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Long-term Follow Up of Patients Treated with D-Penicillamine in the Neonatal Period

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Abstract

Background: In neonatal therapy D-penicillamine (D-PA) was first recognized to have a potential benefit for neonatal hyperbilirubinemia in the early 1970s. Controlled, randomized clinical trials confirmed the effectiveness of D-PA in the treatment of haemolytic disease of the newborn and retinopathy of prematurity. The aim of this study was to explore potential long-term effects of D-PA by measuring health state of adults treated with this drug in the newborn period.

Methods: The self-perceived health and health related quality of life (HRQoL) have been investigated in a cohort of 23-36 years old patients using the EuroQol5D instrument. Self-administered questionnaires were mailed comprising EQ-5D instrument and questions on academic achievements, and presence of neurosensory impairments. The original cohort consisted of 1492 subjects. 518 participants returned the questionnaires, of which 32 had to be excluded due to incomplete responses. As reference, the data of the quality of life survey was used; this study was conducted in the early years of 2000, on a representative sample of 5503 members of a Hungarian population with average achievement [22].

Results: The occurrence of neurosensory disabilities and educational levels on HRQoL were also evaluated. The authors have examined the bias between those who returned complete questionnaires and those who returned incomplete questionnaires. In all age groups of the cohort the mean Visual Analogue Scale (VAS) score was remarkable higher, whereas the mean EQ-5D index was lower than the Hungarian age specific value, which discordance can be explained by the "disability paradox". Significantly more respondents with VLBW compared to their term peers reported to have neurosensory impairment and lower educational level.

Conclusions: The different characteristics of incomplete respondents can lead to large biases and through that way have great influence on HRQoL estimates. Focusing on the potential effects of D-PA, the following facts are verifiable: (i) adults survivors of prematurity can suffer from numerous pathological conditions. Consequently, their health/behaviors were significantly weaker (as it was expected) in comparison with the average population's examined [22] (ii) on the other hand, those adults who were born at term, their health/behaviors were better. This was, however, statistically not significant.

Keywords: D-penicillamine in the neonatal period; Long-term follow up; Health related quality of life

Abbreviations: ASD: Autism Spectrum Disorders; CTR: Controlled Clinical Trial; D-PA: D-Penicillamine; ET: Exchange Transfusion; EQ-5D-3L: EuroQoL-5 Dimensions-3 Levels; NHBI: Neonatal Hyperbilirubinemia; HRQoL: Health Related Quality of Life; QoL: Quality of Life; ROP: Retinopathy of Prematurity; SES: Socio-Economic Status; VAS: Visual Analogue Scale-Introduction

Introduction

D-penicillamine (D-PA) was first recognized to have potential benefit for neonatal hyperbilirubinemia (NHBI) in Department of Pediatrics of Medical School; Debrecen; Hungary in the early 1970 [1]. Later it was reported that D-PA significantly reduced the need for both initial and repeated exchange transfusions (ET) in AB0 hemolytic disease of the newborn [2]. During that time there was a remarkably low incidence of retrolental fibroplasia (RLF) in the infants treated with D-PA in their neonatal period [3]. In 1984-85 two single center; prospective randomized; controlled clinical trials (CTR) were conducted: two hundred and eleven preterm babies of 26 to 33 weeks of gestational age with birth weights <1500 g were enrolled. A 14-day course of D-PA treatment was associated with elimination of all stages of retinopathy of prematurity (ROP) in this cohorts of infants; and no apparent short or long-term toxicity resulted [4,5]. These studies were replicated in other institutes in Hungary; Poland; the US; India and Mexico [6-15]. It is important to note that there was no intolerance or short or long-term toxicity of the medication; in spite of the fact that in the newborn period D-PA was used 10-20 times higher doses than those used in adult. One year longitudinal follow up were done with a cohort of premature babies enrolled in the CTR to assess the long-term; potential adverse effects. Evaluation of the data showed that this drug has no side effects on either mortality or late development [16]. The same result was found in an onset cohort of children; ages 3-4 years who had NHBI and were treated with D-PA [17]. Relative beneficial outcome were observed in children with birth weight 1000 g or less at 8-11 years of age [18]. The aim of this article was to

investigate the self-perceived health and health related quality of life (HROQL) of adults (23-36 years of age) [19,20].

Methods

The authors had the approval by the institution's board (Regional and Institutional Research Ethics Committee of the Medical and Health Science Center of the University of Debrecen) to conduct this long-term follow up study. The study population consisted of 1492 infants born between 1 January 1978 and 31 December 1988 and admitted to the Department of Pediatrics of the University Medical School; Debrecen; Hungary. Detailed questionnaires were mailed to these adults. The questionnaire has comprised of EQ-5D instrument and questions on academic achievements; presence of neurosensory impairments and frequency of hospitalization in childhood (few/several/many times). The HRQoL was measured using the EuroQoL-5 dimensions-3 levels (EQ 5D-3L) instrument. It is one of the generic HRQoL measures developed by an international and interdisciplinary group of researchers (EuroQOL Group); including a descriptive profile and a single index value for health status. The validity of the EQ-5D-3L has been demonstrated for various diseases as well as for the general population [21]. Validated translations are available for more than 30 languages; including Hungarian [22]. The descriptive system covers five health domains (mobility; self-care; usual activities; pain/discomfort; and anxiety/depression). The standard and most widespread version of the EQ-5D-3L has three levels: no problems; some problems; severe problems. The VAS records the respondents self-rating for their current HRQoL on a graduated (0-100) scale; with higher scores for higher HRQoL. This scale provides a direct valuation of the respondents current health state; whereas the descriptive system can be converted into a weighted health status index by applying scores from the EQ-5D preference weights elicited from general population samples. These weights lie on a scale on which full health has a value of 1 and dead a value of 0 [23]. The questionnaire was identified only by a study code; providing the anonymity. Perinatal data regarding birth weights; gestational age at birth; and Apgar scores originated from the patients' medical records. In total; 518 participants returned the questionnaires. 32 patients had to be excluded due to incomplete responses. In the latter group 10 parental or institutional feedbacks has been identified since the recipients could not complete the questionnaires due to severe disabilities. In other 6 cases we became aware of death of the recipient trough the survey. They were very preterm with severe disabilities; 4 of 6 died in infancy; the remaining two subjects died later (19 month and 11 years of age) in an institution. The final sample thus consisted of 486 participants. Their characteristics are given in Table 1 the response rate was 34.86%.

Health judgement

"Health is a state of complete physical; mental; and social well-being not merely the absence of disease; or infirmity." -World Health Organization [24].

Age groups were categorised based on the HRQOL survey: 18-24; 25-34; 35-44 years for EQ-5D index [25] and the VAS [26]. According to Educational Qualifications respondents were classified into three groups: (1) with elementary school at best were coded as elementary qualification (2) those with secondary school were coded as intermediate qualification (3) and those with tertiary education were coded as high qualification [27]. In regard to the remarkable proportion of prematurity in our cohort and the high rate of very low birth weight we decided to analyze the effects of prematurity; particularly that of the very low birth weight (VLBW) infants; on HRQoL; including their educational level and the rate of neurosensory impairment [28,29].

The measure of respondents' health has been compatible with the World Health Organization's definition		
	N	%
Total sample	486	100
Gender		
Male	245	50.4
Female	241	49.6
Age groups		
<24 years	154	31.7
25-34 years	307	63.2
35<years	25	5.1
Maturity at birth		
Term birth	165	34
Premature birth	321	66
VLBW	82	16.9
32 weeks<	152	31.2
32 weeks ≥	169	34.8

Apgar scores at 5 minutes		
7 ≤	454	93.4
7>	32	6.6
Perinatal morbidities		
congenital anomaly	19	3.9
Educational level		
Elementary	65	13.4
Intermediate	253	52.1
High	167	34.4

Table 1: General characteristics of the study population.

Statistical analysis

EQ-5D index values were calculated by the coefficients for the European population as derived using the VAS method. Observed problem prevalence values were compared to the national reference using exact tests based on the binomial distribution. EQ-5D VAS and index estimates were compared to the national reference using two-sample t tests and median regression. EQ-5D VAS and index estimates were compared across levels of observed categorized variables using Wilcoxon's rank-sum tests or Kruskal-Wallis tests. Other continuous outcomes were also compared across categories using these methods or; alternatively; two-sample t tests or analysis of variance. Problem prevalence in EQ-5D dimensions was compared across levels of observed categorical variables using Fisher's exact tests.

Results and Discussion

The detailed data; as results of this long-term follow up study; are presented on Tables 1-5 below; in the same order as the questionnaires.

The aim of our research was to explore potential long-term effect of D-PA; by measuring health state of adults; who received DPA treatment in the newborn period. We investigated the self-perceived HRQL in our cohort using the EQ-5D instrument. In all age groups of the cohort the mean VAS score was remarkable higher than the Hungarian age specific value; the difference reached statistical significance in the group 25-34 years. In opposite the mean EQ-5D index was in all age groups lower than the Hungarian age specific value; the difference was statistically significant in the age group 18-24 years (p=0.0005). Table 1 shows the general characteristics of the study population.

The majority (66%) of participants in our cohort was born prematurely and 16.9% of those were VLBW infant. As it is well known; survivors of prematurity suffer from numerous pathological conditions: cerebral palsy; respiratory illnesses; behavioural problems; hearing and vision abnormalities; lower intelligence quotients; postnatal growth difficulties; mental retardation; attention disorders; developmental disability; autism spectrum disorders (ASD); attention deficit hyperactivity disorder; epilepsy and depression [30]. The discordance between the self-perceived health status (VAS score) and a single index value for health status (EQ-5D index) derived from 0 five health domains can be explained by the "disability paradox" which has been termed by Albrecht and Devleiger [31]. Using different methods for evaluation of QoL; data show that former premature young adults; even though they have impairments; declare their QoL to be quite high; comparable to their term peers **Table 2.** [32].

	Cohort			Control group			
Age groups	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**p-value**
18-24 years all	154	85.733	15.244	826	83.4	0.5	0.0594
Male	76	88.276	13.314	413	84.2	0.6	0.0093
Female	78	83.256	16.629	413	82.599	0.7	0.7284
25-34 years all	306	85.029	15.099	936	81.2	0.5	<0.0001
Male	157	84.133	16.632	468	81.7	0.7	0.0687
Female	149	85.973	13.284	468	80.099	0.1	<0.0001
35-44 years all	25	80.8	15.921	990	75.5	0.6	0.109
Male	12	81.25	16.804	495	76.099	0.8	0.3112
Female	13	80.384	15.74	495	75	0.8	0.241

Table 2: Comparison of VAS scores of the cohort with previous data of Szende *et al.* [22].

The mean VAS score of our cohort is greater than that of the youngest age group in Hungary; which age group has the highest VAS score not only in Hungary; but internationally too [22]. In our cohort the EQ-5D index was significantly lower only in the age group 18-24 years compared to the identical Hungarian age group; whereas in the other two age groups the difference was not remarkable **Table 3.**

	Cohort			Control group			
Age groups	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**p-value**
18-24 years all	154	0.8809	0.19579	826	0.937	0.005	0.0005
Male	76	0.89535	0.18329	413	0.942	0.007	0.0296
Female	78	0.86683	0.20745	413	0.932	0.006	0.0069
25-34 years all	306	0.91435	0.14783	936	0.922	0.004	0.3665

Male	157	0.90757	0.16274	468	0.935	0.005	0.0364
Female	149	0.92149	0.13047	468	0.90799	0.007	0.2089
35-44 years all	25	0.867	0.18523	990	0.897	0.005	0.426
Male	12	0.90441	0.14745	495	0.90099	0.007	0.9375
Female	13	0.83246	0.21447	495	0.889	0.006	0.3606

Table 3: Comparison of EQ-5D indexes of the cohort with previous data of Szende *et al.* [22].

The interpretation of that phenomenon is still uncertain. Both the mean VAS score and the mean EQ-5D index were lower by respondents with premature birth compared to the identical data of respondents with term birth; but the difference was not statistically significant. Significantly more respondents with prematurity (p=0.025); especially those with ELBW (p=0.016) reported to have a neurosensory impairment. Lower educational level was detected by respondents with prematurity (p=0.249); the difference reached statistical significance by respondents with VLBW (p=0.008). In our cohort statistically significant decrease of VAS score and EQ-5D index values were found for persons with neurosensory impairment. Recent research similarly to our results showed important effect of neurosensory impairments on HRQoL Table 4 [33].

	Study sample	Control group	p-value
Age	**18-39 years**	**18-39 years**	

	% of any problems	% of any problems	
Walking			
Total sample	6.2	3.7	0.0076
Self-care			
Total sample	3.3	0.7	0.0001
Daily routine			
Total sample	5.3	2.9	0.004
Pain/discomfort			
Total sample	14.2	18.4	0.0163
Depression/ anxiety			
Total sample	28.2	21.9	0.0012

Table 4: Comparison of problems reported in health domains of EQ-5D-3L of the cohort with previous data of Szende *et al* [22].

In this study in all health dimensions significantly more problems were reported in lower qualification groups than in higher educated groups and respondents in lower qualification groups had significantly lower VAS score and EQ-5D index values in **Table 5.**

	VAS score			EQ-5D index			
Educational level	**N**	**Mean**	**SD**	**p-Value**	**Mean**	**SD**	**p-value**
Elementary	65	76.476	21.273	0.0007	0.81881	0.2206	0.0001
Intermediate	252	86.003	14.877	0.0951	0.91158	0.1526	0.3568
High	167	87.113	11.04	0.4992	0.92204	0.1457	0.0647

Table 5: VAS scores and EQ-5D indexes according to educational levels.

The negative effect of lower educational level was more pronounced in men both in the five health domains and in the health state scores. Educational level is one of the most important indicators of socioeconomic status (SES) **Table 6.**

		VAS score			EQ-5D index		
	N	**Mean**	**SD**	**p-Value**	**Mean**	**SD**	**p-Value**
Full term	165	85.915	13.849	0.5178	0.91634	0.15239	0.1368
Premature	320	84.581	15.841	0.5178	0.8936	0.17373	0.1368
VLBW	82	83.702	16.681	0.4188	0.90751	0.17623	0.3905

Table 6: HRQoL according to maturity.

Lower educational level was detected by respondents with prematurity (p=0.249); the difference reached statistical significance by respondents with VLBW (p=0.008). The association between lower SES and lower HRQoL is well known; it was verified by several studies worldwide [34,35]. Similary to our results Mielck et al. [36] reported more pronounced association between HRQoL and educational level in men. That observations need confirmation in future research. Our results represent only one third of the original cohort. Both non responses and partial responses decrease the statistical power of this study partly by reducing the sample size. On the other hand the different characteristics of non and incomplete respondents can lead to large biases and through that way have great influence on HRQoL estimates [37]. Based on the analysis of our data in the subgroup of incomplete respondents the rate of VLBW subjects; the frequency of congenital anomalies and neurosensory impairments was significantly higher; whereas the educational level was also significantly lower compared to complete responders **Table 7.**

	Complete respondents	Incomplete respondents	p-value
	rate%	rate%	
Total sample	93.8	6.2	
Birth characteristics			
Premature birth	66	76.7	0.3182
VLBW	16.9	63.2	0.0012
Health state			
Central nervous system disorder	1.5	6.3	<0.0001
Neurosensory impairment	5.2	31.3	<0.0001
Congenital anomaly	6.6	57.1	<0.0001
Educational level			
Elementary	13.4	44	0.0003
Intermediate	51.9	44	0.539
High	34.4	12	0.0273

Table 7: Comparison of characteristics of participants with complete and incomplete response.

These characteristics explain that in the subgroup of incomplete respondents significantly more problems were reported in all EQ-5D dimensions; and significant decrease of VAS score and EQ-5D index values were detected. The magnitude of the biases was large in that subgroup. Long term follow up studies generally suffer from biases originated from attrition [38]. Postal questionnaire follow up compared to face-to-face interviews results in further losses. Dropout subjects may have different characteristics relating for instance to cognitive functions; impairments and SES [39]. In a recent research Verrips et al. [40] evaluated changes in HRQoL in a cohort of VLBW or very preterm (<32 weeks of gestation) children between ages 14 and 19; and identified correlates of HRQoL at age 19. Their results represented less than half of the original cohort; and their data showed non-participants had lower SES and more handicaps and also that; in participants; these factors were negatively related to HRQoL. We agree with the hypothesis of Verrips et al.; results based on the available data may show only a positive tip of the iceberg; due to loss to follow-up. This study has a number of limitations. Beside the remarkable dropout ratio as referred to above our cohort was hospital based and selected on the basis of neonatal DPA treatment. According to the formerly used indication of neonatal DPA administration significant part of our cohort was preterm subject.

Conclusion

Despite its limitations our study is unique; because research to explore health state of adults; who were treated with D-PA in the neonatal period has not been performed before to our knowledge. Moreover our study provides valuable clinical data regarding the late outcome for premature infants from the first decade of neonatal intensive care in Hungary. The cohort of this study includes remarkable number of adult born preterm and VLBW subject respectively. Based on the subgroup analysis significantly more respondents with VLBW compared to their term peers reported to have neurosensory impairment and significantly lower educational level was detected by those with VLBW. In our cohort statistically significant decrease of VAS score and EQ-5D index values were found for persons with neurosensory impairment as well as lower qualification. At the same time those adults who were born at term; their health/behaviors were markedly better. This was; however; statistically not significant. The reported rate of childhood hospitalizations increased with decreasing gestational age; but the difference did not reach statistical significance.

Addendum

This study embraces only 10 years of the >40 years history of D-PA therapy in the neonatal period [41]. Two comments; with not so convincing scientific evidence; rather than interesting observations are as follows: (1) it was our privilege to follow a number of children who are now adults; including sons and daughters of our relatives; colleagues; close friends. They are now highly educated persons working in health care (mostly as physicians); bank; computer; music-art; diplomacy (knowledge of 4 languages) and building industry; et cet. (2) During long-term follow up studies (3-36 years, N=550) we found only 1 ASD in the children and adults who were treated with D-PA in their neonatal period patients so far ["New Prevalence Numbers for 2014: 1 in 45 US Children have autism" [42]. This 30 years old male patient was born as a premature infant and had a serious hyperbilirubinemia. He was treated with D-PA without success; because exchange transfusion was necessary to perform [43].

References

1. Lakatos L, Kover B (1974) D-Penicillamine therapy in the neonatal hyperbilirubinaemias. A preliminary report. Hungarian J Med 115: 307-11.

2. Lakatos L, Kover B, Oroszlan G, Vekerdy Z (1976) D-penicillamine therapy in ABO hemolytic disease of the newborn infant. Eur J Pediatr 123: 133-7.
3. Lakatos L, Hatvani I, Karmazsin L, Alberth B, Oroszlan G (1980) Does D-penicillamine decrease the incidence of retrolental fibroplasia? A preliminary report. Hungarian Ophthalmology 117: 9-12.
4. Lakatos L, Hatvani I, Oroszlan G, Balla G, Karmazsin L et al. (1986) Controlled trial of D-Penicillamine to prevent retinopathy of prematurity. Acta Paediatr Hung 27: 47-56.
5. Lakatos L, Lakatos Z, Hatvani I, Oroszlan G (1987). Controlled trial of use of D-Penicillamine to prevent retinopathy of prematurity in very low-birth-weight infants. Physiologic foundations of perinatal care 2: 9-23.
6. Dolinay T, Szombathy G, Lakatos L, Kover B (1974) Use of D-Penicillamine in the therapy of neonatal hyperbilirubinemia. Orv Hetil 115: 1431-2.
7. Korányi G, Kovács J, Voros I. (1978) D-penicillamine treatment of hyperbilirubinaemia in preterm infants. Acta Paediatr Acad Sci Hung 19: 9-16.
8. Szuts A, Lechner E (1999) ABO haemolytikus betegség konzervatív kezelése. Gyermekgyógyászat 50: 67-9.
9. Nagy A; Felszeghi E (2000) Per os D-Penicillaminnal és fototerápiával sikeresen kezelt Rh-isoimmunisation. Gyermekgyógyászat 51: 81-3.
10. Rokicki W (1989) D-Penicillamine - A New Drug For Prevention And Treatment In Neonates. Polish - Przeg Ped 19: 229-33.
11. Christensen RD, Alder SC, Richards SC, Lambert DK, Schmutz N, et al. (2007) D-Penicillamine administration and the incidence of retinopathy of prematurity. J Perinatol 27: 103-11.
12. American Academy of Pediatrics, Commitee on fetus and newborn. (1963) Pediatrics 31: 878-80
13. Phelps DL, Lakatos L, Watts JL (2001) D-Penicillamine for preventing retinopathy of prematurity in preterm infants. Cochrane Database Syst Rev 1: CD001073
14. Qureshi MJ, Kumar M (2013) D-Penicillamine for preventing retinopathy of prematurity in preterm infants. Cochrane Database Syst Rev 9: CD001073.
15. Aldana-Valenzuela C. Personal communication during a lecture-tour in Mexico (2008).
16. Vekerdy-Lakatos S, Lakatos L, Oroszlán G, Itzes B (1987) One year longitudinal follow-up of premature infants treated with D-Penicillamine in the neonatal period. Acta Paediatr Acad Sci Hung 28: 9-16.
17. Vekerdy ZS, Lakatos L, György I (1980) 3-4 years follow-up of children treated with D-Penicillamine in the neonatal period. Gyermekgyógyászat 31: 45-52.
18. Vekerdy-Lakatos Z, Lakatos L, Ittzes-Nagy B (1989) Infants weighing 1000 g or less at birth. Outcome at 8-11 years of age. Acta Paediatr Scand Suppl 360: 62-71.
19. Lund LK, Vik T, Lydersen S, Løhaugen GC, Skranes J, et al. (2012) Mental health quality of life and social relations in young adults born with low birth weight. Health Qual Life Outcomes 10: 146-58
20. Pyhälä R, Wolford E, Kautiainen H, Andersson S, Bartmann P, et al. (2017) "Self-reported mental health problems among adults born preterm: a meta-analysis". Pediatrics 139: e20162690.
21. EQ-5D-3L | Available modes of administration.
22. Szende A, Nemeth R (2003) Health-related quality of life in the hungarian population. Orv Hetil 144: 1667-74.
23. Rabin R, de Charro F (2001) EQ-5D: a measure of health status from the EuroQol Group. Ann Med 33: 337-43.
24. Constitution of WHO: principles definition of health-WHO
25. Handbook of Disease Burdens and Quality of Life Measures. (2010) Editors: Preedy VR; Watson RR; Chapter 5: Gusi N, Olivares PR, Rajendram R The EQ-5D Health-Related Quality of Life Questionnaire. Springer New York; Online ISBN 978-0-387-78665-0, 87-99.
26. Wewers ME, Lowe NK (1990) A critical review of visual analogue scales in the measurement of clinical phenomena. Res in Nurs Health 13: 227-36.
27. Johnstone M, Lee C (2009) Young Australian Women's Aspirations for Work and Family: Individual and Sociocultural Differences. Sex Roles 61: 204-20.
28. Cole C, Hagadorn J, Kim C, Binney G, Casey P, Fiascone J, et al. (2002) Criteria for Determining Disability in Infants and Children: Low Birth Weight. Summary. Evidence Reports/Technology Assessments; No. 70. Agency for Healthcare Research and Quality (US).
29. Hack M, Flannery DJ, Schluchter M, Cartar L, Borawski E, et al. (2002) Outcomes in Young Adulthood for Very-Low-Birth-Weight Infants. N Engl J Med 346: 149-57
30. Kodjebacheva GD, Sabo T (2016) Influence of premature birth on the health conditions; receipt of special education and sport participation of children aged 6-17 years in the USA. J Public Health 38: e47–54
31. Albrecht G, Devleiger PJ (1999) The disability paradox: high quality life against all odds. Soc Sci Med 48: 977-88.
32. Saigal S (2014) Functional outcomes of very premature infants into adulthood. Semin Fetal Neonatal Med. 19: 125-30.
33. Saigal S, Ferro MA, Van Lieshout RJ, Schmidt LA, Morrison KM (2016) Health-related quality of life trajectories of extremely low birth weight survivors into adulthood. J Pediatr 179: 68-73.e1
34. Luo N, Johnson JA, Shaw JW, Feeny D, Coons SJ (2005) Self-reported health status of the general adult U.S. population as assessed by the EQ-5D and health utilities index. Med Care 43: 1078-86.
35. König HH, Bernert S, Angermeyer MC, Matschinger H, Martinez M, Vilagut G, et al. (2009) Comparison of population health status in six european countries: results of a representative survey using the EQ-5D questionnaire. Med Care 47:255-61.
36. Mielck A, Vogelmann M, Leidl R (2014) Health-related quality of life and socioeconomic status: inequalities among adults with a chronic disease. Health Qual Life Outcomes. 12: 58.
37. Coste J, Quinquis L, Audureau E, Pouchot J (2013) Non response; incomplete and inconsistent responses to self-administered health-related quality of life measures in the general population: patterns; determinants and impact on the validity of estimates - a population-based study in France using the MOS SF-36. Health Qual Life Outcomes. 11: 44-58.
38. Cooke RW (2004) Health, lifestyle, and quality of life for young adults born very preterm. Arch Dis Child 89: 201-6.
39. Wolke D, Söhne B, Ohrt B, Riegel K (1995) Follow-up of preterm children; important to document dropouts. Lancet. 345: 447.
40. Verrips G, Brouwer L, Vogels T, Taal E, Drossaert C, et al. (2012) Long term follow-up of health-related quality of life in young adults born very preterm or with a very low birth weight. Health Qual Life Outcomes. 10: 49.
41. Lakatos L, Balla G (2016) D-Penicillamine in the neonatal period. : Chelation as neuroprotectant in the neonatal period. A book. LAMPERT Academic Publishing ISBN-13: 978-3-659-86459-9.
42. Latest Autism statistics - Talk about curing Autism (TACA) (2017).
43. Lakatos L, Pataki I, Balla G, Vekerdy-Nagy Z (2017) Penicillamine - preventing or "curing" autism spectrum disorders in the neonatal period?. EC Paediatrics 6: 51-2.