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Review

Nutritional Aspects of Depression

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Abstract
Several nutrition, food and dietary compounds have been suggested to be involved in the onset and maintenance of depressive disorders and in the severity of depressive symptoms. Nutritional compounds might modulate depression associated biomarkers and parallel the development of depression, obesity and diabetes. In this context, recent studies revealed new mediators of both energy homeostasis and mood changes (i.e. IGF-1, NPY, BDNF, ghrelin, leptin, CCK, GLP-1, AGE, glucose metabolism and microbiota) acting in gut brain circuits. In this context several healthy foods such as olive oil, fish, fruits, vegetables, nuts, legumes, poultry, dairy and unprocessed meat have been inversely associated with depression risk and even have been postulated to improve depressive symptoms. In contrast, unhealthy western dietary patterns including the consumption of sweetened beverage, refined food, fried food, processed meat, refined grain, and high fat diary, biscuits, snacking and pastries have been shown to be associated with an increased risk of depression in longitudinal studies. However, it is always difficult to conclude a real prospective causal relationship from these mostly retrospective studies as depressed individuals might also change their eating habits secondarily to their depression. Additionally specific selected nutritional compounds, e.g. calcium, chromium, folate, PUFAs, vitamin D, B12, zinc, magnesium and D-serine have been postulated to be used as ad-on strategies in antidepressant treatment. In this context, dietary and lifestyle interventions may be a desirable, effective, pragmatical and non-stigmatizing prevention and treatment strategy for depression. At last, several medications (pioglitazone, metformin, exenatide, atorvastatin, gram-negative antibiotics), which have traditionally been used to treat metabolic disorders showed a certain potential to treat depression in first randomized controlled clinical trials.

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Introduction

By the year 2020, depression is projected to reach second place in the ranking of disability adjusted life years calculated for all ages by the World Health Organization [1]. Depression is a multifaceted condition with diverse biological and environmental causes and has therefore been bidirectionally associated with a 1.5 to 6 fold risk to develop cardiovascular diseases, diabetes, epilepsy, stroke, Alzheimer`s dementia and cancer [2-8]. Depression is highly associated with obesity, metabolic syndrome and type-2 diabetes, indeed, it has even been discussed to classify depression as metabolic syndrome type II [9-20]. Interestingly, obesity is prospectively related to depression and depression is predictive for the development of obesity [9-20]. In conclusion, depression is a strong and statistically significant predictor of dietary quality and body mass index, i.e. higher scores in depressive symptomatology are associated with lower scores in dietary quality and an increased body mass index [21].

Nutritional influence on hormonal and neurotransmitter state

Biological systems of nutritional influence and depression are highly connected, i.e. nutrition activates hormonal, neurotransmitter and signaling pathways in the gut which modulate brain functions like appetite, sleep, energy intake, neurogenesis, reward mechanisms, cognitive function and mood [2, 20, 22-25] see Fig. 1. These changes again modulate eating behavior and might chronically result in stress-related disorders, affective disorders and dementia. Some relevant known players of this complex interacting system are for example ghrelin, leptin, the lipid endocannabinoid system, insulin growth hormone (IGF), insulin, advanced glycosylation endproducts (AGEs), corticosteroids, cholecystokinin (CCK), neuropeptide Y (NPY), glutamate, glucose, insulin, GABA, gastrin-releasing peptide and brain-derived neurotrophic factor (BDNF) [2, 20, 22-60].

CCK is a classical gut hormone released in the small intestine when fats and proteins are ingested. CCK is, however also a transmitter in central and intestinal neurons. Of note, CCK is one of the most powerful experimental panic inductors and its bolus injection leads to panic attacks and increased stress hormones [26, 29, 30]. The blockade of CCK can be exerted by antidepressant drugs, reverses depressive behavior, prevents HPA axis hyperactivity and can even lead to mania [26, 29, 30].

Another intermediator is gastrin-releasing peptide, which acts in the hippocampus and in the amygdala, where it regulates synaptic plasticity, neurogenesis and aspects of anxious and depressive behavior [27].

NPY was initially described as a cotransmitter of sympathetic neurons because it stimulates stress response, food intake, sleep and inflammatory processes [28, 35]. In this context, NPY integrates complex somatic symptoms of depression and anxiety states and has been found to play a role in the pathomechanisms of both anxiety and depression [35].

BDNF is a mediator of food intake control via reward-related behavior [25], modulates vagal afferent gastrointestinal impulses and thereby drives overeating and weight gain associated with increased meal size and frequency [2, 31]. The deletion of BDNF leads to obesity, hyperphagia, overeating, weight gain and abdominal adipositas [31], which are often clinically often observed symptoms in depressed individuals. BDNF is involved in the vulnerability to depression and the effects of antidepressant treatment [2, 25, 32, 33]. Additionally, BDNF modulates neuronal plasticity, forms neuronal networks, promotes neurogenesis, synaptogenesis and resilience to depressive disorders [33, 34, 37].

Despite growing evidence on the biology of ghrelin, relatively little is known about the exact molecular pathways responsible for the biosynthesis and release of ghrelin [38]. The consumption of low amounts of carbohydrates increases ghrelin [38]. Ghrelin regulates central system development and mood, exerts antidepressant effects in mice and men, influences the reward behavior and displays dopaminergic properties [2, 39, 40].

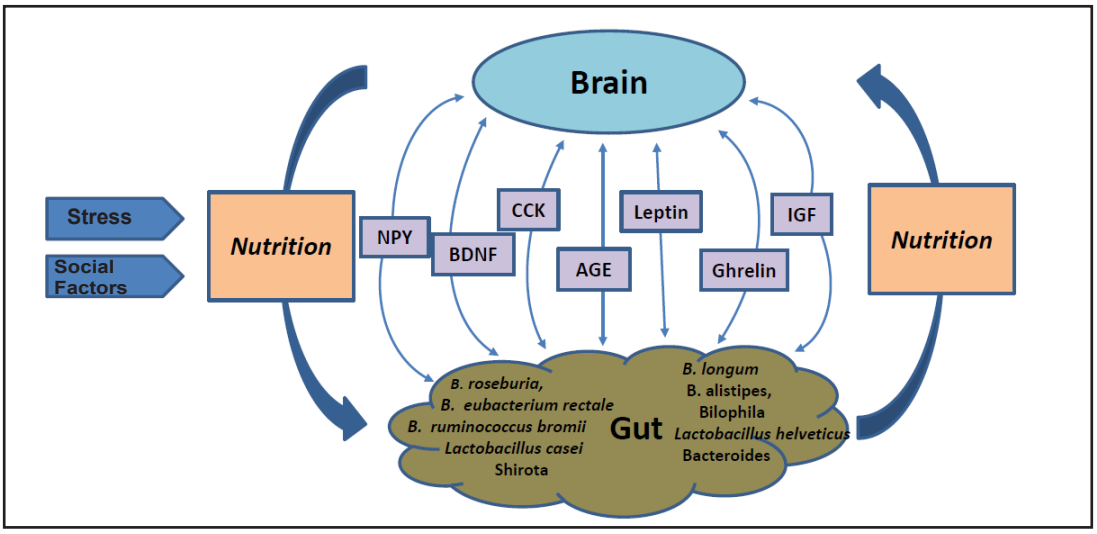

Fig. 1. Environmental, social and psychological factors change the composition of nutrition which is consumed. The compounds of nutrition consumed again change gut microbiota and milieu. Gut hormones again change mood and stress level.

Antidepressant effects were reported following ghrelin administration in mice and men [41, 42].

Leptin has been associated with increased body fat and can be triggered by specific macronutrients, i.e. a high-concentration-fructose diet [43]. Indeed, there might be specific macronutrients which are able to induce leptin resistance independently of the amount of body fat [43]. Leptin is highly associated with depressive symptoms, sleep disturbances, reward behavior, hippocampal plasticity, decreases the basal and feeding-stimulated dopamine release (also in neurons of the ventral tegmental striatum), increases locomotor activity and increases food intake [2, 39, 44-47]. Similarly as BDNF [48-51], leptin acts also via the glycogen synthase kinase-3beta which is a key regulator in controlling hippocampal cell proliferation, mood and response to psychiatric medications [2, 44, 45].

Due to the fact that IGF regulates hippocampal neurogenesis and sensitizes central insulin signaling, its absence leads to depressive symptoms, i.e. a blockade of peripheral IGF reduces exercise induced neurogenesis [52-56]. Correspondingly, in animal models of rats and mice an antidepressant trial of IGF was comparable with the behavioral effects of serotonergic antidepressants and improved frontal cortex neuroplasticity [53, 57]. In line with this an intranasal administration of IGF has been discussed as a plausible and promising treatment option of depression [58].

Chronically impaired peripheral glucose metabolism is connected with late life depression [59]. Indeed, diabetes has been shown to affect the incidence of depression and depressive symptoms are predictive of poor glycemic control in type 2 diabetes mellitus patients and the development of diabetes [5, 12, 16, 60]. In a large population based cohort study depressive symptoms have been shown to be significantly associated with glucose metabolism [12]. In line with this, hyperglycemia and poor glycemic control as measured by glycosylated hemoglobin have been found to reduce hippocampal brain volume 61]. In this context, poor glycemic control was found to be associated with both, poorer memory function and smaller hippocampal volumes [62]. In a recent cross-over, double-blind, placebo-controlled resting state functional imaging study, glucose ingestion induced significantly greater elevations in plasma glucose, insulin, GLP-1 and GIP, while feelings of fullness increased and prospective food consumption decreased relative to fructose. Furthermore, imaging findings suggest that glucose and fructose induce dissociable effects on resting state functional connectivity within the basal ganglia/limbic network, which are probably mediated by different insulin levels [63].

Moreover, hyperglycemia is thought to contribute to elevated serum concentrations of AGEs [64]. AGEs are prooxidant, cytotoxic substances contributing to chronic inflammation and diabetic complications [64-66]. AGEs correlate with insulin resistance and inflammation, which is changed in depressive patients [20, 64]. Also altered cytokine levels had been repeatedly reported in depressed patients [67]. Interestingly, a recent proteomic study suggests that AGEs are involved in first episode major depressed patients, who have not been treated with antidepressants [68]. Indeed, an optimization of the glycemic control and associated prevention strategies might modify not only depression but also the occurrence of dementia [59].

Insulin resistance has further been linked to phosphoinositide 3-kinase (PI3K) signaling which again is central in the development of depressive symptoms [48-51, 69]. Inhibition of PI3K leads to inactivity, memory loss and depressive and anxious behavior [48-51, 69].

Nutrition directly influences intestinal microbiota, which again appear to influence the development of neurotransmitter brain systems and modulate affective and stress-related disorders and pain perception [70-74]. Perturbations and disturbances of microbiota with dietary changes or prebiotics, probiotics or antibiotics can lead to addictive or depressive behavior [75, 76]. Consequently, restoring a disturbed gut microbiome might be a desirable treatment strategy for depression, especially as most of the clinically depressed patients additionally suffer from obesity, weight loss or gain, appetite disturbances and constipation [77-79]. In rodents the use of Lactobacillus sp., Bifidobacteria sp., L. helveticus, B. longum, L. rhamnosus, L. helveticus and Lactobacillus farciminis helped in the reduction of anxiety and depressive symptoms [78].

A first randomized controlled clinical trial shows that a 3-week consumption of a probiotic-containing drinks containing *Lactobacillus casei Shirota* can significantly improve mood at least in healthy volunteers [80]. Similarly, a 30-day consumption of a probiotic mixture containing *Lactobacillus helveticus* and *B. longum* reduced anxiety and depressive symptoms and cortisol in healthy persons [81]. In a randomized controlled trial *L. casei Shirota*, decreased anxiety but not depressive symptoms as measured via the BDI in patients with chronic fatigue syndrome [80] .

Interestingly, also prebiotics result in healthy controls in lower cortisol levels at awakening and improved attention to positive stimuli in an emotional recognition task [82].

The analysis of fecal microbiota of depressed patients revealed an overrepresentation of Bacteroidales, underrepresentation of the Bacteroidetes phylum and Oscillibacter an underrepresentation of Lachnospiraceae and Alistipes and a decrease in Bacteroidetes [76, 78]. Alistipes have been shown to be easily modified by a dietary intervention, where natural food consisting entirely of animal or plant products is used, increases the abundance of biletolerant microorganisms (Alistipes, Bilophila and Bacteroides) and decreases the levels of Firmicutes, which are able to metabolize dietary plant polysaccharides (Roseburia, Eubacterium rectale and Ruminococcus bromii) [74] .

Association studies between depression and dietary habits

In several prospective partly large studies an unhealthy western dietary pattern was associated with an increased prevalence of depression [83-103]. Moreover, the consumption of sweetened beverage, refined food, fried food, processed meat, refined grain, and high fat intake, biscuit snacking and pastries have been shown to be associated with an increased risk of depression in longitudinal studies [83-103] .

In recapitulation, in a recent large study with about 4500 healthy controls, specific dietary patterns (healthy; unhealthy; sweets; 'Mexican' style; breakfast) predicted 39.8% of the total variance of depression incidence with or without diabetes [91].

On the other hand healthy foods such as the *Japanese diet* (fruit, soy products, vegetables, green tea) or *Mediterranean diet* or other healthy diets containing high amounts of olive oil,

fish, fruits, vegetables, nuts, legumes, poultry, dairy, unprocessed meat have been inversely associated with depression risk [83-103].

However, most of the present studies are retrospective studies, where the exact mechanisms linking mood and meal cannot fully be explained and remain rather correlative, as behavioral changes might determine meal choice long before depression finally occurs. Therefore prospective randomized controlled studies on dietary effects are needed, with one starting at the moment in Australia [90]. In a quasi-experimental study, which examined the impact of a vegan diet on emotional well-being and productivity a weekly dietary instruction for 18 weeks resulted in an improvement in depression, anxiety, and productivity in 292 individuals [94]. Interestingly, vegetarians reported better mood than omnivores despite their negligible intake of EPA/DHA [96, 97], which has also been confirmed in a parallel arm, interventional two-week randomized controlled trial [96, 97] on a 2 week subclinical level in healthy volunteers who consumed vegetarian food [96, 97]. In a comparative study between a high- and a low-sucrose, low-fat, hypoenergetic diet 43% of the total daily energy versus 4% intake was sucrose. In this study in 42 women no differences have been found concerning mood and depression and hunger scores [98].

Prospective controlled randomized studies on diet and depression

In a prospective cohort study to investigate the relations between dietary glycemic index, glycemic load, and other carbohydrate measures (added sugars, total sugars, glucose, sucrose, lactose, fructose, starch, carbohydrate) and depression in 87,618 postmenopausal women a progressively higher dietary glycemic index was found to be associated with increasing odds of incident depression [99]. Higher consumption of dietary added sugars was associated with increasing odds of incident depression [99]. Higher consumption of lactose, fiber, nonjuice fruit, and vegetables was significantly associated with lower odds of incident depression [99]. In elderly subjects a dietary coaching might be effectfull and result in a decrease in depressive symptoms and an enhanced well-being over 2 years and even less hospital admissions [100, 101]. In a further randomized controlled trial, the mediterranean diet combined with nuts reduced the risk for depression [92]. In sixty subjects with metabolic syndrome a six month weight loss programme reduced not only body fat mass but depressive symptoms, anxiety, leptin and CRP and increased dopamine and serotonine [102]. Another study focused on long term effects of a low protein diet on depressive symptoms and the quality of life in elderly patients with Type 2 diabetes [103]. After randomly selection, patients were enrolled in a 30 months low protein diet on either 6 days a week or seven days a week. Although Creatine Clearance similarly decreased in both groups, depression score and cognitive outcome improved significantly more in the seven days a week group than in the 6 days a week [103]. Using evidence from a randomized depression prevention trial for older adults, it has been confirmed that coaching in healthy dietary practices are effective in the protection of episodes of major depression and in the reduction of depressive symptoms to an extent from 40% to 50% [100].

Special nutritional compounds which could influence depression risk

Intakes of magnesium, calcium, iron, and zinc were inversely associated with the prevalence of depressive symptoms [104]. Zinc and magnesium are potent antagonists of the NMDA receptor and the deficiency of both of them may lead to functional NMDA receptor hyperactivity. Several animal and human studies have shown that low dietary zinc plays a role in the reduction of depression. Recently, two prospective cohorts show that high dietary zinc intake was associated with a decreased incidence of depression in both men and women [105]. In a randomized, blinded and placebo-controlled study, zinc supplementation was shown to improve mood states and reduce anger and hostility [106].

Magnesium gates the activity of NMDA receptors and indeed magnesium restriction is associated with reduced amygdala-hypothalamic protein levels of GluN1-containing NMDA complexes [107, 108]. A preclinical study showed that magnesium reduced depressive symptoms and increased the concentration of a NMDA receptor subcomponent (GluN2B) in the prefrontal cortex [109]. At least in animal trials, highly dosed magnesium increases plasticity and neurogenesis [110]. Moreover, in one randomized study magnesium proved to be comparably effective in the treatment of depression as imipramine, which is an extensively used, tricyclic and highly effective antidepressant drug [111]. Therefore it has been hypothesized that oral administration of magnesium might support an antidepressant effect [112, 113].

Increased polyunsaturated fatty acid (PUFA) and monounsaturated fatty acid (MUFA) concentrations, and high concentrations of plasma total n-3 fatty acids, docosahexaenoic acid, eicosapentaenoic acid, α-linoleic acid, and linoleic acid, were associated with lower scores in the depression scale used [113, 114]. Accordingly, fish consumption has been associated with resilience to depression [115]. However, about 97 double-blind, placebo-controlled, randomized controlled trials on the treatment of depression with PUFAs have been performed since 1965 [116]. In a recent meta-analysis no significant effects of omega-3 FA have been been found in the treatment of depression [116]. Most of the investigations have been performed in small samples and data are mixed [117]. However, the positive effects of fish consumption on depressive disorders might not be exclusively connected with PUFAs as e.g. tyrosine is present in high concentrations in many fishes (160% in tuna when compared with chicken) [118, 119]. Tyrosine is a biological precursor of dopamine, norepinephrine, and epinephrine, a component of thyroxine and triiodothyronine (hypothyreosis is common in 30% of depressive patients) and its deficiency has been implicated in depression [119-122].

Chromium plays a crucial role in glucose and fat metabolism and improves insulin sensitivity in the hypothalamus, which enhances hypothalamic function by increasing glucose use, leading secondarily to an increased synthesis of serotonin, norepinephrine and melatonin [2, 123]. Three pilot trials of chromium indicate an antidepressant effect in patients with unipolar depression when used as adjunctive or monotherapy [2, 124-126].

According to the observation that oxidative stress and inflammation have been connected to the pathophysiology of depression subjects with a diagnosis of major depression consume less fruits, legumes, nuts and seeds, vitamin C, beta carotene, lutein, and zeaxanthin than controls [127]. In two to 28-day lasting, randomized, double-blind, placebo controlled studies, vitamin C was found to have an equivalent effect as a very strong antidepressant medication, i.e. amitriptyline 150 mg/d [128, 129]. In a recent placebo controlled randomized clinical trial adding vitamin C to citalopram did not increase the efficacy of citalopram in major depressed patients [128].

Several reports indicate a high prevalence of folic acid deficiency among patients suffering from psychiatric conditions such as depression, bipolar disorder and cognitive dysfunction disorders [2, 129]. Adequate levels of folate are essential for proper brain functioning [2, 130, 131]. Folate, with vitamins B12 and B6 as catalysing cofactors, influences cognitive performance and mood [2, 132,-134]. Treatment with vitamin B6, vitamin B12, and folic acid reduces the hazard of a major depressive episode compared with placebo among survivors of a stroke and reduces the risk to re-experience a major depressive episode for 7 years about 50% [133, 134]. Several trials have demonstrated efficacy of folic acid in the treatment of unipolar depression [2, 135]. However, in a recent meta-analysis of 52 randomized controlled trials the number of available trials remains small and heterogeneity between studies high. The results of these meta-analyses suggest that treatment with folate and vitamin B12 does not decrease the severity of depressive symptoms over a short period of time, but may be helpful in the long-term management of special populations [133, 134].

In a randomised, double blind, parallel group, placebo-controlled trial in which participants, aged 14-24 years, at increased familial risk of mood disorder, were randomized to folic acid (2.5 mg daily) or identical placebo liquid for a maximum of 36 months the incidence

of mood disorder in the folic acid and placebo groups were 14.3% and 17.9% respectively [136]. This effect was not statistically significant, however, there was post-hoc evidence that folic acid delayed the time to onset of mood disorder in those participants who became unwell [136].

In a cohort of 1745 pregnant Japanese women a higher intake of levels of yogurt and calcium was independently related to a lower prevalence of depressive symptoms during pregnancy [137]. The amount of calcium is proportional to the quantity of activated CaMKII [138]. A calcium influx during LTP induction triggers the activation of calcineurin and Calcium/calmodulin-dependent protein kinase II (CaMKII) in dendritic spines [138]. CaMKII activation has been linked to antidepressant treatment mechanisms [139]. However, there is no direct causal link between central effect and peripheral absorbed calcium, so in a recent epidemiological study the supplementation of vitamin D and calcium in about 36.000 postmenopausal women no significant effect on mood outcome has been observed [140].

In a large sample of 12.500 adults higher vitamin D values showed less incidence for depressive disorders and also depression related personality traits seem to correlate with vitamin D serum level, i.e. vitamin D is connected to openness and extraversion [141, 142]. In terms of treatment vitamin D has been suggested to be helpful in subgroups of depressed persons, i.e. patients with saisonal affective disorder, less activity and older age [143].

It has been shown that D-serine interacts with the GluN1 unit of the NMDA receptor. In animal studies a single and acute D-serine administration leads to several behavioural effects of an antidepressant-like type which are for example reduced immobility in the forced swim test beneath many others [144]. Elevated D-serine concentrations in the central nervous system might lead to a depression-protected phenotype in mice [145]. Authors from these preliminary basic research studies suggest that chronic dietary D-serine supplementation might lead to improvement of mood disorders [145].

However, nutritional interventions for major depression have not been studied extensively yet and there are only pilot studies available. Therefore, to the knowledge of the author, there is no high level evidence (large prospective RCTs, meta-analyses) for an effective nutritional intervention for the treatment of major depression. Accordingly, the current standard treatment guidelines do not include any nutritional aspect for the prevention or treatment of major depression.

Experimental medications focusing primarily on metabolic aspects and successful in antidepressant treatment

At least in terms of cardiovascular protection recent meta-analyses show that several medications (statins, aspirin, beta-blockers, fibrates, niacin, ACE inhibitors) do not reach the effect size of successful life style interventions as *Mediterranean* diet, consumption of fruits and vegetables, moderate alcohol use, smoking cessation and physical activity [146]. However, the adherence to life style modifications might be less feasible for depressed patients. However, a recent randomized, double-blinded, multicentre, two arm-parallel clinical trial, with a 12 month follow-up showed in a sample of 273 primary care patients that hygienic-dietary written recommendations on diet, exercise, light exposure and sleep hygiene were not successful [147]. In the last years several medications focusing on metabolic abnormalities have been proposed in the treatment of depression.

Pioglitazone, which is an insulin sensitizer acts as adjunctive therapy of depressive symptoms in mice and men [148, 149]. In a parallel-arm, double-blind, placebo-controlled design in 138 healthy, overweight women food take inhibitors N-oleyl-ethanolamine (NOE) and epigallocatechin-3-gallate (EGCG) improved insulin resistance and depressive symptoms and binge eating with a high significance [150]. Furthermore, green tea extract consisting of polyphenols, particularly catechins such as EGCG, caffeine, and theanine share an overlap in activity of at least one biochemical pathway, the N-methyl-D-aspartate receptor (NMDAR) pathway. Along this line, beneficial effects of green tea on cognitive functioning [151], in

particular, on working memory processing at the neural system level suggested changes in short-term plasticity of parieto-frontal brain connections [152]. Additionally, evidence was found that the insulin sensitizer pioglitazone in a double-blind placebo-controlled study in 40 patients with major depression showed superiority over placebo during the course of the trial. Therefore the authors state that pioglitazone is a safe and effective adjunctive short-term treatment in patients with moderate-to-severe MDD even in the absence of metabolic syndrome and diabetes [153]. Resulting from a present clinical study in depressive patients with diabetes mellitus treated with metformin authors raise the possibility that supplementary administration of antidiabetic medications may enhance the recovery of depression [154].

Statins have anti-obese properties and their use was associated with a significant reduced occurrence of depression at least in individuals who have had a cardiac event in a prospective clinical trial [155]. In a placebo controlled clinical trial, augmentation of citalopram with atorvastatin improved depressive symptoms assessed with the Hamilton depression rating scale [156]. Also a GLP-1 analogue therapy, i.e. exenatide has been discussed to exert antidepressant properties [157]. As compared with new insulin, treatment satisfaction, well-being score and the Hospital Anxiety and Depression Scale scores were significantly reduced in exenatide as compared with insulin-treated patients. Although exenatide and insulin appear to have similar efficacy for the treatment of type 2 diabetes mellitus, exenatide affects both physiological and psychological parameters and might be used as an adjunctive therapy for depression in the context of diabetes [157]. In addition, the use of gram-negative antibiotics has been discussed to offer a potential therapeutic approach for the adjuvant treatment of depression [158].

Disclosure Statement

None of the contributing authors state any conflict of interest.

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