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Placebo in the Guise of Evidence-Based Medications

Kanıta Dayalı İlaçlar Kisvesinde Plasebo

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ABSTRACT

Placebo therapy can be beneficial and ethically justifiable; but it is not a sufficient reason to publish biased information. Certain journals are selecting reliable reports but others are publishing biased materials and rejecting criticism. Publication series of questional reliability are sometimes continued without making references to published comments. Theories have been construed for promotion of some drugs and dietary supplements without proven effectiveness. This review is a collection of examples, when substances with unproven effects and unclear action mechanisms are directly or indirectly presented by professional publications as evidence-based medications. Some of the topics might be not completely clarified, so that arguments provided here can induce a constructive discussion.

Keywords: Placebo, hormesis, nutrition, phytoestrogens, soy, osteoarthritis, acetylcysteine

ÖZET

Plasebo tedavisi faydalı ve etik olarak uygun olabilir; ancak taraflı bilgi yayınlamak için yeterli bir neden değildir. Bazı dergiler güvenilir raporlar seçmekteyken, diğerleri taraflı materyal yayınlayıp eleştiriyi reddetmektedir. Yayınların güvenilirliği bazen yayınlanan yorumlara atıfta bulunulmaksızın halen sorgulanmaktadır.Etkinliği kanıtlanmamış bazı ilaçların ve diyet takviyelerinin tanıtımı için teoriler oluşturulmaktadır. Bu derleme, etkileri kanıtlanmamış ve etki mekanizmaları belirli olmayan maddelerin profesyonel yayınlar tarafından doğrudan veya dolaylı olarak kanıta dayalı ilaçlar olarak sunulduğu örneklerin bir derlemesidir. Bazı konular tam olarak açıklığa kavuşturulamayabilir, dolayısıyla bu şekilde burada sunulan argümanlar yapıcı bir tartışmayı tetikleyebilir.

Anahtar kelimeler: Plasebo, hormon, beslenme, fitoöstrojenler, soya, osteoartrit, asetilsistein

Introduction

It is evident for a reviewer of scientific literature that the quality of argumentation in some areas of medical and biological research deteriorated during last decades. Another tendency is that substances without proven effects and questionable treatments have been advertized, and corresponding products marketed in the guise of evidence-based medications. Scientific publications are needed to register these drugs and treatments to obtain permissions for the practical use; accordingly, such publications appeared, sometimes apparently being fabricated. Patients can be influenced not only by the advertizing but also by professional publications. In Russia, the marketing of placebos under the guise of evidence-based medications is not infrequent, while artificial theoretic concepts are used for that purpose.

The placebo therapy can be beneficial and ethically justifiable[1]; but it is not a sufficient reason to publish biased information in support of the placebo marketing. Note that some substances without proven effects are quite expensive. Several examples are discussed in this review, when drugs and dietary supplements with unproven effects and unclear action mechanisms are directly or indirectly presented as evidence-based medications. The conclusions of this review are partly based on theoretic considerations. In conditions of abundant literature with declared and non-declared conflicts of interest, when it is increasingly difficult to distinguish between relable and unreliable reports, theoretic considerations gain in importance.

Not only questionable data have been published but also theoretic concepts construed. An example is hormesis – a concept of biphasic dose-response to various pharmacological and toxicological stimuli; typically, low-dose exposures induce a beneficial response, while higher doses cause toxicity[2]. Theoretically, hormesis as a general principle is conceivable only for factors that are present in the natural environment, having induced an evolutionary adaptation, so that a deviation in either direction from an optimum would

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be harmful.[3] So it is, for example, for light or atmospheric pressure, different kinds of stress, numerous chemical substances and elements[2,4]. However, there are no reasons to expect a hormetic (biphasic) dose-response pattern a priori for factors that are absent in the natural environment.

A response to a pharmacological agent generally tends to increase with the increasing dose and concentration. The placebo effect does not depend on concentrations. Homeopathic remedies can be extremely diluted. Homeopathy claims a curative reaction from a small dose of a drug, of which high doses cause symptoms similar to those from which the patient is suffering. Homeopathy has never been grounded on empirical scientific evidence[5]. Nonetheless, homeopathic medications have been proposed, patented and used in diverse diseases e.g. tuberculosis, acute pneumonia, viral infections and myopia[6-9]. In particular, it is precarious when homeopathic medications are applied using invasive methods e.g. intraarticular injections[10]. If homeopaths have useful empirical knowledge, it should be discussed in the professional literature and tested by scientific methods. Suggestions that homeopathy is based on hormesis create an illusion that homeopathy employs a scientific concept.

Some noxious agents can have cumulative effects or act synergistically with other factors, for example, on the cells with a limited ability of cellular regeneration such as cardiomyocytes or neurons. It can be of particular importance in conditions when such cells are pre-damaged e.g. by ischemia so that even a mild additional impact would act according to a no-threshold pattern without hormesis. Under such circumstances, which are not uncommon especially in gerontology, the hormesis concept can be dangerous if used in the clinical thinking[11]. For example, it is obviously not indicated to injest small doses of ethanol, a known hormetic agent, by a patient with hepatic failure. Nonetheless, certain publications describing hormesis as a general biological principle[12,13], can be cited in support of homeopathy and placebos, in gerontology and other fields of medicine. This can pave the way for homeopathy and placebos as inexpensive substitutes of evidence-based medications. It should be stressed that all clinically significant effects, hormetic or not, must be tested according to the principles of evidence-based medicine.

Phytoestrogens and soy products

Phytoestrogens (PE) are plant-derived substances with a structural similarity to estradiol[14,15]. The most extensively studied PE are isoflavones and coumestans. Isoflavones are present in various edible plants being most abundant in soybeans. Some inedible plants also contain PE, in particular, red clover. Remarkably, PE are used for compensation of estrogen deficiency in menopause; however, their estrogenic potential does not prevent from the use of soy in infant formulas, other foodstuffs and pediatric parenteral nutrition.

The consumption of PE and soy foods has been associated with health benefits[16]; however, the potential adverse effects on the reproductive and endocrine systems seem to be underappreciated[14,17]. Some epidemiological studies suggest that dietary intake of PE may contribute to the decreased incidence of postmenopausal cardiovascular diseases and thromboembolic events[18], and that PE are significantly more effective than placebo in reducing the frequency and severity of hot flashes[19]. The evidence of clinically relevant biological effects from observational studies and randomized trials has, however, been generally lacking[20,21]. Several reviews concluded that there are no reliable arguments in favor of PE efficacy against menopausal symptoms[22,23] and that current evidence does not generally support their use[24]. The utility of PE in alleviating vasomotor symptoms has failed the test in randomized clinical trials[25]; "Efficacy of PE on menopausal vasomotor symptoms is similar to placebo"[26]; "Definite conclusion on possible beneficial health effects of PE cannot be made"[15], etc. The analysis of earlier findings from enrichment the diet with soy protein has failed to confirm beneficial cardiovascular effects by way of lipid lowering, vasodilatation or lipoprotein oxidation[27]. In particular, there are little data to support the claim that PE protect against menopausal osteoporosis[15,28,29].

The use of PE as an alternative for the hormone replacement therapy is not advocated also because of insufficient and conflicting data about safety[30]. Sporadic reports show adverse effects and interactions with other medications[31]. Moreover, soy is one of the most allergenic foods; so that for some people it is essential to avoid it[15,32]. Conventional menopausal hormone therapy remains the only treatment that consistently had a greater effect than placebo in published controlled trials[33]. It was pointed out that most high quality studies

had shown no clear benefit and some potential for harm, further research being necessary to make recommendations[33].

The theoretical basis for the use of PE for menopausal hormone replacement appears doubtful. The biological action of estrogens is mediated by receptors. It is therefore unclear, why the plant-derived analogs must be used instead of the natural or synthetic hormones that are complementary to receptors. Another reasonable question: "Why should soy or red clover products containing isoflavone be recommended, if the positive effects are only negligible but the adverse effects serious?"[34] Moreover, commercial PE preparations often contain a mixture of ingredients of unclear nature and concentration. Such mixtures can exert undesirable effects, depending on their composition and the patient's condition[35]. Therefore, the concept of PE as a "natural and safe" alternative to estrogens[25] is unfounded: these substances are in fact less natural for humans than endogenous hormones.

The following controversies should be stressed: PE are used for compensation of estrogen deficiency in the menopause; and, at the same time, their estrogenic potential does not prevent from the use of soy in infant formulas and other foodstuffs as well as for pediatric parenteral nutrition. Moreover, the use of soy as animal fodder may result in accumulation of PE and their active metabolites such as equol in meat and other animal products. Equol, a PE metabolite with the relatively high estrogenic potential, is produced by intestinal bacteria in sheep, cows, pigs and domestic fowl[36,37].

Adverse effects associated with the intake of soy have been overviewed[14,38-40]. Perturbations of the reproductive health and feminizing effects in men are regarded to be of small scale[38]. It was reported on abnormal uterine bleedings in women consuming soy products[14], subtle gender-related behavior changes in girls[41] and gynecomastia in a man[42]. A cross-sectional study of 11,688 women showed that high intake of isoflavones was related to an increased risk of never becoming pregnant and remaining childless[43]. Hormonal effects of PE may lead to fertility problems possibly due to the influence on menstrual cycle, oocyte quality and endometrial receptivity[39]. An association between soy exposure and early menarche was reported[44], although there have been contradicting data[38]. Animal data demonstrate that soy isoflavones, at doses and plasma levels attainable in humans including infants, can alter the structure and function of neuroendocrine pathways in both sexes[14]. Relevant doses of PE have an impact on the differentiation of ovaries and fertility in animals[45]. Alterations of male sexual development and deficits in the sexual behavior were noticed in rats[46]. Note that the feminizing effect of soy products may be subtle, detectable only in large populations by statistical methods. Moreover, there is increasing evidence that some PE e.g. genistein can exert androgenic effects[47], which is not surprising as PE are plant substances with accidental similarity to human hormones, so that their effects cannot be predicted a priori. It was suggested that isoflavones are selective estrogen receptor modulators and, as such, are different from estrogens. It is questionable, however, whether such modulating effects, also referred to as "endocrine-disrupting properties of soya"[14], are desirable in infants receiving soy formulas and for other consumers of soy products[48]. Parents should be aware of possible estrogenic effects if they choose to feed their infants with soy-based formula[14]. Besides, it should be mentioned that soy-based oil emulsions were identified as one of the major causative factors of cholestasis related to the pediatric parenteral nutrition; further details and references are in[49].

Another contradiction: it was stated that "findings from a recently published metaanalysis and subsequently published studies show that neither isoflavone supplements nor isoflavone-rich soy affect total or free testosterone levels. Similarly, there is essentially no evidence from the nine identified clinical studies that isoflavone exposure affects circulating estrogen levels in men"[50]. In a case report on gynecomastia associated with soy consumption by a man it was noted: "After he discontinued drinking soy milk … his estradiol concentration slowly returned to normal"[42]. The statements that there was "no conclusive interaction between soy or isoflavone intake and free testosterone concentrations"or "a systematic review of literature showed that effect of soy on sex hormones in pre- and post-menopausal women had very small"[38] are in fact non-informative because PE, being estrogen analogs, exert estrogenic effects on their own, independently on the levels of the endogenous estradiol or other hormones.

It was not the purpose of this review to pass final judgments on the effects and safety of PE. The aim can be seen within a broader perspective: marketing of herbal placebos and other substances with unproven

effects under the guise of evidence-based medications, corroborated by research of questionable reliability and spurious theoretic concepts. In Russia, PE are sometimes promoted by misquoting foreign publications[51]. A supposed anti-atherogenic effect of some PE was confirmed by experiments with cell cultures. In these experiments, the ability of serum to induce accumulation of cholesterol in cultured cells was interpreted as an indicator of serum atherogenicity[52-54]. No references have been made by the authors to the published criticism of their works[55].

Scientifically questionable methods and theories are sometimes used for the official registration and patenting of drugs, dietary supplements and treatment methods e.g.[54,56]. As a result, substances with unproven efficiency are sometimes offered to patients, who are misinformed not only by advertising but also by some scientific papers. As for PE, these substances are used to compensate for estrogen deficiency in menopause; but their estrogenic potential does not prevent from the use of soy in infant formulas and other foodstuffs. As mentioned above, the feminizing effect of soy products may be subtle, detectable only statistically in large populations. This matter should be clarified by independent research.

Glycosaminoglicans in osteoarthritis

Chondroitin (Ch) is a glycosaminoglycan and glucosamine (Ga) is an aminosaccharide acting as a substrate for the biosynthesis of glycosaminoglycans. Ch undergoes hydrolysis in the intestine; being administered orally, it can be regarded as a source of precursors for glycosaminoglycans. Hyaluronic acid (HA) is a glycosaminoglycan used for intra-articular injections. These substances are named chondroprotectives and applied for the therapy of osteoarthritis. The oral preparations have been discussed within the group of Symptomatic Slow-Acting Drugs in Osteoarthritis (SYSADOA)[57]. This name seems to be suboptimal: oral glycosaminoglycans and their precursors are aimed primarily not to alleviate symptoms but to compensate for a supposed deficiency of constituents/precursors of cartilage or synovial fluid. The evidence in favor of their chondroprotective effectiveness is conflicting. Many studies have been supported by the industry. There is skepticism in the scientific community[58]. For example, a meta-analysis concluded that "Ch, Ga, and their combination do not have a clinically relevant effect on perceived joint pain or on joint space narrowing"[59]. Another key remark: "Given that there is an effect, understanding the biochemical basis of this effect might lead to more useful supplements"[60]. The biochemical basis is largely unclear. Glycosaminoglycans and their precursors are not irreplaceable; they are produced by the body also in vegetarians, who receive no immediate precursors. It appears doubtful that oral supplementation of Ch or Ga can shift the balance between synthesis and degradation in the whole body so that it would be significant for the cartilage turnover. Furthermore, the sources such as shellfish chitin and fungi for Ga, cartilage from mammals, birds or fish for Ch and contaminants can impart undesirable properties to the preparations[61,62]. The criteria of efficacy are largely subjective, which means that improvements can be caused by a placebo effect. It is known that pain measurements in clinical trials are difficult, which can contribute to exaggeration of treatment effects. A great part of the treatment successes of osteoarthritis can be attributed to a placebo effect[63]. Admittedly, there are many studies and reviews reporting effectivity of chondroprotectives compared to placebo, but reliability is often questionable due to declared or non-declared conflicts of interest. Quality of research and possible influence by the industry must be taken into account defining inclusion criteria for studies into meta-analyses and reviews.

In regard to the intra-articular injections of HA, a meta-analysis concluded that "currently available evidence suggests that intra-articular GA is not clinically effective"[64]. Another meta-analysis and systematic review concluded that in patients with knee osteoarthritis, intra-articular HA is associated with a small, clinically irrelevant benefit and an increased risk for adverse events[63,65]. The evidence remains inconsistent and controversial[66]. Action mechanisms of intra-articular HA are hardly understandable including the "lubrication at the joint surfaces"[67] i.e. viscosupplementation. Viscosity changes in consequence of HA injections can be measured (e.g. adding HA to cadaverous synovial fluid) or approximately calculated, knowing viscosity of synovial fluid, of injected solution, and corresponding volumes. Both pre- and post-treatment viscosity indicators were reported to be within the range of normal values[68]. In any case, the lubrication effect cannot last long: no explanation has been proposed for the discrepancy between the short intra-articular half-life of injected HA and the reported duration of the clinical carry-over effect. The intra-articular half-life of Hyalgan (sodium hyaluronate) is about 17 h; the low molecular weight component of

Synvisc (Hylan G-F 20 constituting about 90% of the preparation) has a half-life of 1.5 days; the minor component with a higher molecular weight - 8.8 days[68]. The rheological effect of exogenous HA in the joint is supposed to last less than 1 day[69]. The carry-over effect after the treatment cessation lasted reportedly from 3 months with oral chondroprotectives to 6-9 months with intra-articular injections[70]. The half-life of HA preparation with artificial cross-linking was reportedly up to 4 weeks[71]; but again, there are no reasons to expect a much longer carry-over effect. A short-term functional improvement (if any) due to the viscosupplementation may reinforce the placebo effect by the mechanism of Pavlovian conditioning thus contributing to alleviation of subjective symptoms. It is known that invasive procedures can exert a pronounced placebo effect. However, a placebo must have no adverse effects by definition; otherwise it is named pseudoplacebo[72]. In particular, the intra-articular therapy of hip osteoarthritis[73] is burdened by complications due to the proximity of important anatomical structures[74].

HA is a polymer; according to the law of mass action, its local enrichment would displace the chemical equilibrium toward low-molecular precursors i.e. reduction of viscosity. Therefore, suppositions about "induction of biosynthesis of endogenous HA"[57] by injections of the same substance are unfounded. As for molecular mechanisms studied in vitro, their clinical relevance is questionable, among others, because of generally higher concentrations of tested substances in vitro than in vivo. Note that Ch, Ga and HA were chosen for supplementation therapy; and a probability of their specific e.g. anti-inflammatory action[75] or "inhibition of chondrodegenerative enzymes"[76] would be a priori be the same as for substances taken at random.

In Russia, Ch, Ga and HA are named chondroprotectors. These drugs are prescribed to osteoarthritis patients, among whom are elderly people with low incomes. Many patients purchase the drugs for a prolonged use[77,78]. Chondroprotector-containing ointments and preparations for intra-articular injections have been patented[73,79]. In the author's opinion, it would be equivalent to recommend to osteoarthritis patients a diet rich in natural glycosaminoglycans: animal joints, chicken wings and legs etc. This idea is not new, it was discussed at conferences. To support the placebo effect, patients can be advised that such diet would saturate their bodies with precursors of cartilage similarly to drugs. In this connection, it might be informative to study the prevalence of osteoarthritis in vegetarians, who receive no supply of glycosaminoglycans and their direct precursors. Effectiveness of a dietary supplementation of natural glycosaminoglycans compared to Ch and Ga preparations can be tested for osteoarthritis in animals, particularly dogs, giving them food rich in cartilage. A recent review concluded that potential benefits from Ga and Ch in canine osteoarthritis can neither be confirmed nor denied[80]. Unfortunately, not only human but also animal studies are at risk of funding bias due to sponsorship[80].

Flavonoids as venoactive drugs

This section addresses the reported phlebotonic activity of some flavonoids (Fls) recommended for the treatment chronic venous insufficiency and varicose veins, both conditions having considerable socioeconomic impact[81]. Supplementation of Fls as drugs or nutritional supplements versus enhanced consumption of citrus fruit is also discussed. Fls constitute a major part of dietary polyphenols; they are found in many fruits, vegetables, and cereals[82,83]. Some supposedly venoactive Fls (rutin, escin, quercetin) were obtained from medicinal plants. Today, the micronized purified flavonoid fraction (MPFF) consisting of 90% diosmin and 10% hesperidin is widely used and prescribed[84]. Diosmin is synthesized from hesperidin extracted from oranges[85]. In the US, preparations of Fls are classified as dietary supplements, and in some European countries - as drugs, which does not necessarily mean an extensive use. In Scandinavian counties, drugs are rarely prescribed for chronic venous disease[86]. In Spain, for certain phlebotonics (calcium dobesilate, chromocarbe and naftazone) the indication for the use in chronic venous insufficiency has been withdrawn, and for several other phlebotonics, such as aminaftone, diosmine, hidrosmine, escin and some rutosides, the use for exacerbations of chronic venous insufficiency has been limited to 2-3 months[87].

The following effects of venoactive Fls have been discussed: phlebotonic, anti-edematous, anti-inflammatory, and anti-oxidative. The action mechanisms are not well established[85,87,88] and not clearly understandable theoretically. Smooth muscles (SM) of large and medium-sized veins studied in vitro have no tone and do not relax under the impact of vasodilators[89]. Lumina of collapsed veins are slit-like, circular

SM bundles are narrow, alternatimg with connective tissue. In post-thrombotic syndrome and varicose veins, where Fls are generally recommended, venous lumina are distended, SM being atrophic and replaced by connective tissue[81,90]. This testifies against any significant phlebotonic effect of Fls; in particular, its durability is doubtful, which pertains also to a supposed potentiation of the norepinephrine action[85,89,90]. The vasoconstrictive effect of norepinephrine is transient; its blood concentration fluctuates e.g. in stress, whereas Fls have been proposed for the treatment of chronic conditions such as venous insufficiency and varicose veins. At the same time, there were reports on the inhibition by quercetin of vascular contraction induced by norepinephrine[91]. A significant phlebotonic action seems to be improbable without a concomitant influence on the arterial tonus. If Fls considerably enhanced the action of norepinephrine or otherwise cause vasoconstriction, it would elevate the blood pressure[88]. Although some degree of venous tone does exist[92,93], there is no convincing evidence that the tone can be significantly influenced by Fls. If vasoconstriction is indeed favorable for patients with venous diseases, known vasoconstrictive agents could be used instead of Fls with unproven efficiency.

There are objective assessment methods of pharmacologic effects on the vascular bed e.g. using isolated veins[93]. For example, dihydroquercetin did not modify the basal tone of isolated rat veins[94]. It was reported on the basis of experiments with rat femoral veins that diosmin heightens the sensitivity of SM to calcium, which could explain the phlebotonic action[95] (the study was supported by manufacturers). On the contrary, hesperetin (the aglycone form of hesperidin) induced vasodilatation in humans and hypertensive rats[96,97]. The vasorelaxing effect was demonstrated also for eriodictyol, a flavonoid from lemon[97]. Overall, the quality of studies on this topic is regarded to be poor, beneficial effects being often exaggerated[88,98]. The most rigorously conducted trial did not show any additional benefit from Fls in the treatment of venous leg ulcers[98]. Among positive results, subjective improvements (quality of life, pains, cramps, sensation of swelling, heavy legs) are often reported[85,90,99,100], which may be caused by a placebo effect. Admittedly, an improvement of venous hemodynamics under the influence of MPFF has been reported, confirmed by strain gauge plethysmography and ankle circumference measurements in patients with chronic venous insufficiency[84,100-103]. The data of foot volumetry were unconvincing[86,104].

Mechanisms of supposed anti-inflammatory and anti-edematous effects of Fls are hardly comprehensible. It can be asked in this connection why, instead of the Fls with unproven efficiency, known anti-inflammatory or diuretic drugs are not used vein diseases[101]. Furthermore, the anti-oxidative capacity of Fls has been discussed. In general, antioxidants are regarded to be far from scientifically founded clinical application[105]. In any case, it is incomprehensible why antioxidants should be used in conditions associated with tissue hypoxia, such as venous insufficiency.

Adverse effects of Fls are reported to be mild to moderate across studies. The most common events are skin lesions e.g. eczema, gastrointestinal disturbances and hypertension[87,98]. In this connection, the role of Fls as repellents, protecting plants from herbivores, should be mentioned. Certain Fls were reported to be toxic for insects or other organisms[83,106,107]. Presumably, Fls are mild toxins stimulating endogenous defense mechanisms[108] so that their abundant intake may be associated with adverse effects especially under conditions of compromised defense mechanisms e.g. in chronic disease or advanced age. Moreover, concentrations of Fls in drugs and nutritional supplements are higher than in a typical diet. Excessive amounts of polyphenols reaching the colon may cause dysbiosis[109].

Despite the arguments presented above, there are numerous publications reporting favorable effects of Fls in venous diseases. Many studies were sponsored by the industry. Obviously, verification in large-scale independent experiments is needed. Should the useful properties of Fls be confirmed, the question will arise whether drugs and dietry supplements can be replaced by enhanced consumption of citrus fruits as a dietary source of Fls. Data on concentrations of different Fls in citrus juices are presented in the review[82]. Remarkably, some commercial citrus juices contain more Fls than hand-pressed ones[82] probably due to the forceful pressing and use of pulp. However, some commercial products in the former SU, labeled as citrus juices, are diluted, contain added syrup and artificial flavors.

In conclusion, the data in favor of the phlebotonic action of Fls are inconsistent, clinically significant effects being hardly comprehensible theoretically. The effectiveness of venoactive drugs needs verification in large-

scale studies protected from conflicts of interest, using objective methods such as measurements of supramaleolar circumference, plethysmography, water volumetry and modern optoelectronic methods.

Acetylcysteine as a mucolytic drug

Acetylcysteine (N-acetyl-L-cysteine or NAC) is considered to be a mucolytic drug; however, this is not well documented[110,111]. There is probably a placebo effect reinforced by the Pavlovian conditioning if NAC had been administered together with expectorants or inhalations. It was pointed out that all positive findings about NAC in chronic obstructive pulmonary diseases have come from studies either investigating small numbers of cases or conducted in patients groups not representative of wider populations[112]. The Bronchitis Randomized on NAC Cost-Utility Study (BRONCUS) showed that NAC is ineffective in preventing deterioration of the lung function in patients with chronic obstructive pulmonary disease (COPD)[113]. It was concluded that there had been no randomized controlled trials demonstrating a benefit from inhaled NAC in the treatment of any airway diseases[114-117], and that no data have convincingly demonstrated an improvement of mucus expectoration, while there is a risk of epithelial damage when NAC is administered as aerosol[117]. At the same time, a systematic review found that the treatment with mucolytics reduced the frequency of exacerbations in patients with COPD, whereas some studies had applied NAC[118]. The latter findings were supported by a pharmaco-epidemiologic study[119], although there was a concern that reported benefits resulted from bias[120]. The 2013 Cochrane review found no grounds to recommend both nebulized and oral NAC for patients with idiopathic cystic fibrosis[115]. According to a recent review, NAC failed to provide benefits in terms of important indices for the treatment evaluation of cystic fibrosis such as the forced vital capacity and percentage of predicted carbon monoxide diffusing capacity; neither did the NAC treatment influence the death rate[121]. It was concluded that there was no evidence in favor of either nebulized or oral NAC for the routine treatment of cystic fibrosis[121,122].

The efficiency of NAC is especially doubtful if the substance is taken per os. A slight increase in radioactivity of bronchial secretions after the oral intake of ^{35}S-NAC does not prove that there was a chemically active agent in the bronchial contents.[123] NAC was not detected in airway secretions and bronchoalveolar lavage fluid, while cysteine concentrations did not increase in the lavage fluid following an oral intake of NAC[111,117,122124,125]. This suggests that oral NAC is unlikely to have any mucolytic properties. A controlled, double-blind study investigating oral NAC showed no significant differences in lung function and mucociliary clearance or sputum viscosity compared to the control or placebo[122,126]. This is not surprising as the oral bioavailability of NAC is low (4-10%), the substance being metabolized in the gut, liver and other tissues, while about 30% of the clearance occurs via kidneys[117,122,127].

A separate topic is the use of NAC for the treatment of microbial infections accompanied by the formation of biofilms. Antibiotic resistance of bacteria in biofilms contributes to the chronicity of infections[128]. Biofilms were shown to be responsible for both acute and chronic conditions of the upper respiratory tract, sinusitis, otitis media, tonsillitis and adenoiditis[129]. Difficulties of biofilm eradication with systemic antibiotics have led to consider non-antibiotic therapies including NAC. It was reported on the mucolitic efficiency of NAC against bacterial biofilms on the tonsils[130,131], obviously, because it is easier to achieve an efficient concentration in the nose, throat and oral areas than in the bronchi. There have been in vitro studies reporting that NAC at relatively high concentrations lowers the sputum viscosity[132,133]. The evidence from in vitro studies indicates that NAC interferes with the biofilm formation enhancing potencies of antibiotics[134-136], which may be an efficient tool in the nose, throat and oral areas[137].

Apart from the mucolytic action, NAC was supposed to possess antioxidative, anti-inflammatory, antimicrobial and anticancer activity[137-140]. Data on anti-inflammatory effects of NAC are limited and the mechanism is not readily understandable. The supposed antimicrobial activity should be tested by microbiological methods and compared with that of antibiotics. A priori, the supposition about a significant antimicrobial activity of NAC seems to be speculative. As mentioned above, a synergism with antibiotics in biofilm eradication may be of clinical significance in localizations, where sufficient concentrations of NAC can be achieved. Antioxidative effects have been discussed elsewhere[105,141]; in any case, they are not directly related to the supposed mucolytic activity of NAC.

In conclusion, there are reasons to doubt effectiveness of NAC, especially if taken orally, as a mucolytic agent beyond the placebo effect. The matter can be clarified by in vitro viscosimetry of sputum with NAC concentrations comparable to those in vivo, and measurements of NAC concentrations in expectorated sputum from patients receiving the substance per os and with inhalations.

Calf hemodialysate

Highly purified calf hemodialysate (HPCH), known as Actovegin or Solcoseryl, has been discussed as a medication for certain neurological and other conditions[142-149]. Actovegin is a deproteinized hemodialysate manufactured from calf blood by ultrafiltration; it is registered for clinical use in some countries of Asia and Europe including Russia but not in the US[149]. Actovegin was reported to have beneficial effects on the cognitive performance in poststroke patients; it has also been prescribed in peripheral arterial disease and diabetic polyneuropathy[149]. A hypothesis is proposed here that reported effects of HPCH are caused by its nutritive value and placebo effect. HPCH is a mixture of normal serum components so that a specific action can hardly be expected. HPCH contains oligopeptides, amino acids, nucleotides, microelements etc., thus being of nutritive value. The recommended dose around 2 g/day is a negligible addition to the whole day's diet, but if injected intravenously it may produce an immediate effect especially in conditions of protein-energy undernutrition, acting synergistically with the placebo effect and reinforcing the latter by way of Pavlovian confitioning. As for the oral intake, beef contains the same substances as HPCH, especially if not overcooked[150]. Oligopeptides and amino acids are preferable nutrients for diabetics, which may contribute to the favorable action of HPCH reported in diabetes mellitus[143]. HPCH and some other meat-derived substances having a nutritive value (carnosine, taurine) are consumed by athletes[151]; but HPCH has proven itself neither ergogenic nor enhanced functional capacity in exhaustive tests[152].

HPCH applied topically was reported to be beneficial for wound healing and skin lesions caused by ionizing radiation[153-155]. The underlying mechanism may be a supply of nutrients for regenerating tissues, which is outside the scope of this review. The nutritive value of HPCH can also explain neuroprotective effects after a hypoxic injury in rats and in neurons cultured from embryonic rat brains[156,157]. It is not surprising that added serum components contribute to the viability of cell cultures; this effect must depend on the culture medium composition. Further experiments should compare HPCH with other nutritive substances e.g. homologous serum, meat broth or preparations for parenteral nutrition containing amino acids and oligopeptides. A favorable effect of HPCH in stroke patients[144] may be caused by a nutritional supplementation, which is known to reduce morbidity and mortality after stroke[158]. Efficiency of HPCH as well as of other meat-derived substances such as carnosine and taurine[141] in patients with dementia, depression, other mental and neurological disorders[145-148,159] should be further studied as possible markers of malnutrition and protein deficiency e.g. among inhabitants of homes for the aged and psychiatric hospitals. Malnutrition is known to be associated with impaired cognition[160].

Apart from its nutritive value, HPCH probably acts as placebo, the more so as many registered variables have been subjective (cognition, perception etc.) and evaluated by questionnaires[143,144,149]. Certain trials reporting efficiency of HPCH were randomized, placebo-controlled and double-blind but sponsored by the industry. Many substances with unknown action mechanisms show efficiency under such conditions.

Conclusion

Examples presented in this review might appear haphazardly collected, but all of them can be discussed, to some extent, within the scope of scientific misconduct (SM). Since 1998, several cases of SM in medical research in the former SU have been commented, including invasive procedures with questionable indications, trimming of quantitative data, etc.[161,162] As discussed in this review, a special kind of SM is a marketing of placebos and substances with unproven effects under the guise of evidence-based medications, supported by dubious research. The published examples are only a tip of the iceberg. Considering the ongoing "improvement" of fraudulent skills, scientists, editors, and authorities must jointly combat SM. A response to SM requires national and international bodies to provide leadership and guidelines, while whistleblowers need a safe, confidential place to report SM[163].

The deception is objectionable on the grounds that it limits autonomy and breaches trust; these grounds possibly do not apply to placebos when they are prescribed within appropriate ethical limits[164], although it can be problematic both on the professional and the ethical level[165]. In other words, placebo therapy with misinformation of a patient can be beneficial and ethically justifiable[1]; but it is still not a sufficient reason to publish biased and misleading information. In conclusion, the following statement should be agreed with: "…doubts will further raise the question if patients should spend their money for useless drug with no clear mechanism of action which shows no or little evidence of its efficiency."[142]

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