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LEADING ARTICLE

Nutritional Psychiatry: From Concept to the Clinic

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Abstract
The field of 'nutritional psychiatry' has evolved with rapidity over the past several years, with an increasing amount of dietary or nutrient-based (nutraceutical) intervention studies being initiated, and more preclinical and epidemiological data being available. This emergent paradigm involves the clinical consideration (where appropriate) of prescriptive dietary modification/improvement, and/or the select judicious use of nutrient-based supplementation to prevent or manage psychiatric disorders. In the last several years, significant links have increasingly been established between dietary quality and mental health (although not all data are supportive). Maternal and early-life nutrition may also affect the mental health outcomes in offspring. In respect to nutraceutical research, like with many recent conventional drug studies, results are fairly mixed across the board, and in many cases there is not emphatic evidence to support the use of nutraceuticals in various psychiatric disorders. This may in part be due to a preponderance of recent studies within the field revealing marked placebo effects. Due to current indicators pointing towards mental disorders having an increasing burden of disease, bold and innovative approaches on a societal level are now required. In light of the widespread use of nutrient supplements by those with and without mental disorders, it is also critical that scientifically rigorous methodologies be brought to bear on the assessment of the efficacy of these supplements, and to determine if, or what dose of, a nutrient supplement is required, for whom, and when, and under what circumstances. More simple studies of additional isolated nutrients are not of great benefit to the field (unless studied in supra-dosage in an individualised, biomarker-guided manner), nor, based on recent data, is the research of 'shotgun' formulations of nutraceuticals. The next critical step for the field is to design psychiatric interventional studies for both dietary modification and nutraceuticals, based on more of a personalised medicine approach, using biomarkers (e.g. nutrient deficiencies, inflammatory cytokine levels, genomic assessment, microbiome analysis) and a person's dietary patterns and individual macro/micronutrient requirements.

1 Introduction

'Nutritional psychiatry' (NP) has evolved with rapidity over the past several years, with an increasing amount of dietary or nutrient-based (nutraceutical) intervention studies being initiated, and more preclinical and epidemiological data being available. The emergent paradigm of NP involves the clinical consideration (where appropriate) of prescriptive dietary modification/improvement, and/or the select judicious use of nutrient-based supplementation to prevent or

Key Points

'Nutritional psychiatry' as a distinct field has grown in recent years, with a range of data showing varying levels of evidence for the impact of diet on mental health, and the select use of various nutraceuticals for assistance in treating a range of psychiatric disorders.

More recent research is finding that complex nutraceutical formulations may not necessarily be more beneficial for treating mood disorders, and a more targeted personalised biomarker-guided approached is advised.

Clinician education and public policy is advised to reflect current findings regarding the importance of nutrition in the maintenance of mental health.

Early intervention studies are advised to assess the potential of nutritional medicine for addressing the tumescence of mental disorders.

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manage psychiatric disorders. It is widely understood in the field that investment into new psychiatric medications has slowed, while our recognition of the immense burden of mental disorders has grown [1, 2]. Due to this, there is now an urgent need to increasingly identify modifiable targets to reduce the incidence of mental disorders. The paradigm shift of NP offers an additional treatment approach via the targeting of key modifiable elements, for the prevention and treatment of mental disorders. However, this approach should be regarded as part of an integrated model involving other important lifestyle medicine elements, including physical activity and prescriptive exercise, regulation of sleep and relaxation, and consideration of several other health promotion activities [3, 4]. Significant changes in dietary habits (along with an increased sedentary lifestyle, and alcohol, drug/tobacco use), and an increased chronic allostatic load for most urbanised people, have resulted in an epidemic of ill-health [5]. The major noncommunicable diseases, including mental disorders, are estimated to cumulatively cost the global community US$47 trillion over the years to 2020 [6]. Due to this, a shift in clinical treatment and policy within the field of mental health is needed, having a greater focus on the importance of nutrition [7].

The purpose of this review is to provide a platform to discuss where the field of NP is currently positioned in its endeavours to move towards a more integrated paradigm within psychiatry, whereby nutritional considerations can be considered mainstream. It provides an update since an international collaboration of academic authors from the membership of the International Society for Nutritional Psychiatry Research (ISNPR) published an index paper on the emergent field in 2015 [8]. This personal perspective briefly outlines the current state of evidence, as well as presents limitations and challenges, while presenting a vision for the next crucial steps for the field.

2 Nutritional Psychiatry as a Construct

In contemporary academic literature, the concept of nutrition (in respect to diet, nutritional deficiencies, and obesity) being considered within psychiatry is evident in a *Nutrition Reviews* commentary around the early 1950s [9, 10]. Discussion was provided on how "certain neuropsychiatric disorders are accompanied by grossly inadequate or excessive food intakes", with additional reference to "nutritional deficiencies which result in neuropsychiatric symptoms". In more recent years, a group of research and clinician academics formed the ISNPR. Several years ago, authors from the ISNPR published a suite of papers outlining elements concerning the field (in addition to a consensus position statement) [5, 8, 11, 12], with more recent updates also provided on the progress of the field [13, 14]. As detailed in the ISNPR position statement published in *World Psychiatry* [12], one of the key platforms articulated "… *we advocate that evidence-based nutritional change should be regarded as an efficacious and cost-effective means to improve mental health. In addition to dietary modification, we recognise that nutrient-based (nutraceutical) prescription has the potential to assist in the management of mental disorders at the individual and population level. Many of these nutrients have a clear link to brain health, including: omega-3s, B vitamins (particularly folate and B12), choline, iron, zinc, magnesium, S-adenosyl methionine (SAMe), vitamin D, and amino acids. While we advocate for these to be consumed in the diet where possible, additional select prescription of these as nutraceuticals may also be justified*".

The advocation of dietary modification is regarded for modern societies to shift back towards a traditional whole-food dietary pattern, comprising higher intakes of foods such as vegetables, fruits, seafood, whole grains, lean meat, nuts, and legumes, with avoidance of processed foods (including trans fats, and refined carbohydrates and sugars). This is due to the understanding that aside from the brain requiring an immense supply of macronutrients, the diet (or supplementary nutrients) provide a range of critical co-factors and phytochemicals that additionally may have important effects which may modify brain and mental health. These effects include antioxidant, neurogenesis, anti-inflammatory, and microbiome- and immune-modifying activities [13]. The field of NP seeks to understand the mechanisms underpinning the influence of diet and its potential application, in addition to the use of select nutraceuticals to address nutrient deficiencies, and for the modulation of specific neurobiological pathways.

3 Current Data in the Field

In the last several years, significant links have increasingly been established between dietary quality and mental health. The effect of this link may be apparent via the quality of both maternal nutrition and the early-life nutrition of babies and toddlers potentially affecting subsequent childhood mental health [15]. Data suggest that severe maternal macronutrient deficiencies during critical developmental periods of pregnancy may be implicated in the pathogenesis of depressive and psychotic disorders in offspring [16, 17]. Many epidemiological studies, including longitudinal studies (in maternal cohorts and their offspring, children, adolescents, and adults), have demonstrated significant associations between healthy dietary patterns and a reduced risk and prevalence of symptoms such as depression [18]. Furthermore, systematic reviews have tentatively found a relationship between 'unhealthy' dietary patterns and poorer mental health in children, adolescents, and adults [19]. As an example, the

results from the large European PREDIMED study demonstrated a reduced risk for incident depression in people with type 2 diabetes who were randomised to a Mediterranean diet with nuts, compared with a low-fat diet control group [20]. Recent data from the MoodFOOD prevention study have shown that in a sample of participants ($n = 990$), those with subsyndromal depressive symptoms and a history of depression have higher levels of emotional and uncontrolled eating, and lower levels of cognitive restrained eating compared with those without a former depression diagnosis [21]. Our recently published meta-analysis of 16 eligible randomised controlled trials (RCTs; $n = 45{,}826$) found that dietary interventions significantly reduced depressive symptoms ($g = 0.28$, 95% confidence interval [CI] 0.10–0.45, $p = 0.002$) [22]. However, no effect for dietary interventions was observed on anxiety outcomes ($g = 0.10$, 95% CI − 0.04 to 0.24, $p = 0.15$). Thus, given the early age of onset for mood disorders, early dietary intervention is indicated as a key modifiable interventional target for preventing the potential incidence of many common mental disorders, in particular in those with emerging metabolic or inflammatory conditions [20, 23].

There are data (with varying levels of evidence) also suggesting that select nutraceuticals may provide an array of neurochemical modulatory activities that are beneficial in managing various psychiatric disorders. For example, there are dozens of double-blind RCTs in the field utilising a range of nutrients for mood disorders: omega-3 fatty acids, *S*-adenosyl methionine (SAMe), *N*-acetyl cysteine (NAC), zinc, B vitamins (including folic acid), and vitamin D [24–26]. A specific example of a nutraceutical that is the most studied and has a variety of clinical trials providing supportive evidence concerns omega-3s (in particular eicosapentaenoic acid; EPA) for disorders such as major depressive disorder (MDD) and bipolar depression (as adjunctive interventions). This is especially pertinent regarding its adjunctive use, with a meta-analysis revealing a highly significant effect with a moderate to strong clinical effect size compared with placebo [27].

In respect to taking a 'meta-view' of the nutraceutical data across the field, we recently conducted an umbrella review that was led by Firth et al. [28]. We identified, synthesised and appraised a total of 33 meta-analyses of RCTs ($n = 10{,}951$) reporting on the efficacy and safety of nutrient supplements in common and severe mental disorders. The strongest evidence was found for omega-3 (in particular EPA) as an adjunctive treatment for MDD, and, to a lesser extent, attention-deficit/hyperactivity disorder (ADHD), with evidence lacking for schizophrenia. Positive effects from RCTs of high-dose methylfolate was revealed in MDD. There was emergent evidence for NAC as a useful adjunctive treatment in mood disorders and schizophrenia.

4 Limitations and Challenges

While advances have been made in terms of academic contributions, and an inaugural NP conference occurring in Washington DC in 2017 (with the next conference due in London in October 2019) [29], there are still a range of challenges in the field at present. In respect to nutraceutical research, like with many recent conventional drug studies, results are fairly mixed across the board, and in many cases there is not emphatic evidence to support the use of nutraceuticals in various psychiatric disorders. This may in part be due to a preponderance of recent studies within the psychiatric field revealing marked placebo effects [30]. This is not limited to pharmaceutical studies, and, for example, our recent nutraceuticals studies in the treatment of MDD have shown a placebo response rate (> 50% reduction on the depression scale) of over 50% [31, 32]. The result of such high placebo response rates is that in studies with modest sample sizes, a response rate would need to be approximately > 60% in order to statistically separate from placebo to provide a significant effect. This is fairly unheard of within the field of psychiatry.

Our original ISNPR perspective was that an ideal approach in nutraceutical studies may often involve combining nutrients together to match the natural physiological requirements of the body, and to also better reflect the broad array of nutrients that are present in food. In essence, this perspective implies that such a prescriptive approach may potentially improve people's responses beyond an effect garnered from isolated nutrients [8]. Indeed, in some instances, data show that a synergistic effect from combined nutrients may be of benefit, for instance from a complex micronutrient formulation for psychiatric disorders [33]. For example, an 8-week, double-blind RCT involving 80 adults with ADHD revealed a significant effect on self and observer rating symptom scales in favour of the micronutrient over placebo [34]. However recent research, including our own, has shown that, for example in depression, 'more is not necessarily better' when it comes to complex formulations [31]. Mood disorder clinical trials have recently been conducted showing that nutraceutical combinations (regardless of being based on sound mechanistic effects) may not have a more potent effect, and in some cases placebo has been more effective [31, 35, 36]. These combinations commonly involve nutrients such as omega-3, folate-based nutrients, NAC, vitamin D, B vitamins, selenium, and various minerals.

In regard to dietary data, there is the challenge with analysing large data sets in respect of assessment quality and diversity, while smaller pooled studies often showing marked methodological differences. For example, most studies assessing the relationship between dietary quality and mental health outcomes have used a range of assessment

scales as a way of analysing a person's diet [19, 37], many of which are open to recall bias. In particular, use of the Food Frequency Questionnaire (used commonly) is subject to an individual's recall bias and does not capture the dietary difference of many—it does not elucidate a range of beneficial phytonutrients that occur from a variety of plant-based sources. A theoretical gold standard approach would be to match, weigh, and biochemically analyse a participant's food and beverage consumption, however the cost and logistics of this are practically prohibitive. In terms of intervention studies, while laudable, they are impossible to adequately blind, and are fraught with expectancy bias from participants who may be psychologically primed towards a positive belief about the potential effect of dietary change. Regardless, the recent interventional studies (*cf.* [38]) such as the SMILES study have the advantage of being able to ascertain whether clinician prescription of a wholefood diet in those with poorer quality diets may have beneficial effects.

5 Future Foci

While the current limitations are outlined above, there are several considerations that may address these and advance the field enough to provide more concrete guidelines for both clinicians and the public. In regard to the challenge of undertaking interventional diet studies, more precision is needed to interrogate potential mediating biomarkers. In particular, the effect of modulating inflammation (which is evident in many psychiatric disorders) is quite tantalising. Recent data increasingly show that a pro-inflammatory diet may be linked, for example, to mood and psychotic disorders, while an 'anti-inflammatory' diet may be potentially protective [23, 39, 40]. A more fine-tuned methodological approach combining an analysis of inflammatory biomarkers and microflora in larger intervention studies using an 'anti-inflammatory' diet (high in a range of fruits and vegetables and essential fatty acids), alongside 'hard' depression outcomes, including clinician-rated assessments, would be of great benefit to the field. This can be further augmented with neuroimaging techniques, and assessment of relevant pharmacogenetics and gene expression analysis. It is also important to test baseline nutrient levels (of the studied nutraceutical) and consider exclusion of high-nutrient status participants (or at least stratify between groups based on this, also covarying for such during later statistical analyses). Finally, it is crucial for more nutritional medicine studies to focus on early intervention in order to assist in addressing the actual tumescence of mental disorders.

Aside from applications in dietary research, the aforementioned can be extended to the nutraceutical field, where a personalised medicine approach to research and clinical prescription is also advised. The nutraceutical 'shotgun' approach is increasingly being found to be no more effective than placebo, and it may be that a more targeted approach based on prescribing due to specific nutrient deficiencies or biological aberrations linked to the mental disorder may be of most benefit. To this end, science needs to advance to provide greater understanding as to the individual biological underpinnings of psychiatric disorders, with clinical trials of specific nutraceuticals being prescribed based on this information. For example, a person with depression may present with high inflammatory markers (e.g. C-reactive protein, tumour necrosis factor-α, and interleukin-6) and thus may be more appropriate for omega-3 [41], or, for instance, someone with a poor antioxidant status may find NAC of more benefit [25]. However, it is recognised that not all data are currently supportive of biomarker-informed treatment [42], and that various subtypes of mood disorders with varying pathogenic influences exist.

Every subfield often believes they have the silver bullet, however it is evident to date that no specific intervention is indeed that within psychiatry, and thus the field of NP also needs to be recognised to sit within a larger overarching treatment paradigm—a truly 'integrated care' model approach, as advocated by myself and colleagues [43, 44]. For example, this is especially evident with depression, where the psychosocial influence on mood is inescapable. As mentioned, high placebo response rates are common, and it is unlikely that any nutraceutical intervention (or pharmaceutical intervention) can constantly surpass placebo response rates of > 50% reduction in affective disorder studies. One potential reason for this could involve inflated 'expectancy bias' that may occur because participants are increasingly recruited from internet-focused advertising, which may target psychologically primed people via search algorithms. This issue was raised by some academics critiquing recent dietary and nutraceutical depression studies [31, 45, 46], highlighting that targeted web-based recruitment may selectively recruit people with an expectancy bias towards the advertised active intervention. However, this is a concern more broadly for all current clinical trials that use web-based recruitment and selective advertising. Due to this, more precision is often needed in trial designs, in addition to covariance in data analysis with a baseline assessment of participant bias (using a relevant assessment scale, or excluding participation in those with high-expectancy bias). Non-targeted opaque advertising may also assist in reducing the participation of those with strong belief in the effectiveness of nutritional interventions; however, in consideration of how challenging it is to recruit for psychiatric studies, this may not be feasible.

In terms of general translation of the field more broadly, given the current changes related to growing/rapid urbanicity and globalisation of the food industry, resulting in profound

shifts away from traditional dietary patterns, there is still a clear imperative to fully determine how dietary modification/improvement and/or multinutrient interventions can influence mental health. The current state wherein populations in both developed and emerging economies preferentially consume nutrient-poor, energy-dense, highly processed foods is detrimental. In essence, many societies are nutritionally undernourished while being overfed. More assertive action is required to influence governments to take more forthright actions to both improve the quality of food and promote healthier dietary practices (within the context of their culture). This is critical in order to address the substantial burden of disease, including mental ill health, resulting from unhealthy processed diets laden with sugars, trans fats, and low in fibre and nutrients. While there is significant lobbying pressure by parts of the food industry on government, courage is needed by politicians to address the literal 'elephant' in the room. While it is recognised that freedom of choice should not be curtailed, there are policies that can be enacted in the same way in which smoking was approached. Such policies are advised to stimulate significant public change in dietary habits back towards a traditional wholefood diet, educating the public and clinicians about the role of nutrients in the brain, and the link between nutrition and mental health.

6 Conclusions

Psychiatry is at a critical juncture, with the current pharmacologically focused model having achieved only modest benefits in addressing the global burden of poor mental health. Current indicators point towards mental disorders having an increased burden of disease that will continue to rise globally over the coming decades [2]. Due to this, bold and innovative approaches on a societal level are needed now. Over the last several years there has been a rapid growth in high-quality research related to nutrition and mental health and, increasingly, the impact of the NP field is growing and is influencing clinical practice. In light of the widespread use of nutrient supplements by those with and without mental disorders, it is also critical that scientifically rigorous methodologies be brought to bear on the assessment of the efficacy of these supplements, and to determine the most suitable applications. More simple studies of additional isolated nutrients are not of great benefit to the field (unless studied in supra-dosage in an individualised biomarker-guided manner), nor, based on recent data, is the research of 'shotgun' formulations of nutraceuticals. The next critical step for the field is to design psychiatric interventional studies for both dietary modification and nutraceuticals, based on more of a personalised medicine approach, using biomarkers (e.g. nutrient deficiencies, inflammatory cytokine levels, genomic assessment, microbiome analysis) and a person's dietary patterns and individual macro/micronutrient requirements. Early intervention research is also needed to study nutritional intervention at the crucial developmental stage.

From this resultant research, the evidence needs to be communicated to clinicians and the wider public, the former via implementation through educational institutions and the latter via public health campaigns. Formal education to clinicians from a broad range of fields should include training focusing on the role of diet and nutrients on brain function and mental health. We are currently at the precipice of a renaissance where nutrition is increasingly being regarded as a key pillar of mental health, and, over time, public policy will no doubt reflect this evolving recognition.

Compliance with Ethical Standards

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