Review

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Prolactinoma: Navigating the Dual Challenge of Side Effects and Treatment Strategies - A Comprehensive Review

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Abstract

This narrative review provides a succinct exploration of prolactinoma, the most common pituitary adenoma, focusing on its epidemiology, clinical manifestations, and therapeutic interventions. Beginning with an overview of its prevalence and aetiology, the review delves into the gender distribution and familial associations of prolactinoma. Clinical presentations, including endocrine disruptions, reproductive health issues, and metabolic disturbances, are examined, emphasizing their impact on hormonal regulation and cardiovascular health. The narrative then navigates through pharmacological treatments, surgical interventions, and radiation therapy, highlighting their efficacy, side effects, and long-term management challenges. Strategies to mitigate side effects and optimize treatment outcomes are discussed, emphasizing the importance of multidisciplinary collaboration in prolactinoma management. This review is a concise yet comprehensive resource for healthcare professionals and researchers, providing insights into prolactinoma's clinical complexities and therapeutic nuances to guide optimal patient care strategies.

Keywords: dopamine agonists, emerging therapies, hormonal disorders, individualized therapy, pharmacological therapy, prolactinoma, surgical interventions

Introduction

Prolactinoma is the most common secretory tumour of the pituitary gland, accounting for up to 40% of all pituitary adenomas[1]. Both males and females are affected by prolactinoma, which has a general prevalence of 50 cases per 100 000 people and an incidence of 3–5 cases per 100 000 people per year. It is more common in hypogonadal subjects because higher prolactin levels cause central inhibition of gonadotropes through kisspeptin neurons[2]. Although its precise aetiology is unknown, most of these tumours arise sporadically and can also be a component of familial disorders[3]. Tumours less than 10 mm are categorized as microadenomas, while larger ones are called macroadenomas. Microadenomas are more common than macroadenomas (57.4% vs. 42.6%)[4].

HIGHLIGHTS

- Dual challenge: Managing prolactinoma entails balancing treatment efficacy with the burden of side effects, presenting a dual challenge for clinicians.
- Treatment modalities: This review explores various treatment modalities for prolactinoma, including surgery and dopamine agonists, highlighting their pros and cons.
- Individualized therapy: Emphasis is placed on the importance of individualized therapy, considering patient demographics and tumour characteristics for optimal treatment outcomes.
- Emerging options: The review discusses emerging treatment options and potential future directions in prolactinoma management, offering insights into novel therapeutic avenues.
- Optimization strategies: Future research should prioritize optimizing treatment strategies to minimize side effects while maximizing therapeutic benefits, ultimately improving patient outcomes in prolactinoma management.

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Serum prolactin (PRL) levels over the customary upper limit of the normal range are referred to as hyperprolactinemia. Several physiological, pharmacological, or pathological variables can contribute to this frequent clinical finding. Prolactinomas, also known as PRL-secreting adenomas, are the most common aetiology among pathogenic causes[5]. Usually, microprolactinomas form more frequently in women in their third to fifth decades of life[6]. Nonetheless, the prevalence of macroprolactinomas is higher in men and older women[7]. 4–8% of pituitary adenomas in people over 65 are caused by prolactinomas[8]. However, there is a lack of precise information on their prevalence.

Prolactinomas arise from the monoclonal expansion of pituitary lactotrophs, which are typically benign and frequently noninvasive[3]. Classical signs and symptoms of hyperprolactinemia include hypogonadism, galactorrhea, and/or adenoma mass effects, primarily visual field loss[9]. Age and gender have an impact on clinical presentation as well. Headache, growth failure, and defects in the visual field are the most common signs during the prepubertal period, while during puberty, galactorrhea, hypogonadism, or pubertal arrest are more typical[10]. Pharmacological therapy is effective in most prolactinomas, and the mainstay of care typically consists of dopamine agonists (DA)[6], Cabergoline being the most commonly used drug to regulate prolactin levels and reduce tumour mass[9]. Aggressive prolactinoma (APRL) is a subset of aggressive pituitary tumours (APTs) that are more invasive and proliferative than typical prolactinomas and usually develop resistance to standard treatments, thus requiring radiation therapy and surgery. However, this class of prolactinoma shows a higher risk of early recurrence post-surgery or during traditional medical management[11,12].

Prolactinomas are notorious for the vast effects they have throughout multiple organ systems. Excess PRL may hasten the emergence of disorders related to insulin and glucose metabolism[13]. Evidence suggests that high PRL levels promote the increase of the surrogate index of insulin resistance (HOMA-IR) and the reduction of the surrogate index of insulin sensitivity, either in obese or lean patients, linking the pathogenesis of impaired glucose tolerance and hyperinsulinemia in patients with hyperprolactinemia[14]. Newly diagnosed pituitary tumours are frequently associated with obesity, of which prolactinoma is no exception[15,16]. However, the fundamental relationship between obesity and prolactinoma is poorly understood[17,18]. Owing to its association with insulin resistance, hyperglycaemia, dyslipidemia, weight gain, obesity, systemic arterial hypertension, atherosclerosis, and endothelial dysfunction, there is concern for an increased risk of cardiovascular disease in patients presenting with hyperprolactinemia[19].

The study aims to comprehensively review the current landscape of prolactinoma management, focusing on treatment modalities, including dopamine agonists, surgery, and radiation therapy, and exploring associated side effects. Additionally, the study aims to identify novel therapeutic approaches and advancements in precision medicine for prolactinoma treatment. Through this review, we seek to provide insights into the efficacy, safety, and long-term outcomes of different treatment options, with the ultimate goal of informing clinical practice and improving patient care.

Methodology

This narrative review was conducted to explore various aspects of prolactinoma management, including treatment modalities and associated side effects. PubMed/MEDLINE and Google Scholar databases were searched for relevant articles published up to 2023. The search utilized keywords such as “prolactinoma,” “treatment,” “dopamine agonists,” “surgery,” “radiation therapy,” “cabergoline,” “bromocriptine,” and “side effects.” Articles were included discussing treatment modalities, outcomes, side effects, and novel therapeutic approaches for prolactinomas. The articles’ titles, abstracts, references, and citations were screened to ensure their relevance to the topic under investigation.

Understanding prolactinoma

Prolactinoma ranks as one of the most prevalent tumours of the pituitary gland, accounting for ~40% of all pituitary adenomas. It exhibits a higher incidence among females, primarily affecting women aged 20–50. However, beyond age 50, its occurrence becomes equally distributed between genders[9].

Prolactinomas, based on their size, are divided into microadenoma and macroadenoma; microadenoma is less than 1 cm, and macroadenoma is more than or equal to 1 cm[20]. Up to 80% of prolactinomas are microadenomas. Meanwhile, the malignant counterpart is rare. Generally, women present most commonly with microadenoma and men with macroadenoma[21].

Females with prolactinoma encounter infertility, galactorrhea, and menstrual abnormality, as well as decreased libido and dyspareunia, while men present with low sex drive, erectile dysfunction, and premature ejaculation[22,23]. An excess of serum prolactin for a long period can lead to impaired glucose tolerance, hyperinsulinemia, insulin resistance, atherogenic dyslipidemia, subclinical atherosclerosis, endothelial dysfunction, and increased weight[24].

Prolactinoma occurs when there is a somatic mutation, leading to the monoclonal expansion of lactotrophs. In adenoma, primarily prolactinoma mutation of fibroblast growth factor 4 receptor, as well as overexpression of pituitary transforming genes, are found. Most are sporadic but can also be part of a familial syndrome. Fifteen to sixty percent of individuals with multiple endocrine neoplasia 1 can have pituitary gland adenoma, predominantly prolactinoma[22,25]. Prolactinoma is unusually involved in multiple endocrine neoplasia 1, where they behave more aggressively than sporadic prolactinomas[26].

Prolactinomas are often sharply demarcated with no sign of invasion; some behave aggressively and spread to surrounding structures, with signs of pleomorphism and increased cellularity. To call it a malignant prolactinoma, there must be distal extracranial involvement. Prolactinoma’s most involved site is the anterior pituitary’s lateral part. Microadenoma, which is usually within the Sella turcica, does not compress the adjacent structure and produces symptoms mainly due to high levels of prolactin; in contrast, macroadenoma expands, compressing the local structure like optic chiasm leading to visual field defect, cavernous sinuses causing headache and cranial nerve palsy[27].

Prolactin level correlates with the adenoma size; an adenoma less than 1 cm will have a serum prolactin level less than 200 ng/ml. If the size is greater than 1 cm, the serum prolactin level is over 200 ng/ml. Suppose there is a disparity between the size of

prolactinoma and prolactin level. In that case, it may be due to a poorly differentiated prolactinoma, or there could be a large cystic component in the adenoma[22,28]. The hypothalamus mainly regulates prolactin secretion and has a mostly inhibitory effect on prolactin secretion. Considering different reasons for hyperprolactinemia is crucial, as they are raised in many other physiological and pathological states besides prolactinoma[9].

To approach the diagnosis, start by checking the prolactin level, and if raised, a pregnancy test should be performed in women of childbearing age; serum TSH level and a comprehensive metabolic panel are recommended. Other pituitary gland hormones, like ACTH, LH, FSH, testosterone, or estradiol, should be checked to exclude hypopituitarism and co-secreting tumours[29–31]. Rule out physiological causes of prolactinoma, such as breastfeeding, food intake, sleep, exercise, and stress. We will have to eliminate other possible pathological conditions, such as chronic kidney failure and liver failure, by performing renal function tests and liver function tests. Drugs such as antidepressants, dopamine receptor blockers, birth control pills, neuroleptics, gastrointestinal medications, and antipsychotics could be a source of hyperprolactinemia and, hence, should be excluded[20]. There is a phenomenon called the hook effect, in which there is raised prolactin, which, when measured, gives a false low level of prolactin. If there is any suspicion about the reading, serial dilution of the serum prolactin sample should be performed and repeated once for a second time[32]. If the prolactin level is high and the prolactin level is low, it is due to macroprolactin, a high molecular weight prolactin. Thus, in asymptomatic hyperprolactinemia, the level of macroprolactin should be assessed[33]. To Confirm the diagnosis, gadolinium-enhancing MRI should be performed to discover the tumour size. Computed tomography (CT) is not as productive in recognizing microadenoma and the extent of the macroadenoma; nonetheless, it can be performed in situations where MRI is contraindicated or inaccessible[34].

Common side effects associated with prolactinoma itself

Prolactinoma, a benign tumour of the pituitary gland causing elevated levels of prolactin, is associated with a spectrum of side effects ranging from reproductive and menstrual disturbances to neurological and psychological manifestations.

This study delves into the distinctive adverse effects of prolactinomas on both men and women. Comprising 40% of pituitary adenomas, prolactinomas cause irregularities, amenorrhoea, galactorrhea, weight gain, infertility, hypogonadism, decreased libido, and depression[34]. Macroadenomas can produce headache, vomiting, lower chiasmatic sickness, and ophthalmoplegia due to compression of surrounding structures. Tumours greater than 10–15 mm with suprasellar spread induce significant vision field loss. Giant prolactinomas (1–5% of instances) larger than 40 mm can infiltrate essential locations such as the cavernous sinus, leading to advanced chiasmatic syndrome. The conclusion underlines the typical features of the inferior chiasmatic syndrome, including the greater prevalence of macroprolactinomas in men, probable diagnostic delays, and a usually optimistic prognosis with accessible medicinal therapies such as dopamine agonists. This information is an excellent resource for understanding the complex impacts of prolactinomas in therapeutic settings[34].

Furthermore, this prolactinoma study investigates how the illness impacts body composition, lipid metabolism, and hormone levels. Analyzing 21 prolactinoma patients and 30 controls, the study reveals that prolactinoma is associated with a higher BMI, greater body fat in men, and worse lipid profiles (higher Low-density lipoprotein, lower High-density lipoprotein). Glucose metabolism remains essentially unaltered. The study stresses the significance of monitoring and controlling the metabolic hazards linked with prolactinoma[35].

In a retrospective population-based study, researchers aim to investigate the relationship between prolactinoma and incident cardiovascular disease. Studying 2233 patients with prolactinoma and 10 355 matched controls over six years using data from The Health Improvement Network (THIN) database, they found that females with Prolactinoma show no elevated risk of Cardiovascular disease. In contrast, males with prolactinoma had a considerably higher risk. These findings highlight a gender-specific link between prolactinoma and increased Cardiovascular disease risk in men, although the mechanism has yet to be identified[36].

A cross-sectional case-control study examines the incidence of newly diagnosed autoimmune thyroid disorders in female prolactinomas. Analyzing 260 females from a single tertiary referral hospital, the study finds that prolactinoma patients had a considerably greater frequency of autoimmune thyroid disorders compared to healthy participants. Subclinical hypothyroidism is significantly more common in prolactinoma patients. The findings emphasize the necessity of routine screening for autoimmune thyroid illnesses in female prolactinoma patients at diagnosis[37].

Lastly, a case report describes the unusual incidence of aneurysmal subarachnoid haemorrhage (SAH) and epistaxis in a 61-year-old man with untreated prolactinoma. The patient arrived with major epistaxis, amaurosis, nausea, and an intense headache. Imaging detected SAH as well as a minor internal carotid artery pseudo aneurysm linked with the prolactinoma. The study underscores the importance of carefully considering associated hazards, even in untreated prolactinomas[38].

Pharmacological treatment and associated challenges

Prolactinomas, the most common type of pituitary adenomas, often require pharmacological intervention to regulate hormone levels. Dopamine agonists, including bromocriptine and Cabergoline, have emerged as the first-line treatment due to their ability to stimulate dopamine receptors, thereby inhibiting prolactin secretion and reducing tumour size.

Efficacy of dopamine agonists

Dopamine agonists have shown remarkable efficacy in the management of prolactinomas. Cabergoline, in particular, has demonstrated superiority over bromocriptine in normalizing prolactin levels and inducing tumour shrinkage[39]. Studies report a high success rate in achieving biochemical remission and restoring gonadal function with dopamine agonist therapy[40].

Side effects of dopamine agonists

While dopamine agonists are effective, they are associated with various side effects. Common side effects include nausea, dizziness, headache, and gastrointestinal disturbances[41]. Long-term use of these agents may lead to complications such as valvular heart disease and impulse control disorders[42]. Regular monitoring for adverse effects is crucial to ensure patient safety and treatment compliance.

Challenges in long-term management

A significant challenge in the long-term management of prolactinomas is the development of drug resistance to dopamine agonists. Some patients may exhibit persistent elevation of prolactin levels and inadequate tumour shrinkage despite treatment[43]. The mechanisms underlying drug resistance are complex and may involve alterations in dopamine receptor expression or signalling pathways.

Long-term treatment adherence poses another challenge, as patients may experience intolerable side effects or become noncompliant with medication regimens. Strategies to enhance treatment adherence, including patient education and regular follow-up, are essential to optimize outcomes[44].

Alternative pharmacological treatments

Prolactinomas, the most common pituitary adenomas, are traditionally managed with DAs. However, some patients experience adverse effects or show resistance to DAs, necessitating the exploration of alternative pharmacological treatments. This review critically examines the existing literature on alternative drugs and their implications in prolactinoma management.

Somatostatin analogues

Somatostatin analogues, such as octreotide and lanreotide, have emerged as potential alternatives. These agents inhibit prolactin secretion by binding to somatostatin receptors. Adverse effects include gastrointestinal disturbances, gallstones, and transient glucose intolerance. Their efficacy in prolactinoma management may be limited compared to DAs[39].

Dopamine antagonists

Dopamine antagonists, like haloperidol and pimozide, offer an indirect approach by blocking dopamine receptors. Despite being less common in prolactinoma treatment, they are considered in DA-intolerant patients. Adverse effects include extrapyramidal symptoms, limiting their widespread use[45].

Gonadotropin-releasing hormone (GnRH) agonists

GnRH agonists, exemplified by leuprolide and goserelin, indirectly decrease prolactin production by suppressing gonadotropin secretion. However, long-term use can lead to menopausal symptoms and bone loss, posing challenges in their continuous application[42].

Selective oestrogen receptor modulators (SERMs)

SERMs like tamoxifen and raloxifene act by blocking oestrogen receptors, reducing prolactin levels. Although less effective than DAs, they are considered in specific cases. Adverse effects encompass hot flashes and thromboembolic events, necessitating careful patient monitoring[40].

Tyrosine kinase inhibitors

Tyrosine kinase inhibitors like cabozantinib and sunitinib are under investigation and are showing promise in reducing prolactinoma growth. However, hypertension and gastrointestinal disturbances have been reported as potential adverse effects, warranting further research into their long-term safety and efficacy[46].

While DAs are the mainstay for prolactinoma treatment, alternative pharmacological approaches provide valuable options, particularly in cases of intolerance or resistance. Understanding the efficacy, adverse effects, and treatment challenges associated with somatostatin analogues, dopamine antagonists, GnRH agonists, SERMs, and tyrosine kinase inhibitors is crucial for tailoring treatment strategies to individual patient needs. Further research is essential to define the role of these alternative drugs in the evolving landscape of prolactinoma management.

Surgical intervention: addressing challenges and complications

Prolactinoma, although a benign pituitary tumour, may require surgical intervention if medical treatment fails to produce satisfactory results. Surgical interventions for prolactinomas can be broadly categorized into two main types: trans-sphenoidal surgery and alternative surgical methods, such as transcranial surgery, which are less common. Additionally, surgery may be the primary treatment option for exceptional cases, including pituitary adenoma, craniopharyngioma, Rathke's cleft cyst, meningioma, and chordoma[47].

Trans-sphenoidal surgery

Also known as endoscopic pituitary surgery, this procedure involves accessing the pituitary gland through the sphenoid sinus, a hollow space in the skull behind the nasal passage and beneath the brain. Typically, a neurosurgeon and an otorhinolaryngologist collaborate to perform this surgery. The surgeon makes a small incision inside the nose and opens the rigid walls of the sphenoid sinus with delicate instruments to reach the pituitary gland. Specialized instruments are then used to remove the tumour, while an endoscope provides visualization of the tumour and surrounding structures for assessment. In some cases, intraoperative MRI may obtain real-time images to monitor tumour removal progress[47,48].

Effectiveness and complication rates of the procedure

Trans-sphenoidal surgery is generally considered a safe procedure with a complication rate of less than 1%[49]. It boasts a high remission rate, averaging around 67% and exceeding 90% for microprolactinomas. The recurrence rate is relatively low, ranging from 5 to 20%[50]. Given these statistics, trans-sphenoidal surgery for prolactinomas is regarded as a relatively safe option. The success of the surgical procedure depends on factors such as tumour size, extent of removal, and preservation of surrounding healthy tissues[51].

Table 1

Compares trans-sphenoidal and transcranial surgeries for prolactinoma treatment, highlighting their pros and cons.

Procedure	Pros	Cons
1. Trans-sphenoidal surgery	The procedure of the first-choice Complications are less common Complications are less severe The procedure is less invasive More cost-effective	Usually ineffective if the tumour has metastasized to distant areas of the brain. Usually ineffective if the tumour is large.
2. Transcranial surgery	More effective for large tumours The most effective treatment for cases where the tumour has metastasized to distant areas of the brain	Complications are more common. Complications are more severe. The procedure is more invasive. Less cost-effective

Alternative surgical approaches

Alternative surgical approaches, particularly transcranial surgery, also known as craniotomy, are less common for prolactinoma treatment. This method involves making an incision on the scalp and then removing a section of bone to access the tumour. The surgeon then removes the affected area while minimizing damage to surrounding tissues. Finally, the removed bone piece is replaced, and the incision is closed[52,53]. Table 1 compares Trans-sphenoidal and Transcranial Surgeries for prolactinoma treatment, highlighting their pros and cons.

Complications of the procedures

Although considered safe treatment options for prolactinomas, both major types of surgical interventions are associated with rare but significant complications. These include vision loss, infections, cerebrospinal fluid leakage, hormonal imbalances, nasal deformities, damage to the normal pituitary gland, diabetes insipidus, and anaesthesia-related complications[54].

Comparison of advantages and disadvantages between trans-sphenoidal and transcranial surgeries

Trans-sphenoidal and transcranial surgeries each have their own set of advantages and disadvantages. Trans-sphenoidal surgery offers a less invasive approach with a shorter recovery time and lower risk of complications such as damage to surrounding structures. However, it may be less effective for larger tumours. On the other hand, transcranial surgery provides better access to larger tumours but carries a higher risk of complications and longer recovery time[55].

Management of the complications

Preoperative evaluation by an otorhinolaryngologist is crucial to assess the patient's suitability for surgery and minimize risks. Patients should refrain from taking any medications, including over-the-counter drugs, without consulting their doctor. Various laboratory tests, including blood tests, chest X-rays, and heart rhythm tests, may be required before surgery. Additionally, dietary restrictions may be prescribed leading up to the surgery based on the patient's medical history and comorbidities[55].

Surgical resection of prolactinomas is generally safe and can effectively achieve therapy and biochemical control in many patients. Educating patients about the likelihood of postoperative remission based on various indicators is important for informed decision-making[56].

Radiation therapy: navigating challenges and complications

Conventional radiation therapy

Pharmacological treatment using dopamine agonists is the primary approach for managing prolactinomas due to their effectiveness in normalizing prolactin levels, reducing tumour size, and restoring gonadal function[57]. However, some individuals may exhibit resistance to dopamine agonists, necessitating the exploration of additional therapies for therapeutic purposes[58]. Surgical and radiation therapies come into play in such cases.

Radiation therapies serve as an alternative option when conventional treatments fail to manage tumour growth or prolactin levels adequately. They are considered a last resort option when other approaches have proven ineffective[59]. These therapies are particularly beneficial for patients experiencing persistent hypersecretion of growth hormone after unsuccessful surgical intervention, providing a targeted approach to managing the condition and improving outcomes[60]. In cases of prolactinomas, radiation therapy is typically reserved for patients with inoperable macroadenomas or those extending into critical regions near the optic apparatus[61,62].

Giant prolactinomas, characterized by their significant size and extensive growth beyond the sella turcica, present unique management challenges. While dopamine agonists are the first-line treatment, additional therapeutic approaches such as radiation therapy and chemotherapy with temozolomide may be necessary for optimal tumour control and hormone normalization[63]. Radiation therapy also offers an alternative for individuals intolerant to dopamine agonists like Cabergoline and bromocriptine[64].

With advancements in imaging techniques, stereotactic radiosurgery, such as Gamma Knife radiosurgery, has become increasingly popular. This intervention has shown excellent efficacy and safety, leading to symptom relief and significant tumour shrinkage in most patients[65,66]. Additionally, stereotactic radiosurgery has been associated with lower rates of new-onset hypopituitarism[67]. Notably, discontinuation of dopamine agonists before treatment may enhance the benefits of radiosurgery, as dopamine agonists may interfere with radiological interventions[68].

Strategies to mitigate side effects

Individualized treatment plan

Dopamine agonists like bromocriptine and Cabergoline are commonly prescribed to manage prolactinomas, a type of tumour associated with elevated levels of prolactin hormone. These medications affect dopamine receptors within the tumour cells, reducing prolactin levels and tumour size. Cabergoline is often preferred due to its higher efficacy and lower incidence of side effects than bromocriptine. However, bromocriptine is considered safer for use during pregnancy. Despite their efficacy, dopamine agonists are typically discontinued during pregnancy, although they may need to be resumed if the tumour shows significant growth. In some instances, hormone replacement therapy with testosterone or oestrogen may be considered for smaller

Table 2

Summarizes medications for prolactinoma treatment, detailing their administration, class, dosage, efficacy, pregnancy category, common side effects, and additional considerations.

Variable	Route	Class	Dosage	Usual dose	Efficacy	Pregnancy category	Side effects	Extra details
Bromocriptine	Oral	D2 receptor agonist	1–2 times/day	2.5–7.5 mg/d	60–80%	B	Nausea, vomiting, nasal congestion, orthostatic hypotension, dizziness, headache, psychosis, impulse control disorder, compulsive behaviour	The first option, according to statistics available among women intending to become pregnant
Cabergoline	Oral	D2 receptor agonist	Bi-weekly	0.5–2 mg	80–90%	B	Same as bromocriptine	More potent and easily tolerable in general, It may require echocardiography to monitor for valvular defect if used in high doses for prolonged periods of time.
Laptanib	Oral	Kinase inhibitor	daily	1250 mg	To be determine	Not applicable	GI disturbances, insomnia, fatigue, acroparesthesias	Also, in the study of patients with CD (Cushing disease)
Quinagolide	Oral	D2 receptor agonist	daily	37.5–75 microgram	Reduction of tumours by more than 80%	X	Nausea, vomiting, headache, dizziness, anorexia, abdominal pain, constipation or diarrhoea, insomnia, oedema, flushing, nasal congestion, and hypotension.	Not used in pregnancy causes spontaneous miscarriage and stillbirth.

GI, gastrointestinal.

tumours that do not exert pressure on surrounding tissues. However, careful monitoring is essential as oestrogen has the potential to stimulate tumour growth. Despite these treatment options, some patients may choose to forego treatment due to the need for long-term medication or the experience of side effects. Additionally, complications such as nasal leakage or bleeding from the tumour may arise during treatment[6]. Table 2 summarizes medications for prolactinoma treatment, detailing their administration, class, dosage, efficacy, pregnancy category, common side effects, and additional considerations.

Nausea, vomiting, fatigue, headaches, and dizziness are among the common side effects associated with dopamine agonists, which may limit their effectiveness. In a study by Webster and colleagues, it was found that 31% of women treated with Cabergoline experienced some degree of nausea, while 50% of those on bromocriptine reported nausea. Severe vomiting was reported by 0% of women on Cabergoline compared to 5% of those on bromocriptine. Additionally, ~30% and 25% of patients reported experiencing headaches and dizziness, respectively, after taking both drugs. Withdrawal from treatment was observed in 3% of patients in the Cabergoline group, while 12% of patients treated with bromocriptine experienced withdrawal overall[25].

In another study, it was found that serum PRL levels returned to normal in 14 out of 16 patients with macroprolactinoma (87.5%) and all 23 patients with macroprolactinomas (100%) after 12 months of quinagolide treatment. MRI tests revealed that 21.7% of patients with microprolactinoma and 25% of patients with macroprolactinoma had a more than 80% reduction in tumour volume[49,69].

The management of side effects involves addressing symptoms as they arise. Nausea and dizziness usually subside temporarily and can be mitigated by taking medication with food or before bedtime. Approximately 5% of patients taking dopamine agonists may experience increased occurrences of compulsive behaviours such as hypersexuality and gambling[69].

Regarding monitoring patients on Cabergoline treatment for prolactinoma, current FDA recommendations suggest undergoing yearly echocardiograms to check for heart valve problems. However, recent research indicates that the risk of Cabergoline causing heart valve issues is minimal. A study involving 40 patients on Cabergoline found that only a small number exhibited heart murmurs during examination, and none had significant valve problems on echocardiograms. Furthermore, a review of multiple studies involving over 1800 Cabergoline-treated patients found only a few cases of confirmed Cabergoline-related valve issues. These findings suggest a low risk of significant heart valve disease unless a murmur is present. Based on this evidence, routine yearly echocardiograms for all Cabergoline-treated prolactinoma patients may need reconsideration. Instead, clinical screening of patients and reserving echocardiograms for those with murmurs, those on higher doses for longer durations, or those over 50 years old may be sufficient[70].

Emerging therapies and future directions

Novel treatment approaches

Somatostatin analogues

Somatostatin receptors (SSTR) immunohistochemistry research revealed that prolactinomas contain all SSTR types, with SSTR5

being the most common and SSTR2A and SSTR1 being the least common[71]. Even though prolactinomas express SSTRs, the somatostatin analogue is not believed to be very effective at suppressing PRL[72]. Ongoing cabergoline treatment may, however, be supplemented with a somatostatin analogue in specific individuals with DA-resistant macroprolactinomas[73].

Selective oestrogen receptor modulators

Estrogens regulate prolactin release and lactotroph cell proliferation. These results are supported by lactotroph hyperplasia, which causes gland enlargement during pregnancy and breastfeeding and implies that estrogens could be useful for treating prolactinomas[74]. When tamoxifen (SERMs) was administered to ten women who had been thought to be resistant to bromocriptine, six of them experienced a moderate decrease in prolactin[75]. Tamoxifen intensifies dopamine agonist's ability to suppress prolactinomas. It has a direct, anti-oestrogen-mediated effect on the suppression and regression of tumour growth. Variations in the doses of tamoxifen, the way it is administered, and the molecular characteristics of the tumours can be responsible for variations in outcomes between cases[76].

TGFB1 system

One well-known inhibitor of prolactin release and lactotroph cell proliferation is transforming growth factor β1 (TGFβ1), which also partially contributes to the inhibitory effect of dopamine[77]. Reduced expression of many TGFβ1 system components and decreased TGFβ1 activity are observed in both human and animal prolactinomas. As a result, regaining TGFβ1 inhibitory function provides an effective treatment approach to bypass dopamine action in DARPs[78].

Blocking the epidermal growth factor (EGF) receptor

The family of transmembrane tyrosine kinase receptors known as the EGF system, which includes EGFR, ErB1, and HER, forms homo and/or heterodimers upon binding ligands and uses intrinsic kinase domains to transduce intracellular signals. It has been demonstrated that EGFR expression is variable in human prolactinomas. In preclinical studies, Gefitinib, an EGFR antagonist, suppressed PRL gene expression, reduced cell proliferation, and lowered the volume and secretion levels of PRLomas rodent xenografts. According to certain publications, EGFR inhibition could be a useful treatment strategy for aggressive or DA-resistant human prolactinomas[79].

Metformin

The diabetes medication metformin, a biguanide, stimulates AMP-activated protein kinase (APMK) and may have antitumor effects. Interestingly, stimulation of AMPK has been shown to inhibit the mammalian target of rapamycin (mTOR), which in turn causes autophagy-dependent cell death in prolactinomas[80].

Advancements in precision medicine

It has been suggested that increased citrullinating enzymes are an early indicator of prolactinoma pathogenesis[81]. Response to DAs has been linked to DRD2 and NGFR expression in prolactinomas. On the other hand, there appears to be no correlation between tumour aggressiveness or DA response and the expressions of PTTG, ERB, and ERA. Prolactinomas exhibit a wide range of responses to DAs, from highly sensitive to resistant[82].

Medical treatments for pituitary adenomas, aside from prolactinomas, often aim to achieve biochemical control rather than complete adenoma removal, as the cure is unlikely[83]. Patient tolerance varies, and therapies may be ongoing or permanent. Research explores targeted proteins and novel epigenetic markers for developing therapeutics. In a recent phase 2a trial on dopamine agonist-resistant prolactinomas, lapatinib, an ErbB1/HER2 tyrosine kinase inhibitor, showed promise in stabilizing disease, albeit without meeting endpoint conditions[84]. Another study evaluated raloxifene, a serum oestrogen receptor modulator, in prolactinoma patients unresponsive to dopamine agonist therapy. Raloxifene reduced serum prolactin levels in most patients, achieving normoprolactinemia in some[85]. Experimental in-vivo gene therapy models, including gene-directed enzyme prodrug therapy, target lactotroph adenomas with potential systemic administration of adenoviral vectors[86–88].

Several other problems need to be solved before gene therapy becomes a reality. These include developing more secure and effective vectors for delivering genes, refining techniques for regulating the expression of transgenes and identifying specific gene targets that can kill cells without necessitating a high rate of proliferation.

Innovations in imaging techniques

The medical sciences now possess a keener sense of vision due to medical imaging, which has profoundly altered the healthcare system. The preferred imaging technique these days is magnetic resonance imaging, which produces excellent images of the hypothalamic-pituitary axis and surrounding structures. Recent technical developments, including the introduction of 3 Tesla MRI, are already extensively used in imaging procedures[89].

The advent of intraoperative MRI seems to be a promising breakthrough that could potentially enhance the results of pituitary surgery[90]. The potential of radiomic analysis to aid in diagnosing, characterizing, and treating these disorders has begun to be shown by its application in the research of PitNETs. Radiomics provides a quantitative, noninvasive instrument that may provide light on previously undiscovered aspects of tumour properties, enhancing diagnostic precision and supporting treatment choices[90].

Patient-centred care and collaborative research

Patient-centred care is the best chance for every patient needing rapid medical attention. The development of service synergies, clinical decision-making regarding care, and precision in managing all patient problems are examples of coordination in services that prioritize interprofessional collaboration and help achieve the primary goal of providing patient-focused services. Table 3 outlines four cases of prolactinoma, detailing patient demographics, tumour characteristics, treatment methods Cabergoline, bromocriptine), and outcomes, highlighting varied clinical presentations and associated complications.

Excellent management, an explicit division of work, team member training for individual responsibilities and team dynamics, and team-supporting organizational policies are linked to improved performance[85].

Table 3

Outlines four cases of prolactinoma, detailing patient demographics, tumour characteristics, treatment methods cabergoline, bromocriptine), and outcomes, highlighting varied clinical presentations and associated complications.

Case Number	Year	Authors	The Focus of the Case	Patient Demographics	Prolactinoma Characteristics	Treatment Approach	Outcome of Treatment
1	2022	Anargyros Ioannis-Vasilakis1 *et al.* [92]	Giant prolactinoma with atypical histological features	15 years old male with short stature, delayed puberty, headache, visual field defects	large atypical, prolactin-secreting pituitary macroadenoma	0.5 mg of Cabergoline orally once a week, and then increasing it gradually to 1.5 mg.	Prolactin levels returned to normal eighteen months following the start of cabergoline therapy, the tumour mass was reduced by nearly half, and the patient's vision improved. DA therapy was well tolerated, except for modest fatigue without postural hypotension.
2	2022	Correa e Castro *et al.* [93]	Compulsive buying, binge eating with Cabergoline for prolactinoma	21-year female presented with galactorrhea, menstrual irregularity, altered field of vision	Microadenoma	Initially patient was treated with 3.5 mg of bromocriptine then CAB was .5 mg per week was introduced.	Initially patient was well tolerated with Cabergoline but after some years of treatment patient showed behavioural changes such as eating without feeling hungry, compulsive buying, and hypersexuality.
3	2018	Caputo *et al.*[94]	Cabergoline associated valvulopathy	A 52-year-old woman with headache, galactorrhea, and secondary amenorrhoea	Macro adenoma	The patient was treated with bromocriptine Because of the limited response to bromocriptine patient underwent two debulking microscopic trans-sphenoidal surgeries with 6 mg weekly cabergoline	Prolactin levels became normal along with reduction in a tumour size but after some years of treatment echocardiogram was performed and the patient showed the three key echocardiography characteristics of CAV were seen on the echocardiogram: new-onset mild to moderate aortic regurgitation and a thickened and constricted valves.
4	2018	Elabd *et al.*[95]	Pneumocepalus with cabergoline treatment for giant Prolactinoma	24-year male with clear fluid nasal discharge, mild to moderate headaches, decreased libido, and spontaneous galactorrhoea	Giant invasive macroprolactinoma	0.25 mg of oral Cabergoline twice weekly	Following 5 weeks of cabergoline medication, the patient complains of an increasing CSF leak, a strong headache, and nausea. In addition to the previously reported invasive and destructive huge macroprolactinoma, an urgent CT scan revealed severe pneumocephalus. and meningitis

CSF, cerebrospinal fluid; CT, computed tomography; DA, dopamine agonist.

The care team may be a powerful tool for achieving better results and patient-centred, collaborative care; nevertheless, team care can also lead to a breakdown in accountability, continuity, and communication. For the people it serves, this fragmentation may lead to a worsened quality of service and results[91].

Conclusion

In conclusion, managing prolactinoma is complex and requires a multifaceted approach across medical disciplines. Despite pharmacological, surgical, and radiation advancements, significant challenges persist, including side effects, treatment resistance, and long-term efficacy. Tailored, multidisciplinary approaches are essential for optimal patient management, highlighting the need for ongoing research to refine treatment strategies and improve outcomes. By addressing these challenges and promoting collaboration among healthcare professionals, we can navigate the complexities of prolactinoma more effectively and enhance the quality of care for affected individuals.

Ethical approval

This paper did not involve patients; therefore, no ethical approval was required.

Consent

This paper did not involve patients; therefore, no consent was required.

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Author contribution

F.Y.: conceptualization; data curation; formal analysis; methodology; writing—original draft. S.A.R.: data curation; investigation; methodology; resources; software; writing—original draft. M.D.: data curation; investigation; methodology; resources; software; writing—original draft. K.I.: methodology; investigation; resources; writing—review and editing. R.A.: methodology; investigation; resources; writing—review and editing. P.K.A.: methodology; investigation; resources; writing—review and editing. M.S.: methodology; investigation; resources; writing—review and editing. FNU T.: methodology; investigation; resources; writing—review and editing. F.Z.H.: methodology; investigation; resources; writing—review and editing. M.I.: methodology; investigation; resources; writing—review and editing. N.K.: methodology; investigation; resources; writing—review and editing. H.H.S.: methodology; investigation; resources; writing—review and editing. T.H.: writing—methodology; investigation; resources; writing—review and editing. M.A.H.: data curation; formal analysis; methodology; project administration; resources; visualization; writing—review and editing.

Conflicts of interest disclosure

The authors declare that there is no conflict of interest.

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