Vilnius University Press

Contents lists available at Vilnius University Press

Acta Medica Lituanica
2023. Online ahead of print

ISSN 1392-0138 eISSN 2029-4174
DOI: https://doi.org/10.15388/Amed.2023.30.2.1

Current and Perspective Approaches to the Treatment of Prolactinomas

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Abstract. ***Background:*** Along with the presence of the 2011 *Endocrine Society Clinical Practice Guidelines* and numerous large-scale studies on the treatment of hyperprolactinemia of different origin, there are some unresolved questions, ambiguous and sometimes contradictory points of view regarding the management of patients with prolactinomas. This overview is devoted to the analysis of the results of modern clinical studies and the approaches towards the management of hyperprolactinemia caused by prolactinoma.

Materials and methods: A systematic research of the literature for the appropriate keywords published mainly for the last 10 years was done; also, a reference list of each selected article was analysed. We included to our review the articles reporting controversial issues or new data on the treatment of hyperprolactinemia.

Results: The review describes various problems arising during the treatment of prolactinoma. The presence of primary and secondary dopamine agonist resistance in each case requires an individual approach, and sometimes may include the use of the antineoplastic agent t*emozolomide*. The side effects of dopamine agonists are discussed, with quite rare ones, including valvulopathy, pathological psychological conditions and cerebrospinal rhinorrhea. The controversial issue of the duration and doses of the drug used to achieve a lasting effect in the treatment of prolactinomas is considered. There are some points connected with the frequency of relapses. Thus, recurrence is correlated to the duration of treatment with dopamine agonists, prolactin levels at diagnosis, and the initial tumor size. Metformin, somatostatin analogues, selective estrogen receptor modulators, tyrosine kinase inhibitors, inhibitors of the mammalian target of rapamycin, epidermal growth factor receptor antagonists are investigated nowadays as potential alternative methods of drug treatment of prolactinomas.

Conclusion: Drug therapy with dopamine agonists makes it possible to achieve the desired results in the vast majority of patients. However, despite the proven safety of this group of medicines, the risk of side effects should still be taken into account. The therapy regimen should be determined by the clinical course of prolactinoma and the patient's response to treatment. Other options of treatment should be considered in patients intolerant to medical therapy, with contraindication or resistance to dopamine agonists, in the case of a malignant tumor. The presence of refractory to any of the applied methods of treatment and aggressive prolactinomas leads to the search for new drugs.

Keywords: hyperprolactinemia, prolactinoma treatment, dopamine receptor agonists, dopamine agonist resistance.

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Received: 23/11/2022. **Revised:** 18/01/2023. **Accepted:** 17/04/2023

Šiuolaikinis požiūris į konservatyvų prolaktinomų gydymą: problemos ir iššūkiai

Santrauka. Nepaisant to, kad turimos 2011 metų Endokrinologijos asociacijos klinikinės praktikos gairės (*Endocrine Society Clinical Practice Guidelines*) ir atlikta daugybė išsamių tyrimų, kaip gydyti įvairios kilmės hiperprolaktinemiją, vis dar lieka neatsakytų klausimų ir kartais nesuderinamų požiūrių, kaip gydyti pacientus, kenčiančius nuo prolaktinomų. Ši apžvalga skiriama šiuolaikinių klinikinių tyrimų rezultatams apibendrinti. Taip pat siekiama apžvelgti požiūrius, kaip gydyti prolaktinomos sukeltą hiperprolaktinemiją.

Medžiagos ir metodai: Buvo atlikta sisteminė per pastaruosius 10 metų publikuotos literatūros apžvalga, remiantis aktualiais raktažodžiais. Taip pat, ištirtas ir visų atrinktų straipsnių nuorodų sąrašas. Į šią apžvalgą įtraukti ir tie straipsniai, kuriuose keliamos kontroversiškos problemos ar pateikiama naujų duomenų apie hiperprolaktinemijos gydymą.

Rezultatai: Šioje apžvalgoje atskleidžiami įvairūs kylantys prolaktinomų gydymo sunkumai. Dėl pirminių ir antrinių dopamino agonistų pasipriešinimo apraiškų kiekvienu atveju reikia individualaus sprendimo, ir kartais šio sprendimo dalis gali būti antineoplastinio agento temozolomido (*temozolomide*) vartojimas. Dopamino agonistų šalutiniai poveikiai jau aptarti; aprašyti net ir tokie reti atvejai, kaip antai valvulopatija, patologinės psichologinės būklės ar cerebrospinalinė rinorėja. Šiame straipsnyje svarstomas probleminis klausimas, kokia turėtų būti vaistų vartojimo trukmė ir dozės, kad būtų pasiektas ilgalaikis prolaktinomų gydymo efektas, nes kai kurie gydymo aspektai yra susiję su recidyvų dažniu. Jie galimai susiję su gydymo dopamino agonistais trukme, nustatytu prolaktino lygiu ir pradiniu auglio dydžiu. Metforminas, somatostatino analogai, selektyvūs estrogeno receptorių moduliatoriai, tirozino kinazės inhibitoriai, žinduolių tiksliniai rapamicino inhibitoriai bei epidermio augimo faktoriaus receptorių antagonistai šiuo metu yra tiriami kaip galimos prolaktinomų gydymo alternatyvos.

Išvados: Medikamentinis gydymas dopamino agonistais leidžia pasiekti norimų rezultatų gydant daugumą pacientų. Tačiau nors šios medikamentų grupės saugumas įrodytas, vis dėlto reikėtų atsižvelgti į gretutinių efektų pavojų. Sprendimą dėl gydymo terapijos reikėtų priimti, atsižvelgiant į klinikinę prolaktinomos gydymo eigą bei paciento reakciją į gydymą. Svarbu apsvarstyti ir kitas gydymo alternatyvas, jei pacientas netoleruoja gydymo medikamentais, jei, gydant piktybinį auglį, atsiranda kontraindikacijų ar būna pasipriešinimas dopamino agonistams. Tiems atvejams, kai nustatomas atsparumas bet kuriam taikytam gydymo metodui ir agresyvioms prolaktinomoms gydyti reikia sukurti naujų vaistų.

Raktažodžiai: hiperprolaktinemija, prolaktinomos gydymas, dopamino receptorių agonistai, dopamino agonistų pasipriešinimas.

Introduction

Nowadays there are ambiguous and sometimes contradictory points of view on the prolactinomas treatment. Its verification is primarily based on the level of serum prolactin (PRL) above the standard upper limit, with the exception of the physiological and iatrogenic genesis of this hormonal disorder [1-6]. In case of the absence of an obvious etiological factor, idiopathic hyperprolactinemia is established [7].

The management of patients with hyperprolactinemia is regulated by the 2011 Endocrine Society Clinical Practice Guidelines for the Diagnosis and Treatment of Hyperprolactinemia, which have not been reviewed since 2011 [8]. However, unresolved issues remain. It relates to the choice of the drug, the duration of the therapy course and possible regimens of administration, as well as approach in case of resistance to the treatment. The purpose of this work was to survey the current approaches to prolactinoma treatment as well as promising areas based on the analysis of relevant publications over the past 10 years.

Methods and Materials

We conducted an analysis of studies that examined different approaches to prolactinoma treatment. Publications were identified by searching MEDLINE/PubMed, Google Scholar and Web of Science without language restrictions from February, 2011 to November, 2022. The following keywords were searched: "Hyperprolactinemia", "Prolactinoma treatment", "Dopamine receptor agonists", "Dopamine agonist resistance". All articles were attentively reviewed by the authors, and only those reporting controversial issues or new data on the treatment of hyperprolactinemia comparing with existing guidelines [8] were included. Additional articles were identified by manually searching the reference lists of pertinent articles.

Results

We identified 127 articles from databases mentioned above. After excluding 71 irrelevant articles based on titles and abstracts, 56 full articles remained for further examination.

Currently, there are three main methods of treatment for prolactinomas, namely: medical, surgical and radiation. A medical (pharmacological) method, which is a priority, is aimed not only at achieving a normal concentration of biologically active PRL, restoring the menstrual cycle, fertility in women and men, but also at reducing the size of the tumor.

As mentioned above, guidelines for the treatment of hyperprolactinemia were adopted in 2011, and these recommendations are still relevant today [8]. According to these guidelines, the use of dopamine agonists (DAs) is recommended as a priority drug therapy. Their efficacy has been confirmed by numerous studies proving their activity in decreasing the level of PRL, reducing the size of the tumor and restoring the function of the gonads in patients with symptomatic PRL-secreting microadenomas or macroadenomas. The first DAs used to treat hyperprolactinemia was bromocriptine. Later, the therapeutic capacity was enriched with cabergoline and quinagolide. The last one is rarely used and the amount of studies on its use is limited. Cabergoline is currently the drug of choice due to its greater efficacy with fewer side effects due to the selective action of the drug at a lower frequency of administration.

Long-term clinical practice has shown that cabergoline normalizes the level of PRL in the blood in 86–92% of cases, leads to regression of pituitary microadenomas in 16–74%, macroadenomas – in 44–91%, helps to restore ovulation in women in 67–89% of cases. However, the average frequency of adverse events with the use of cabergoline in different studies ranged from 13 to 70%, depending on the therapeutic dose [9]. At the same time, it should be emphasized that in the DAs treatment many problems arise, the solution of which does not have an unambiguous answer.

Dopamine Agonist Resistance

Despite a long-term experience in the use of DAs and their proven high efficiency, drugs in this group (bromocriptine, cabergoline, quinagolide) do not give the desired result in some patients. This situation is regarded as DAs-resistance [10].

In general, drug resistance is defined as the failure of an adequate medicine at effective doses to achieve therapeutic targets in a patient who demonstrates both good tolerability and good adherence to treatment. There is no consensus on what exactly can be considered as the goal of therapy – restoration of fertility, reduction of tumor size, normalization of PRL level, etc. That explains the diversity of data on DAs-resistance. Thus, in large invasive or giant adenomas, tumor size reduction and compression relief are considered priority endpoints of therapeutic treatment [11].

Moreover, it should be noted that currently there are no generally accepted criteria for DAs-resistance [10, 12]. Most often, it is defined as the impossibility of achieving normoprolactinemia and

reducing the maximum tumor diameter by less than 50% at the maximum tolerated doses of DAs for at least 3–6 months [10, 12, 13]. The doses vary widely in different patients, but are typically ≥ 15 mg bromocriptine per day, ≥ 2.0 mg cabergoline per week, and ≥ 225 μg quinagolide per day [10].

As with any drug therapy, there are primary resistance to DAs and secondary one, which is less common. In addition, a diagnosis of partial DAs-resistance can be made when, for example, normoprolactinemia is achieved and the tumor size decreases, fertility is not restored [8]. Some patients may experience discordant reactions, i.e. reduction in tumor size without normalization of PRL levels, or can be partially resistant when a person requires higher than typical doses of DAs to get an adequate response. DAs-resistance should be clearly distinguished from intolerance when the side effects of these drugs exclude their use.

In general, the frequency of DAs-resistance among patients receiving therapy with drugs of this group, according to different authors, ranges from 6% to 20% [10, 12, 14]. This indicator varies depending on the drug used and the size of prolactinoma.

Absence of normalization of serum PRL levels as a reflection of primary DAs-resistance is observed in 20–30% of patients treated with bromocriptine, and in approximately 10–15% of patients treated with cabergoline [10, 15, 16]. The inability to achieve at least 50% reduction in tumor size is found in about 30% of cases in patients treated with bromocriptine and in 10–15% of patients treated with cabergoline [16].

Many researchers also consider adenoma size when assessing the risk of DAs-resistance. There is a widespread point of view that macroadenomas, especially with tumor invasion, should be attributed to risk factors for the development of insensitivity to these drugs [8, 10]. This statement is probably based on statistics. DAs-resistance has been observed in less than 10% of patients with microadenomas and in about 15–20% of patients with macroadenomas [10].

This conclusion is contradicted by the data of some investigators. Shimon I. et al. observed patients with giant prolactinomas (adenoma size ≥ 40 mm) and received a positive result during treatment with cabergoline [17]. Summarizing their unique experience in the monitoring and treatment of patients with giant prolactinomas, these authors emphasize the fairly good responsiveness of huge prolactinomas to cabergoline treatment with PRL suppression to normal or close to normal in most cases and achieving a significant tumor shrinkage in many cases. This response was very similar to the reported clinical course of smaller macroprolactinomas.

Along with this, Espinosa E. et al. based on the results of a retrospective study, concluded that cabergoline treatment in patients with giant prolactinomas and macroprolactinomas was effective [18]. According to the obtained data, this therapy led to the normalization of PRL level in 68% and a decrease in tumor volume by more than 50% in 87% of patients with giant prolactinomas, and the cumulative goal of PRL level normalization and tumor reduction > 50% was achieved in 55% of cases in this population. According to these authors, cabergoline treatment was equally effective in patients with giant prolactinomas and in patients with macroprolactinomas in achieving treatment goals, although the average dose of cabergoline was slightly higher in the group of patients with giant prolactinomas (2 vs. 1.5 mg/week). It was argued that in addition to their impressive size and huge amount of secreted PRL, the clinical course of giant prolactinomas does not differ from that of macroprolactinomas. These tumors respond well to cabergoline treatment, and surgery on the pituitary gland is rarely required [18].

The experience in the treatment of prolactinomas indicates that with an increase in the size of the adenoma and its invasiveness beyond the saddle field, the rate of normalization of PRL level gradually decreases to 70–80% in macroprolactinomas and 60–68% with giant PRL-secreting tumors [17, 18, 19].

Vermeulen E. et al. observed DAs resistance in 15.9% of patients with prolactinomas. The authors identified its four significant predictors. In addition to the large tumor volume mentioned above,

predictors established in this study included male sex, long time taken to achieve normal PRL level and presence of a cystic, hemorrhagic and/or necrotic component of tumor tissue. In addition, these authors focused on symptoms associated with mass effect, high baseline PRL level and high contrast capture on MRI [14]. Considering these data, as well as the scoring system suggested by the authors for a particular patient in order to predict the development of resistance to DAs, it should be recognized that each of the proposed criteria has a limited predictive value.

So, the ambiguity of the identified risk factors for the development of resistance to DAs is confirmed by the data of other authors and our own observations [20]. Based on a retrospective assessment of the treatment outcomes in patients with prolactinomas, Araujo-Castro M. et al. argue that large tumor size, but not male gender, is a risk factor for DAs resistance [21].

Our own experience indicates a pronounced therapeutic efficacy in the treatment of macroprolactinoma complicated by compression syndrome in men with average therapeutic doses of cabergoline. At the same time, we observed a young woman with microprolactinoma and the initial absence of any response to the use of DAs, despite an increase in the dose of the drug [20]**.** Szmygin H. et al. also observed a 26-year-old woman with microadenoma, whose treatment was complicated by both primary resistance to all drugs of the DAs group, and their poor tolerance [12].

As noted above, in addition to primary resistance to DAs therapy, one more problem for physicians is the development of a secondary one. It has been described in patients who were initially responsive to treatment with DAs but later resistance developed with elevated PRL levels and sometimes an enlarging tumor volume several years afterwards. Laboy-Ortiz I. E. et al. presented a clinical case of a male patient with prolactinoma who developed drug resistance 13 months after initially effective DAs therapy [22].

So, it should be recognized that the proposed predictors of the development of DAs resistance have been repeatedly refuted by clinical cases and the results of a number of studies. But, apparently, when prescribing treatment to a patient with prolactinoma, these predictors should still be assessed in combination.

The mechanism of DAs resistance is not completely understood. Ongoing studies of the causes and pathogenetic mechanisms of this phenomenon have not yet given unequivocal exhaustive answers. However, in any case of DAs resistance, the problem of its overcoming and prescribing effective treatment arises. [23-24].

To date, several approaches were proposed in the treatment of patients with prolactinoma resistant to DAs. They include increasing the dose or changing for the other drug from this class of meds. The replacement of one DA with the other one is based on their different activities. Tumors that do not respond to bromocriptine or quinagolide often respond to cabergoline [25]. Also, it has been suggested that a standardized, individualized approach with stepwise cabergoline dose increment can normalize PRL levels and reduce prolactinoma size in patients otherwise thought to be resistant to DA [26]. Nevertheless despite the high activity of cabergoline approximately 10% of patients are resistant to this drug [8]. So, changing the drug is not always a solution to the problem of resistance overcoming and achieving the targets in prolactinoma treatment.

Another option for patients who do not achieve normal PRL levels or who do not experience significant tumor shrinkage with standard doses of DA is to increase the dose to the maximum tolerated one followed by surgery [8]. Meanwhile, it should be noted that an increase in the dose, in particular cabergoline, may not only fail to reach the target points of treatment, but also lead to the development of iatrogenic complications.

It is assumed that the ineffectiveness of drug therapy for PRL may be associated with genetic characteristics and variants of the clinical course of the tumor [27].

Management of patients with specific forms of prolactinomas

According to various data, aggressive, refractory, atypical prolactinomas and carcinomas are currently distinguished [28, 29]. At the same time, clear criteria for each of these forms are not strict and unambiguous. Lasol H. et al. define aggressive prolactinomas as radiologically invasive tumors that are incurable by surgery and have an unusually high tumor growth rate due to resistance to DAs, and in some cases are characterized by the occurrence of metastases typical for PRL-secreting carcinoma [28]. Based on the analysis of literature and research data, Moisi M. et al. [29] consider aggressive prolactinomas to be a subset of refractory prolactinomas, the distinguishing features of which are:

- ineffectiveness of DAs therapy and surgical removal of the tumor,
- frequent and early relapses and rapid local growth of the tumorous tissue after surgery or radiotherapy.

Moisi M. et al. also acknowledge that there is debate about what constitutes an "aggressive" adenoma and invasion. In the absence of clear histological features supporting the diagnosis of an aggressive adenoma, the 2004 WHO pituitary tumor classification system defines such cases as "atypical adenomas". They have signs of malignant tumors, but without distant or craniospinal metastases, as seen in pituitary carcinomas [29].

In patients with refractory malignant prolactinomas, temozolomide therapy is suggested [8, 30]. Currently temozolomide is considered to be the best option when optimal standard therapies (high-dose cabergoline, surgery, and radiotherapy) fail. This antineoplastic alkylating agent, which was first used in multiform glioblastoma, is by far the best choice due to its ability to control tumor growth in approximately 50% of treated prolactinomas and improve survival of the patients [28].

Whitelaw B.C. et al. demonstrated a strong association between prolactinomas that were negative by immunostaining for methylguanine methyltransferase and a good response to temozolomide [31]. Contrary to the common approach of using temozolomide as a salvage therapy after all conventional treatments have failed, these authors suggest considering the use of temozolomide at an earlier stage of the treatment algorithm in selected cases.

However, temozolomide therapy has a downside. First, a long-term complete response was observed in a limited subgroup of tumors. No response to temozolomide after three cycles, that is, neither reduction of tumor size nor normalization of PRL level, has been found to be a predictor of poor outcome [29]. Resistance to temozolomide can be primary or occur later in the course of treatment due to the selective elimination of sensitive cells and the persistence of resistant cell populations in a heterogeneous tumor [32]. Despite the positive results of temozolomide treatment of aggressive, refractory prolactinomas, as well as carcinomas, in practice it is very difficult to decide on the optimal timing of the start of therapy with this drug and predict its effectiveness.

Thus, the use of temozolomide, based on presumed future aggression, as primary therapy or instead of radiotherapy, the timing of treatment (immediate or delayed) and combination with other therapies remain controversial [33, 34]. To date, the optimal duration of temozolomide treatment has not been determined, although the current European Society of Endocrinology guidelines suggest at least 6–12 cycles to improve outcomes and increase survival [34].

Considering the poor tolerability of temozolomide in a number of patients, the lack of clear indications for its use in prolactinomas and no clear evidence of its use in combination with other types of treatment, as well as the criteria for initiating and duration of therapy, further research is needed.

In general, DAs-resistant prolactinomas exhibit aggressive course and tend to be large, invasive, hyperangiogenic tumors with high mitotic indices, making them difficult to treat with surgery, radiosurgery, or alternative therapies. This fact justifies the need to look for new therapeutic approaches and treatment algorithms in prolactinomas resistant to DAs [35].

Adverse effects of dopamine agonists

One more challenge in the treatment of prolactinomas with DAs in some patients is development of adverse reactions. The most common DAs side effects are the next:

- systemic and cutaneous symptoms (edema, skin bruising);
- respiratory symptoms (chest pain, respiratory distress, dyspnea, hacking cough);
- gastrointestinal symptoms (dry mouth, loss of appetite, nausea, vomiting, liver failure, constipation, diarrhea);
- cardiovascular symptoms (orthostatic hypotension, arrhythmias, worsening of angina, fibrotic changes in the heart valves with prolonged use of large doses);
- psychological and neurological symptoms (asthenia, fatigue, dizziness, headache, drowsiness (in this connection preference is given to prescribing drugs in the evening), sleep perversion, insomnia, narcolepsy, somnolence, memory loss, hallucination, paresthesia);
- renal symptoms (renal insufficiency) [36-37].

The frequency of occurrence of certain adverse reactions varies in different populations. Such unpleasant side effects as low blood pressure and nausea Castinetti F. et al. refer to the classic and the most well-known ones since DAs were first introduced [36]. Ke X. et al., based on the analysis of the frequency and manifestations of adverse reactions in Chinese prolactinoma patients treated with DAs, noted the predominance of gastrointestinal symptoms, mainly including loss of appetite and nausea with a low overall incidence of side effects [37].

Since 2002, the use of certain DAs in the treatment of Parkinson's disease has been associated with an increased risk of fibrotic valvular disease, which in turn has shaped the direction of research regarding the safety of these drugs in the treatment of patients with prolactinomas. To date, this effect of DAs has been proven to be dose-dependent [8, 36, 38]. When specifically considering the treatment of hyperprolactinemia with DAs, it is clear that the average daily doses are usually 10-fold lower compared with the treatment of patients with Parkinson's disease, and the British Society of Echocardiography, the British Heart Valve Society and the Society for Endocrinology acknowledge notice to the little evidence that DAs pharmacotherapy causes abnormal valvular morphology and dysfunction at doses used to treat hyperprolactinemia [39].

However, due to the necessity of long-term use of DAs high doses in some cases of prolactinoma, it is recommended to monitor the valvular status in these patients for early detection of heart valve disease [8, 40, 41]. Along with mentioned, some clinical observations demonstrated the possibility of heart valves affection when prescribing a low dose of the drug. So, Bhat M.H. et al. gave an example of the cabergoline-induced tricuspid regurgitation in a woman with microprolactinoma who took cabergoline at a low dose [42]. Thus, the decision to discontinue medication should be made only after reviewing a series of echocardiography obtained in the view of drug-induced valvulopathy or carcinoid heart disease [39].

Also, dose-dependent, and therefore very rare is such cabergoline side effect as fibrosis – pleural, pericardial, retroperitoneal. Pleural fibrosis classically manifested with dry cough, dyspnea and edema of the lower limbs [36].

Recently, researchers have begun to pay more attention to the psychosocial side effects of DAs in patients with prolactinoma either de novo after starting DAs therapy or as exacerbations of previously existed psychiatric disorder. It is noted that patients receiving DAs therapy may develop changes in mood and behavior regardless of prior psychiatric history. These pathological psychological conditions include psychosis, mania, anxiety, depression, confusion, auditory hallucinations, hyperactivity, insomnia, nightmares, paranoia, and impulse behavior disorders [36-37, 43-44]. Ioachimescu A.G. et al., according to the data of the studies, noted that patients treated with DAs therapy also experienced a decrease in quality of life and other personality characteristics compared

with the control group [43]. It should be recognized that most endocrinologists are not well aware of the relationship between taking DAs and psychiatric symptoms. Moreover, there are no specific guidelines for the management of patients experiencing psychological problems as a result of DAs therapy [43-44].

Rare but serious complications of DAs therapy include cerebrospinal rhinorrhea, subclinical pituitary apoplexy. Thus, the occurrence of rhinorrhea while taking cabergoline associated with the destruction of the bottom of the saddle by macroadenoma and the pronounced effect of cabergoline on the shrinkage of the adenoma was described in clinic [36]. In addition, the treatment of prolactinoma with DAs is associated with the risk of inducing cystic degeneration, infarction, and intratumoral hemorrhage. Clinical or subclinical pituitary apoplexy is rare but potentially fatal, especially in large macroprolactinomas, where tumor changes caused by DAs can lead to changes in blood flow in the pituitary portal system [38].

The generally accepted point of view is that the risk of developing side effects depends on a particular drug from the DAs group, as well as on treatment parameters (dose, duration of administration) [45].

Experience of prolactinomas DAs treatment suggests that side effects can occur during therapy with any drug of this group – cabergoline, quinagolide or bromocriptine. At the same time, Fachi M.M. et al. point to cabergoline as the safest drug from the DAs group, except for the possible abdominal pain in case of taking it in a dose of 1 mg/week [46].

Regarding bromocriptine treatment Ke H. et al. didn't find the relationship between duration of the treatment, cumulative and maximum daily doses and the development of side effects [37].

The foregoing determines the need for physicians prescribing DAs, including cabergoline, to be aware of the possible risk of developing side effects, even very rare ones. Acknowledgement of these side effects should remind clinicians that while DAs therapy is an accepted and approved treatment for patients with prolactinoma, it may cause a number of complications and careful monitoring is key. On the other hand, the low prevalence of these adverse effects should not call into question the role of DAs in the treatment algorithm for prolactinoma.

Prolactinoma drug therapy regimens and risks of its relapse

The main issues of any pharmacological treatment are its duration and the dose of the drug used to achieve a long-term effect. Considering that adverse effects can be observed at the beginning of treatment, in order to reduce the risk of developing these symptoms, it is recommended to start therapy with low doses, gradually increasing it with further treatment [8, 46-47]. Another approach to determining the initial dose of cabergoline involves the appointment of a high suppressive dose of the drug, in particular, taking into account the basal level of serum PRL [48]. This approach is not generally accepted and is not included in the current international recommendations for the treatment of hyperprolactinemia [8], but we are sure that such method of the treatment should be mentioned here as possible perspective one.

There is also still debate about the optimal duration of treatment and whether to stop treatment, and if so, when. Even when DAs treatment is discontinued as recommended, relapses after discontinuation of the drug occur in a significant proportion of patients. There is a variable rate of recurrence of prolactinomas (from 2% to 80%), which, apparently, is associated with the patients selection criteria, type of DAs used and duration of observation [49]. If more stringent criteria were applied before withdrawal, sustained remission occurred in more than 50% of patients [50].

Salvatori R. has identified main questions that arise when prescribing DAs and remain unanswered [51]. First of all, what is the likelihood of lifelong treatment. Unfortunately, there are currently no data to answer this question prior to initiating therapy due to the lack of reliable predictors

of successful response to DAs therapy. It is assumed that the degree of response to DAs therapy usually becomes apparent within the first few months of therapy, and patients whose PRL levels rapidly decrease are more likely to meet the withdrawal criteria after two years of treatment or more. Secondly, the target levels of PRL have not been finally determined. Thirdly, what is the duration of DAs treatment after which prolongation of therapy is useless. Finally, the probability of success of a second DAs therapy attempt after a failed previous one has not been established [51].

Thus, despite many years of experience in the use of DAs, there remains a sufficient number of questions regarding the optimization of prolactinomas treatment in order to achieve a stable remission of the disease and prevent its relapses.

Promising methods of drug therapy for prolactinomas

Currently, studies are underway to find alternative drug treatments for prolactinomas. Primarily, this is due to the presence of aggressive and DAs-resistant prolactinomas, as well as cases of intolerance to currently available drugs.

There are only few data on the use of metformin in the treatment of prolactinomas. The application of this antidiabetic drug is based on its ability to reduce the proliferation of lactotrophic cells and stimulate their apoptosis both in rat xenografts and in human prolactinoma cell cultures. The need for further studies to assess the potential benefits of metformin in the treatment of prolactinomas, in particular those resistant to DAs, has been substantiated [15, 52].

Somatostatin analogs have also attracted the attention of clinicians as potential agents for the treatment of DAs-resistant prolactinomas. Research in this direction was due to the results of immunochemical mapping of somatostatin receptors (SSTR), which revealed the presence of all their types in prolactinomas. The established variability in SSTR expression with a predominance of SSTR subtype 5 (SSTR5) in prolactinomas seems to determine their sensitivity to somatostatin analogues [15, 52-53]. However, studies of first-generation somatostatin analogues have not demonstrated efficacy in DAs-resistant prolactinomas, and in vitro studies have shown conflicting results [53-54]. At the same time, clinical cases of the successful use of second-generation somatostatin analogs, in particular pasireotide, are presented. Thus, Coopmans E.C. et al. reported a patient with a very aggressive, DAs-resistant prolactinoma in whom long-acting release pasireotide (LAR) therapy was effective. The authors noted that pasireotide LAR treatment had clinical potential for selectively aggressive, DAs-resistant prolactinomas that express SSTR5 [55]. It is assumed that the advantage of pasireotide over first-generation drugs (octreotide and lanreotide) is due to its greater affinity for SSTR5. However, it seems likely that the SSTR expression profile in lactotrophic adenomas is not the only parameter associated with high variability in outcomes. Additionally, studies of the treatment of prolactinomas with somatostatin analogues included a small number of patients. Further studies are needed to clarify the place of these drugs in the treatment algorithm for DAs-resistant prolactinomas.

A number of researches have evaluated the potential role of selective estrogen receptor modulators in prolactinoma patients. According to Choudhary C. et al., the use of raloxifene in addition to DAs led to a more pronounced decrease in PRL levels [56]. At the same time, these authors didn't provide information about the dynamics of the size of the adenoma, and raloxifene was prescribed only along with DAs therapy. Overall, data on the use of selective estrogen receptor modulators in DAs nonresponsive prolactinomas are limited and inconclusive.

Studies are also underway to identify and evaluate the effectiveness of prolactinomas treatment with other groups of drugs, namely tyrosine kinase inhibitors, inhibitors of mammalian target of rapamycin, epidermal growth factor receptor antagonists [15, 52]. The results obtained are preliminary and require further research and careful analysis.

Conclusions

In conclusion, drug therapy with DAs as the preferred treatment for prolactinomas makes it possible to achieve the desired results (normalization of serum PRL levels and shrinking tumor size) in the vast majority of patients. However, despite the proven safety of agonists, the risk of side effects should be taken into account when prescribing these drugs. The dose and duration of therapy should be determined by the clinical course of prolactinoma and the patient's response to treatment. In patients intolerant to, or with contraindication for DAs, or patients with malignant or DAs-resistant tumors other options should be considered, namely surgery and radiation therapy. The presence of refractory to any of the applied methods of treatment and aggressive prolactinomas encourages the search for more effective drugs.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding resources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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