

Nowadays physicians are under economic pressure; therefore therapeutic decisions based on safety, efficacy, and the effectiveness of the medication also require economic analysis. The aim of this review is to discuss data concerning the cost-effectiveness of drug therapy in patients with hormonally active pituitary adenomas, namely growth hormone, adrenocorticotrophic hormone, thyroid-stimulating hormone-secreting pituitary adenomas, prolactinoma and pituitary incidentaloma.

In acromegalic patients using lanreotide is cheaper for health care payers and more convenient for physicians and patients because of the opportunity for self/partner injections, lower clogging risk and possibility of longer intervals between injections, while the efficacy is comparable with octreotide. Patients with prolactinomas should be treated with novel dopamine agonists, such as cabergoline or quinagolide, however, bromocriptine still remains a cheaper and almost as effective alternative.

There are no easy methods or algorithms, but in general, extracting the maximum value from the investment in treatment is essential.

Key words: pharmacoeconomics, lanreotide, octreotide, acromegaly, prolactinoma, ACTH-secreting pituitary adenoma.

Pharmacoeconomic aspects of the treatment of pituitary gland tumours

Jerzy Sowiński, Nadia Sawicka, Katarzyna Piątek, Ariadna Zybek, Marek Ruchała

Department of Endocrinology, Metabolism and Internal Medicine, Poznan University of Medical Sciences, Poland

Introduction

The prevalence of pituitary gland tumours is a matter of recent debate. In the meta-analysis based on data extracted from anatomical studies (including autopsies and imaging studies) pituitary adenomas were found in approximately 17% of the population [1]. However, a community-based, cross-sectional study performed among 81 149 subjects established the prevalence of pituitary adenomas as 77.6 cases per 100 000 inhabitants [2]. These results are supported by a population-based study recently performed in Malta which established a prevalence rate of pituitary gland tumours of 75.67 per 100 000 people [3]. The clinical relevance of pituitary adenomas depends on their size, location, hormonal hyper- or hyposecretion, and visual field loss. Their potentially serious effects require a diagnostic approach based on physical examinations, laboratory tests, and imaging procedures.

In general, a patient with a pituitary adenoma requires treatment of hormonal or visual abnormalities. Pituitary gland tumours resulting in hypersecretion may lead to hyperprolactinemia, acromegaly, and Cushing's disease. The treatment of choice for acromegaly and Cushing's disease is transsphenoidal surgery. Pituitary irradiation is also a therapeutic option when other methods are unsuccessful. Recently, modern medications are also available for treatment. Decisions concerning therapeutic modalities require an individual approach to every patient. However, nowadays physicians are under economic pressure, so therapeutic decisions based on safety, efficacy, and the effectiveness of the medication also require economic analysis. The aim of the paper is to discuss data concerning the cost-effectiveness of drug therapy in patients with pituitary adenomas.

Growth hormone-secreting pituitary adenoma

Acromegaly is a rare disease, which is characterised by an elevated level of growth hormone (GH). In the prevalent cases (nearly 99%), acromegaly is caused by benign, slowly growing pituitary adenoma, which produces excess GH. The annual incidence of acromegaly was estimated as 3.3 cases/million. The worldwide prevalence is approximately 60 per million. Although the incidence is not very high, the costs of lifelong care and treatment of acromegaly and its comorbidities are a noticeable burden for health care payers [4–6]. Due to a slow and insidious onset, the diagnosis is usually delayed and established 7–10 years after the first symptoms occurred [7]. This disease has a chronic and debilitating nature. Untreated disease reduces the life expectancy of patients by approximately 10 years. The most likely cause of death is cardiovascular failure [8, 9]. It is worth mentioning that the decreased GH level and appropriate for age insulin-like growth factor-I (IGF-1) concentration can potentially equalize the mortality between patients with acromegaly and the general population [4]. The patients quality of life (QOL) is decreased, not only due to treatment reasons but also because of immutable

changes including alternation of patient's appearance, which cannot be cured.

Acromegaly is accompanied by many others disorders. Impaired glucose tolerance occurs in 16–46% of patients. Diabetes mellitus prevalence is higher and is estimated at 19–56% of cases. Cardiovascular effects include: arterial hypertension, arrhythmia and concentric biventricular hypertrophy. At diagnosis, arthropathy occurs in up to 70%. Sleep apnoea, among which the obstructive type is the most frequent, brings an additional problem to the patients [4, 10].

Decisions concerning the strategy of management must be individualized for each acromegalic patient. There are some treatment options – surgery, radiotherapy, pharmacotherapy with somatostatin analogues, GH receptor antagonist, and dopamine agonists – which can be used as monotherapy or combined [4, 9]. The goal of medical management is to achieve optimal disease control which is defined as a mean GH level less than 2.5 ng/ml, GH level less than 1 ng/ml during an oral glucose tolerance test (OGTT), and age- and sex-adjusted normal IGF-1 level. However, when pegvisomant is administered, only the IGF-1 level remains as a biochemical marker of disease control [11, 12].

Pharmacological treatment of acromegaly

Among the various methods of treatment, pharmacological management plays an important role in controlling acromegaly. There is a wide range of therapeutic indications: as first-line therapy when the patient prefers to be treated using pharmacological medications and there are contraindications for surgery, and possibly, in very old age. As second-line therapy, when the effect after surgery is not satisfactory, and after radiotherapy until the curing effect occurs [12, 13].

Plöckinger noted that the criteria for the initiation of medical therapy should include not only the elevated markers of biochemical control but also the clinical activity of acromegaly and the patient's subjective activity of disease reported in the AcroQOL questionnaire. (The AcroQOL is an acromegaly specific questionnaire designed to assess the quality of patients' lives) [9, 12].

Primary medicaments used to control acromegaly are somatostatin analogues (SA). Current guidelines for acromegaly management recommend using SA when there is a low probability of cure by performing surgery; after surgery has failed and no biochemical control was achieved; before surgery, when there are severe comorbidities, which may be improved to perform surgery more safely (pre-surgical therapy is still a matter of debate); or after radiotherapy to achieve disease control, until the effect of radiotherapy is satisfactory [6, 12–14].

There are two slow-release SA approved by the U.S. Food and Drug Administration (FDA): lanreotide (Somatuline AUTOGEL® 60, 90, 120 mg) and octreotide (Sandostatin LAR® 10, 20, 30 mg) [15]. Numerous studies have been performed to compare them. Both lanreotide and octreotide have approximately 40–60% efficacy in achieving a biochemical control of acromegaly [12–14]. Moreover, both medications are well tolerated, lead to symptom relief and are effective in reducing tumor size by at least 20% in approximately 75%

of patients suffering from this disease [13, 14, 16]. So far, individual results of therapy are not predictable.

Many symptoms of acromegaly such as headaches, hyperhidrosis, sleep apnoea, arthritic pain and the occurrence of carpal-tunnel syndrome may be relieved during SA therapy [12]. Mortality is decreased due to positive effects on the cardio-vascular system and renal structure and function. Conversely, the quality of life (QOL) of patients, even with controlled disease is not improved [9].

Lanreotide and octreotide are synthetic analogues of somatostatin which are designed to connect with sst2 and sst5 with high affinity [6, 12, 15]. Due to the location of somatostatin receptors not only in the pituitary gland but also in the gastrointestinal tract and pancreas, side effects may be as follows: nausea/vomiting, cholelithiasis, abdominal discomfort, diarrhea, and reduced glucose tolerance. Moreover, injection site reactions such as erythema or swelling may occur. Local side effects can be avoided by warming drugs to room temperature before injection [9, 12, 13, 16].

The half-life of somatostatin is approximately 2 minutes, which is the reason why its use in treatment was rejected. SA have a noticeably prolonged half-life of up to 2 hours. Sandostatin LAR® and Somatuline AUTOGEL® due to a long-acting/slow release form are able to guarantee a suppressing level of SA in serum from 4 to 8 weeks respectively [12]. Pharmacokinetics studies on lanreotide showed that after an injection of depot formulation a stable linear release profile was observed. The mean absolute bioavailability was approximately 70% for all available doses. With increasing doses 60, 90 and 120 mg increasing lanreotide concentrations in serum were achieved. After single administration of Somatuline AUTOGEL® 120 mg the effective concentration level was observed in 56 days following the injection and it was confirmed in many clinical trials [6, 15, 17–22]. Recently the FDA has approved extended dosing intervals for lanreotide and now this SA is administered every 4 to 8 weeks [6]. Octreotide has pharmacodynamics which do not allow an extended dosing interval and the FDA has approved an interval of 4 weeks for this medicament [23].

Aspects of pharmacoeconomics in acromegaly treatment

There is a publication from 2006, which describes the whole cost of management in one patient with acromegaly. Orthopaedic surgery and dental care were included. The total expenditure was approximately \$ 1 000 000, from before the diagnosis up to 25 years later [8]. In Brazil a study comparing the costs of treatment using lanreotide and octreotide was carried out; however, it compared Somatuline LA® and Sandostatin LAR®. Somatuline AUTOGEL® was not available in Brazil in 2008 [24]. Marko *et al.* calculated the annual cost of treatment using SA. To compare the costs, the average dose of lanreotide was assumed as 103 mg/4 weeks and of octreotide as 24 mg/4 weeks. The annual costs of lanreotide and octreotide were \$ 41 216 and \$ 43 526, respectively. Somatuline AUTOGEL® was cheaper in use, at the same efficacy of 60% for both medications. The authors calculated that the illness is diagnosed at an average patient age of 40 years and if treated successfully, the illness does not shorten the

patient's lifetime. Assuming that the life expectancy in the USA is 78.3 years (data from 2010), the average time of treatment for a single patient is 38.3 years, and the costs are: \$ 1 578 567 if lanreotide is administered and \$ 1 667 052 if octreotide is used. The calculation was published in 2010 [9].

As described earlier, lanreotide and octreotide are very similar except for two very important things: the means of application and the opportunity to exceed the time interval between injections for lanreotide. Somatuline AUTOGEL® is a medication which is sold in ready-to-use prefilled-syringes with a low volume of liquid (0.3–0.5 ml) for deep subcutaneous injection [15, 16].

Adelman *et al.* presented results from their research which was designed to compare the administration of lanreotide and octreotide by nurses from Europe and the USA. All points were given on a 10-point scale. For nurses, the most important attributes of medicaments were: the confidence that patient received the full dose (9.5), high product efficacy (9.4), appropriate safety features (9.4), low risk of clogging (8.8) and convenient preparation and injection (8.8). Somatuline AUTOGEL® is in a device which is transparent and thus, enables a check as to whether the whole dose was delivered. 70% of nurses appreciated the fact that the device has an automated needle guard. During 3 years preceding the research, 69% of the nurses had experienced or had heard about clogging with SA; 99% (440/443) occurring when octreotide was being administered. The time of injection preparation and administration was approximately one minute vs. five and a half minutes for lanreotide and octreotide, respectively [23]. Less risk of clogging and a shorter time to prepare and perform the injection are the advantages which make Somatuline AUTOGEL® more convenient to use.

Considering the risk of clogging in the previously described research, Marty *et al.* compared the costs of administration of Somatuline AUTOGEL® and Sandostatin LAR® in France, Germany and the United Kingdom. During the research there were no clogging incidents when lanreotide was injected, whereas clogging occurred in 2.5% of administrations of octreotide. The authors calculated the costs per successful injection for both medicaments in varied doses. Somatuline AUTOGEL® was cheaper than Sandostatin LAR® by € 13–45, € 52–108 and € 127–151 for France, Germany and the United Kingdom, respectively. In France both drugs are the same price, as opposed to Germany and the United Kingdom, where lanreotide is cheaper. To compare cost savings, pounds were converted to euros based on the mean exchange rate in 2010. To calculate the annual cost savings for one patient Somatuline AUTOGEL® 90 mg and Sandostatin LAR® 20 mg were chosen. The results were as follows: € 356.4, € 929.5 and € 1457.5 for France, Germany and the United Kingdom, respectively. These numbers were also multiplied by the number of acromegalic patients treated with SA for each country. The annual cost savings for health care payers could be as high as € 948 236, € 3 176 618 and € 3 645 213 in France, Germany and the United Kingdom, respectively [15].

In contrast to octreotide, which is designed for intramuscular injections, lanreotide is adjusted for self-administration [12]. Approximately 20% of patients treated with SA,

if asked, were willing to accept self-injection and another 20% partner-injection [6, 13]. The efficacy and safety of self/partner injections were compared with injections performed by a healthcare professional and there were no significant differences [13, 25]. A prefilled syringe which requires no reconstitution, allows 100% of willing patients/partners to perform the injection correctly after being trained by a healthcare professional [16, 25]. After the end of the research, 88% of them preferred to continue the self/partner method of administration. The most important advantages of this form of treatment were: the opportunity to save time, lack of necessity to travel to hospital, and increased patient independence [13, 25].

From an economical point of view, less frequent clinical visits for injections could save € 65 per injection (data for Sweden 2012) [25]; indirect costs are also reduced. Patients do not need to spend time and money to travel to hospital. Currently, self-administration of Somatuline AUTOGEL® is approved in most European countries [16].

Pharmacodynamics of lanreotide allows the dose interval to be extended to even up to 8 weeks. Abrams *et al.* noticed the opportunity to reduce the costs of the management of patients with acromegaly. The authors exceeded the intervals between lanreotide injections for the patients with controlled disease up to 6 weeks. This provided the effectiveness of treatment in 78% of patients, although the weekly dose was diminished. The annual cost of treatment was decreased also. Even when the weekly dose was maintained (60 mg per 4 weeks was switched to 90 mg per 6 weeks), the annual cost decreased from € 11 316 to € 9 024 [22]. In the research reported by Plöckinger, Sandostatin LAR® 10, 20, 30 mg administered every 4 weeks was changed to Somatuline AUTOGEL® 120 mg injected every 8, 6 and 4 weeks, respectively. There were no significant differences in GH and IGF-1 concentrations between the medicaments. Hormonal control was achieved in 63.6% of patients with intervals between injections lasting for 8 and 6 weeks. Almost 50% of well-treated patients had injections less frequently than every 4 weeks. With prolonged intervals, the investigators and patients' preference for lanreotide grew. Among 71.4% patients treated with lanreotide every 8 weeks, investigators declared that they would use this frequency of administration in the future. In the group with an interval of 6 weeks, the preference was 54.5% vs. 9.1% for lanreotide and octreotide, respectively. Patients would choose lanreotide compared to octreotide in 57.1% vs. 14.3%, 63.3% vs. 18.2% and 11.8 vs. 41.2% in the 8, 6, and 4 weeks groups, respectively [12]. Carmichael *et al.* noted that among responders to SA who were not treated with the maximum dose of lanreotide, the interval between injections could be extended to 6 or 8 weeks using lanreotide 120 mg. The efficacy of management was similar in each group [16]. The results of the retrospective phase of Lanro-Study were published in 2012 [26]. Lanro-Study is a non-interventional study to assess administration of SA in Poland. All decisions made to change treatment (switching medications, doses and interval time) were not indicated in the study protocol; they only depended on the physicians. The calculated data indicated that lanreotide was injected on average every 5 weeks and

octreotide on average every 4 weeks. The average monthly cost of treatment using lanreotide and octreotide (in various doses and interval time) was € 987.95 and € 1479.23, respectively. Annual costs were € 11 855.40 and € 17 750.78, respectively. The annual cost savings connected with using lanreotide was € 5895.38. (The currency of Poland was converted to euro based on the mean exchange rate from January 2013) [26].

To sum up, using lanreotide is cheaper for health care payers and more convenient for physicians and patients because of the opportunity for self/partner injections, lower clogging risk and possibility of longer intervals between injections, while the efficacy is comparable with octreotide.

Pegvisomant (Somavert®) is the only GH receptor antagonist available in the management of acromegaly. Its mechanism of action is competing with GH for the GH receptor and binding with this receptor without activation. Pegvisomant decreases the IGF-1 level, but increases the GH concentration. Hence, to assess the effectiveness of treatment only the IGF-1 level can be used [9, 27–29].

Pegvisomant should be injected subcutaneously in doses of 20 mg per day in monotherapy. This medicament has a high efficacy, approximately 90–97%, in normalising IGF-1 concentration in serum [9, 12, 13, 28]. However, due to the high cost of treatment (\$ 68 438 annually) it is indicated for use as a third or fourth option for therapy, when others have failed. Administration of this medicament in addition to SA allows the weekly dose to be decreased to 60 mg once per week, but still, the costs of combined therapy are high (\$ 67 189 annually), when lanreotide 120 mg per 4 weeks and Pegvisomant 60 mg per week are administered [9, 12, 27, 28, 30].

Elevation of transaminase levels is a significant adverse reaction during treatment with pegvisomant, noted in more than 10% of patients. Besides that, headaches, vertigo, tremors, diarrhoea, nausea and pain at the injection site may occur. Pegvisomant has no effect on the gallbladder. It also does not decrease the tumour volume [12, 14, 27–29].

Dopamine agonists (DA) were the first medications used in the treatment of acromegaly. Oral administration and the low costs of treatment are the most important advantages of these drugs [12, 13].

Bromocriptine – the first generation of DA in monotherapy was ineffective; the disease was controlled in only 10% of patients [9, 14]. The second generation of DA includes: cabergoline and quinagolide. They are characterised by a longer half-life and fewer side effects than bromocriptine. The current guidelines indicate that only cabergoline should be used for acromegaly. Its efficacy, which was estimated in various studies, varies from 10% to 40% in cases of the most modest elevation of IGF-1 level [9, 12, 14].

Nowadays, the use of DA is limited to situations in which the patient prefers oral treatment, after surgery when elevated prolactin (PRL) accompanies elevated GH and IGF-1 levels, and as additional therapy to SA after multiple treatment failures. In the latter case, the normalized GH and IGF-1 occurred in as many as 50% of patients [9, 14].

Due to the GH receptor being blocked, the GH concentration in serum rises. Only the IGF-1 level is an indicator of the therapeutic efficacy of DA [12].

Side effects of DA are common. The most frequent are: nausea/vomiting, headaches, vertigo, asthenia, diarrhoea, vasospasm, oedema and sleeping disorders [9, 12].

Other pituitary adenomas

Other types of pituitary adenomas producing PRL, adrenocorticotropin (ACTH) or thyroid stimulating hormone (TSH) may also require medical therapy, including SA.

Prolactinoma

Prolactinomas are benign pituitary tumours arising from lactotroph cells of the anterior pituitary, representing almost 40% of all pituitary adenomas. PRL hypersecretion is responsible for many clinical symptoms in female patients, including infertility, menstrual irregularities, reduced libido and vaginal dryness, and in males, including sexual disorders, galactorrhoea and infertility. The so-called “mass effect” may be present, if the large tumour exerts pressure on surrounding tissues, resulting in visual field defects and headaches [31, 32]. Pharmacotherapy remains the widely considered first-line treatment modality for this disorder [33]. Therapeutic options also include observation, transsphenoidal or transcranial surgery and radiotherapy. Since PRL secretion is inhibited by dopamine via the dopamine D2 receptor, normalization of PRL levels is usually achieved with the use of dopamine agonists [31]. Available for over 28 years, this therapy in most cases not only reduces the PRL serum concentration, but also helps to restore gonadal function and decrease the tumor size. The first available and clinically used dopamine agonist was bromocriptine, which has also been the most extensively described and tried over the years. Others, with a longer half-life, such as cabergoline, pergolide and quinagolide have recently become available (in the case of pergolide and quinagolide – not in all countries) [32]. Although the new dopamine agonists are considerably more expensive due to their high efficacy and significantly lower percentage of adverse side effects, they are generally preferred to bromocriptine for the therapy of prolactinomas [34–36]. In a recently published systemic review and meta-analysis of randomized controlled trials comparing cabergoline with bromocriptine, cabergoline provided better rates of normalization for PRL levels and menstruation along with less adverse effects, such as nausea and vomiting and better tumor size reduction than bromocriptine [37]. Gillam *et al.* in 2006 noted that the normalization of the PRL level was achieved in about 70–80% of patients treated with bromocriptine, in 80–90% of those treated with cabergoline and in 70–100% of patients who were taking quinagolide [31]. Additionally, there is a significantly lower risk of recurrence after cabergoline therapy withdrawal in comparison with bromocriptine. Low doses needed to obtain the normal PRL serum concentration are also in favor of cabergoline [38]. As for drug resistance, it should be mentioned that more patients are resistant to bromocriptine than cabergoline, and 85% of bromocriptine-resistant subjects responded to cabergoline or quinagolide with a decrease in PRL level [35, 39]. On the other hand, some cases reported recently described cabergoline-resistant patients who positively responded when switched to high doses of bromocriptine. Although novel DA,

like cabergoline or quinagolide are generally preferred to bromocriptine in the treatment of prolactinomas, mostly because of their better tolerance profile and greater effectiveness, still bromocriptine remains a safe, relatively inexpensive, and well-tolerated alternative [40]. If the cost issue is present and a patient has to pay for the therapy out of his pocket, bromocriptine may and should still be considered, especially, when high doses of drug are needed to reach the normal PRL level. It has been reported that high doses of cabergoline may result in cardiac valve abnormalities, while no such side effects have been described regarding bromocriptine [41]. In conclusion, newly designed and clinically applicable DA are generally preferred in the pharmacotherapy of pituitary PRL-secreting tumours, however, bromocriptine still remains a cheaper and almost as effective alternative, which should be considered when therapy cost is an important issue for a patient.

Adrenocorticotrophic hormone-secreting pituitary adenoma

Pituitary-directed medical treatment of Cushing's disease, i.e. hypercortisolism caused by an ACTH-secreting pituitary tumour, is one of the available medical management types of this disease [32]. Chronic over-production of cortisol by adrenal glands is associated with various features such as metabolic syndrome, hirsutism, easy bruising, muscle weakness, cognitive dysfunction and mood alterations [42, 43]. Reported significant morbidity and increased mortality of patients with hypercortisolism indicates the need for sufficient disease control [44]. Pituitary surgery is widely recommended as a first-line therapy, with a median remission rate between 60 and 90%. However, a frequent tumour recurrence decreases the rate of successful therapy to 25%. It might be even lower in the case of invisible adenomas and macroadenomas [45, 46]. Other therapies applied in the past, such as radiotherapy or bilateral adrenalectomy (being so-called "last chance treatment") are considered to be not highly effective and have many adverse side effects. For that reason, the urgent need for an effective pharmacological intervention emerges. It might be used especially in case of acute complications of very high cortisol levels, as a balancing treatment before the surgery to prevent postoperative complications, or in patients with persistent or recurrent disease. It may also be applied as a temporary therapy that decreases serum concentration of cortisol as long as radiotherapy is not yet effective enough. Medical treatment should also be considered when the risk of operation is high, for example in case of macroadenomas, unfavorable location of tumors and general patient's surgery risk [46]. Available treatment modalities include pituitary-targeted, adrenal-blocking and combined therapy [32]. SA, octreotide and novel multireceptor-targeted pasireotide were evaluated for their efficacy in lowering the ACTH serum concentration. Although octreotide seems not to be helpful due to the lack of ACTH suppression, many performed studies have indicated the potential of pasireotide. Early reported data pointing to the significant suppression of cell proliferation and inhibition in ACTH secretion in primary cultures of human corticotroph tumors, suggested the possible advantages of this therapy [47, 48]. Since

then, many clinical trials have tried to evaluate long-term pasireotide treatment effects, reaching a significant and sustained reduction in ACTH and cortisol levels as well as improvements in blood pressure, BMI, weight and cholesterol in patients with Cushing's disease [49, 50]. To date, pasireotide has been accepted in Europe for the treatment of patients with Cushing's disease after unsuccessful surgery or for whom surgery cannot be undertaken, becoming the only approved medical therapy that treats the direct source of this disorder. Still, this kind of treatment may be considered only for certain group of patients with tumor recurrence or contraindications for surgical therapy, mostly because of the high cost and persistence of this kind of treatment. The surgical management offers, in not that low percentage of cases, a possibility of full recovery when the pharmacotherapy should be sustained for a long time. Additionally, the disadvantages of this kind of therapy include hyperglycemia-related adverse events in almost 73% of subjects, making it not only expensive but also not fully safe [49]. Other available reported treatment modalities are adrenal-blocking drugs including mitotane, etomidate, metyrapone, ketoconazole and mifepristone, and others, such as retinoic acid and PPAR- γ agonists. Interesting are the new possibilities of using dopamine agonists, especially combined with pasireotide. However, further evaluations should be performed to fully confirm the clinical usefulness of this kind of management.

Thyroid-stimulating hormone-secreting pituitary adenoma

Another rare tumour, accounting for less than 2% of pituitary adenomas is TSH-producing adenoma. Overgrowth of the thyrotroph cells stimulates the thyroid gland, causing hyperthyroidism [51]. Over the last few years, medical treatment of these tumours with somatostatin analogues has been proposed and introduced, even though the transsphenoidal surgery remains the first-line therapy. The treatment is based on the presence of somatostatin receptors on the cell membrane of thyrotrophs [52]. Available somatostatin analogues, octreotide and lanreotide, provided a decrease in TSH level in over 80% of cases. Possible future clinical trials with dopamine analogues – bromocriptine and cabergoline – result from detected coexistence of dopamine receptors type 2 on the same cells. The possible clinical correlation between these two receptors may be interesting and requires further evaluation [51, 53].

Pituitary incidentaloma

Nowadays, more and more pituitary tumours that are clinically non-functioning, are incidentally being found during central nervous system imaging in asymptomatic patients. It has been estimated that the majority of these tumours are actually adenomas producing some, sometimes quite small, amounts of hormones, such as gonadotropins, ACTH, GH, PRL or TSH, sometimes even more than one at a time. Due to the lack of clinical symptoms, they are called "silent" adenomas [54, 55]. The Endocrine Society recommends that patients should undergo a complete anamnesis and physical examination. In all patients, laboratory evaluations for

hormone hypersecretion and hypopituitarism are considered as needed. Additionally, all patients with incidentaloma abutting optic nerves or chiasm on MRI should undergo a formal visual field examination. If the tumour does not need to be surgically removed, a follow-up with a clinical assessment is indicated. Magnetic resonance imaging of the pituitary should be performed after 6 months in the case of macroincidentaloma, and after 1 year in the case of microincidentaloma. If the tumor does not change in time, less frequent subsequent imaging studies are suggested [56]. In the case of detected hormone hypersecretion or hypopituitarism, a proper therapy is indicated. However, there are no available data to support routine medical therapy in non-functioning pituitary tumours. The surgical treatment of non-functioning tumours should be considered, according to the newest guidelines, when visual abnormalities such as visual field defect, ophthalmoplegia or lesion abutting the optic nerve on MRI are present. Radiotherapy may be required as an adjunctive method of treatment in progressively growing remnants of the tumor [56, 57]. Still, appropriate evaluation and follow-up are essential in the management of pituitary incidentalomas. Due to increased sensitivity and frequency of performed central nervous system imaging, the cost of incidentally detected lesions constantly rises. In accordance with Randall *et al.*, who estimated the median cost of conservative management of pituitary incidentalomas, the average expense is \$ 6215.28 for males and \$ 6061.78 for females. This cost includes both primary and follow-up endocrine serum studies, imaging, and physician fees. All these all expenses have to be borne even if the tumor remains stable and requires no treatment [58]. The potential health benefits of early intervention in incidentally detected masses, which reduce the risk of hypopituitarism and neurological deficits should be evaluated in future guidelines.

Summary

Undoubtedly, pharmaceuticals and other therapeutic interventions have contributed to the progress in the healthcare of patients with pituitary adenomas. On the other hand, their costs are relevant. Surely, recent focus on reducing the amount of money spent on medical treatment does not translate directly to its costeffectiveness. Pharmacoeconomic evaluation must combine both economic and humanistic aspects of therapy. Potential benefits, the outcome of drug therapy and many other factors should be taken into account for when performing a pharmacoeconomic assessment.

Traditionally, physicians were focused on the clinical outcome of therapy. Nowadays, they are also involved in the economic aspects of therapy. There are no easy methods or algorithms, but in general, extracting the maximum value from the investment in treatment is essential.

The authors declare no conflict of interest.

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Address for correspondence

Nadia Sawicka

Department of Endocrinology, Metabolism and Internal Medicine
Poznan University of Medical Sciences
Przybyszewskiego 49
60-355 Poznań, Poland
e-mail: nyha@o2.pl

Submitted: 4.03.2013

Accepted: 18.04.2013