_{2L}	0.950	75	Partial agonist
D_3	0.80–1.0	86	Partial agonist
D_4	56	49	Partial agonist
D_5	22	?	?
5-HT_{1A}	1.9–20	93	Partial agonist
5-HT_{1B}	479	102	Full agonist
5-HT_{1D}	8.70	68	Partial agonist
5-HT_{2A}	4.6–6.2	94	Partial agonist
5-HT_{2B}	1.2–9.4	123	Full agonist
5-HT_{2C}	5.8–692	96	Partial agonist
5-HT_3	>10,000	–	–
5-HT_4	3,000	?	?
5-HT_6	1,300	?	?
5-HT_7	2.5	?	Antagonist
α_{1A}	288–>10,000	0	Silent antagonist
α_{1B}	60–1,000	?	?
α_{1D}	166	?	?
α_{2A}	12–132	0	Silent antagonist
α_{2B}	17–72	0	Silent antagonist
α_{2C}	22–364	0	Silent antagonist

α_{2D}	3.6	?	?
H_1	1,380	?	?
M_1	>10,000	–	–
SERT	>10,000	–	–
Notes: All sites mentioned, with the exception of α2D-adrenergic, are specific to humans [13]. Cabergoline exhibits Mild affinity (>10,000 nM) toword other types of receptor, including adrenergic beta 1, 2 receptors, adenosine, GABA, glutamate, glycine, nicotinic acetylcholine, opioid, and prostanoid receptors [14,15].			

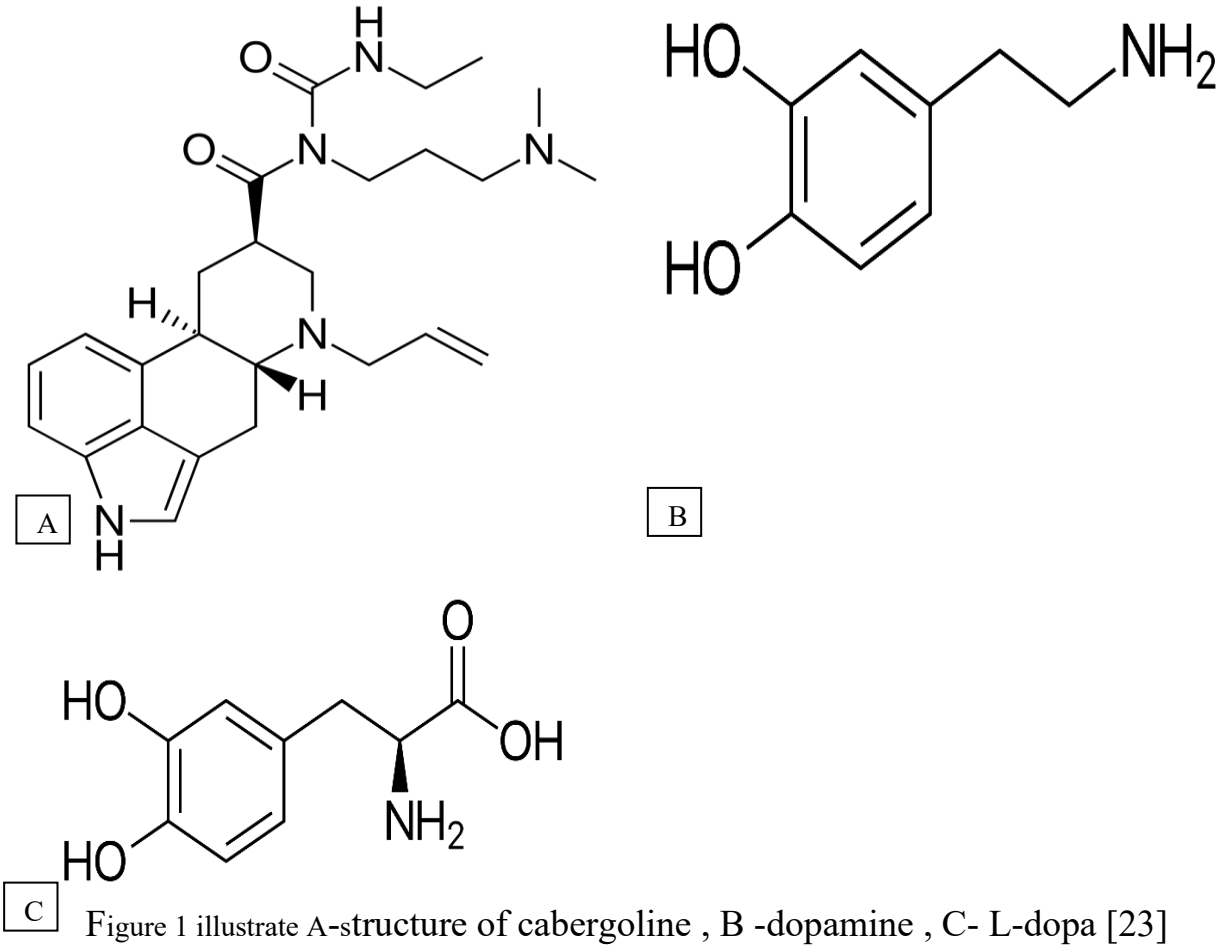

Figure 1 illustrate A-structure of cabergoline , B -dopamine , C- L-dopa [23]

Valvular heart disease:

The use of cabergoline and pergolide, both dopamine receptor agonists, has been associated with an increased risk of valvular heart disease. Studies published in the New England Journal of Medicine on January 4, 2007, linked these medications to the development of valvular heart abnormalities. In response to these findings, the FDA took pergolide off the market in the United States on March 29, 2007 [15].

Cabergoline, however, remains available for use in the United States, primarily for the treatment of hyperprolactinemia, but not for Parkinson's disease. It is worth noting that the risk of valvular heart disease appears to be dose-dependent, and lower doses used for treating hyperprolactinemia have been found to be less likely to lead to

cardiac valve regurgitation or clinically severe valvular heart disease.

As with any medication, caution should be exercised when prescribing cabergoline, especially in patients with preexisting cardiovascular conditions. Regular cardiovascular monitoring and careful evaluation of potential risks and benefits are essential when using cabergoline in clinical practice. Patients on cabergoline should be closely monitored for any signs or symptoms of valvular heart disease, and healthcare providers should remain vigilant in assessing cardiac health during the course of treatment. **[16-18]**.

Adverse Drug Reactions:

Most adverse reactions are dose-dependent especially when used in Parkinson's disease management and restless leg syndrome, which both frequently demand extremely high doses, even more severe adverse effects have been documented; When used to treat hyperprolactinemia, other endocrine problems, or gynecologic causes, where the normal dose is one hundredth to tenth that for Parkinson's disease, the adverse effects are regarded as minor.

To reduce adverse effects, cabergoline should be monitored carefully (2-4 weeks for hyperprolactinemia, frequently considerably longer for other disorders). The medication's exceptionally lengthy bioavailability could make titration dosing methods more challenging and necessitate special safeguards.

The most bearable alternative for treating hyperprolactinemia is cabergoline, however, the more recent and unproven quinagolide may have similar good side effects[17].

- GI tract: Adverse reactions were very common. Patients who reported adverse symptoms made up 53%. Very common symptoms include dry mouth (10%), constipation (22%), and nausea (30%). Gastric irritability (7%), vomiting (5%), and dyspepsia (2%), all occur often.
- Central nervous system (CNS) and psychiatric disturbances: 51 percent of individuals were impacted overall. Vertigo (27%), sadness (13%), and sleep difficulties (somnolence 18%, sleeplessness 11%) are also very common. Hallucinations (4%) and dyskinesia (4%) are frequent.
- Cardiovascular: Some side effects were reported by about 30% of individuals. The most prevalent edemas were non-specific (2%), peripheral (14%), and hypotension (10%). Palpitations occurred in 4.3%, arrhythmias in 4.8%, and angina pectoris in 1.4% of cases[18].

Contraindications:

- An allergy to ergot derivatives
- Children (without prior clinical training)
- Significantly deteriorated liver health or cholestasis
- Using cabergoline concurrently with medications that are mostly metabolized by CYP450 enzymes, such as erythromycin and ketoconazole, as this may cause cabergoline plasma levels to rise (even though cabergoline undergoes very little CYP450 metabolism)[17].

It is essential to steer clear of the following conditions: severe cardiovascular illness, Raynaud's disease, gastroduodenal ulcers, active gastrointestinal bleeding, and hypotension.

Pregnancy & Lactation:

The impact of this drug on lactation and pregnancy is a subject of relatively little

research. When pregnancy is anticipated, the associated drug bromocriptine in some situations may be an alternative[19].

Pregnancy: Initial findings indicate that patients who were on cabergoline during pregnancy showed a slightly higher incidence of congenital defects [Reference required]. However, a separate study reported that exposure to cabergoline during early pregnancy did not result in an increased risk of miscarriage or fetal malformation [10].

Lactation: Cabergoline was discovered in the mother's milk of rats. It is typically not advised to breastfeed if/when cabergoline medication is required because it is unknown if this effect also happens in humans.

Lactation suppression: Cabergoline (Dostinex), a drug, is occasionally used to inhibit lactation in some nations[20].

Therapeutic Uses:

Therapeutic Uses of Cabergoline - Dopamine Receptor Agonist:

Cabergoline, a dopamine receptor agonist, has found several therapeutic applications owing to its ability to interact with dopamine receptors in the central nervous system[21]. This medication has been widely studied and utilized in the following therapeutic areas:

1. Hyperprolactinemia: Cabergoline is primarily employed in the treatment of hyperprolactinemia, a condition characterized by elevated levels of prolactin hormone in the blood. It effectively inhibits prolactin secretion from the pituitary gland, thus reducing prolactin levels in the body. By restoring prolactin levels to normal, cabergoline helps alleviate associated symptoms such as menstrual irregularities, galactorrhea (abnormal milk production), and infertility [22]. It is considered a first-line treatment for hyperprolactinemia due to its high efficacy and favorable tolerability.

2. Parkinson's Disease: Cabergoline has shown promise as an adjunct therapy in Parkinson's disease. By stimulating dopamine receptors, it helps to improve motor symptoms, such as rigidity, bradykinesia (slowness of movement), and tremors, which are characteristic of this neurodegenerative disorder. It is particularly beneficial in cases where other dopamine agonists or levodopa treatments may have limitations or adverse effects [23].

3. Restless Legs Syndrome (RLS): Restless legs syndrome is a neurological disorder characterized by an irresistible urge to move the legs, often accompanied by uncomfortable sensations. Cabergoline, as a dopamine receptor agonist, has been investigated for its role in managing RLS symptoms. It helps in reducing sensory and motor symptoms, leading to improved sleep quality and overall quality of life for affected individuals.

4. Prolactin-Secreting Pituitary Adenomas (Prolactinomas): Cabergoline is the treatment of choice for prolactin-secreting pituitary adenomas (prolactinomas), a type of benign tumor of the pituitary gland. By lowering prolactin levels, it can lead to a reduction in tumor size and alleviate symptoms associated with tumor compression on nearby structures [24].

5. Off-Label Uses: In addition to its approved therapeutic uses, cabergoline has been explored for various off-label applications. Some of these include the management of acromegaly (excessive growth hormone production), treatment-resistant major depressive disorder, and as an adjunct therapy in certain cases of male infertility associated with high prolactin levels.

Conclusion

Cabergoline, as a dopamine receptor agonist, holds significant therapeutic potential in various medical conditions. Its efficacy in treating hyperprolactinemia, Parkinson's disease, and restless legs syndrome has been well-established. Additionally, it plays a crucial role in managing prolactin-secreting pituitary adenomas. However, careful clinical supervision is essential due to its potential side effects and interactions. Cabergoline's therapeutic benefits make it a valuable option in the field of neurology and endocrinology, warranting further research and exploration of its applications in other medical areas.

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Author Contributions

All Authors contributed equally in this article

References:

1. Elks J, editor. The dictionary of drugs: chemical data: chemical data, structures and bibliographies. Springer; 2014 Nov 14. pp. 204–.

2. Fischer J, Ganellin CR (). *Analog-based. John Wiley & Sons*; 2006. *p. 533. ISBN 9783527607495.*

3. Brar SS, Khan SS, Sandhu GK, Jorgensen MB, Parikh N, Hsu JW, Shen AY. Incidence, mortality, and racial differences in peripartum cardiomyopathy. The American journal of cardiology. 2007 Jul 15;100(2):302-4. DOI:10.1016/j.amjcard.2007.02.092

4. Sliwa K, Bauersachs J, Arany Z, Spracklen TF, Hilfiker-Kleiner D. Peripartum cardiomyopathy: from genetics to management. European Heart Journal. 2021;42(32):3094-102.

5. Honigberg MC, Givertz MM. Peripartum cardiomyopathy. Bmj. 2019 Jan 30;364. DOI: 10.1136/bmj.k5287

6. Pearson GD, Veille JC, Rahimtoola S, Hsia J, Oakley CM, Hosenpud JD, Ansari A, Baughman KL. Peripartum cardiomyopathy: national heart, lung, and blood institute and office of rare diseases (National Institutes of Health) workshop recommendations and review. Jama. 2000 ;283(9):1183-8. DOI: 10.1001/jama.283.9.1183

7. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowski P, Poole-Wilson PA, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM): The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaborati. Eur J Heart Fail . 2008;10(10):933–89. DOI: 10.1016/j.ejheart.2008.08.005

8. Sliwa K, Blauwet L, Tibazarwa K, Libhaber E, Smedema J-P, Becker A, et al. Evaluation of bromocriptine in the treatment of acute severe Peripartum cardiomyopathy: A proof-of-concept pilot study. Circulation. 2010;121(13):1465–73. DOI: 10.1161/circulationaha.109.901496

9. Hilfiker-Kleiner D, Haghikia A, Berliner D, Vogel-Claussen J, Schwab J, Franke A, et al. Bromocriptine for the treatment of peripartum cardiomyopathy: a multicentre randomized study. Eur Heart J. 2017;38(35):2671–9. DOI: 10.1093/eurheartj/ehx355

10. Al-Hussaniy HA, Al-kuraishy AA, Jalil HJ. Evaluation of the efficacy of adrenergic neurons inhibition through various surgical and therapeutic regimens on controlling blood pressure and circadian rhythm in patients with uncontrolled hypertension. Journal of Clinical Trials and Experimental Investigations. 2022 ;1(3):106-13.

11. *Fariello RG. Pharmacodynamic and pharmacokinetic features of cabergoline: rationale for use in Parkinson's disease. Drugs. 1998;55:10-6. DOI:* 10.2165%2F00003495-199855001-00002

12.

13. Hoeppner LH, Wang Y, Sharma A, Javeed N, Van Keulen VP, Wang E, Yang P, Roden AC, Peikert T, Molina JR, Mukhopadhyay D. Dopamine D2 receptor agonists inhibit lung cancer progression by reducing angiogenesis and tumor infiltrating myeloid derived suppressor cells. Molecular oncology. 2015;9(1):270-81. DOI: 10.1016%2Fj.molonc.2014.08.008

14. *Millan MJ, Maiofiss L, Cussac D, Audinot V, Boutin JA, Newman-Tancredi A. Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. I. A multivariate analysis of the binding profiles of 14 drugs at 21 native and cloned human receptor subtypes. Journal of Pharmacology and Experimental Therapeutics. 2002;303(2):791-804.* DOI: 10.1124/jpet.102.039867

15. *Sharif NA, McLaughlin MA, Kelly CR, Katoli P, Drace C, Husain S, et al. Cabergoline: Pharmacology, ocular hypotensive studies in multiple species, and aqueous humor dynamic modulation in the Cynomolgus monkey eyes. Exp Eye Res . 2009;88(3):386–97. DOI: 10.1016/j.exer.2008.10.003Newman-Tancredi A, Cussac D, Audinot V, Nicolas J-P, De Ceuninck F, Boutin J-A, et al. Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. II. Agonist and antagonist properties at subtypes of dopamine D(2)-like receptor and alpha(1)/alpha(2)-adrenoceptor. J Pharmacol Exp Ther. 2002;303(2):805–14. DOI: 10.1124/jpet.102.039875*

16. *Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. N Engl J Med. 2007;356(1):29–38. Available from: 10.1056/NEJMoa062222*

17. *Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. N Engl J Med. 2007;356(1):39–46. DOI: 10.1056/NEJMoa054830*

18. Al-Hussaniy HA. The Effect of MicroRNA-409-3p for Treatment and Response to Tumor Proliferation of Lung Cancer Cell Lines (In Vitro). Asian Pacific Journal of Cancer Prevention: APJCP. 2022 Sep;23(9):3151.

19. *25. Colao A, Abs R, Bárcena DG, Chanson P, Paulus W, Kleinberg DL. Pregnancy outcomes following cabergoline treatment: extended results from a 12-year observational study. Clin Endocrinol (Oxf). 2008;68(1):66–71 DOI: 10.1111/j.1365-2265.2007.03000.x*

20. UK electronic Medicines Compendium Dostinex Tablets Last Updated on eMC December

23. Farid NF, Abdelwahab NS. Development and validation of different chromatographic methods for analysis of cabergoline in the presence of its degradation products: studying degradation profile. Chromatographia. 2019;82(10):1555-69.

22. Budayr A, Tan TC, Lo JC, Zaroff JG, Tabada GH, Yang J, et al. Cardiac valvular abnormalities associated with use and cumulative exposure of cabergoline for hyperprolactinemia: the CATCH study. BMC Endocr Disord . 2020;20(1):25. DOI: 10.1186/s12902-020-0507-8

23. Lin S, Zhang A, Zhang X, Wu ZB. Treatment of pituitary and other tumours with cabergoline: New mechanisms and potential broader applications. Neuroendocrinology. 2020;110(6):477–88. DOI: 10.1159/000504000

24. Kizilgul M, Duger H, Nasiroglu NI, Sencar E, Hepsen S, Akhanli P, et al. Efficacy of cabergoline add-on therapy in patients with acromegaly resistance to somatostatin analogs treatment and the review of literature. Arch Endocrinol Metab. 2022; DOI: 10.20945/2359-3997000000481

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