Vicent Balanzá-Martínez [1,2,3,4]

Nutritional supplements in psychotic disorders

[1] Unitat Docent de Psiquiatria i Psicologia Mèdica, Departament de Medicina, Universitat de València, Valencia
[2] Unitat de Salut Mental de Catarroja, Valencia
[3] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto Carlos III, Madrid
[4] International Society for Nutritional Psychiatry Research (ISNPR)

There is growing interest about the potential of diet and nutrients to improve the mental health of the population and for the treatment of psychiatric disorders. In the case of schizophrenia, the limitations of antipsychotic drugs to achieve adequate rates of clinical remission and functional recovery have promoted the search for complementary approaches. This narrative review approaches the dietary patterns and interventions in schizophrenia, efficacy of specific nutrients and therapeutic modulation of the gut microflora by probiotics. As a whole, schizophrenia patients follow a low-quality diet and are exposed to deficiencies in various nutrients that are essential for brain functioning. Although clinical trials with nutritional supplements are still limited and have inconsistent results, specific nutrients, as Omega-3, vitamin D and Group B vitamins can be useful as complementary strategies in the treatment of schizophrenia. It is hoped that the initiation of personalized medicine strategies, such as stratification and using a clinical staging approach, will make it possible to identify the subgroups of patients who can obtain maximum benefit from dietary and nutritional interventions.

Key words: Schizophrenia, Psychotic disorders, Diet, Nutrients, Omega-3, Vitamins

Actas Esp Psiquiatr 2017;45(Suppl. 1):16-25

Suplementos nutricionales en los trastornos psicóticos

Existe un interés creciente en el potencial de la dieta y los nutrientes para mejorar la salud mental de la población y para el tratamiento de los trastornos psiquiátricos. En el caso de la esquizofrenia, las limitaciones de los fármacos antipsicóticos para lograr tasas adecuadas de remisión clínica y recuperación funcional han impulsado la búsqueda de abordajes complementarios. En esta revisión narrativa se abordan los patrones dietéticos y las intervenciones dietéticas en esquizofrenia, la eficacia de nutrientes específicos y la modulación terapéutica de la microflora intestinal mediante probióticos. En conjunto, los pacientes con esquizofrenia siguen dietas de pobre calidad y están expuestos a deficiencias en varios nutrientes esenciales para el funcionamiento cerebral. Aunque los ensayos clínicos con suplementos nutricionales son aún escasos y con resultados inconsistentes, nutrientes específicos, como los Omega-3, la vitamina D y las vitaminas del grupo B, pueden ser útiles como estrategias complementarias en el tratamiento de la esquizofrenia. Se espera que la puesta en marcha de estrategias de medicina personalizada, como la estratificación y una perspectiva de estadiaje clínico, posibilite identificar a los subgupos de pacientes que puedan obtener el máximo beneficio de las intervenciones diéteticas y nutricionales.

Palabras clave: Esquizofrenia, Trastornos psicóticos, Dieta, Nutrientes, Omega-3, Vitaminas

Correspondence:
Vicent Balanzá Martínez
Unitat Docent de Psiquiatria i Psicologia Mèdica
Departament de Medicina
Facultat de Medicina
Avda. Blasco Ibáñez 15
46010 Valencia (Spain)
Tel.: +34 963864168
E-mail: vicente.balanza@uv.es

INTRODUCTION

Psychotic disorders and specifically schizophrenia represent an important public health problem due to their prevalence and associated incapacity. Schizophrenia is a neurodevelopmental disorder with a complex etiopathogeny. The dopaminergic hypothesis is currently considered the final common pathway[1] in which interaction of many genetic and environmental factors converge as well as different molecular mechanisms, standing out among them low grade systemic inflammation and oxidative stress.[2] Administration of antipsychotic drugs is the basis of the treatment, however their efficacy in terms of clinical remission beyond those of the positive symptoms and functional recovery is limited. Thus, there is growing interest in therapeutic interventions that go beyond the dopaminergic neurotransmission.[3]

Although it has been proposed that some nutritional deficiencies would participate in the etiopathogenic mechanisms of schizophrenia, nutrition has been a minority intervention in psychiatry.[4] However, advances that are important to our understanding on the influence of diet and nutrition on brain functioning and on the cellular and molecular mechanisms involved in psychiatric disorders have occurred in the last decade.[4,5] The growing interest on the potential influence of diet and nutrients for mental health could also be contextualized within the recent changes observed in the Western societies, with a relative abandonment of high quality dietary patterns, as those of the Mediterranean diet, and the discovery of anti-inflammatory and anti-oxidant properties of various nutrients.[6]

This narrative synthesis provides an update of the scientific knowledge on the growing role of diet and nutrition in the treatment of psychotic disorders. To do so, the dietary patterns and interventions have been reviewed as well as the efficacy of specific nutrients, standing out among them Omega-3 fatty acids and vitamins. Finally, therapeutic modulation of gut microflora through innovating approaches is addressed.

DIETARY PATTERNS AND INTERVENTIONS IN SCHIZOPHRENIA

Suffering a psychotic disorder reduces life expectancy by up to about 25 years compared to the general population, a large part of this difference being due to cardio-metabolic problems.[7] The metabolic syndrome is one of the most common medical comorbidities of psychotic disorders. Genetic vulnerability, ethnic differences, side effects of antipsychotic drugs and unhealthy life habits, such as sedentary life style, diet and alcohol and tobacco abuse, converge in its multifactorial etiology.

A recent systematic review of 32 studies on dietary patterns of patients with schizophrenia concluded that these patients tend to follow diets having poor quality, characterized by excess calories and processed foods, rich in saturated fats, refined sugar and salt, and low intake of fruits and fiber, compared with healthy individuals.[8] In the general population, all these factors have been associated with the development of metabolic syndrome or its components, such as insulin resistance, dyslipidemia and high blood pressure. Furthermore, surveys conducted in Spain and Australia have shown the most patients with psychosis eat less than 4 daily rations of fruit and vegetable, which are the rations recommended by the WHO.[9,10] Several factors represent a barrier for patients with schizophrenia to follow a healthy diet, such as weight increase associated with antipsychotics, low social-economic status, negative symptoms and substance abuse, especially tobacco.[10]

However, dietary pattern is a modifiable factor and is a therapeutic target for improvement of both mental health and, above all, physical health of patients with schizophrenia. There are existing recommendations and consensus of the experts for the care and monitoring of physical health.[11] In the research facet, it is a very contrasted fact that nutritional interventions forming a part of a multi-component program of life habits have mostly been aimed at weight loss in the chronic phase of schizophrenia or its prevention in the early phases.[12] A recent meta-analysis concluded that nutritional interventions are effective for improving physical health of patients with serious mental disorders.[13] Specifically, they reduce anthropometric measures, such as weight, body mass index and abdominal circumference. Efficacy of the interventions increases when directed by dietitians and administered in an individual format, which would make it possible to contemplate the incorporation of dietetics and nutrition specialists into the mental health teams in the middle term.[13]

Interventions aimed at modifying life habits, including diet, still do not form a part of the care package offered to this group routinely in our setting and its implementation is an urgent need since they are already feasible.[12,13] There are different levels of intervention in the clinical practice: a) dietary-nutritional education in group format; b) individualized nutritional counseling, using for this the same elements that promote cardiometabolic health in the general population; c) training in healthy shopping skills and cooking as one more component of the rehabilitation programs.[14,15]

The recommendations would include, for example, progressive replacement of low quality diets for healthy ones, such as the Mediterranean one, which have

demonstrated clinical benefits in other areas of medicine.[5] However, this hypothesis has not been investigated by adequate clinical trials in psychotic disorders up to date. A recent pilot study pointed out that the implementation of a 3-month psychoeducation intervention is possible within the context of a rehabilitation program and is also effective to modify dietary habits of patients with severe mental disorder.[14] On the contrary, the impact of excluding certain nutrients on the mental health of patients with psychotic disorders has been studied for decades. This is the case of diets without gluten and/or casein. Various series of clinical trials have described a significant resolution of the psychotic symptoms after the introduction of said diets.[16,17] Given that elimination of gluten and milk has been associated with negative results in other studies, the current scientific evidence is inconsistent and it is likely that exclusion diets only provide benefits to the subgroup of patients with schizophrenia who also have gluten hypersensitivity.[18,19]

The poor quality of the diets indirectly suggests that patients with schizophrenia would be subjected to deficiencies in several essential nutrients, a hypothesis that will be discussed in the following sections of the review. The nutrients most investigated in schizophrenia have been Omega-3 polyunsaturated fatty acids and various vitamins.

OMEGA-3 POLYUNSATURATED FATTY ACIDS

There are two main types of polyunsaturated fatty acids in the human body: those of the Omega-6 series, such as arachidonic acid (AA), which are derived from linoleic acid, and those of the Omega-3 series, which are derived from alpha-linolenic acid. The latter include eicosapentaenoic acid (EPA) and docosahoxaenoic acid (DHA). All of them are important components of the phospholipid cell membrane and are essential for survival of the human body. However, as the body cannot synthesize them, they must be obtained through diet.[20] On the molecular level, Omega-3 EPA and DHA have properties that are of interest in psychotic disorders. They improve dopaminergic and serotoninergic neurotransmission. They decrease micro-inflammatory and oxidative stress. They modulate functioning of the mitochondria, which is the main source of oxidative stress. They protect against toxicity due to apoptosis and they regulate gene expression of BDNF.[21]

Diverse data converge in pointing out the association between Omega-3 fatty acids and schizophrenia. In the first place, fatty acid deficiency in the erythrocyte membrane and in the post-mortem brain tissue of patients with schizophrenia has been described repeatedly. A recent meta-analysis of 18 studies has confirmed the presence of alterations in Omega-3 fatty acids (DHA and docosapentaenoic) and Omega-6 (AA), independently of treatment with antipsychotics.[22] The decrease of the proportion of Omega-3 in these tissues has been associated with poor therapeutic response[23] and greater severity of the negative symptoms.[24] Furthermore, it has been suggested that a baseline deficiency in the body content of Omega-3 is a predictive variable for the development of psychosis in adolescents with high risks.[25] In this sense, the phospholipid hypothesis of schizophrenia formulated by David Horrobin[26,27] postulated that inadequate amounts of phospholipids in the neuronal membrane would contribute to the alterations in the neuronal functioning or survival that are characteristics of the schizophrenia in vulnerable subjects.

In any case, this deficiency represents a risk factor that is potentially treatable or reversible by adequate supplementation. The clinical trials with nutritional supplements of Omega-3 for the treatment of schizophrenia and other psychotic disorders have been recently reviewed.[28-31] The efficacy of the Omega-3 to treat psychotic symptoms would be different in the different stages of the schizophrenia.[30] Most of the trials have enrolled samples of patients in chronic phase, while in more recent times, investigator interest has been directed towards first psychotic episodes (FPE) and prevention in subjects at high risk for psychosis. The seven trials conducted in chronic phase have used ethyl-EPA supplements during short periods, going from 8 to 12 weeks, obtaining inconsistent results. It has been described that the use of Omega-3 in patients with psychotic flareups or who abandon antipsychotic treatment was associated with clinical deterioration.[30]

Three trials were performed with patients with first psychotic episode (FPE).[32-34] Peet et al. observed that monotherapy with 2 g daily during 12 weeks had a significant effect on the clinical severity measured with the PANSS scale, on the need to begin antipsychotic treatment before the appearance of psychotic symptoms and on the response rate.[32] It is important to indicate that in said trial the patients were either not taking antipsychotic drugs or had only been taking them recently. On the contrary, the addition of this same daily dose of EPA using flexible doses of antipsychotics was not associated with a significant clinical improvement in another 3-month trial of patients with FPE.[33] In the most recent trial, supplementation during 26 weeks with fish oil rich in EPA+DHA (2.2 g daily) was significantly better than placebo to reduce the clinical severity evaluated with the PANSS scale and to increase the rate of response and functionality of patients with FPE.[34]

Three other clinical trials used a prevention approach in subjects with high risk for psychosis.[35-37] In a pilot study performed in a singe center, 81 adolescents and young persons with ultra-high risk for psychosis were randomly administered 1.2 g of a combination of EPA+DHA or placebo for 12 weeks. At the end of the additional follow-up of 40

weeks, two of the 41 subjects from the experimental group (4.9%) and 11 of the 40 subjects from the control group (27.5%) progressed to psychosis so that monotherapy with Omega-3 significantly reduced the risk of developing psychosis in this population.[35] In the trial follow-up, the effects of the supplementation with Omega-3 on the risk of developing psychosis and psychiatric morbidity in general was maintained for an average of 6.7 years.[36] However, a more recent multicenter trial with 304 individuals at high risk for psychosis[37] did not confirm the results of the pilot trial. Administration of 1.4 g daily of EPA+DHA or placebo for 6 months in combination with cognitive-behavioral therapy had similar results for the reduction of the risk of psychosis. It stands out that both groups obtained a relevant clinical and functional improvement and a low conversion rate to psychosis (19.5%). Thus, the authors speculate with the possibility that psychosocial intervention has a possible ceiling effect, above which administration of Omega-3 does not provide additional benefits.

That is, the Omega-3 seem to be more effective in the early phases of schizophrenia than in the chronic phase of the disease. These differences, according to the disease stage, could be due to the neuroprotective effects of Omega-3 in the early phases, which, however, would not be effective for reversing the neurobiological changes established in the more advanced stages of the disease.[30] It has been indicated that the alterations in the metabolism of Omega-3, which are already present in the early course of schizophrenia, decrease with the disease progression and can be reversed with atypical antipsychotics in patients with FPE, but not during the chronic phase.[38]

The trials conducted with Omega-3 supplements for treatment of schizophrenia have several limitations:[30,31] The size of the samples is generally relatively reduced and there is significant heterogeneity in regards to the diagnosis, duration of the intervention and the doses used. Furthermore, the trials have not always evaluated the baseline levels of Omega-3, which could represent a confounding factor.

Omega-3 can provide additional benefits, such as improving tolerability of the antipsychotics. In one of the FPE trials,[33] supplementation with ethyl-EPA was associated with a 20% decrease of the antipsychotic dose and reduction of the sexual and extrapyramidal side effects. A possible reduction of the risk of tardive dyskinesia in patients with chronic schizophrenia was also suggested.[39] In the second place, the Omega-3 have the potential to improve the physical health of the patients with psychotic disorders.[21] Beneficial effects have been described in the cardiovascular diseases, metabolic syndrome, autoimmune and inflammatory diseases, which are frequent comorbidities in patients with psychotic disorders. In this sense, preliminary data support that addition of Omega-3 significantly reduces the triglyceride levels in patients with schizophrenia treated with clozapine.[40] Finally, all the trials performed coincide in pointing out that this is a safe and well-tolerated intervention in general, with minimum gastrointestinal side effects.

In summary, patients with schizophrenia generally have a potentially treatable Omega-3 deficiency, but the results of the clinical trials performed are inconsistent and efficacy seems to vary according to the disease stage. Currently, sufficient scientific evidence does not exist in favor of or against recommending supplementation with Omega-3 in psychotic disorders, on the contrary to that which occurs with unipolar depression. From a clinical staging approach, it has been suggested as a possible indicated prevention in subjects with high risk for psychosis and secondary prevention after a FPE. Furthermore, the Omega-3 represent a well-tolerated intervention with potential to improve physical health of the patients with schizophrenia.

VITAMINS

Vitamins are organic compounds that the human body cannot synthesize in adequate amounts, so they need to be obtained through the diet. The efficacy of interventions with vitamins in schizophrenia has been reviewed recently.[41,42] In the following, we summarize the most relevant information on vitamin D, group B vitamins, vitamin A and antioxidant vitamins C and E.

Vitamin D

Besides its known role in the regulation of calcium metabolism and bone health, it is currently known that vitamin D is a neurosteroid hormone that is key for brain development and functioning.[43] It has anti-inflammatory properties and capacity to regulate the immune system, neurotransmission and neuroprotection through receptors present in the neurons and glial cells.[44]

Vitamin D is obtained from the diet and more importantly, it is synthesized after skin exposure to ultraviolet B light (UV-B). At present, it is considered that vitamin D deficiency, evaluated by determining serum levels of 25-hydroxyvitamin D, reaches dimensions of a world pandemic since most individuals do not consume the necessary doses in their diet and are not exposed to the UV-B amount needed for its synthesis.[45] Two recent meta-analyses show that patients with schizophrenia have an important vitamin D deficiency compared to the general population although it is comparable to that of patients with other psychiatric disorders.[46,47] The prevalence of vitamin D deficiency affects almost two thirds of the patients (65.3%) with an average deviation of 5.91 ng/mL regarding healthy controls.[47] Fur-

thermore, in an extensive sample of patients with schizophrenia and psychotic spectrum disorders, it was established that vitamin D deficiency is associated, on the one hand, with greater depressive, cognitive and especially negative type symptoms[48,49] and, on the other hand, with the metabolic syndrome and cardiovascular risk factors.[50]

The possible role of said deficiency in the etiology of schizophrenia was proposed two decades ago[51] and has been analyzed in several observational type epidemiological studies, although the data have been contradictory up to date.[52] In the first place, several environmental factors of risk involved in the etiopathogeny of schizophrenia, as the effect of the season of birth, latitude and migratory status, have been related with vitamin D deficiency because its skin synthesis from sun exposure is less efficient during the winter, in higher latitudes and in colored persons.[47] In the second place, vitamin D deficiency in early stages of life has been related with a greater risk of schizophrenia. In a case-control study in the Danish population, low neonatal levels of vitamin D were associated with a two times greater risk of developing schizophrenia in later stages of the life.[53] The fact that this study found that hypervitaminosis would also increase the risk suggests a curvilineal relation between both factors. On the other hand, maternal levels of vitamin D were not associated with the risk of psychosis at the age of 18 years in a cohort study conducted with more than 2000 mother-child dyads in the United Kingdom.[54] In the third place, the risk would persist in the adult age. According to a cohort study of women in the general Swedish population (n=33,623), those women having a higher dietary intake of vitamin D presented a 37% lower risk of developing psychotic type symptoms compared with the group having lower intake, after controlling confounding variables.[55]

Although the observational data suggest a consistent relationship, they do not make it possible to establish causality relations. In other words, it is not known if vitamin D deficiency represents a possible etiological factor for schizophrenia or whether it is the result of the disease and/or its treatment. Association may also be due to confounding factors associated to schizophrenia and vitamin D deficiency, such as unhealthy life habits (sedentary life, insufficient exposure to sun light, poor diet, smoking habit), urbanicity, poverty and overweightness/obesity. For example, an inverse relation has been documented between serum levels of this vitamin and body mass index.[56]

In regards to the intervention, in a Finnish cohort study of more than 9000 subjects, supplementation with at least 2000 IU daily of vitamin D during the first year of life was associated to a 77% reduction in the risk of schizophrenia at the age of 31 years in relation with having received lower doses (RR=0.23), although the effect was only observed in the males.[57] In a small, uncontrolled study, conducted in 18 immigrants with schizophreniform disorders, lower doses (1000 IU) added to the antipsychotic treatment, were not associated with significant changes in the psychiatric symptoms.[58] In a small 8-week open-label trial, supplementation with 2000 IU of vitamin D had no significant impact on weight, glucose and the lipids in patients with schizophrenia treated with antipsychotics.[59] This is in line with the inconsistent results described in the general population.[60] However, at present, there are no controlled trials with random selection that have evaluated the impact of the vitamin D supplements on psychotic symptoms.[42]

In summary, there is a close association between schizophrenia and vitamin D deficiency. This indicates the need to monitor frequently its serum levels in the routine care of this population. However, neither its etiological role nor the possible improvement of the psychotic symptoms have been clearly established. Thus, vitamin D supplementation is not indicated at present for all the patients with schizophrenia. Rigorously designed clinical trials that would make it possible to establish more precise recommendations need to be conducted. However, it seems that there are critical vital cycles for the brain development, as the pregnancy and puerperium, as subgroups of patients who could benefit from vitamin D supplements, such as those with prominent negative symptoms and perhaps those with metabolic syndrome.

Group B vitamins

The group B vitamins, as folate and vitamin B12, act as coenzymes in numerous enzymatic processes of cell metabolism and are essential for the development and functioning of the nervous system. These vitamins play a key role in the monocarbonate metabolism, by which they donate methyl groups for the synthesis of macromolecules, neurotransmitters and hormones.[61]

Due to their participation in methionine-homocysteine metabolism, most of the studies have focused on cobalamin (vitamin B12), folate (B9) and to a lesser degree, pyridoxine (B6). A deficiency of these vitamins can increase homocysteine levels. Homocysteine is a toxic amino acid that negatively affects brain functioning through inhibition of methylation and increasing oxidative stress, DNA damage and neurotoxicity.[62] Hyperhomocysteinemia has been associated with greater risk of cardiovascular disease, depressive disorders and cognitive deterioration,[61] as well as schizophrenia.[63]

Recent meta-analyses have concluded that patients with schizophrenia generally have a folate deficiency compared with healthy controls,[64] while the results are less consistent in favor of a vitamin B12 deficiency.[65] On the other hand, maternal folate deficiency has been related with a posterior increased risk of schizophrenia and, on the other

hand, low levels of folate in patients with schizophrenia have been associated with greater severity of the negative symptoms.[66] Folate deficiency may be due to an inadequate supply in the diet but also to genetic polymorphisms related with its metabolism. Thus, supplementation with folate is more effective to improve the negative symptoms in patients with genetic vulnerability for folate metabolism alterations, specifically the carriers of the low functioning variants in the gene that codes the methylenetetrahydrofolate reductase gene (MTHFR) enzyme.[67] However, it must be indicated that the effect of these polymorphisms would be reduced and currently the association between variants as MTHFR *C677T* and risk of schizophrenia is considered to be debatable.[61,63]

The seven trials with vitamin B group supplements (including folate and vitamins B12 and B6) for the treatment of schizophrenia have recently been meta-analyzed.[42] The conclusion is that they are moderately more effective than the placebo to improve the psychiatric symptoms, although without demonstrating a specific efficacy in the clinical dimensions of the positive and negative symptoms.[42] Furthermore, greater efficacy was observed in the trials that used higher doses, a combination of several vitamins and in the early stages of schizophrenia.

On the other hand, the administration of group B vitamins would be effective to reduce hyperhomocysteinemia. In a placebo-controlled trials with cross-over design, the administration during 3 months of a cocktail of the three vitamins mentioned decreased the elevated levels of homocysteine more than the placebo in a sample of 42 patients with schizophrenia.[68] Said decrease was also associated to clinical and neurocognitive improvement.

That is, there are indications that supplements of the group B vitamins, especially folate and vitamin B12, can improve the general symptoms of schizophrenia. This efficacy could be especially relevant in specific subgroups of patients, for example, those with genetic vulnerability for folate metabolism disorders and those with hyperhomocysteinemia.

Other vitamins

Vitamin A plays an essential role in the processes of neuronal differentiation and migration during neurodevelopment. According to a cohort study, low maternal levels of vitamin A during the second quarter of pregnancy were associated with a three times greater risk for the subsequent appearance of disorders of the schizophrenic spectrum in children.[69] Up to date, no clinical trials in schizophrenia have been conducted with this vitamin.

On their part, *vitamins C and E* are considered antioxidants. The six trials that have studied the effects of these vitamins, administered separately or combined, have not found significant improvement of the psychotic symptoms, according to a recent meta-analysis.[42]

THE MODULATION OF THE MICROBIOTA-GUT-BRAIN AXIS WITH THERAPEUTIC PURPOSE

One of the most recent frontiers of knowledge is the role of the gut-microbiota and microbiota-gut-brain axis in mental health. From the theoretical point of view, interventions aimed at modulating the gut microbiota with therapeutic purposes have a potential application in psychotic disorders (for review[70]). In other areas of medicine such approaches include diet and the nutrients reviewed as well as the use of probiotics, prebiotics, antibiotics and fecal transplantation.[71] Clinical trials in schizophrenia are still limited and have focused on diet and probiotics, always in combination with antipsychotics.[72] Modification of the diet can change both the composition and activity of the gut microflora. However, the difficulty existing to achieve a significant change in patients with schizophrenia suggests the use of the so-called psychobiotics, that is, probiotics and/or prebiotics.[73] Prebiotics are non-digestible dietary fiber that promote growth and improve the functioning of the probiotics in the gastrointestinal tract. However, clinical trials still have not been conducted in schizophrenia.[70]

Probiotics are microorganisms, generally bacterias, which when provided in adequate amounts, confer a benefit in the host. Administration of bacteria of the *Lactobacillus* and *Bifidobacterium* genera can improve mood state and reduce response to stress and anxiety in humans.[6] As schizophrenia is associated with an alteration in the immuno-inflammatory response and in metabolism, probiotics constitute a promising therapeutic approach. The only two clinical trials with probiotics in psychotic disorders were performed by the same team.[74,75] To do so, they recruited patients with schizophrenia or schizoaffective disorder in chronic phase and with residual symptoms, whose severity was at least moderate, and treated with antipsychotics. Supplementation during 14 weeks of one tablet with a combination of *Lactobacillus Rhamnosus* GG and *Bifidobacterium animalis lactis* Bb12 (n=33) was not more effective than the placebo (n=32) to reduce the clinical severity when evaluated with the PANSS scale. However, the administration of the probiotic was well tolerated and was associated to a significant reduction in the incidence of severe gastrointestinal discomfort, which is a relatively frequent comorbidity in this population.[74] These results could be explained by the molecular parameters analyzed in the second trial.[75] Administration of this same probiotic was associated with an increase of the brain-derived neurotrophic factor (BDNF) neurotrophin, an improvement in the indicators of integrity of the intestinal epithelium and immunomodulatory effects. Al-

though these data are preliminary, it would be interesting to continue evaluating the efficacy of the psychobiotics, especially in the earliest stages of schizophrenia, such as FPE. Furthermore, the demonstrated effects of the probiotics to improve obesity and dyslipidemia[76,77] make up further grounds for the conducting of more clinical trials in schizophrenia.

FINAL CONSIDERATIONS

The future of psychiatry requires a multimodal approach, in which nutritional factors represent a key element to achieve better results in health, functioning and quality of life.[4] Dietary modification is the ideal approach, but in the case of schizophrenia, it is a considerable challenge. Interventions with formulae that combine several nutrients have greater potential than those based on a single nutrient. Diet and nutrients have the added value of their potential to improve physical health and reduce the gap in life expectancy that currently exists in schizophrenia.

Patients with schizophrenia generally have deficiencies in several essential nutrients for brain functioning, so that a practical involvement for the clinicians is to identify them by certain tests. However, the association described between schizophrenia and nutritional deficiency does not necessarily imply a causal relationship and, in fact, does not always show demonstrated efficacy in the trials with supplementation. This situation is analogue to other areas of the nutritional medicine,[78] and therefore it should not discourage going forward in psychiatry research.

Clinical trials with nutritional supplements for the treatment of schizophrenia are relatively scarce, except in the case of Omega-3 fatty acids. Furthermore, there is marked heterogeneity between the trials and methodological rigor can be improved. Most of the studies have recruited samples having a reduced size, have evaluate efficacy of the nutrients during relatively short periods and do not always adequately control confounding, demographic and habits of life variables.

Although the results are not completely consistent, specific nutrients, such as Omega-3, vitamin D and group B vitamins, may be useful as complementary strategies in the treatment of schizophrenia. An important conclusion of this review is that the nutrients analyzed are not going to improve the psychotic symptoms of the whole group of patients with psychosis. However, it is very likely that they will do so in specific subgroups. This is consistent with the marked heterogeneity of the psychotic disorders on the etiopathogenic, clinical and prognostic level. The challenge consists in identifying those patients that may obtain the maximum therapeutic benefit, for which the response predictors are key factors.

In this sense, future clinical trials should use therapeutic stratification strategies aided by biomarkers.[42,79] In such a way, the selection of more homogeneous samples of patients with specific polymorphisms, specific clinical syndromes and baseline nutritional deficiencies will make it possible to confirm, for example, the efficacy of vitamin D to improve negative symptoms or that of folate in genetically vulnerable patients. On the other hand, from a clinical staging approach, it is foreseeable that supplementation with nutrients would be more effective in the early phases of schizophrenia. In short, a recommendation is made to initiate personalized medicine strategies, such as stratification and staging, in order to transfer the results of the research to the clinical practice. The recently created *International Society for Nutritional Psychiatry Research* (ISNPR) is sponsoring research of high methodological quality in order to continue advancing in this young scientific field and to establish therapeutic recommendations to improve the mental health of the general population and of the patients with psychiatric disorders.[4,79]

ACKNOWLEDGMENTS

The conducting of this work was supported by project PI16/01770 (PROBILIFE) of the Instituto de Salud Carlos III.

REFERENCES

1. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III--the final common pathway. Schizophr Bull. 2009; 35(3):549-62.
2. Davis J, Moylan S, Harvey BH, Maes M, Berk M. Neuroprogression in schizophrenia: Pathways underpinning clinical staging and therapeutic corollaries. Aust N Z J Psychiatry. 2014;48(6):512-29.
3. Brown HE, Roffman JL. Emerging treatments in schizophrenia: highlights from recent supplementation and prevention trials. Harv Rev Psychiatry. 2016;24:e1-e7.
4. Sarris J, Logan AC, Akbaraly TN, Amminger P, Balanzá-Martínez V, Freeman MP, et al. Nutritional Medicine as Mainstream in Psychiatry. The Lancet Psychiatry. 2015;2(3):271-4.
5. Gómez-Pinilla F. Brain foods: the effects of nutrients on brain function. Nat Rev Neurosci. 2008;9(7):568-78.
6. Logan AC, Katzman M, Balanzá-Martínez V. Natural environments, ancestral diets and microbial ecology: is there a modern "paleodeficit disorder"? Part I. J Physiol Anthropol. 2015 Jan 31;34:1.
7. Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature mortality among adults with schizophrenia in the United States. JAMA Psychiatry. 2015;72(12):1172-81.
8. Dipasquale S, Pariante CM, Dazzan P, Aguglia E, McGuire P, Mondelli V. The dietary pattern of patients with schizophrenia: a systematic review. J Psychiatr Res. 2013;47(2):197-207.
9. Simonelli-Muñoz AJ, Fortea MI, Salorio P, Gallego-Gomez JI, Sánchez-Bautista S, Balanza S. Dietary habits of patients with

schizophrenia: a self-reported questionnaire survey. Int J Ment Health Nurs. 2012;21(3):220-8.
10. Hahn LA, Galletly CA, Foley DL, Mackinnon A, Watts GF, Castle DJ, et al. Inadequate fruit and vegetable intake in people with psychosis. Aust N Z J Psychiatry. 2014;48(11):1025-35.
11. Sáiz Ruiz J, Bobes García J, Vallejo Ruiloba J, Giner Ubago J, García-Portilla González MP; Grupo de Trabajo sobre la Salud Física del Paciente con Esquizofrenia. Consenso sobre la salud física del paciente con esquizofrenia de las Sociedades Españolas de Psiquiatría y de Psiquiatría Biológica. Actas Esp Psiquiatr. 2008;36(5):251-64.
12. Hjorth P, Davidsen AS, Kilian R, Skrubbeltrang C. A systematic review of controlled interventions to reduce overweight and obesity in people with schizophrenia. Acta Psychiatr Scand. 2014;130(4):279-89.
13. Teasdale SB, Ward PB, Rosenbaum S, Samaras K, Stubbs B. Solving a weighty problem: systematic review and meta-analysis of nutrition interventions in severe mental illness. Br J Psychiatry. 2017;210(2):110-8.
14. Bogomolova S, Zarnowiecki D, Wilson A, Fielder A, Procter N, Itsiopoulos C, et al. Dietary intervention for people with mental illness in South Australia. Health Promot Int. 2016 Jul 31. pii: daw055.
15. Teasdale SB, Samaras K, Wade T, Jarman R, Ward PB. A review of the nutritional challenges experienced by people living with severe mental illness: a role for dietitians in addressing physical health gaps. J Hum Nutr Diet. 2017 Apr 17. doi: 10.1111/jhn.12473.
16. Dohan FC, Grasberger JC. Relapsed schizophrenics: earlier discharge from the hospital after cereal-free, milk-free diet. Am J Psychiatry. 1973;130:685-8.
17. Jackson J, Eaton W, Cascella N, Fasano A, Warfel D, Feldman S, et al. A gluten-free diet in people with schizophrenia and anti-tissue transglutaminase or anti-gliadin antibodies. Schizophr Res. 2012;140:262-3.
18. Kalaydjian AE, Eaton W, Cascella N, Fasano A. The gluten connection: the association between schizophrenia and celiac disease. Acta Psychiatr Scand. 2006;113:82-90.
19. Severance EG, Prandovszky E, Castiglione J, Yolken RH. Gastroenterology issues in schizophrenia: why the gut matters. Curr Psychiatry Rep. 2015;17:27.
20. Su KP, Balanzá-Martínez V. Role of Omega-3 fatty acids in mood disorders. In: McNamara RK, ed. The Omega-3 Fatty Acid Deficiency Syndrome: Opportunities for Disease Prevention. New York: Nova Science Publishers; 2013, pp. 315-36. ISBN: 978-1-62417-716-3
21. Balanzá-Martínez V, Fries GR, Colpo GD, Silveira PP, Portella AK, Tabarés-Seisdedos R, et al. The therapeutic use of Omega-3 fatty acids in bipolar disorder. Exp Rev Neurother. 2011;11(7):1029-47.
22. Hoen WP, Lijmer JG, Duran M, Wanders RJ, van Beveren NJ, de Haan L. Red blood cell polyunsaturated fatty acids measured in red blood cells and schizophrenia: a meta-analysis. Psychiatry Res. 2013;207(1-2):1-12.
23. Sumiyoshi T, Higuchi Y, Matsui M, Itoh H, Uehara T, Itoh T, et al. Membrane fatty acid levels as a predictor of treatment response in chronic schizophrenia. Psychiatry Res. 2011;186(1):23-7.
24. Sethom MM, Fares S, Bouaziz N, Melki W, Jemaa R, Feki M, et al. Polyunsaturated fatty acids deficits are associated with psychotic state and negative symptoms in patients with schizophrenia. Prostaglandins Leukot Essent Fatty Acids. 2010;83(3):131-6.
25. Amminger GP, Schäfer MR, Klier CM, Slavik JM, Holzer I, Holub M, et al. Decreased nervonic acid levels in erythrocyte membranes predict psychosis in help-seeking ultra-high-risk individuals. Mol Psychiatry. 2012;17(12):1150-2.
26. Horrobin DF. The membrane phospholipid hypothesis as a biochemical basis for the neurodevelopmental concept of schizophrenia. Schizophr Res. 1998;30:193-208.
27. Horrobin DF, Glen AI, Vaddadi K. The membrane hypothesis of schizophrenia. Schizophr Res. 1994;13:195-207.
28. Fusar-Poli P, Berger G. Eicosapentaenoic acid interventions in schizophrenia: meta-analysis of randomized, placebo-controlled studies. J Clin Psychopharmacol. 2012;32(2):179-85.
29. Chia S, Henry J, Mok Y, Honer W, Sim K. Fatty acid and vitamin interventions in adults with schizophrenia: a systematic review of the current evidence. J Neural Transm (Vienna). 2015;122(12):1721-32.
30. Chen AT, Chibnall JT, Nasrallah HA. A meta-analysis of placebo-controlled trials of omega-3 fatty acid augmentation in schizophrenia: Possible stage-specific effects. Ann Clin Psychiatry. 2015;27(4):289-96.
31. Bozzatello P, Brignolo E, De Grandi E, Bellino S. Supplementation with Omega-3 Fatty Acids in Psychiatric Disorders: A Review of Literature Data. J Clin Med. 2016;5(8):pii: E67.
32. Peet M, Brind J, Ramchand CN, Shah S, Vankar GK. Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. Schizophr Res. 2001;49(3):243-51.
33. Berger GE, Proffitt TM, McConchie M, Yuen H, Wood SJ, Amminger GP, et al. Ethyleicosapentaenoic acid in first-episode psychosis: a randomized, placebo-controlled trial. J Clin Psychiatry. 2007;68:1867-75.
34. Pawełczyk T, Grancow-Grabka M, Kotlicka-Antczak M, Trafalska E, Pawełczyk A. A randomized controlled study of the efficacy of six-month supplementation with concentrated fish oil rich in omega-3 polyunsaturated fatty acids in first episode schizophrenia. J Psychiatr Res. 2016;73:34-44.
35. Amminger GP, Schäfer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch Gen Psychiatry. 2010;67:146-54.
36. Amminger GP, Schäfer MR, Schlögelhofer M, Klier CM, McGorry PD. Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study. Nature Communications. 2005;6:7934.
37. McGorry PD, Nelson B, Markulev C, Yuen HP, Schäfer MR, Mossaheb N, et al. Effect of ω-3 Polyunsaturated Fatty Acids in Young People at Ultrahigh Risk for Psychotic Disorders: The NEURAPRO Randomized Clinical Trial. JAMA Psychiatry. 2017;74(1):19-27.
38. McEvoy J, Baillie RA, Zhu H, Buckley P, Keshavan MS, Nasrallah HA, et al. Lipidomics reveals early metabolic changes in subjects with schizophrenia: effects of atypical antipsychotics. PLoS One. 2013;8:e68717.
39. Emsley R, Niehaus DJH, Koen L, Oosthuizen PP, Turner HJ, Carey P, et al. The effects of eicosapentaenoic acid in tardive dyskinesia: a randomized, placebo-controlled trial. Schizophr Res. 2006;84:112-20.
40. Caniato RN, Alvarenga ME, Garcia-Alcaraz MA. Effect of omega-3 fatty acids on the lipid profile of patients taking clozapine. Aust N Z J Psychiatry. 2006;40(8):691-7.
41. Brown HE, Roffman JL. Vitamin supplementation in the treatment of schizophrenia. CNS Drugs. 2014;28(7):611-22.
42. Firth J, Stubbs B, Sarris J, Rosenbaum S, Teasdale S, Berk M,

et al. The effects of vitamin and mineral supplementation on symptoms of schizophrenia: a systematic review and meta-analysis. Psychol Med. 2017;47(9):1515-27.
43. Cui X, Gooch H, Groves NJ, Sah P, Burne TH, Eyles DW, et al. Vitamin D and the brain: key questions for future research. J Steroid Biochem Mol Biol. 2015;148:305-9.
44. Kalueff AV, Tuohimaa P. Neurosteroid hormone vitamin D and its utility in clinical nutrition. Curr Opin Clin Nutr Metab Care. 2007;10(1):12-9.
45. Ferder M, Inserra F, Manucha W, Ferder L. The world pandemic of vitamin D deficiency could possibly be explained by cellular inflammatory response activity induced by the renin-angiotensin system. Am J Physiol Cell Physiol. 2013;304:C1027-39.
46. Belvederi Murri M, Respino M, Masotti M, Innamorati M, Mondelli V, Pariante C, et al. Vitamin D and psychosis: mini meta-analysis. Schizophr Res. 2013;150(1):235-9.
47. Valipour G, Saneei P, Esmaillzadeh A. Serum vitamin D levels in relation to schizophrenia: a systematic review and meta-analysis of observational studies. J Clin Endocrinol Metab. 2014; 99(10):3863-72.
48. Nerhus M, Berg AO, Kvitland LR, Dieset I, Hope S, Dahl SR, et al. Low vitamin D is associated with negative and depressive symptoms in psychotic disorders. Schizophr Res. 2016;178(1-3):44-9.
49. Nerhus M, Berg AO, Simonsen C, Haram M, Haatveit B, Dahl SR, et al. Vitamin D deficiency associated with cognitive functioning in psychotic disorders. J Clin Psychiatry. 2017 May 9. doi: 10.4088/JCP.
50. Lally J, Gardner-Sood P, Firdosi M, Iyegbe C, Stubbs B, Greenwood K, et al. Clinical correlates of vitamin D deficiency in established psychosis. BMC Psychiatry. 2016;16:76.
51. McGrath J. Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia? Schizophr Res. 1999;40(3):173-7.
52. Taylor AE, Burgess S, Ware JJ, Gage SH, Richards JB, Davey Smith G, et al. Investigating causality in the association between 25(OH)D and schizophrenia. Sci Rep. 2016;6:26496.
53. McGrath JJ, Eyles DW, Pedersen CB, Anderson C, Ko P, Burne TH, et al. Neonatal vitamin D status and risk of schizophrenia: a population-based case-control study. Arch Gen Psychiatry. 2010;67(9):889-94.
54. Sullivan S, Wills A, Lawlor D, McGrath J, Zammit S. Prenatal vitamin D status and risk of psychotic experiences at age 18 years-a longitudinal birth cohort. Schizophr Res. 2013;148(1-3):87-92.
55. Hedelin M, Löf M, Olsson M, Lewander T, Nilsson B, Hultman CM, et al. Dietary intake of fish, omega-3, omega-6 polyunsaturated fatty acids and vitamin D and the prevalence of psychotic-like symptoms in a cohort of 33,000 women from the general population. BMC Psychiatry. 2010 May 26;10:38.
56. Saneei P, Salehi-Abargouei A, Esmaillzadeh A. Serum 25-hydroxy vitamin D levels in relation to body mass index: a systematic review and meta-analysis. Obes Rev. 2013;14(5):393-404.
57. McGrath J, Saari K, Hakko H, Jokelainen J, Jones P, Järvelin MR, et al. Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study. Schizophr Res. 2004;67(2-3):237-45.
58. Dealberto MJ. Clinical symptoms of psychotic episodes and 25-hydroxy vitamin D serum levels in black first-generation immigrants. Acta Psychiatr Scand. 2013;128(6):475-87.
59. Thakurathi N, Stock S, Oppenheim CE, Borba CP, Vincenzi B, Seidman LJ, et al. Open-label pilot study on vitamin D(3) supplementation for antipsychotic-associated metabolic anomalies. Int Clin Psychopharmacol. 2013;28:275-82.
60. Chiang M, Natarajan R, Fan X. Vitamin D in schizophrenia: a clinical review. Evid Based Ment Health. 2016;19(1):6-9.
61. Mitchell ES, Conus N, Kaput J. B vitamin polymorphisms and behavior: evidence of associations with neurodevelopment, depression, schizophrenia, bipolar disorder and cognitive decline. Neurosci Biobehav Rev. 2014;47:307-20.
62. Kennedy DO. B vitamins and the brain: mechanisms, dose and efficacy- a review. Nutrients. 2016;8(2):68.
63. Nishi A, Numata S, Tajima A, Kinoshita M, Kikuchi K, Shimodera S, et al. Meta-analyses of blood homocysteine levels for gender and genetic association studies of the MTHFR C677T polymorphism in schizophrenia. Schizophr Bull. 2014;40(5):1154-63.
64. Wang D, Zhai JX, Liu DW. Serum folate levels in schizophrenia: A meta-analysis. Psychiatry Res. 2016;235:83-9.
65. Cao B, Wang DF, Xu MY, Liu YQ, Yan LL, Wang JY, et al. Vitamin B12 and the risk of schizophrenia: A meta-analysis. Schizophr Res. 2016;172(1-3):216-7.
66. Song X, Fan X, Li X, Kennedy D, Pang L, Quan M, et al. Serum levels of BDNF, folate and homocysteine: in relation to hippocampal volume and psychopathology in drug naïve, first episode schizophrenia. Schizophr Res. 2014;159(1):51-5.
67. Roffman JL, Brohawn DG, Nitenson AZ, Macklin EA, Smoller JW, Goff DC. Genetic variation throughout the folate metabolic pathway influences negative symptom severity in schizophrenia. Schizophr Bull. 2013;39(2):330-8.
68. Levine J, Stahl Z, Sela BA, Ruderman V, Shumaico O, Babushkin I, et al. Homocysteine-reducing strategies improve symptoms in chronic schizophrenic patients with hyperhomocysteinemia. Biol Psychiatry. 2006;60(3):265-9.
69. Bao Y, Ibram G, Blaner WS, Quesenberry CP, Shen L, McKeague IW, et al. Low maternal retinol as a risk factor for schizophrenia in adult offspring. Schizophr Res. 2012;137(1-3):159-65.
70. Caso J, Balanza-Martinez V, Palomo T, Garcia-Bueno B. The microbiota and gut-brain axis: contributions to the immunopathogenesis of schizophrenia. Curr Pharm Des. 2016; 22(40):6122-33.
71. Fond G, Boukouaci W, Chevalier G, Regnault A, Eberl G, Hamdani N, et al. The "psychomicrobiotic": Targeting microbiota in major psychiatric disorders: A systematic review. Pathol Biol (Paris). 2015;63:35-42.
72. Arroll MA, Wilder L, Neil J. Nutritional interventions for the adjunctive treatment of schizophrenia: a brief review. Nutr J. 2014;13:91.
73. Dinan TG, Stanton C, Cryan JF. Psychobiotics: a novel class of psychotropic. Biol Psychiatry. 2013;74:720-6.
74. Dickerson FB, Stallings C, Origoni A, Katsafanas E, Savage CL, Schweinfurth LA, et al. Effect of probiotic supplementation on schizophrenia symptoms and association with gastrointestinal functioning: a randomized, placebo-controlled trial. Prim Care Companion CNS Disord. 2014;16(1). pii: PCC.13m0157.
75. Tomasik J, Yolken RH, Bahn S, Dickerson FB. Immunomodulatory effects of probiotic supplementation in schizophrenia patients: a randomized, placebo-controlled trial. Biomark Insights. 2015; 10:47-54.
76. Guo Z, Liu XM, Zhang QX, Shen Z, Tian FW, Zhang H, et al. Influence of consumption of probiotics on the plasma lipid profile: a meta-analysis of randomised controlled trials. Nutr Metab Cardiovasc Dis. 2011;21:844-50.
77. Kadooka Y, Sato M, Ogawa A, Miyoshi M, Uenishi H, Ogawa H, et al. Effect of Lactobacillus gasseri SBT2055 in fermented milk on abdominal adiposity in adults in a randomised controlled trial.

Br J Nutr. 2013;110:1696-703.
78. Roffman JL, Lamberti JS, Achtyes E, Macklin EA, Galendez GC, Raeke LH, et al. Randomized multicenter investigation of folate plus vitamin B12 supplementation in schizophrenia. JAMA Psychiatry. 2013;70(5):481-9.
79. Sarris J, Logan AC, Akbaraly TN, Amminger GP, Balanzá-Martínez V, Freeman MP, et al. International Society for Nutritional Psychiatry Research (ISNPR) consensus position statement: nutritional medicine in modern psychiatry. World Psychiatry. 2015;14(3):370-1.