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Changes in the Prescribing habits of insulin in Bulgaria

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Abstract

BACKGROUND: The prescribing habits of insulin in Bulgaria at national level were analyzed during 1991-1994 and published in 1997 but the authorization of lots of new medicines and introduction of health insurance fund (NHIF) in 2000 changed treatment patterns.

OBJECTIVE: To analyze the prescribing habits of insulin and to compare them with the previous study as well as with the contemporary diabetes therapy.

METHODS: The sample of 29,281 prescriptions for 2,440 patients was collected in 2004 and systematized according to the share of the prescribed insulin by international nonproprietary name (INN), duration of action, trade names, manufacturer, dosage forms and number of prescribed defined daily doses (DDD). The pharmacotherapy cost was calculated on the basis of the average monthly cost of ambulatory prescription.

RESULTS: There is an increase with approximately 39,400 insulin users for 10 years period. During 2004 the consumption in DDD/per patient/per day was 1.46 DDD. The percentage of prescribed different action modes of insulin presented in DDD was 51% premixes (mix of short acting and long acting insulin), 17% short acting human insulin, 25% long acting human insulin, 7% human insulin analogues (genetic modified insulin).

In comparison with the study published ten years ago the changes in the prescribing patterns are in the complete replacement of the animal insulin with the human ones, introduction of the human analogues and changes in the internal structure of prescribing patterns pointing at switch mainly towards the intensified therapeutic regime.

The changes in the prescribing practice and introduction of the new insulin and therapeutic schemes lead to the increase in the cost of ambulatory drug therapy paid by the NHIF at 23,345,280 Euro in 2004.

CONCLUSIONS: The changes in the insulin prescribing could be evaluated as significant improvement in the therapeutic practice and close to the contemporary requirements but there is still delay in the introduction of the intensified therapy for all patients. The usage of insulin analogues also lag behind in comparison with the economically developed countries.

Key words: Prescribing habits, Diabetes therapy, Insulin prescribing, Pharmacotherapy cost, diabetes in Bulgaria

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Introduction

During the past decade a tremendous improvement has been observed in the diabetes therapy that changes the treatment patterns all over the world [1-7]. The new technologies in the development of human insulin products made diabetes therapy more convenient to the patients by mimic the physiological (basal and postprandial) insulin secretion and thus have decreased the frequency and severity of diabetes complication [1-10]. Combined with the constantly rising number of patients, diabetes nowadays reaches the epidemic proportion in economic, social and clinical terms [11-14]. Researches are also focusing on the impact of the new criteria for diabetes on the pattern of disease that make the distinction among the type of diabetes not so straightforward [15]. The necessity of constant monitoring and evaluation of the changes in treatment patterns is doubtless, especially in transition countries due to financial and clinical reasons [16-21].

The prescribing habits of insulin for diabetic patients in Bulgaria at national level were analyzed during 1991-1994 and published in 1997 but the authorization of lots of new medicines and the establishment of the obligatory health insurance system in 2000 changed treatment patterns [22-26].

The **objective** of this study is to analyze the prescribing habits of insulin and to compare them with the previous study, as well as, with the contemporary diabetes therapy. [22]

Three main questions have been discussed in this study:

- What are the main changes in the insulin prescribing?
- Have the changes in the insulin prescribing matched the contemporary antidiabetic therapy requirements?
- How have the changes in the insulin prescribing affected the cost of insulin therapy?

Materials and methods

Data sources for the study

The main data source was the electronic database of the National Health Insurance Fund in Bulgaria (NHIF) [23-24]. The database collects information at national level about the ensured patients, the average cost per prescription for different diagnoses, including diabetes, hospitalized patients and general health indicators. The sample of 29,281 prescriptions for 2,440 patients was collected in 2004. For the registered 74,880 insulin users a sample of 2000 patients is sufficient to provide representativeness within the 95% CI. It was selected every

30 patient from the NHIF database, thus reaching 2440 patients, and all the prescriptions per patient were collected. According to the current legislation every patient receives 1 prescription per month for a monthly therapy that's why the number of prescriptions is 29,281 (2440 x 12).

Prescribing practice analysis

The collected prescriptions have been systematised according to the prescribed insulin (human insulin and insulin analogues) by international nonproprietary name (INN), the mode and prolongation of action, insulin trade names, manufacturer, dosage forms and number of prescribed defined daily doses (DDD). The structure of the insulin prescribing has been compared with that of 10 years ago.

Cost of therapy

The cost of the insulin therapy has been calculated from the NHIF point of view on the basis of the average monthly cost of ambulatory prescription for insulin users paid by the fund on national, as well as, regional level. To evaluate the relevance among the standard and prescribing practice the cost of ambulatory prescriptions has been compared to the cost of all 15 theoretically possible intensified dosage regimes, according to the authorized for sale insulin in the country [27].

Results

The changes in the diabetes morbidity

According to NHIF database for 2004, there are 74 880 insulin users (type 1 and type 2 diabetic patients), which on average is 104 insulin users per 10,000 insured inhabitants. The total number of insured is 7,746,385. The regional separation of patients is irregular (from 39 to 187 per 10,000) and in general, the bigger regions account for the higher prevalence (Mean 103.64; SD 28.95; n=28). In comparison with the study published in 1997 (data for 1991-1994), there has been an increase of approximately 39,400 insulin users for the 10 years period. It is important to clarify that the Bulgarian population decreased from 8,9 to 7,8 millions during the period 1993 – 2004 [28]. In the previous study there were only type 1 diabetic patients on insulin therapy while nowadays the insulin has been prescribed also for type 2 diabetes in case of pure glycemic control.

Prescribing habits

Within the collected sample of 29,281 prescriptions in 2004 the monthly prescription (N = 12 months) of different dosage forms (vial, cartridge, pre-filled pen) is at mean of 3,149 (standard deviation SD 515) for long acting insulin ; premixes are 7,338 dosage forms (SD 1338); short-acting insulin is 1,350 dosage forms (SD 499) and for insulin analogues 980 dosage forms (SD 385) – Table I.

Table I Descriptive statistics for average monthly prescribed dosage forms of insulin action modes

		Long acting human insulin	Short acting human insulin	Premixes human insulin	Human insulin analogues
N	Valid	12	12	12	12
	Missing	0	0	0	0
Mean		3148,92	1350,83	7338,17	980,25
Std. Error of Mean		148,709	144,184	386,152	111,222
Median		3273,00	1168,50	7725,00	872,50
Std. Deviation		515,143	499,467	1337,668	385,285
Minimum		1617	524	3344	262
Maximum		3681	2201	8386	1734

*N valid – 12 months, 0 missing (no missing data)

The higher percentage (57%) of the prescribed premixes and long acting insulin (25%) is suggesting an existence of proportion of patients on conventional therapy (Table II). A little decrease of premixes prescribing was shown at the end of 2004. The national consultant on endocrinology considered most of the type 1diabetes patients (95%) to be on intensified therapeutic regime, so the conventional therapy should correspond to the type 2 diabetic insulin users [29]. There was also a decrease in the proportion of prescribed long-acting human insulin at the end of the year, as a consequence of increasing prescription of short- and long-acting analogues (Table II) [22].

Table II Insulin consumption in DDD and dosage forms per type of insulin in 2004

Type of Insulin	Total number of prescribed dosage forms	Relative share	Total number of DDD prescribed	Relative share
Long acting human insulin	39,262	25%	322,200	**25%**
Premix (human insulin)	88,058	57%	667,213	**51%**
Short acting human insulin	16,210	10%	214,485	**17%**
Human insulin analogue	11,763	8%	88,223	**7%**
Total	155,293	100%	1,292,121	100%

The insulin analogues possess marketing authorization in the country since recently and this can explain why their market share has been very low.

In 2004 for the observed sample of 2,440 patients were prescribed 51,684,840 IU (international units) of insulin, which is 1,292,121 DDD (insulin DDD = 40 IU) (Table II). Thus the consumption in DDD/per patient/per day was 1,46 DDD. In comparison, the previous published study evaluated the yearly needs of insulin as 532,754,000 IU that correspond to 13,318,850 DDD for 36,490 patients (1 DDD/per patient/per day).

The comparison among the the proportion of different modes of prescribed insulin in dosage forms and DDD reveals that the percentage of prescribed insulin in DDD and dosage forms have some small differences. The differences are 51% vs 57% for premixes (difference 6%), 17% vs 10% for short acting insulin (difference 7%) and 7% vs 8% for insulin analogues (difference 1%) and did not change for the long acting insulin (Figure 1). These differences could be explained with the fact that different dosage forms have different number of IU (vials 400 IU vs cartridges, pre-filed pens 300 IU) but in general the all dosage forms follow the recommended therapeutic standards for necessary quantity of insulin per patient.

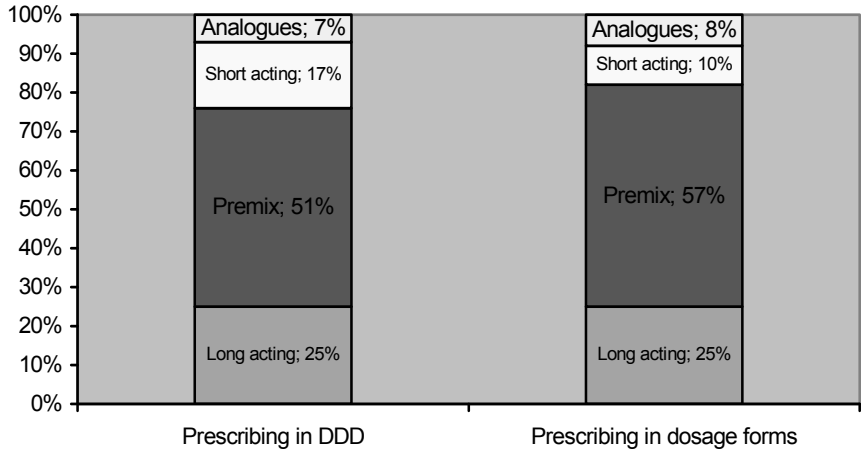

Figure 1. Proportion among different modes of prescribed insulin in dosage forms and DDD

Based on the comparison with the previous study, three main changes in the insulin prescribing patterns among 1994 and 2004 studies could be formulated. The first one is the complete replacement of the animal insulin that was domestically produced with the human ones. In 1992, 1993, 1994 the expenditures spent on animal insulin was respectively 85%, 92% and 38%. In 1993 the animal insulin, as a number of dosage forms, was prescribed in 58% of the observed prescriptions, the short acting insulin in 34% of prescriptions, in 8%-premixes and in 0.11% of prescriptions was prescribed the long acting insulin. The second change is the introduction in 2002 of the human insulin analogues that started to account for 8% of all prescribed dosage forms in 2004. The third change is in the internal structure of the prescribing patterns that is characterized by the constantly rising prescribing of intensified insulin therapy.

Considering the manufacturers, the relative market share of NovoNordisk is 85% of all prescribed dosage forms, followed by Eli Lilly with 10% and Sanofi-Aventis -5% (2004 year). Novo Nordisk became also a market leader, with near 60% market share in value terms, in 1994, after the replacement of the domestically produced animal insulin.

The cost of the insulin therapy

Insulin is 100% reimbursed by the NHIF for patients with type 1 and 2 diabetes. The average monthly cost paid by the NHIF in 2004 per insulin

prescription for all 28 country regions was 31.13 Euro (SD 2.43; min 25.94; max 34.74). At the same time the average monthly cost per reimbursable prescription (for all reimbursed by the NHIF diseases) was 7.77 Euro. It is obvious that the ambulatory cost of insulin therapy is 4 times higher than the ambulatory cost of all reimbursed diseases. On the basis of average monthly cost the yearly cost per insulin prescriptions per patient accounted for 373.56 Euro (31.31 Euro x 12 months).

This stimulates us to see what the expenditures will be if all patients are on intensified therapy or if the insulin analogues are included as a standard therapy for all patients. We have calculated that there could be 15 possible theoretical intensified therapeutic schemes if all compatible authorized for sale dosage forms are combined in the proportion 2/3 short acting to 1/3 long acting (27 IU + 13 IU = 40 IU DDD). Apart from them, 9 schemes include insulin analogues. The average yearly cost per patient using the theoretically possible scheme without insulin analogue is 327.85 Euro and 407.60 Euro if there is insulin analogue included in the scheme (Table III).

Table III The yearly patient cost of treatment with intensified therapeutic schemes

	The yearly cost of theoretical intensified treatment schemes without insulin analogues	The yearly cost of theoretical treatment schemes with insulin analogues
N Valid	6	9
Mean	327,8467	407,6011
Median	311,9150	421,2100
Std. Deviation	59,93955	62,78120
Variance	3592,749	3941,479
Minimum	266,09	318,62
Maximum	421,43	492,86

* There are 6 theoretical possible combinations of intensified schemes and 9 of schemes with analogues

Because of the small difference between the current yearly treatment cost per patient presented above (373.56 Euro) and the average yearly costs (367.73 Euro) of both theoretically possible types of treatment schemes, we can consider that the switch of all patients (type 1 and type 2) to intensified therapy

will not increase significantly the financial burden for the NHIF. The total cost for ambulatory insulin therapy for all diabetic patients paid by the NHIF in 2004 accounted for 23,345,280 Euro (74,880 x 373.56 =27972172,8 Euro). The maximum possible increase will be with 1,188,000 Euro (367.73 x 74,880 = 27535622,4 Euro;) yearly if all insulin users are switched to intensified therapy. If all insulin users are switched to therapy that include insulin analogues the respective treatment cost will be 30,521,088 Euro (407.60 Euro x 74,880) with increase of 7,175,808 Euro.

Discussion

The changes in the insulin prescribing in Bulgaria could be recognized as significant improvement in the therapeutic practice and close to the contemporary requirements but there is still a delay in the introduction of the intensified therapy for all diabetic patients, indicated for this therapy [11,12,23,25,30]. According to prescribing share of insulin analogues their introduction in the current therapy at national level lags behind in comparison to the economically developed countries.

Despite the existing proportion of patients with prescribed conventional regime, the yearly cost per patient paid by the NHIF is close to that of the intensified regimes even higher in comparison to schemes that do not include analogues. It seems that some patients are treated still old fashioned and it could increase the future long-term expenditures due to higher risk of complications [11,20]. Also, the conventional therapy is not recommended by the Bulgarian Endocrinology Society [23,25]. It is evidently necessary to be clarified the differences among the recommendations of the Endocrinology Society and the Health Insurance Fund medicines policy, for the different standards of the insulin therapy of diabetes 1 and 2 patients.

In our study we have as a major limitation the fact that the NHIF records all insulin users under the same disease ICD code E 10 Insulin-dependent diabetes mellitus (International classification of diseases (ICD) [37] without separation for type 1 and type 2 diabetes. Because of that we could not distinguish clearly which patients are on intensified or conventional therapy and to analyze the connection between the type of diabetes and the prescribing patterns. So we could not confirm that all type 1 diabetes patients were on intensified therapy and because of that we could not evaluate the real financial impact that the diabetes complication could have had [11,16,19]. On the other hand, 10 years ago only type 1 diabetic patients were insulin users and probably because of the pure control of diabetes in 2004 nowadays we have such a tremendous growth in the number of insulin users that also increases current

and future costs for the society. The other possible reason for the higher increase of the number of insulin users in this 10 year period could be the fact that the NHIF fully reimburses only insulin products and not the per oral hypoglycemic medicines that are partly reimbursed, and we could assume therefore., that physicians and diabetic patients with type 2 diabetes both prefer to switch on insulin in case of pure glycaemic control.

Conclusion

Analysis of the prescribing habits and evaluation of their impact on the cost of therapy is extremely important evidence for the establishment of the contemporary reimbursement policy and therapeutic standards for diabetic patients.

References

1. Worker C.1999. "Novel therapeutic strategies." Drugs Sep; 2(9):848-52.
2. McCormack JG. 2006 "Applying science to drug discovery." Biochem Soc Trans. Apr; 34 (Pt 2): 238-42
3. Philips JC, Radermecker R. 2005 "Update on new insulins." Rev Med Suisse. Aug 24;1(30):1936-8, 1940-1.
4. Klonoff DC. 2003 "Technological advances in the treatment of diabetes mellitus: better bioengineering begets benefits in glucose measurement, the artificial pancreas, and insulin delivery." Pediatr Endocrinol Rev. Dec;1(2):94-100
5. Fritsche A, Haring H. 2004 "At last, a weight neutral insulin?" Int J Obes Relat Metab Disord. Sep;28 Suppl 2:S41-6.
6. Handrean S., N. Younis. "Insulin detemir: a new basal insulin analogue Diabetes." Obesity and Metabolism Online Early doi:10.1111/j.1463-1326.2005.00487.x
7. Hermansen K., Fontaine P., Kukolja K, Peterkova V., Leth G., Gall AM. 2004."Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulin's (NPH and regular human insulin) in basal-bolus therapy for patient with type 1 diabetes." Diabetologia 47: 622-629
8. Coughlin C., M. Nelson. 2003. "Incidence and cost of medically treated hypoglycemia in diabetic patients enrolled in managed care." J Managed Care Pharm 9(2):185
9. Nordfeldt S, Jonsson D.2001. "Short-term effect of severe hypoglycemia in children and adolescents with type 1 diabetes. A cost-illness study." Acta Paediatr Feb; 90 (2):137-42.

10. Rossetti P, Pampanelli S, Fanelli C, Porcellati F, Costa E, Torlone E, Scionti L, Bolli GB. 2003. “Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime: a 3-month comparison between administration of NPH insulin four times daily and glargine insulin at dinner or bedtime.” Diabetes Care May; 26(5):1490-6
11. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. (UKPDS 33). Lancet. 1998 Sep 12;352(9131):837-53.
12. Lasker RD. 1993. “The diabetes control and complications trial. Implications for policy and practice.” N Engl J Med Sep30;329(14):1035-6.
13. International Diabetes Federation, St Vincent Declaration, Available from http://www.idf.org/e-atlas/home/index.cfm?node=71 (Accessed 17 February 2004)
14. Gruber W, Lander T., Leese B., Songer T., Williams R. 1997. “The Economics of diabetes and diabetes care: a report of the diabetes health economics study group. Eds. Geneva, International F-Diabetes Federation-World Health Organization” 1268—1275
15. Keen H. 1998 “Impact of new criteria for diabetes on pattern of disease.” Lancet Sep 26; 352 (9133):1000-1.
16. Licciardone JC, Kotsanos JG, Brinkman-Kaplan V, Cooper T, Jordan JE, Wishner KL. 1997. “Resource utilization and work or school loss reported by patients with diabetes: experience in diabetes training programs.” Am J Manag Care May; 3(5):777-82.
17. Allicar MP, Megas F, Houzard S, Baroux A, Le Thai F, Augendre-Ferrante B. 2000. “Frequency and costs of hospital stays for hypoglycemia in France in 1995.” Presse Med Apr 1;29(12):657-61.
18. Gray A, Raikou M, McGuire A, Fenn P, Stevens R, Cull C, Stratton I, Adler A, Holman R, Turner R. 2000. “Cost effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomised controlled trial (UKPDS 41).” BMJ May 20;320(7246):1373-8.
19. Caro J.J., A.J. Ward, J.A. O’Brien. 2002. “Lifetime costs of complications resulting from type 2 diabetes in the US.” Diabetes care 2002, (22); 3: 476-481
20. Wagner EH, Sandhu N, Newton KM, McCulloch DK, Ramsey SD, Grothaus LC. 2001. “Effect of improved glycemic control on health care costs and utilization” JAMA Jan 10;285(2):182-9.
21. Truter DI. 1998. “An investigation into antidiabetic medication prescribing in South Africa.” J Clin Pharm Ther 23: 417-22
22. Dimitrova Zl., I.Getov, A. D. Ivanova, G. Petrova. 1997. “Trends in Antidiabetic Drugs consumption in Bulgaria.” Journal of social and administrative pharmacy vol.14, 1, 1997, 52-56

23. NHIF, Country strategy for diabetes treatment and prevention, Ministry of health and National health Insurance fund, Bulgaria, available from: http://www.nhif.bg –(assessed January 2003)
24. NHIF. The yearly activities report for 2004. www.nhif.bg (assessed March 2006)
25. Bulgarian scientific endocrinology association. Methodological guideline for the treatment of Diabetes mellitus. Sofia. 2004
26. NHIF. National program "Endocrine diseases. Diabetes mellitus." www.nhif.bg/nrd/ nrd2000files/appendixes/assp3 (assesed January 2003)
27. Ministry of health, National Drug Price List 2003, available from: http://www.mh.government.bg (assessed December 2003)
28. NSI. National Statistic Institute of Bulgaria www.nsi.bg (assessed December 2004)
29. Tankova Tz. 2006. "Contemporary aspects of insulin therapy, Scientific Conference on Insulin and Diabetes." Bankya 24-25 March
30. Rosenstock J. 2004. "Basal insulin supplementation in type 2 diabetes; refining the tactics." Am J Med Feb 2;116 Suppl 3A:10S-16S.
31. International classification of diseases. ICD 10. Available at: www.who.int/classifications/apps/icd/icd10online (Accessed 2004)

Promene u navici propisivanja insulina u Bugarskoj

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Kratak sadržaj

U ranijem periodu urađena je analiza navika u propisivanju insulina u Bugarskoj u periodu 1991-1994. godine. Rezultati su publikovani 1997. godine. Od tada do danas došlo je do značajnih promena na tržištu i uvođenja novih preparata insulina. Takođe, 2000. je došlo do promena u Nacionalnom fondu zdravstvenog osiguranja. Zbog svega ovoga, napravljena je nova analiza. Prikupljeno je 29281 recepata koji su propisani za 2440 pacijenata tokom 2004. Urađena je statistička obrada podataka po različitim kriterijumima: INN, dužina delovanja, zaštićeno ime, proizvođač, farmaceutski obliki, broj prepisanih dnevnih doza.

Na osnovu ovakve analize, zaključeno je da je u proteklom periodu došlo do značajnih promena u navici propisivanja insulina u Bugarskoj. Ovakve promene su u skladu sa unapređenjem farmakoterapijske prakse, kao i sa trenutnim stručnim zahtevima. Treba raditi na uvođenju intenzivne terapije za sve pacijente kod kojih je ona opravdana. Primena analoga insulina i dalje zaostaje u poređenju sa ekonomski razvijenim zemljama. Treba navesti da je poslenjih deset godina u Bugarskoj došlo do značajnog porasta broja pacijenata koji koriste insulin (do 39 400 pacijenata).