

*medicinski tretman***NOVI NI VO TERAPIJATA NA  
AUTIZMOT***Vladimir E. TRAJKOVSKI*Filozofski fakultet  
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U{te nema specifi~ni lekovi vo tretmanot na autizam. Golem broj metodologije bile iskoristeni vo evaluacijata na bezbednosta i efikasnost na farmakolo{ki te tretmani kaj decata i vozasni te so autizam. Vo studijete se osobeno zna~ajni dva parametra, a toa se postoeve "slepi #i kontrolni grupi. Studijete so najvisok kvalitet gi koristat dvete-"slepã#i kontrolna procedura podjednako. Tie treba da bidat izvedeni vo pove}e mesta i da so dr`at gol em broj subjekti.

I strauvawata {to gi procenuvaat lekovite, predlo`eni vo tretmanot na autizam, postojano se vo porast. Zabele`li vo e zabrzano istaknuvawe na potrebata od testirawe na lekovite i podobra informacija za tretmanite, koja treba da bide pobrzo dostapna otkolku vo minatoto. Vo ovoj trud }e bidat diskutirani slednite vidovi lekovi i vidovi terapii: mo`nidni tretmani so lekovi-kako {to se oksitocin, tetrahydrobiopterin i ampakini te, hormonska terapija, antigabina terapija, vitaminskite terapii, dimetilglicinot, alfa lipoi~nata kiselina i terapiite so dijeta.

**Klu~ni zborovi:** autizam, terapija, studii.

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*medical treatment***INOVATIONS IN THERAPY OF AUTISM***Vladimir E. TRAJKOVSKI*Faculty of Philosophy  
Institute of Special Education and Rehabilitation**Abstract**

There is no specifically marked medicine for the treatment of autism. A number of approaches have been used in evaluating the safety and efficiency of pharmacological treatments of both children and adults with autism. Two study parameters are particularly important, the presence of "blind" and control groups. The highest quality studies utilize equally "blind" and control procedures as well. They have to be performed at multiple sites with a large number of subjects.

Research evaluating medicine proposed for treatment of autism, is on the increase. There is accelerated emphasis on medicine testing and better information on treatments should be more available than in the past. In this article, the following classes of medicine and therapies will be discussed: possible future medicine treatments - such as oxytocin, tetrahydrobiopterin and ampakines, hormone therapies, anti-yeast therapies, vitamin therapies, dimethylglycine, alpha lipoic acid and diet therapies.

**Key words:** autism, therapy, studies.

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## **Voved**

Autizmot pretstavuva pervazivno razvojno naru{ uvawe { to se javuva vo ranoto detstvo i se karakterizira so naru{ uvawa vo socijalnata i komunikativnata sfera, namaleni interesi i povtoruvako odnesuvawe (1).

Autizmot bi trebalo da bide dijagnostificiran do voзраст od 18 meseci. Ranata intervencija e mnogu va`na za podobar ishod. Terapiite vkluuvaat defektolo{ki tretman, logopedski tretman, okupacijska i bihejvi oralna terapija. U{te nema specifi~ni lekovi vo tretmanot na autizmot. Nema farmakolo{ki tretman {to bi poka`al markantno podobruvawe na jadrovite simptomi kako {to se socijalno, govornoto i kognitivnoto naru{uvawe kaj autizmot. Medicinski te vidovi terapii ~esto im ovozmo`uvaat na autisti~ni te indivi dui da `iveat nadvor od institucii te (2).

Istra`uvawata {to gi procenuvaat lekovi te i koi bile predlo`eni vo tretmanot na autizmot, postojano se vo porast. Zabele`livo e zabrzano istaknuvawe na potrebata od testirawena lekovi te i podobra informacija za tretmanite {to treba da bide pobrzo dostapna otkolku vo minatoto.

**Celta na ovoj trude** da prika`e neкои novi vidovi biomedicinski tretmani {to se koristat vo svetot.

### **1. Vidovi tretmani koi mo`e da se koristat vo idnina**

**Oksitocinot** e mal peptiden hormon, sostaven od devet aminokislini {to, normalno, se sekretira od majkata pri raaweto i doeweto na deteto. Vo animalnite studii bilo najdeno deka toje asociiran so socijalno odnesuvawe. Koga bil inektiran kaj `ivotnite, oksitocinot go zgolemi lni vnoto socijalno odnesuvawe, a koga bile dadeni negovi blokatori, toga{se namalilo nivnoto socijalno odnesuvawe i bila izbegnuvana socijalnata interakcija (3).

Podatocite kaj ~ovekot uka`uvaat na mo`na uloga na oksitocinot vo tretmanot na autisti~ni te simptomi.

## **Introduction**

The autism is pervasive developmental impairment that occurs in early childhood characterized with impairments in social and communicative sphere, reduced interests and repeated behavior (1).

The autism has to be diagnosed up to the age of 18 months. Early intervention is very important for better results. The therapies include special education and rehabilitation treatment, treatment of speech therapist, occupational and behavioral therapy. There is no specifically marked medicine for the treatment of autism. There are no pharmacological treatments, which indicate noticeable improvement of core symptoms such as social, speech and cognitive impairments of autism. Medical therapies often enable autistic individuals to live outside the institutions (2).

Research evaluating medicine proposed for treatment of autism, is on the increase. There is accelerated emphasis on medicine testing and better information on treatments should be more available than in the past.

**The aim of this article** is to present some new types of biomedical treatments used in the world.

### **1. Treatments that could be used in future**

**The oxytocine** is a tiny peptide hormone consisted of nine amino acids that mother normally secretes during child's birth and breast-feeding. The animal studies associate it with social behavior. When oxytocine was injected in animals, it increased their social behavior, and when its blockers were used then their social behavior and social interaction were reduced (3).

Human data show that the role of oxytocine in treatment of autistic symptoms is possible.

Vo edna studija bile i spituвани koncentracii te na oksitocin kaj 29 deca so autizam i 30 izednani po voзраст deca bez autizam. Decata so autizam i male poniški ni voa na oksitocin. Decata bez autizam poka`ale poviški ni voa so tekot na voásta, { to ne bilo slu~aj i kaj decata so autizam (4). Hollander i sor. napravile dvojno-slepa, placebo-kontrolirana studija na infuzija so oksitocin kaj adulti, dijagnostici rani kako autizam ili Asperger-ov sindrom. Tie zabele`ale namaluvawe na repetitivnoto odnesuvawe kaj 13 od 15 nabuduвани subjekti koi primile infuzija so oksitocin. Za razlika od niv samo 6 od 15 ~lenovi na placebo-grupata poka`ale namaluvawe na repetitivnoto odnesuvawe. Ne bile najdeni razliki vo nesakanite efekti me|u oksitocinskata i placebo-grupata. Ovie avtori uka`ale i na toa deka socijalnoto odnesuvawo`e da se podobri so oksitocinski otretman (5).

**Tetrahydrobiopterin (R-BH4)** e drug lek, istra`uvan vo tretmanot na autizmot. Toje hemisko soedinenie e potrebno za sinteza na neurotransmiterite, kako { to se serotoninot i drugite kateholamini. Vo edna otvorena pilot-studija { est predu~ili { ni deca so autizam bile tretirani so R-BH4. Roditelite soop{tile za podobruvawe vo kontaktot so o~ite, vo`elbata za interakcija i vo brojot na zborovi. PET-skenovite poka`ale 10% zgol emuvawe vo vrzuvaweto na dopamin D2 receptorot vo n. caudatus i vo putamen. N. caudatus i putamen se komponenti na sistemot na bazalni te ganglii i se polywa dlaboko vo mozokot { to primaat razli~ni impulsi od korata na mozokot, gi procesiraat tie impulsi i gi vra}aat do motornata kora. N. caudatus vlijae na motivacionite procesi, a putamen e povrzan so nesvesnata koordinacija na ednostavnoto senzomotorno odnesuvawe. Bi dej}i samo edna studija e sprovedena za ovoj lek, neophodni se i drugi istra`uvawa za da se proceni negovata bezbednost i efikasnost (6).

One study examined the concentrations of oxytocine in 29 children with autism and 30 children at the same age without autism. The children with autism had lower level of oxytocine. The children without autism showed higher level while growing up which was not the case in children with autism (4). Hollander et al. made double "blind", placebo-controlled study of infusion with oxytocine in adults, diagnosed as autism or Asperger syndrome. They noted declined repeating behavior in 13 of 15 observed subjects who received infusion with oxytocine. Contrary to them, only 6 of 15 members of placebo group showed declined repeating behavior. There were no differences of unwanted effects between oxytocine and placebo groups. These authors indicated that the social behavior could be improved with oxytocine treatment (5).

**Tetrahydrobiopterin (R-BH4)** is another medicine examined in the treatment of autism. It is a chemical compound necessary for synthesis of neuro-transmitters, such as serotonin and other catecholamines. In one open pilot study, six preschool children with autism were treated with R-BH4. The parents reported improvement in eye contact, willing for interaction and number of words. PET-scans showed 10% increase in binding of dopamine D2 receptor in n. caudatus and in putamen. N. caudatus and putamen are components of the basal ganglion system and they are areas deep in the brain, which receive different impulses from the brain cortex, process those impulses and return them back to the motor cortex. N. caudatus influences the motivating processes and putamen is connected with unconscious coordination of simple sense-motor behavior. Since there is only one study carried out on this medicine, other researches are necessary to evaluate its safety and efficiency (6).

**Ampakini** se relativno nova klasa lekovi { to ja poka-uvaat aktivnost na AMPA-receptorot. Ovie receptori pomagaaat vo prenesuvawe na glutamatnite signali vo mozokot. Studii te poka`uvaat deka ovie zoni vo mozokot se pomalku aktivni i imaat pomala gustina na AMPA-receptori. Tielekovi ja podobri le memorijata kaj pacienti te so Alchajmerova bolest. CX516 e ampakini { to ima efekt vrz kognitivni te i bihejvioralnite simptomi kaj indidui so Fragilen X sindrom i autizam (7).

## 2. Hormonska t erapija

**Sekretinot** e polipeptid, sostaven od 27 aminokiselini, { to se sekretira vo tenkoto crevo kako odgovor na hl orovodorodnata kiselina od `eludni kot. Sekretinot se apsorpira vo krvta i go predizvikuva pankreasot da sekretira bikarbonati { to ja neutraliziraat kiselinata vo crevoto. Sekretinot ja namaluva cirkulacijata vo crevoto i umereno go inhibira crevniot motilitet, so { to go zabavuva dvi`eweto na crevnata sodr`ina. Poradi negovite za{titni i smiruvaki efekti na crevoto, sekretinot e koristen kako del od dijagnostiki testovi, sproveduvani za da gi evalui raat pri ~ini te na gastrointestinalnite naru{uvawa; kako na primer, hroni ~nata dijarea i sindromot na iritabilni creva.

Decata so autizam, kako i drugi te deca { to imaat gastrointestinalni problemi, mo`e da primat sekretin pri dijagnostiki testirawe. Eden pacient so autizam, Peter Beck, na voзраст od ~etiri godini, primil sekretin pri laboratoriskoto testirawe, sprovedeno za da se vidat pri ~ini te za negovata hroni ~na dijarea. Za tri nedeli davawe infuzija so sekretin odnesuvaweto markantno mu se promeni lo. Peter mo`el da izre~e preku 100 zborovi, da ka`e kusi re~enici, da odgovara na pra{awata i go podobril kontaktot so o~ite. Negovata dijarea, isto taka, se podobri la (8). Vo edna druga studija se soop{teni sli ~ni vidovi podobruvawa na simptome, predizvikuj i

**Ampakines** are relatively new medicine class, which increase the activity of AMPA-receptor. These receptors help the transfer of glutamate signals in the brain. The studies show that these areas in the brain are less active and with less density of AMPA-receptors. They improved the memory of patients with **Alzheimer** disease. CX516 is ampakine which influences cognitive and behavioral symptoms in individuals with fragile X syndrome and autism (7).

## 2. Hormonal therapy

**The secretin** is polypeptide, consisted of 27 amino acids secreted in small intestine as a reaction to the chloro-hydrogen acids from the stomach. The secretin is absorbed in the blood and challenges the pancreas to secrete bicarbonates, which neutralize the acid in the intestine. The secretin reduces the circulation in the intestine and moderately inhibits intestine motion, slowing down the movement of intestine content. Because of its protective and relaxing effects on the intestine, the secretin is used as a part of diagnostic tests conducted to evaluate the reasons for gastro-intestinal impairments; for example: chronic diarrhea and syndrome of irritable intestines.

Children with autism, as other children with gastro-intestinal problems, can be treated with secretin while diagnostic testing. A patient with autism, Peter Beck, at the age of 4, was treated with secretin in laboratory testing carried out to find the reasons for his chronic diarrhea. After three-week treatment of secretin infusion, the behavior remarkably changed. Peter could pronounce more than 100 words, compose short sentences, reply questions and he improved eye contact. His diarrhea improved, too (8). In another study, similar symptom improvements are registered, causing interest for secretin therapy in autism.

interes za sekretin not kako mo`na terapija za autizem. Vo ova studija se uka`uva deka sekretin not mo`e da ja podobri sostojbata so crevnata li gavica, odnosno da ja normalizira, so { to se onevozm`uva golemi te proteini, ili toksini da pominat od crevata vo krvta, so { to se prevenira sindromot na propu{tlivi creva (9). Koga se vnesuva vo terapevtski dozi, sekretin not se dava intravenski. Obi~no se dava vo pomali dozi vo vremetraewe od { est nedeli, a vo gol ema doza se dava edine~no. Dodeka vo neкои studii nema izve{tai za nesakani efekti, neкои drugi uka`uvaat deka e mo`no javuvawe na osip po ko`ata, generalizirano crvenilo na glavata, vratot i gradite vedna{ po infuzijata, treska, tahikardija, povra}awe i zgolemena razdrazljivost. Edno od najnovite istra`uvawa gi otf rla naodite na onie studii kade { to sekretin not nepoka`al nikakov korisen efekt, ili imal nesakani dejstva. Ova dvojno-slepa, placebo-kontrolirana i vrstena studija poka`uva deka sekretin not gi podobruva simptome kaj decata so autizam { to imaat hroni~na dijarea mnogu pove}e otkolku kaj onie deca { to go nemaat ovoj problem. Janet Kern i kolegite prou~uvale 19 deca so autizam davaj}i mu na sekoje dete edna infuzija na sekretin (2CU/kg) i edna infuzija na placebo solen rastvor. Istra`uvavite izvestile deka kaj 5 mom~iwa so hroni~na dijarea do{lo do namaluvawe na iritabilnosta, voznemirenosta, plae~eweto, hiperaktivnosta, koga tie bile tretirani so sekretin, a nemale odgovor na placebo, dodeka drugite lica nemale odgovor ni na sekretin, ni na placebo. Kako dopolnuvawe na ova, decata so autizam i hroni~na dijarea poka`ale podobruvawe vo re~nikot i namaluvawe na stereotipnoto odnesuvawe. Pritoa bilo zabele`ano edno vlo{uvawe kaj edno dete bez gastrointestinalni simptomi, kaj kogo do{lo do eskalirawe na bihejvi oralnite problemi. Na krajot, tie zaklu~uvaat deka mo`ebi ima subtip na deca so autizam ili pervazivno razvojno naru{uvawe i hroni~na dijarea koi imaat polza od sekretin not (10).

This study shows that secretin can improve the condition of intestinal mucus, i.e. normalize it disabling the big proteins or toxins to pass from intestines into the blood, which prevents the syndrome of porous intestines (9). When inserted in therapeutic doses, the secretin is applied intravenously. It is usually applied in smaller doses in duration of six weeks, or once if it is a bigger dose. Some studies show no side effects while others report possible occurrence of skin rash, generalized blush on head, neck and chest immediately after the infusion, as well as fever, tachycardia, vomiting and increased irritability. One of the latest researches rejects the findings of the studies where secretin did not show any useful effect nor had unwanted activities. This double "blind", placebo controlled and cross-examined study shows that secretin improves symptoms in children with autism and chronic diarrhea much better than in those children without this problem. Janet Kern and colleagues studied 19 children with autism, giving each child an infusion with secretin (2CU/kg) and one infusion of placebo salty solution. The researchers reported that 5 boys with chronic diarrhea reduced the irritability, anxiety, crying, hyperactivity when treated with secretin, and did not respond to placebo, while others did neither respond to secretin nor placebo. Additionally to this, children with autism and chronic diarrhea showed improvement in vocabulary and reduction of stereotype behavior. The aggravation was noticed in one child without gastrointestinal symptoms who showed escalation of behavioral problems. At the end, they concluded that there was a subtype of children with autism or pervasive developmental impairment and chronic diarrhea, who benefited the secretin (10).

### 3. Antigabi~na i fungicidna terapija

**Probiotic** se mikroorganizmi { to se koristat vo terapevtski celi za da go kontroliraat razmno`uvaweto na gabi te, fungi te i bakterii te vo crevata. I ma stotici razli~ni vidovi polezni bakterii koi se dostapni vo farmacevtski te ku}i, a neкои od ni v se: *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus bulgaricus*, *Lactobacillus salivarius*, *Lactobacillus termophilus* i *Lactobacillus plantarum*. Drugi polezni vidovi gi vku~uvaat: *Bifidobacterium bifidum* i *Streptococcus faecium* (da ne se pome{ a so *Streptococcus faecalis*, koj e patogena bakterija). Ovi e vidovi bakterii mo`e da se najdat vo razli~ni formi, kako { to se suspenziji, pra{oci, kapsuli i tableti. Ovi e produkti mo`e da pomognat vo kontrola na gabi te i patogenite bakterii od rodot *Clostridia* vo crevni ot trakt. Se prepore~uva si mul tana upotreba na probiotici te so fungicidna terapija. Gabi te se del od crevni ot ekosistem i tie gi dr`at drugite organizmi pod kontrola. Dokolku ne se zemaat probiotici simu~l tano so fungicidni lekovi, toga{ mo`e da se slu~i da dojde do razmno`uvawe na patogenite bakterii.

Druga va`na postapka e kontrola na razmno`uvaweto na gabite preku **dijeta**, odnosno isfrlawe na {e}erite, poradi nivni ot pottiknuva~ki efekt na razmno`uvaweto na gabi te. Osnovno pravilo vo elimi~nacijata na {e}erite e: toa { to e slatko, da ne se jade. Listata na ograni~eni hrani vku~uva: bonboni, sladole, torti, blagipiti, ~okolada i ovo{ni sokovi. Otkako deteto }e po~ne so ova di eta se ~ini deka vodata }e mu stane glavni pijalok. Site vidovi {e}er treba da bidat elimini rani, vku~uvaj}i go i medot, i sirupite, i ovo{ni ot {e}er i rafinirane {e}eri. Nekoi avtori prepore~uvaat kompletna elimini cija, dodeka drugi prepore~uvaat povremena. Ponekoga{ , mo`ebi, }e bide potrebno dodavawe vitamini C ako deteto e naviknato da pije sok od portokal koj, isto taka, e elimini ran. Ovo{ jeto mora da bide otstraneto od ishranata za eden mesec za da se zabrza elimi naci jata na gabi te.

### 3. Anti-yeast and Fungicide Therapy

**Probiotic** is a microorganism used in therapeutic aims to control growth of yeast, fungi and intestinal bacteria. There are hundreds of different useful types of bacteria available in pharmaceutical houses, such as: *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus bulgaricus*, *Lactobacillus salivarius*, *Lactobacillus termophilus* and *Lactobacillus plantarum*. Other useful types are *Bifidobacterium bifidum* and *Streptococcus faecium* (not to be confused with *Streptococcus faecalis*, which is pathogen bacteria). These types of bacteria can be found in different forms, such as suspensions, powders, capsules and pills. These products can help to control yeasts and pathogenic bacteria from the family *Clostridia* in intestinal tract. Simultaneous use of Probiotic with fungicide therapy is recommended. The fungi are part of intestinal eco system and they control other organisms. If Probiotic is not simultaneously used with fungicide medicine, then a growth of pathogenic bacteria can occur.

Another important procedure is the control of bacteria growth through **diet**, i.e. ejecting of sugar because of its stimulating effect on bacteria growth. The basic rule for sugar elimination is not to eat sweets. The list of restricted food includes candies, ice cream, cakes, sweet pies, chocolate, and fruit juices. When starting with this diet, it seems that water becomes the main drink for the child. All types of sugar should be eliminated including honey, syrups, fruit sugar and refined sugar. Some authors recommend complete while others recommend temporary elimination. Sometimes, however, it is necessary to add vitamin C if the child is used to drinking orange juice, which is also eliminated. The fruit must be eliminated from the diet in a period of one month in order to fasten the elimination of fungi.

Deserti te { to sodr`at mnogo { e}er treba da bi dat i sf rleni na neopredel eno vreme. Vo toj slu~aj glavni izvori na jagl enhi dra-ti }e bidat kompir ite, gravot, p~enkata, sladok tropski kompir, brokola i dr. Si te vi dovi meso i riba se dovol eni vo i shrana-ta. Dietata, isto taka, treba da bide kom-bi ni rana so f ungi ci dna terapi ja, { to dava dvapati pogol em ef ekt vo el i mi naci ja ta razmno`eni te crevni gabi, otkol ku ako di-etata se kori sti bez f ungi ci dnata terapi ja. **Nistatin** e eden od najstari te i najbezbedni f ungi ci dni lekovi. Negovata bezbednost se dol`i na f aktot { to toj ne se apsorbi ra vo krvotekot vo dozi koi naj~esto se pri pi { u-vaat. Re~isi 100% od nistatinot se el i mi -niraat vo fecesot. Zaradi toa { to ne vle-guva vo krvta, toj e bezbeden i ne mo`e da predizvika nekoj seriozni nesakani de-jstva. Mnogu od decata so autizam ne sakaat da zemat kapsuli, zaradi { to najdobra op-cija e davawe vo forma na suspenzija. Naj~esto suspenzije na nistatin se f or-mulirani da sodr`at 100.000 edinici vo 1ml. Ako se dade vo 48 pati pogol emi dozi od prepora~anite, toga { mo`e da dade ne-sakani ef ekti vo smisl a na zgol emena agre-sivnost.

**Amfotericin B** mo`e da bide mnogu toksi~en ako se dade intravenski. Zatoa, pak, daden oral no toj e mo { ne bezbeden lek. Koga }e se dade oral no, negovata bezbednost se sporeduva so ona na ni stati not, bi dej}i toj lo { o se apsorbi ra od GI T (11).

#### 4. Vitaminoterapija

Vo 18 studii, sprovedeni za evaluacija na dejstvoto na **vitamin B6** kaj licata so au-tizam, toj poka`al pozitivni rezultati. Nitu eden nesakan ef ekt ne bil soop { ten vo tie studii. Ova e pove}e od zna~en rezultat za ef i kasnost i bezbednost, oso-beno ako se znae deka drugi te lekovi { to se davaat kaj autizmot poka`ale nekonzisten-tni rezultati i imale rizik od nesakani ef ekti.

The deserts, which consist of much sugar, should be eliminated forever. In that case, main sources of carbohydrates are potatoes, beans, corn, sweet potatoes, broccoli and others. All kinds of meat and fish are allowed in the diet. The diet should be combined with fungicide therapy, which shows twice bigger effect in elimination of intestinal fungi growth, than if the diet is used without it.

**Nystatin** is one of the oldest and the safest fungicide medicine. It is safe due to the fact, that it is not absorbed in the circulation of the blood in mostly prescribed doses. Almost 100% of Nys-tatine is eliminated in feces. Because it does not enter the blood, it is safe and cannot cause any se-rious and unwanted activities. Many autistic chil-dren do not want to take capsules and the best op-tion is a suspension. Most frequently, suspension of Nystatin is formulated to contain 100.000 units in 1 ml. If it is applied in 4 - 8 times bigger doses than the prescribed one, then it can show unwanted effects of increased aggressiveness.

**Amphotericin B** can be very toxic if applied in-travenously. If applied orally, it is a very safe medicine. When applied orally, its safety is com-pared to the one of Nystatin because it is badly absorbed from GIT (11).

#### 4. Vitamin Therapy

In 18 studies implemented for evaluation of influ-ence of **vitamin B6** on people with autism, it showed positive results. There were no unwanted effects, reported in these studies. It has been more than a significant result for the efficiency and safety, especially when it is known that other medicine applied in autism showed inconsistent results and had unwanted effects.

Istran`uvawata za upotrebatana vitamin B6 po-nale vo 60-tite godini od minatiot vek. Vo 1966 godina dvajca britanski nevrolozi - A.F. Heeley i G.E. Roberts - soopti-le deka kaj 11 od 19 deca so autizam na le abnormalni metaboliti vo urinata pri upotrebatana triptofanski test. Davajji im po 30 mg tableta vitamin-B6 do lo do normalizirane na nivnata urina. Vo taa studija ne bile napraveni bihevioralni ispituvawa. Germanski otru`uva V.E. Bonisch vo 1968 godina izvestil deka kaj 12 od 16 deca so autizam imalo znaitelno podobruvawe vo povedenieto koga im bilo dadeno visoki dozi vitamin-B6 od 100 mg do 600 mg dnevno. Trojca od negovite pacienti prvpat prozborele po davaweto na vitamin-B6 vo ovoj otvoren kliniki obid.

Po izdavaweto na knjigata "Infantile autizam" od dr Bernard Rimland vo 1964 godina, toj po-nal da prima stotici pisma od roditelitelite koi se obidete so megavitaminska terapija kaj nivnite deca so autizam. Vo pralni kot, to toj im go pratile na okolu 1000 roditeli, otkril deka 57 eksperimentirale so visoki dozi na vitamini. Mnogi na od nivni deli poze tivni rezultati kaj nivnite deca. Kako rezultat na toa, Rimland po-nal golema studija so preku 200 deca so autizam na koi im dal megadozi na vitamin-B6, niacinamid, pantotenska kiselina i vitamin-C. Vitaminite bile smesteni vo edna multipna tableta, specialno dizajnirana za ova studija. Na krajot od studijata, po etiri meseci, bilo jasno deka vitamin-B6 bil najvni otod site 4 ispituvani vitamini i deka vo nekoj slu-i dovel do izvonredno podobruvawe. Vitamin-B6 poka`al znaitelno podobruvawe kaj 30% do 40% od decata. Samo nekolku od decata poka`ale minorni nesakani efekti (razdrazljivost i uvstvitenost na zvukovi), notie is-eznale koga bil dodaden magnezium. Magneziumot ne samo togi eliminiira nesakani te efekti, tuku toj esto go podobruva govorot i povedenieto. Dve godini podocna toj drugi dvajca istran`uva i nicirale vtora eksperimentalna studija za megavitaminskata terapija, koncentrirajji se na vitamin-B6 i magnezium.

The research on the use of vitamin B6 started in the 60s of the last century. In 1966, two British neurologists - A.F. Heeley and G.E. Roberts - reported that 11 of 19 children with autism found abnormal metabolites in the urine using triptophan test. Applying each patient 30 mg tablet of vitamin B6 they succeeded in normalizing the urine. This study did not make any behavioral investigations. The German researcher V.E. Bonisch in 1968 reported that in 12 of 16 children with autism showed significant behavioral improvement when they were applied high doses of vitamin B6 from 100 mg to 600 mg per day. Three of his patients could talk for the first time after applying vitamin B6 in this open clinical trial.

After the publication of the book "Infantile autism", Dr. Bernard Rimland in 1964 started receiving hundreds of letters by parents who had tried megavitamin therapy on their children with autism. In the questionnaire he had sent to about 1000 parents, he found out that 57 had experimented with high doses of vitamins. Most of them saw positive results with their children. As a result of this, Dr. Rimland started a large study with over 200 children with autism who were given mega doses of vitamin B6, niacinamid, pantotenic acid and vitamin C. The vitamins were put in a multi type tablet, specially designed for this study. At the end of the study, after four months, it was obvious that the vitamin B6 was the most important one of the four examined vitamins and that in some cases it brought excellent improvements. The vitamin B showed considerable improvement with 30% to 40% of the children. Only a few children showed minor unwanted effects (irritable and sensitive to sounds) which disappeared when magnesium was added. Magnesium, not only eliminates unwanted effects, but it frequently improves speech and behavior.

Two years later, he and two other researchers initiated a second experimental study for megavitamin therapy, concentrating on vitamin B6 and magnesium.



Toj bil dvojno-slep placebo-kontroliran eksperiment kaj 16 deca so autizam i povtorno imalo statistiki-znane rezultate. Dozi te se dvel emeju 300 mg i 500 mg dnevno.

Vo dvete studii decata pokaale irok rang na izvonedni rezultati so vitamin B6. Tie imale podobar kontakt so oite, pokaual e pogolem interes kon svetot okolu niv, pomalku bile besni, govorot bil podobar i, op{ to zemenostanal e ponormalni.

Francuski te istrauva-i, predvodeni od prof. Gilbert LeLord, napravile dopolnitelno istrauvawe so vitamin B6 i magnezium. Nivniot eksperiment go sprovele vrz 44 hospitalizirani deca so autizam. Ottoga{ i maat publicirano pove}e studii, kade { to ja ispituvaa upotrebata na vitamin B6 so magnezium ili bez nego kaj deca i adulti so autizam. Vo nivni te studii davan e 1 gram dnevno vitamin B6 i polovina gram magnezium. LeLord i sor. neodamna gi rezimirale rezultate od 91 pacient, kade { to zabeleale: kaj 14% markantno podobruvawe, kaj 33% podobruvawe, 42% bile bez podobruvawe i kaj 11% vlo{ uvawe na klini-kata slika. Vo site nivni studii ne bile zabeleani nesakani dejstva.

Drugi dve studii od istrauva-ki te grupivo SAD, predvodeni od Thomas Gualtieri i sor. na Uni verzi tetot vo Severna Karolina i George Ellman i sor. od Sonoma, dr`avnata bolnica vo Kalifornija, imale pozitivni rezultati kaj paci entite so autizam (12).

**Vitamin C** e va`en antioksidant i mo`e da bide od golema polza kaj decata so autizam. Toj e vitamin rastvorliv vo voda i zatoa mnogu retko mo`e da se zabele i vistsinska toksinost, osven { to mo`e da se formiraat kristali na askorbinskata kiselina vo urinata, koga toj se koristi vo ekstremno visoki dozi. Vitamin C treba da po~ne da se dava vo doza od 5-10 mg/kg/dnevno so postepeno poka-uvawe na dozata. Avtorite postavile hipoteza deka dejstvoto se dol`i na pretpostaveni te dopaminergiki efekti na vitamin C. Kako i da e, rezultate od ova studija u{ te ne se povtoreni (13).

That was a double "blind", placebo-controlled experiment with 16 children with autism and again there were statistically significant results. The doses ranged from 300 mg to 500 mg per day.

In both studies, the children showed wide range of excellent results with vitamin B6. They had better eye contact, showed bigger interest for the world around them, were less furious, their speech was improved, they became more normal in general.

The French researchers led by Professor Gilbert LeLord additionally examined vitamin B6 and magnesium. Their experiment was carried out with 44 hospitalized children with autism. Since then, they have published a large number of studies, examining the use of vitamin B6 with magnesium or without it, both with children and adults. In their studies, a daily dose of 1 g. vitamin B6 and half a gram magnesium was applied. LeLord and associates have summarized their results recently with 91 patients and stated 14% with noticeable improvement, 33% with improvement, 42% without improvement and 11% with worse clinical picture. In all their studies, unwanted actions have not been noticed.

Other two studies of the research groups from USA, led by Thomas Gualtieri and associates at the University of North Carolina and George Ellman with associates from Sonoma, the state hospital in California, has positive results in patients with autism (12).

**Vitamin C** is an important antioxidant and could be of great benefit for children with autism. The vitamin is soluble in water and therefore real toxicity is rarely noticeable, except formation of crystals in ascorbic acid in the urine when used in extremely high doses. Vitamin C has to be applied with starting daily dose of 5/10 mg/kg and with gradual increase of the dose. The use of vitamin C has been examined in a small double "blind", placebo-controlled cross-examined study, where a slight alleviation of the symptoms has been found in schoolchildren with autism. The authors have put forward hypothesis that the action is due to assumed dopaminergic effects of vitamin C. The results of this study have not been repeated again (13).

**Folnata kiselina** je pol ezna za upotreba kaj autizmot. Golemi ot francuski istra`uva~ Jerome Lejeune izvestil deka davawe na okolu 250 mikrogrami folna kiselina na kilogram telesna te`ina dnevno doveduwa do golemi podobruvawa kaj neкои deca so autizam. Toj daval folna kiselina na iljadnici mentalno retardirani deca (naj~esto so Down-ov sindrom) po 20 mg dnevno vo razli~ni studii, bez da ima ni kakvi { tetni i nesakani efekti (14).

### 5. Dimetilglicin (DMG)

Dimetilglicinot je supstancija so sladok vkus, opi{ana kako prirodna, ednostavna sestojka so nepoznati, nepo`elni i nesakani efekti. DMG je dostapen vo mnogu prodavnici za zdrava hrana vo SAD. Toj legalno je klasificiran kako hranлива supstancija. Se upotrebuwa vo pove}e formi, a naj~esto kako sitni tableti od 125 mg. Vkusot mu je prijaten i decata brzo gi xvakaat tableti te.

Mnogu studii imaat doka`ano deka DMG ja zasiluwa efikasnosta na imunitet sistem, gi podobruwa fizi~kite i atletskite performansi kaj lu|eto i `ivotnite i ima {i rokrang na polezni efekti. Toj je mnogu bezbeden. Mo`e da se sretne vo mnogu mal i koli~estva vo kafeavio i oriz i crniot drob. Hemiski i fiziolo{ki toj priloga na vitamini rastvorlivi vo voda, kako na primer, vitamini te od B-grupata. Glavnata pri~ina {to toj ne je klasificiran kako vitamin je toa deka nema specifi~ni simptomi povrzani so deficiet na DMG.

Mnozi na roditeli izvestile deka u{te vo prvite denovi od po~etokot na terapijata so DMG, povedeni eto na decata zabele`itelno se podobri lo~bil zabele`an podobar kontakt so o~ite, govorot bil podobren i decata poka`uval e pogolemi interes i mo`nost za zboruvawe.

Za predutili{ni deca se prepore~uwa za po~etok polovina od 125 mg tableta ili kapsula zaedno so pojadokot, a za pogolemi deca po edna tableta.

**Folic acid** is useful when applied for autism. The great French researcher Jerome Lejeune reported that a dose of 250 mg of folic acid at one kilogram of corporal weight per day showed great improvements in some children with autism. He applied a daily dose of 20 mg folic acid to thousands of mentally retarded children (mostly with Down syndrome) in different studies without any harmful and unwanted effects (14).

### 5. Dimethyl-glycine (DMG)

DMG is a substance with sweet taste described as natural, a simple component with unknown and unwanted effects. DMG is available in many healthy food stores in USA. It is legally classified as nutritious substance. It is used in many forms mostly as small tablets of 125 mg. They are tasteful and children quickly chew them.

Many studies have proved that DMG enhances efficiency of the immunity system, improves physical and athletic performances, both in people in animals, and has a wide range of useful effects. It is very safe. It is present in small quantities in brown rice and the liver. From the aspect of chemistry and physiology, it is soluble in water like vitamins, as for example vitamins of B group. The main reason it has not been classified as vitamin is the fact that it has not specific symptoms related to the deficit of DMG.

Since the very beginning of the therapy with DMG, many parents reported that their children's behavior considerably improved, they had better eye contact, improved speech, showing greater interest and abilities for talking.

At the beginning, pre-school children are recommended a daily dose of half of 125 mg tablet or capsule when having breakfast, and older children one tablet.

Postepeno treba da se zgoleduva dozata od edna na ~etiri tableti dnevno, a za vozrasni te od 2 na 8 tableti dnevno. Ako se pojavi po~etno zgoleduvawe na hi peraktivnost (to se javuva kaj 5-10% od slu~ajte), toga dozata treba da se namali. Vo toj slu~aj, se dodava 800 mikrogrami folna kiselina. Se prepore~uva davawe na DMG 23 nedeli, po~to dodavawe na B6 i magnezium to, isto taka, treba da po~ne postepeno (12).

### **6. Alfa-lipoi~na kiselina**

Alfa-lipoi~nata kiselina e ditiol masna kiselina, koja pretstavuva prirodni vrzuvaki agens i mo~en antioksidans. Taa bila upotrebuвана vo Germanija pri tretmanot na dijabeti~na nevropatija so odli~ni rezultati. Nejni te antioksidantni efekti mo~e osobeno da bi dat od pomo~ kaj decata so autizam. Se po~nuva so doza od 1-3 mg/kg/dnevno i se poka~uva do 10 mg/kg/dnevno. Alfa-lipoi~nata kiselina e prirodni produkt na ~ovekite kletki i zaradi toa ima minimalna toksicnost. Ispituvani te dozi nad 25 mg/kg/dnevno, davani pove~e od 3 godini kaj vozrasni lica, ne poka~ale toksicnost. Alfa-lipoi~nata kiselina mo~e da go olesni odstranuvaweto na `ivata od intracelularno do ekstracelularno. Toa mo~e da bi de mnogu pol ezno za mobiliziraweto na `ivata to ovozmo~uva dostapnost na DMSA da ja vrze `ivata (15).

### **7. Diet a slobodna od gluten i kazein**

Gluteni te se proteini to se sre~avaat vo rastitelni ot svet i pripa~aat na potklasata monokotiledoni. Vo ova semejstvo se p~enicata, ja~menot, ovesot, `rta i nivni te derivati. Kazeinot e fosforprotein od ml ekoto, ~ija molekularna struktura e mnogusli~na so onaa na glutenot.

Ima sigurni podatoci deka neкои od lu~eto so autizam se intolerantni kon hrana to sodri gluten i kazein, pri to reagiraat so mnogu fizi kalni i bihejvoralni problemi, kako to se: glavobolka, bolka vo `eludni kot, gadewe, vris kawe i plawe,

The dose has to be continuously increased from 1 to 4 tablets daily, and for adults 2 to 8 tablets per day. The dose has to be reduced if initial increase of hyperactivity occurs (noticed at 5 – 10% of cases). In that case, 800 mg folic acid is added. DMG is recommended to be applied for 2-3 weeks, then gradually adding B6 and magnesium (12).

### **6. Alpha-Lipoic Acid**

Alpha-lipoic acid is dithiol fatty acid, which is a natural binding agent and powerful antioxidant. It was used in Germany on the treatment of diabetic neuropathy with excellent results. Its antioxidant effects can be a great benefit in children with autism. The treatment starts with a daily dose of 1-3 mg/kg and it increases to 10 mg/kg. Alpha-lipoic acid is a natural product of human cells and therefore it has minimal toxicity. The examined doses of more than 25 mg/kg daily applied for more than 3 years with adults, did not show any toxicity. Alpha-lipoic acid can alleviate the removal of mercury from intracellular to extra-cellular. That can be very useful for mobilization of mercury, which enables DMSA to bind mercury (15).

### **7. Diet Free of Gluten and Casein**

Glutens are proteins present in flora and belong to the subclass monocotyledons. In this family are wheat, barley, oats, rye and their derivatives. Casein is phosphor protein in milk with very similar molecule structure to gluten.

There are certain data that some people with autism are intolerant towards food that contains gluten and casein and they respond with many physical and behavioral problems such as headaches, stomachaches, nausea, screaming and crying, sleeping problems, hyperactivity, aggression, high

problemi vo spi eweto, hi perakti vnost, ag-resija, pre~uvstvi tel nost kon zvukovi, zamor, depresija, crevni problemi (di jareja, opsti paci ja, gasovi), u{ ni i nf ekci i duri i konvul zi i. Za da se podobri ova a si mptoma-tologija treba da se izbegnuvaat oni e vi-dovi hrana { to gi so dr` at glutenot i ka-zei not.

Tretmanot so di eta bez gluten i kazei n po-drazbi ra pri dr` uvawe kon odredeni pra-vi la { to treba da se po~i tuvaat:

- di etata mora da se sproveduva konti nui - rano i dosledno;
- nau~ete go deteto deka hranata ne e samo zadovol stvo, tuku i i zvor na zdravje;
- odnapred bi dete gotovni na i sku{ eni ja i i majte dobra zamena za sekoj vi d hrana;
- odnapred obezbedi te dobra i vkusna hrana za deteto;
- zdravjeto na deteto neka bi de pri ori tet i cel oto semejstvo neka ja zema i stata hrana kako i deteto;
- povrzete se so drugi lu|e { to pri me-nuvaat vakva di eta;
- vni mavajte na saboteri te vo i shranata;
- poka`ete í na sredi nata deka sakate na deteto da mu pomognete, a ni kako deka sakate da mu go smeni te na~i not na ` i vot;
- i spi tuvajte go toa { to treba da vl eze vo detski ot organi zam, vkl u~uvaj}i gi lekovi - te, vi tami ni te i drugo;
- sadovi te za gotvewe na hranata i pri bo-rot za jadewe mora da bi dat posebni ;
- produkti te koi se upotrebuvaat mora da bi dat posebno skl adi rani ;
- da se izvestat rodnini te za cel i te na di etata i da se zamolat da ne i m davaat na decata tajno od zabranetata hrana;
- nikako ne predavajte se bidej}i na krajot }e bi dete zadovol ni od rezul tati te.

Prehranbeni produkti { to **mo`e** da se koristat vo di etata bez gluten i kazei n se sledni ve:

sensitivity to sounds, fatigue, depression, in testinal problems (diarrhea), obstipatio, gases), ear infections and other convulsions. Food containing gluten and casein should be avoided in order to improve these symptoms.

The treatment with a diet free of gluten and casein means obeying certain rules that have to be re-spected:

- The diet has to be carried out continuously and persistently;
- Teach your child that food is not only pleasure, but source of health;
- Be ready for temptations in advance and have good replacement for any kind of food;
- Provide, in advance, good and tasty food for your child;
- The health of your child has to be a priority and the whole family has to use the same food as your child;
- Contact with other people who use the same diet;
- Take care of nutrition saboteurs;
- Show people that you want to help your child and not to change the child's life;
- Examine everything which enters your child's organism, including medicine, vitamins and so on;
- The dishes for preparing food and cutlery have to be special;
- The used products have to be separately stored;
- To inform the relatives about the aims of the diet and to ask them not to give the child secretly the forbidde n food;
- Do not give up because, at the end you will be satisfied with the results.

Food products that **can** be used in the diet free of gluten and casein are the following:

- **Izvori na proteini:** svinško meso, jagne{ ko meso, tel e{ ko meso, june{ ko meso, pile{ ko meso, meso od misirka, patka, fazan, rakovi, {kolki, tuna, pastrmka, losos, sardi ni, jajca, rasti tel ni protei ni - soja, lu{ pi od soja, jogurt od soja.
- **Bra{ na:** ori zovo bra{ no, soi no bra{ no, skrob od p~enka, p~enkarno bra{ no, gri z, bra{ no od le}a, bra{ no od grav, bra{ no od kosteni, bra{ no od proso.
- **Zelen-uk** zel ena sal ata, praz, luk, mor-kov, celer, magdonos, bel kompi r, domati, spana}, cvekl o, zel ena pi perka, gra{ ok, bo-ranija, soja, grav, krastavica, tikva, tik-vi ci, zel ka, karf i ol, p~enka, trupka.
- **Ovo{ je** kru{ ki, duwi, smokvi, porto-kal i, mandari ni, jagodi, mal i nki, kapi nki, ananas, di wa, lubeni ca, kokos, urmi, boro-vinki, kajsi i, praski, slivi, suvi slivi, cre{ ni.
- **Pijalaci:** ovo{ ni sokovi, sok od mor-kov, sok od cvekl o, sok od domati.
- **Zrnest i i senkast i produkt i:** orevi, son~ogledovi semki, semki od tikva, bade-mi, le{ ni ci, susam, lebl ebi i, ki ki ri ki.
- **Drug:** ~ist kakao, ~okolado za gotvewe (bez mleko), margarin bez kazein, al kohol en ocet, ovo{ en ocet (bez jabol ko i grozje, a ako se sproveduva di eta na gabi, toga{ ne smee ni vi nski ocet).

Prehranbeni produkti { to **ne smee** da se zemaat vo di etata bez gluten i kazein, se sledni ve:

- mleko i mle~ni proizvodi (si rewe, krem-si rewe, jogurt, pavlaka, ki sel o mle-ko);
- p~eni ca i proi zvodi od p~eni ca (teste-ni ni, p~eni ~na pasta, bra{ na);
- ja~men i proi zvodi od ja~men (bra{ no);
- oves i proi zvodi od ovesot (bra{ no);
- 'r` i proizvodi od 'r` (16).

### Zaklu-ok

Bi omedi ci nskata terapija na autizmot e aktuel en metod i su{ ti nski e da se sf ati

- **Protein sources:** pork, lamb, veal, beef, chicken, turkey, duck, pheasant, crabs, seashells, tuna, trout, salmon, sardines, eggs, vegetable pro-teins – soybean, soybean shells, soybean yoghurt.
- **Flour:** rice flour, soybean flour, starch, corn flour, groats, lentil flour, bean flour, chestnut flour, millet flour.
- **Vegetables:** lettuce, leek, garlic, carrot, celery, parsley, white potatoes, tomatoes, spinach, beet, green paprika, peas, green beans, soybean, bean, cucumber, pumpkin, squash, cabbage, cauliflower, corn, rape.
- **Fruit:** pears, quince, figs, oranges, mandarins, strawberries, raspberries, blackberries, pineapple, melon, water melon, coconut, dates, bilberries, apricots, peaches, plums, prunes, cherries.
- **Drinks:** fruit juices, carrot juice, beet juice, tomato juice.
- **Grains and seeds:** nuts, sunflower seeds, pumpkin seeds, almonds, hazelnuts, sesame, chick-pea, peanuts.
- **Other:** pure cocoa, cooking chocolate (without milk), margarine free of casein, vinegar, fruit vine-gar (without apple and grapes, and in diet with fungi, then wine vinegar must not be used).

Food products that **must not** be used in diet free of gluten and casein are the following:

- milk and milk products (cheese, feta cheese, yoghurt, cream, sour milk);
- Wheat and wheat products (pastas and flour);
- Barley and barley products (flour);
- Oats and oat products (flour);
- Rye and rye products (16).

### Conclusion

Biomedical therapy of autism is a current method and it is essential to consider that medicine is not

deka lekovi te ne se zameni za drugi te vidovi tretman na autizam. Golem broj deca so primena na ovie lekovi stanuvaa pomirni, pomalku hi peraktivni, so zgolemo vnimanie, reducirana agresija i avtoagresija, dodeka nezainteresirani te deca stanuvaa pootvoreni.

Analizirani te vidovi biomedicinski terapii mo`ebi, u{ te nemaat dokazana vrednost, no vo nekoj studiji imale pozitivni rezultati, odnosno vodile kon pobruvawe na autisti~nata simptomatologija. Sekako, potrebni se natamo{ ni istra`uvawa zaradi doutvrduvawe na vi{tinskata vrednost na ovie lekovi. Vo na{ata sredina mnogu od navedeni te lekovi voop{ to ne se zemaat. Zatoa se nametnuva potrebata od ponuvawe na terapijata na autizam so nekoj od ovie vidovi tretmani vo na{ava dr`ava.

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