 doi:10.20944/preprints202108.0369.v1

Article

Gut hormones as potential therapeutic targets or biomarkers of response in depression: the case of motilin

Ravi Philip Rajkumar [1]

[1] Professor, Department of Psychiatry, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India; ravi.psych@gmail.com
* Correspondence: ravi.psych@gmail.com; Tel.: +91 413 229 6280

Abstract: Recent research has identified the gut-brain axis as a key mechanistic pathway and potential therapeutic target in depression. In this paper, the potential role of gut hormones as potential treatments or predictors of response in depression is examined, with specific reference to the peptide hormone motilin. This possibility is explored through two methods: (a) a conceptual review of the possible links between motilin and depression, including evidence from animal and human research as well as clinical trials, and (b) an analysis of the relationship between a functional polymorphism (rs2281820) of the motilin (MLN) gene and cross-national variations in the prevalence of depression. It was observed that (a) there are several plausible mechanisms, including interactions with diet, monoamine, and neuroendocrine pathways, to suggest that motilin may be relevant to the pathophysiology and treatment of depression, and (b) there was a significant correlation between rs2281820 allele frequencies and the prevalence of depression after correcting for multiple confounding factors. These results suggest that further evaluation of the utility of motilin and related gut peptides as markers of antidepressant response is required, and that these molecular pathways represent potential future mechanisms for antidepressant drug development.

Keywords: depression; gut-brain axis; motilin; serotonin; gamma-aminobutyric acid; gonadal hormones; hypothalamic-pituitary-thyroid axis; antidepressants; macrolide antibiotics

1. Introduction

Depression is one of the most common mental disorders, affecting over 25 million individuals worldwide, with an estimated 12-month prevalence of 5.5-6% and a lifetime prevalence of 11-15% across countries [1, 2]. Depression is estimated to be one of the leading causes of disability at a global level; it is the fourth leading cause of disability in adolescents and the sixth in adults [3]. Though effective treatments for depression have been developed, the efficacy of pharmacological treatments is modest in many patients [4], with only half of patients showing a significant response, and one-third responding completely to a given drug [5]. Besides, these medications are frequently associated with troublesome adverse effects, particularly in certain age groups [6, 7]. Though several psychological interventions have an efficacy comparable to that of medications, unsatisfactory responses are often observed, and these treatments may not be easy to deliver or access in low- and middle-income countries [8, 9]. An important limitation of existing antidepressant medications is that they are largely based on the monoamine hypothesis of depression, in which depressive symptoms are considered to arise from dysregulation of brain noradrenergic, serotonergic and dopaminergic pathways [10]. Contemporary models of depression, while recognizing the importance of these mechanisms, have identified a variety of other molecular and cellular processes involved in the pathogenesis of this disorder. These include changes in neuroendocrine and stress-related pathways, alterations in neural plasticity and neurogenesis, activation of immune-inflammatory pathways, and the involvement of transmitters other than

 doi:10.20944/preprints202108.0369.v1

monoamines, such as glutamate, gamma-aminobutyric acid (GABA), and neuropeptides [11-14]. It is now increasingly recognized that further advances in the treatment of depression are likely to arise from research targeting these pathways and mechanisms [15]. The efficacy of novel antidepressants such as ketamine, which targets glutamatergic receptors, and brexanolone, a progesterone derivative acting through GABA receptors, provides some support for this perspective [16, 17].

In recent years, evidence for a important role of the gut-brain axis in the pathophysiology of depression has accumulated. Research in animal models as well as human subjects has shown that gut-brain interactions, involving the gut microbiome as well as neural and endocrine mechanisms, are involved in modulating emotions and social behaviour [18]. Stress can alter the composition of the gut microbiome, while modification of the microbiome may enhance resilience through stress via gut-brain signaling [19]. Communication between the gut and brain is mediated through several mechanisms, including afferent signals transmitted through the vagus nerve, changes in immune-inflammatory activity, and changes in the metabolism of specific amino acids and fatty acids [20]. Evidence of interactions between stress and gut microbiota leading to changes in intestinal permeability and immune-inflammatory activation, as have been documented in patients with depression [21]. A recent analysis of over 3,000 patients with major depressive disorder found that over 70% of patients reported at least one gastrointestinal symptom; in these patients, the severity of these symptoms was significantly associated with suicidal ideation and attempts [22]. Investigations of the mechanisms linking the brain and gut in patients with depression have largely focused on changes in the gut microbiome, particularly in response to pharmacological treatment, in both animal models and human subjects [23, 24]. It is likely that several biological pathways mediate the link between changes in gut microbiota and depressive symptomatology, including adrenal and gonadal steroid hormones and cytokines [25].

More recently, it has been proposed that the group of hormones known as *gut peptides* or *gut hormones* may play an important role in brain-gut signaling in this disorder. These hormones are a heterogeneous group of peptide hormones, whose primary function is to regulate various aspects of gastrointestinal function; however, receptors for these hormones have also been discovered in various other sites, such as the central and autonomic nervous system and immune cells [26]. There is preliminary evidence that some of these hormones, such as ghrelin, neuropeptide Y, glucagon-like peptide 1 and cholecystokinin, are related to the stress response and the emergence of depressive symptomatology in humans [27]. Among these hormones, ghrelin has received the most attention from researchers to date. This peptide hormone was initially identified as the endogenous ligand for receptors stimulating the release of growth hormone (GH), hence its name ("GH-releasing agent") [28]. Subsequently, ghrelin has been noted to play an important role in the regulation of appetite and food intake, sleep, mood, cognition, and responses to stress [29]. Ghrelin has been found to alleviate depressive-like behaviours caused by chronic stress in animal models [30, 31]. Studies in human subjects have found elevated ghrelin levels in patients with depression, though these findings appear to be influenced by factors such as gender and the severity of depressive symptoms [32, 33]. It is not clear if these findings should be taken to imply a direct causal link between ghrelin and depression, or whether they represent a compensatory response in the face of chronic stress or severe depression [34]. Motilin, a 22-amino acid polypeptide hormone, has significant structural similarities to ghrelin, is co-secreted with ghrelin from specific cell types, and has similar effects on growth hormone secretion and gastrointestinal motility [35, 36, 37]. Despite these similarities, there is little literature examining a possible link between motilin and depression in humans. In this paper, several converging lines of evidence are presented to suggest that such a link is biologically plausible, and that motilin may have promise both as a marker of response to existing antidepressants, as well as a potential therapeutic target.

2. Materials and Methods

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 18 August 2021 doi:10.20944/preprints202108.0369.v1

The current study was carried out in two stages. In the first stage, existing literature on the relationship between motilin and depression was reviewed through a search of the PubMed and Scopus databases. Search terms included "motilin" and "depression" "major depression", or "depressive disorder". As this approach yielded only a small number of relevant citations, a conceptual review of possible mechanistic links between motilin and depression was undertaken, using the existing literature on gut-brain axis interactions in depression as a guide. Based on this, further searches were carried out pairing "motilin" with the following search terms **(Table 1):**

Table 1. Search terms used for the conceptual review of links between motilin and depression.

Mechanistic pathway and supporting references	Search terms used
Neuroendocrine axes [25, 38]	"cortisol", "corticotropin-releasing hormone", "corticotropin-releasing factor", "CRH", "CRF", "hypothalamic-pituitary-adrenal axis", "growth hormone", "thyroid", "thyroxine", "thyroid-stimulating hormone", "thyrotropin-releasing hormone", "luteinzing hormone", "follicle-stimulating hormone", "estrogen", "estradiol", "progresterone", "progestin" and "testosterone"
Stress and stress responses [34]	"stress", "stressor", "stress response", "stress sensitivity" and "resilience"
Monoamine neurotransmitters [10]	"monoamine", "serotonin", "dopamine", "noradrenaline" or "norepinephrine", with and without "receptor*"
Other relevant neurotransmitters [14]	"gamma-aminobutyric acid", "GABA", "glutamate", "neuropeptide" and "neuropeptides" with and without "receptor*"
Immune and inflammatory pathways [12]	"immune", "inflammation", "inflammatory", "cytokine*" and "chemokine*"
Neurotrophic factors [11]	"brain-derived neurotrophic factor", "BDNF", "neural plasticity", and "neuroplasticity"
Diet [39]	"diet*", "sugar", "refined sugar", "probiotic*", and "prebiotic*"
Studies of antidepressants [24]	"antidepressant*" paired with "tricyclic", "serotonin reuptake inhibitor", "selective serotonin reuptake inhibitor"

The citations obtained through these searches were examined and those of possible relevance to depression were included in this review.

As the evidence obtained in the first stage showed evidence of several possible biological mechanisms linking motilin and depression in humans, a further test of this hypothesis was undertaken in a second stage using allele frequency data. Though subject to certain important limitations, this method has been used to identify associations between the prevalence of depression and other genetic variants of interest, such as polymorphisms of the serotonin transporter (5-HTTLPR), monoamine oxidase A (MAO-A) and mu opioid receptor type 1 (OPRM1) genes [40, 41]; these associations have subsequently been confirmed in research involving samples of patients with depression [42, 43, 44].

The *rs2281820* C/T polymorphism of the motilin (*MLN*) gene, located on the short arm of chromosome 6 was selected for analysis. This polymorphism was studied as it has been shown to have functional consequences, and has been associated with disorders of gallbladder motility in humans [45]. Data on the frequencies of the *MLN rs2281820* polymorphism for samples obtained from 26 distinct countries was obtained from the Allele Frequency Database, which provides free access to data on 664,708

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 18 August 2021 doi:10.20944/preprints202108.0369.v1

distinct genetic polymorphisms obtained from a wide range of populations and samples [46, 47]. Allele frequencies in ALFRED are expressed as proportions for each allele. For example, the data on the *rs2281820* polymorphism in sample of 1950 Estonian subjects was expressed as 0.516 for the *C* allele and 0.484 for the *T* allele. Where more than one sample was available from a given country, the weighted mean of the allele frequency for all samples from that country was used for analysis.

Information on the estimated prevalence of depression for these countries was obtained from the World Health Organization's Global Health Estimates for the year 2017 [48]. To correct for the effect of other factors influencing cross-national variations in depression [39, 41, 49, 50], the following potential confounding factors known to be associated with such variation were included in the analysis: gross national income (expressed as dollar values using the Atlas method), distance of each country's capital city from the equator (as a proxy marker for climate), estimated level of cultural individualism-collectivism, and per capita sugar consumption (expressed as kilocalories per capita per day). Data on gross national income was obtained from 2018 estimates by the World Bank [50]. Data on cultural individualism-collectivism was obtained from the Hofstede Institute's data on cross-national variations in culture [51]. Information on sugar consumption was obtained through a database query from the Food and Agricultural Organization's FAOSTAT database for the year 2016 [52].

The above variables were tested for normality using the Shapiro-Wilk test. Except for per capita sugar consumption and prevalence of depression, none of the study variables conformed to a Gaussian distribution ($p < .05$, Shapiro-Wilk test); accordingly, these variables were converted to an approximately normal distribution using a natural logarithmic transformation.

Following transformation, bivariate correlations between *MLN rs2281820* allele frequency and the prevalence of depression, as well as correlations between these variables and potential confounders, were examined. Finally, multivariate regression analyses using both the direct ("enter") and stepwise methods were carried out to confirm whether the link between *MLN* allele frequencies and depression remained significant after correcting for confounding variables. Given the exploratory nature of this analysis and the low sample size, all variables significantly associated with depression at $p < .1$ or lower were included in the regression analyses.

3. Results

3.1. Conceptual analysis of the links between motilin and depression

a) Gastrointestinal motility: Patients with depressive episodes have high rates of co-occurring gastrointestinal symptoms, many of which, such as constipation and dyspepsia, indicate an impairment in gastrointestinal motility [22]; historically, the presence of these symptoms has been associated with more severe forms of depression [53]. Studies using electrogastrography to analyze the activity of gastric smooth muscle have found evidence of gastric dysrhythmia in patients with depression; in these patients, there was also evidence of an association between this abnormality and symptoms suggestive of sympathetic activity [54, 55]. In contrast, low concentrations of motilin stimulate gastrointestinal motility through the facilitation of cholinergic activity [56], suggesting a contrast or even an antagonism of sorts between the two processes.

Functional gastrointestinal disorders, such as functional dyspepsia (FD) and irritable bowel syndrome (IBS), are associated with significantly high rates of comorbid depression, estimated at 20.9% in FD and 23.3% in IBS [57, 58], representing an approximately 1.5 to 2-fold increase over the prevalence of depression in the general population [59]. In FD, which is characterized by specific symptoms of gastric dysmotility, rates of comorbid depression increase threefold in patients with more severe symptoms [58]. Likewise, patients with depression have a two-fold risk of developing irritable bowel syndrome, particularly following an acute gastrointestinal infection [60]. Altered patterns of motilin secretion have been observed in both FD and

 doi:10.20944/preprints202108.0369.v1

IBS, particularly in patients with more severe symptoms [61-64]. An increase in motilin release in response to stress, in comparison with healthy volunteers, has been observed in patients with IBS [65], while higher motilin levels in patients with FD have been associated with reduced negative affect and increased positive affect [66]. More notably, clinical trials have found that both the antidepressant mirtazapine [67] and certain phytochemicals [68, 69] improve both depressive and gastrointestinal symptoms in patients with FD, and that all these pharmacological agents are associated with significant increases in plasma motilin post-treatment. Functional constipation, a functional gastrointestinal disorder usually diagnosed in children and adolescents, is also associated with elevated rates of depression [70]; children with this disorder have reduced serum motilin levels when compared to healthy controls [71].

Though no definitive conclusions can be drawn from these results, they are consistent with the possibility that motilin is associated with gastrointestinal symptoms in depressed patients, that changes in motilin levels may be a biomarker of response in patients with comorbid FD and depression, and that some antidepressants may have a significant effect on motilin levels. The last of these points will be discussed further under "Antidepressants" below.

b) Neuroendocrine axis functioning: The hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-thyroid (HPT) and hypothalamic-pituitary-gonadal (HPG) axes have all been implicated in the pathophysiology of depression to a certain extent [25, 38]; in addition, there is evidence of blunted growth hormone release in patients with depression [72]. There is preliminary evidence of relationships between motilin and several components of these endocrine axes.

HPA axis. Among the hormones involved in the regulation of the HPA axis, corticotropin-releasing hormone (CRH, also known as corticotropin-releasing factor or CRF) is considered to play a central role in several processes related to depression, including overactivity of the HPA axis and reduced neural plasticity [73]. In an animal study, direct injection of CRH into the cerebral ventricles led to suppression of motilin secretion, while intravenous administration was associated with a blunted gastric response to motilin despite normal circulating motilin levels [74]. Exposure to experimental stress in a rat model was associated with increased peripheral levels of both motilin and cortisol [75]. Though interesting, these results require confirmation in human subjects.

HPT axis. Though motilin has primarily been isolated from gastrointestinal and nervous tissue, recent research has found evidence of motilin synthesis and release in the thyroid gland, both in animals and in humans. Studies in rats have found that thyroidectomy is associated with lower motilin levels and reduced gastrointestinal motility, and that electrical stimulation of the hypothalamic paraventricular nucleus (PVN) led to increased motilin release from the thyroid gland [76]. These findings are relevant because constipation is a common symptom of hypothyroidism, a condition frequently associated with depression in both its subclinical and clinical forms [38, 77]; it is possible that reduced motilin levels may be associated with both these sets of symptoms. Though no studies of motilin levels exist in human subjects with hypothyroidism, a study of patients with hyperthyroidism found lower levels of plasma motilin compared to controls, as well as a negative correlation between thyroxine (T4) and motilin levels; plasma motilin showed a tendency to normalize following treatment in these patients [78]. These results suggest that either an excessive or deficient functioning of the HPT axis may be associated with alterations in motilin levels; though no direct link with depression can be demonstrated, depression is a common comorbidity in patients with hyperthyroidism as well as hypothyroidism [79, 80].

HPG axis. Evidence for a link between motilin and HPG axis functioning has been obtained primarily from animal models and research in women. In a female rat model, both central and peripheral administration of motilin resulted in a decrease in the levels of luteinizing hormone (LH) [81]; in contrast, motilin levels were higher during the luteal phase of menstrual cycles [82]. This suggests that LH may increase motilin levels,

while motilin may reduce LH through a feedback regulatory mechanism [81]; alternately, both may vary in relation to levels of progesterone, as a significant positive correlation between progesterone and motilin was found in the latter study [82]. These results are of significance given the following observations regarding depression in women: (i) the established associations between depressive symptoms and the late luteal phase of the menstrual cycle, including exacerbations of pre-existing depression as well as phasic symptoms [83, 84], (ii) increased rates of gastrointestinal symptoms in women with a pre-menstrual exacerbation of depression [84], (iii) evidence that exogenous progesterone analogues can induce depression, particularly in the post-partum period [85], (iv) evidence that reduced LH or elevated follicle-stimulating hormone (FSH) levels may be associated with an increased risk of depression, as well as a poorer response to antidepressants, in post-partum or post-menopausal women [86, 87]. Though a definitive conclusion cannot be drawn from this data, there are suggestions of links between FSH, LH, progesterone and motilin which may be of relevance to depression, particularly in woman.

Growth hormone. Reduced growth hormone secretion, both at rest and in response to exercise or neurotransmitter receptor agonists, has been documented in children, adolescents and adults with depression [72, 88-90]. Motilin is a potent stimulator of growth hormone release, and has been considered by some authors to be a physiological growth hormone-releasing factor (GRF) [35, 91]. Though the exact significance of changes in growth hormone levels in depression is a matter of debate, it has been suggested that stress-induced changes in monoamine transmission may underlie these alterations [92], while antidepressant treatment may result in a normalization of GH release patterns [93]. There is also some evidence that administration of ghrelin, which is similar to motilin both structurally and as a GRF, results in reductions in depressive symptoms in parallel with increases in GH levels [94]; it is plausible that effects of this sort may be discovered for motilin as well.

In summary, there is at least indirect evidence suggesting that further investigations of the interactions of motilin with endocrine parameters, particularly those involving the thyroid and gonadal axes and growth hormone release, may yield clues to a better understanding of the pathophysiology and treatment of depression.

c) Stress and stress responses: As mentioned earlier, concurrent elevations in motilin and cortisol were observed in an animal model of acute stress [75], while elevated motilin levels were observed following exposure to an experimental stressor in patients with IBS [65]. Exposure to a stressor over a period of 10 days was also associated with increased motilin levels in a rat model, and this was associated with an increased frequency of bowel movements [95]. In contrast, a more prolonged (21 days) exposure to experimental stress in mice was associated with a significant reduction in motilin levels compared to a “non-stressed” control group; this was associated with reduced gastric emptying and intestinal propulsion [96]. These results suggest that acute and chronic stress may have differential effects on motilin levels, which may be mediated through the dysregulation in HPA axis functioning induced by exposure to a chronic stressor [97]. An alternate mechanism that may link stress and motilin is the sympathetic nervous system, as stellate ganglion blockade has been found to reduce cortisol levels and increase motilin levels in patients undergoing laparoscopic surgery for colorectal cancer [98]. Finally, in an animal model of chronic stress – the “forced swimming test” (FST), which is used to model depression – rats exposed to FST showed reduced motilin levels, which were associated with both depression-like behavioral changes and reduced gastrointestinal motility [99]. Though caution is required in applying these findings to human subjects, they do suggest that depression resulting from chronic stress may be associated with reduced levels of motilin.

d) Monoamine transmitters: There is evidence that the release of motilin is regulated by monoamine transmitters such as serotonin and norepinephrine, and that the effects of motilin on gastrointestinal motility may be mediated, at least in part, through these transmitters. Dopamine appears to increase motilin secretion when

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 18 August 2021 doi:10.20944/preprints202108.0369.v1

infused intravenously after a meal, whereas it has the opposite effect in fasting subjects, causing a decrease in plasma motilin levels [100, 101]. The blockade of D_2 dopamine receptors by domperidone is also associated with a rapid increase in plasma motilin [102]. Serotonin (5-HT) increases the release of motilin [103], and the effects of motilin on upper gastrointestinal motility are partially mediated by 5-HT3 receptors; blockade of these receptors antagonizes the effects of motilin on gastrointestinal smooth muscle contraction [104]. While there are no studies directly examining the effect of noradrenaline on motilin secretion, this transmitter is known to reduce gastric motility [105], and artificially induced sympathetic blockade is associated with an increase in motilin levels [98]. These results suggest that a complex balance exists between monoaminergic activity and motilin release at the level of the gut; however, there is no direct evidence as yet for such effects at a central level.

e) Other neurotransmitters: Though primarily considered a regulator of gastrointestinal motility, receptors for motilin have been identified at various other sites, including the vagus nerve and specific brain regions [56]. At a central level, motilin receptors have been identified on neurons of the lateral vestibular nucleus in rabbits, where they exert inhibitory effects and appear to act in an additive manner with gamma-amino butyric acid (GABA); immunocytochemical studies also suggest that motilin and GABA may be co-localized and released together by some subsets of neurons, such as cerebellar Purkinje cells [106]. Subsequently, motilin receptors were found to be expressed at high levels in the basolateral nucleus of the mouse amygdala, a brain region involved in stress susceptibility, fear and anxiety responses. Motilin, as well as the motilin agonist erythromycin, increases GABAergic transmission in this area, resulting in reduced anxiety-like responses to stress [107]. This finding may be significant in the light of evidence of structural and functional abnormalities of the basolateral amygdala in patients with depression [108, 109]. Motilin receptors have also been identified in other brain regions that have been implicated in the pathophysiology of depression [110], such as the hippocampus and hypothalamus [112]. In all these brain regions, motilin may act to enhance GABAergic neurotransmission; research in the last two decades has found evidence of reduced GABA levels in multiple brain regions in patients with depression [14], and it has been suggested that the activation of motilin receptors may represent a potential therapeutic target in such situations [107]. Motilin receptors have also been identified on the vagus nerve, where they appear to enhance cholinergic activity at muscarinic receptors [113]. This mechanism may also be of relevance, as vagal signaling has been identified as a potential pathway linking gut and brain in depression [20] and vagus nerve stimulation may be a useful therapeutic option in some patients with this disorder [114]. Finally, there is evidence that a peripherally administered motilin agonist, erythryomycin, can alter the activity of several key brain regions, including the orbitofrontal cortex, limbic structures, hypothalamus, caudate nucleus and putamen [115]. Though the exact neurotransmitters mediating this response have not been identified, this finding provide further evidence of the central effects of motilin on brain circuits involved in appetitive and hedonic behaviours, whose functioning is altered in patients with depression [110].

f) Immune and inflammatory pathways: Relatively little research has examined the interplay between motilin and immune system function. However, the administration of the putative anti-inflammatory cytokine interleukin-11 (IL-11) was associated with an increase in the expression of motilin messenger RNA (mRNA), as well as increased motilin levels, in a rabbit model. This effect appeared to be mediated both by a direct effect of IL-11, and an indirect effect of IL-11 on leptin release, which in turn stimulated motilin synthesis and release [116]. Though there is no evidence directly linking IL-11 to the pathogenesis of depression, changes in IL-11 expression may be a significant predictor of response to antidepressant medications [117]. Given that certain antidepressant medications produce significant changes in motilin levels [67], an analysis of the relationship between these two molecules may aid in identifying markers of antidepressant response.

 doi:10.20944/preprints202108.0369.v1

g) Neurotrophic factors: There is increasing evidence that alterations in neural plasticity may represent a final common pathway through which stressful life events influence the onset and duration of depressive episodes [118]. A key molecule that may mediate this process is brain-derived neurotrophic factor (BDNF), which promotes hippocampal neurogenesis and neural plasticity. Functional polymorphisms of the BDNF gene are significantly associated with the risk of developing depression after exposure to stressors [119], and depression is associated with a modest but significant decrease in serum BDNF levels compared to healthy controls [120]. In an animal model of depression using the forced swimming test, rats exposed to this chronic stressor showed significant decreases in plasma levels of both BDNF and motilin [99], which occurred in parallel with increases in CRH and cortisol. On the other hand, BDNF levels may be increased by the activation of GABAergic pathways [121], which is one of the key central effects of motilin. These indirect links between motilin and BDNF require examination in human subjects with and without depression.

h) Diet. Among the dietary factors investigated in relation to depression, there is consistent evidence of a link between the levels of sugar consumption and the prevalence of this disorder [39, 122, 123]. A study of healthy volunteers found that consumption of a meal with a high glycemic index was associated with a blunted release of motilin compared to a meal with a low glycemic index [124]. Similarly, the consumption of glucose in diabetic patients undergoing a glucose tolerance test resulted in a significant decrease in plasma motilin [125]. In contrast, the administration of prebiotics resulted in increases in motilin levels in an animal model of constipation [126]. These findings suggest that a significant relationship exists between certain dietary components and motilin secretion, which may merit further examination when examining dietary gut-brain axis relationships in depression.

i) Antidepressants: A study of healthy volunteers receiving low-dose (37.5 mg) amitryptiline, a tricyclic antidepressant which is also effective in functional gastrointestinal disorders, found no evidence of a significant change in motilin levels [127]; this may reflect the complex pharmacology of this agent, which includes inhibition of serotonin and noradrenaline reuptake as well as muscarinic receptor blockade. However, in a study examining tricyclic antidepressants as a group, depressed patients receiving these drugs showed significant elevations in basal plasma motilin [128]. Among selective serotonin reuptake inhibitors, fluoxetine was not associated with significant changes in motilin levels or gastrointestinal motility in an animal model of chronic stress [129], and paroxetine had no significant effect on motilin levels in human patients [67]. In contrast, the newer antidepressant mirtazapine, which increases monoamine release and blocks specific serotonin receptor subtypes, appeared to increase motilin levels in patients with a functional gastrointestinal disorder; this increase was associated with improvements in both gastrointestinal and depressive symptoms [67]. These findings suggest that different antidepressant classes have distinct effects on plasma motilin levels, and that investigation of the relationship between changes in plasma motilin and antidepressant response may be warranted.

It is also of note that macrolide antibiotics, which act as motilin receptor agonists, have been associated with the emergence of manic symptoms, including a report of a “switch” to mania in a patient with depression [130, 131]. Though the true frequency of such effects is unclear, they represent another possible point of convergence between motilin receptor activation and the pharmacological effects of antidepressants [132].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 18 August 2021 doi:10.20944/preprints202108.0369.v1

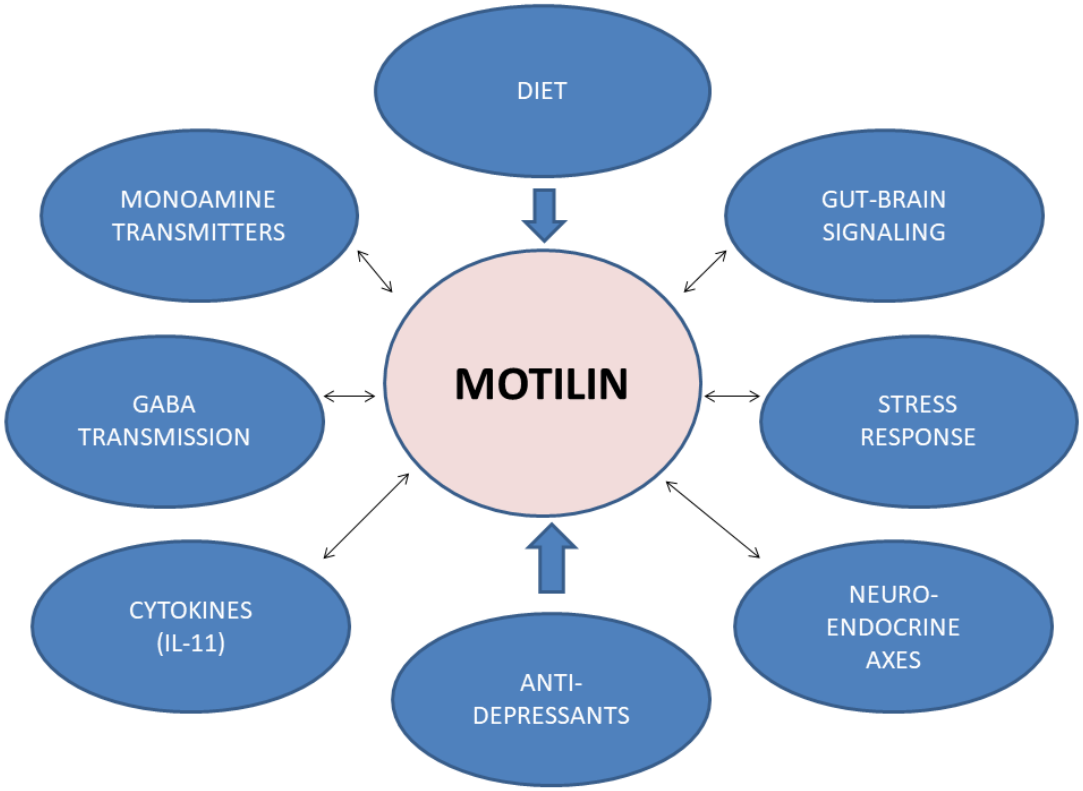

Figure 1. Illustration of the relationships identified between motilin and various factors or processes relevant to the pathogenesis and treatment of depression. Block arrows indicate external factors; line arrows indicate physiological processes. Abbreviations: GABA, gamma-aminobutyric acid; IL-11, interleukin-11.

j) Summary: There is evidence for direct or indirect links between motilin and several mechanisms relevant to depression and antidepressant drug response, though much of this evidence has emerged from experimental research and requires verification in clinical settings. These pathways are summarized in **Figure 1.** The mechanisms reviewed above may not exhaust all the possible links between motilin and depression; for example, there is preliminary evidence of interactions between motilin and the composition of the gut microbiota [133], and between levels of motilin and the peptide transmitter neuropeptide Y [67, 126], which has also been identified as having a protective effect against depression [134].

3.2. Correlations between MLN rs2281820 allele frequencies and the prevalence of depression across countries

Data on a total of twenty-six countries was analyzed: Belarus, Cambodia, China, Colombia, Denmark, Estonia, Finland, France, Hungary, Ireland, Italy, Japan, Kazakhstan, Kyrgyzstan, Mexico, Moldova, Nigeria, Peru, the Russian Federation, South Korea (Republic of Korea), Spain, Ukraine, the United Kingdom, the United States of America, Uzbekistan and Vietnam. The estimated prevalence of depression in these countries ranged from a minimum of 3.4% (Cambodia) to a maximum of 6.3% (Ukraine), with a mean prevalence of 4.8±0.7%. The estimated allele frequency (C allele) of the MLN rs2281820 functional polymorphism ranged from a minimum of 46.3% (Colombia) to a maximum of 94.4% (South Korea), with a mean of 63.2±14.8%.

Bivariate correlations between the estimated prevalence of depression, rs2281820 C allele frequency, and potential confounding variables are presented in **Table 2**. It was observed that there was a significant negative correlation between MLN rs2281820 C allele frequency and the estimated prevalence of depression, as well as a positive correlation between distance from the equator and the prevalence of depression; there were non-significant trends ($.05 < p < .1$) for positive relationships between depression

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 18 August 2021 doi:10.20944/preprints202108.0369.v1

and both gross national income and per capita sugar consumption. MLN rs2281820 C allele frequency was not significantly correlated with any of the confounding factors, though there was a trend towards a negative correlation with sugar consumption.

Table 2. Bivariate correlations between MLN rs2281820 allele frequency, estimated prevalence of depression, and other confounding factors.

Variable	1 Depression, prevalence	2 MLN rs2281820, C allele frequency (ln)	3 Gross national income (ln)	4 Individualism-collectivism (ln)	5 Distance from the equator (ln)	6 Per capita sugar consumption
1	-	-.41* (.037)	.38 (.053)	.34 (.116)	.49* (.012)	.38 (.053)
2		-	-.19 (.365)	-.28 (.190)	.07 (.754)	-.34 (.091)
3			-	.75* (<.001)	.47* (.016)	.53* (.005)
4				-	.56* (.005)	.36 (.091)
5					-	.15 (.452)

Abbreviations: ln, natural logarithmic transformation; MLN, motilin gene. * denotes significance at $p < .05$.

The following variables were included in multivariate linear regression analysis as independent variables: MLN rs2281820 C allele frequency, distance from the equator, gross national income (all log-transformed), and per capita sugar consumption. The results of this analysis are presented in **Table 3**. It was found that both rs2281820 allele frequency and distance from the equator remained significantly associated with the prevalence of depression, confirming the results of the bivariate analyses. Variance inflation factors were less than 2 for all variables, ruling out significant multicollinearity. This model had an adjusted R^2 value of 0.358, indicating that it explained roughly 36% of cross-national variation in the prevalence of depression.

As a further test of this finding, stepwise linear regression was carried out using the same four independent variables. Similar results were obtained, with rs2281820 allele frequency ($\beta = -.45$, $p = .010$) and distance from the equator ($\beta = .52$, $p = .003$) included in the final model, and gross national income and sugar consumption excluded. The adjusted R^2 value for this model was 0.384, indicating slightly greater precision than for the model including all four variables.

Table 3. Multivariate linear regression analysis of variables associated with the prevalence of depression.

Variable	Regression coefficient (β)	Significance level	Part correlation	Variance inflation factor
MLN rs2281820, C allele frequency (ln)	-.38	.037*	-.36	1.15
Distance from the equator (ln)	.48	.015*	.42	1.33
Gross national income (ln)	-.01	.950	-.01	1.78
Per capita sugar consumption	.19	.359	.15	1.53

Abbreviations: MLN, motilin gene; ln, natural logarithmic transformation indicates statistical significance at $p < .05$.

4. Discussion

 doi:10.20944/preprints202108.0369.v1

Gut peptides represent a promising line of research in the quest to improve our understanding of gut-brain links in common mental disorders, and particularly in depression [26, 27]. Though a systematic evaluation of the role of motilin in this process is yet to be undertaken, the existing evidence suggests that motilin has significant interactions with several key molecules and pathways that are considered to play a role in the onset and maintenance of this disorder. These include monoaminergic transmitters, neuroendocrine axes, and – more speculatively – processes such as neural plasticity and immune / inflammatory regulation. Much of this evidence is derived from research in animal models in depression; however, the existing data in human subjects is consistent with this evidence. Because of its ability to influence afferent signaling from the gut to the brain through the vagus nerve [113], and its ability to induce central effects even when administered peripherally [115], it may act as a mediator in processes linking gut-related events, such as those pertaining to diet or microbiota, to changes in brain functioning. The fact that motilin levels increase in human subjects being treated with certain groups of antidepressants suggests that there may be at least an indirect association between changes in the levels of this hormone and the response to these drugs [128, 129]. Finally, the analysis of population-level genetic data related to a functional polymorphism of the *MLN* gene suggests that this factor may influence variations in the prevalence of depression, perhaps in combination with environmental and lifestyle factors such as exposure to stress or particular dietary practices.

Should motilin be considered a "depressant" or "antidepressant" molecule from an endogenous point of view? There is insufficient evidence to provide a definitive answer to this question. The preponderance of evidence suggests that elevated motilin levels are correlated with processes or events that are opposed to depression [67, 91, 107], while low or dysregulated levels of motilin seem to be associated with processes related to depression, such as chronic stress and unhealthy dietary practices [96, 99, 124]. The available evidence seems to suggest an inverse relationship between motilin and depression, though it is likely that this association will not follow a simple linear pattern. A key question for future research in this field is whether these reported associations are epiphenomenal, or whether alterations in central or peripheral motilin play a more direct role in depressive disorders.

When considering the potential relationship between the motilin gene and cross-national variations in depression, it is instructive to consider the factors that are commonly cited as underlying these variations. Apart from genetic variations across populations, these factors include diet [39, 123], socioeconomic factors such as economic inequality [49], cultural values and practices [41], altered gut microbiota and immune-inflammatory activity caused by changes in exposure to pathogens [135]. To a greater or lesser extent, all these factors interact with gut peptides, at least in principle. Socioeconomic and cultural factors are key influencers of stress, stress sensitivity and resilience [136, 137], and altered patterns of motilin release in response to acute and chronic stress may influence susceptibility to depression at the individual and population level. The possible link between diet and motilin, and in particular with sugar consumption, represents another possible area of interaction that is relevant to the development of depression. Finally, though such research is in its early stages, evidence of a link between motilin and the composition of the gut microbiome [133, 138] may be particularly relevant to models that link changes in pathogen exposure and gut microbiota, such as the Pathogen Host Defense (PATHOS-D) or "Old Friends" models of depression [135, 139]. Thus, variations in the release or activity of motilin, mediated through genetic variants, may interact with multiple environmental factors in influencing the risk of depression. However, given that we know little about the functional consequences of motilin gene polymorphisms and their peripheral or central effects in humans, this hypothesis should be subjected to careful testing.

Evaluating the potential of motilin as a biomarker for response to antidepressants would require a consideration of several factors. First, there is evidence that some antidepressants cause an increase in motilin levels during short-term treatment;

 doi:10.20944/preprints202108.0369.v1

however, it is not known if these levels return to a lower or "baseline" value with more prolonged treatment. Second, though an association between changes in motilin and reductions in depressive symptoms was reported in one study, the patients in this study had a comorbid functional gastrointestinal disorder [67]; it is not clear if such an association exists in patients with depression alone, or only in the sub-group of patients with depression and prominent gastrointestinal symptoms. Third, correlations between basal motilin level, or changes in this parameter (in terms of, for example, percentage changes from a baseline value) and objectively defined response to an antidepressant (in terms of a specified percentage reduction in symptom scores) need to be examined in future studies. Finally, as shown by the negative findings with serotonin reuptake inhibitors, it is possible that this measure may be useful in assessing responses to only certain antidepressant drugs or drug groups.

Finally, when considering the therapeutic potential of drugs acting via motilin receptors in patients with depression, certain clues may be obtained from clinical trials of drugs acting on the motilin receptor in other conditions. Macrolide antibiotics, which act as agonists of the motilin receptor, are commonly used to treat disorders of gastric motility. The presence of depressive symptoms in these disorders is generally associated with a poorer response to treatment in these patients [140], but it is not known if treatment with macrolides improves depressive symptoms in parallel with improvement in upper gastrointestinal symptoms. Exposure to higher or longer courses of macrolide antibiotics such as azithromycin and clarithromycin has been associated with an increased risk of depression in certain clinical scenarios [141, 142]; however, it is not possible to conclude whether these effects are due to the actions of these drugs at the motilin receptor, or to their effects on the intestinal microbiome [143]. There have also been numerous reports of new-onset mania associated with the use of these drugs [130, 131, 144, 145], also providing indirect evidence of a possible association between peripheral motilin receptor activation and mood disorders. In this connection, it is also noteworthy that peripheral administration of erythromycin to healthy subjects resulted in a decrease in growth hormone levels, an action opposite to that of centrally administered motilin [146]; it is thus possible that peripheral and central motilin receptor activation may have distinct effects on mood. On the other hand, azithromycin has been observed to exert antidepressant effects in a mouse model of depressive-like behavior when administered peripherally [147]; while these findings cannot be generalized directly to patients with depression, it may be possible that motilin receptor agonists have distinct actions in depressed and non-depressed individuals. Though more selective motilin agonists have been developed [148], data on their use in clinical samples is limited. Moreover, it is possible that centrally acting agonists may have more beneficial effects [107]. In conclusion, though it would be premature to conduct clinical trials of existing motilin receptor agonists in patients with depression, there are several promising lines of enquiry that follow from the existing evidence: (a) assessment of changes in depressive symptoms in patients receiving motilin agonists for an existing indication, such as diabetic gastroparesis, (b) assessment of changes in mood in patients receiving macrolide antibiotics for infectious diseases, (c) evaluation of motilin or motilin agonists, both centrally and peripherally administered, in animal models of depression, and finally (d) the development and testing of centrally acting motilin receptor agonists in depressive or anxiety disorders. Even if such strategies do not directly lead to the approval of a specific drug, they would deepen our understanding of the role that this gut peptide and related molecules play in gut-brain "cross-talk" in depression. This could in turn lead to the development of novel therapeutic approaches aimed at targeting gut-brain axis dysfunction in this disorder.

The work presented here is subject to certain important limitations. Concerning the first stage, these include: a paucity of relevant studies in patients with depression, difficulties in extrapolating findings from animal models of depression, the indirect nature of much of the available evidence linking motilin to the pathophysiology of depression, the lack of replication of the available positive findings, and the lack of

literature linking motilin to those mechanisms, particularly alterations in the microbiome, that are considered to be more relevant in depression. Moreover, more fundamental details of the physiological significance of motilin in relation to brain functioning, when compared to other relevant peptides such as ghrelin and somatostatin, and the interactions between them, require elucidation [149]. For the associations reported in the second stage of this work, key shortcomings include: a relatively small sample size, reliance on estimates of the prevalence of depression rather than direct epidemiological research, the possibility that other confounding factors may have been overlooked in the analysis, the limitations of inferring causation from population-level associations [150], and our lack of knowledge regarding the functional consequences of the *MLN* polymorphism being analyzed, particularly in terms of gut-brain axis functioning.

5. Conclusions

Despite the limitations enumerated above, the possibility of a link between motilin and several key physiological processes related to depression is biologically plausible and supported to an extent by the evidence available to date. Though it is not possible to draw definitive conclusions from this evidence, it is likely that a more in-depth understanding of the functions of motilin in gut-brain signaling, both in healthy subjects and in patients with depression. This would improve our understanding of this disorder and could lead to novel strategies – either based on direct modulation of motilin receptor activity or on indirect approaches such as dietary modification or the administration of probiotics – to normalize gut-brain functioning and improve recovery rates in patients with depression. The relationship between antidepressant use, symptomatic response, and plasma motilin levels may also merit further examination, both as a marker of response and as a potential means of distinguishing responders and non-responders to drug treatment in depression.

Author Contributions: Conceptualization, methodology, formal analysis, data curation, writing—original draft preparation, writing—review and editing, R.P.R.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable, as this study is based on a critical literature review and analysis of publicly available, country-wise data.

Informed Consent Statement: Not applicable

Data Availability Statement: The data used for the analyses in this study is available to the public, and its sources have been cited as references 47, 48, 51, and 52. A complete data sheet is available from the author on reasonable request.

Acknowledgments: None.

Conflicts of Interest: The author declares no conflict of interest.

References

1. Bromet, E., Andrade, L.H., Hwang, I., Sampson, N.A., Alonso, J., de Girolamo, G., de Graaf, R., Demyttenaere, K., Hu, C., Iwata, N., Karam, A.N., Kaur, J., Kostyuchenko, S., Lepine, J-P., Levinson, D., Matschinger, H., Mora, M.E.M., Browne, M.O., Posada-Villa, J., Viana, M.C., Williams, D.R., Kessler, R.C. Cross-national epidemiology of DSM-IV major depressive episode. *BMC Medicine* **2011**, *9*, 90.
2. Liu, Q., He, H., Yang, J., Feng, X., Zhao, F., Lyu, J. Changes in the global burden of depression from 1990 to 2017: findings from the Global Burden of Disease study. *J Psychiatr Res.* **2020**, *126*, 134-140.
3. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* **2020**, *396*, 1204-1222.

4. Guo, X., McCutcheon, R.A., Pillinger, T., Mizuno, Y., Natesan, S., Brown, K., Howes, O. The magnitude and heterogeneity of antidepressant response in depression: a meta-analysis of over 45,000 patients. *J Affect Disord.* **2020**, *276*, 991-1000.
5. Rush, A.J., Jain, S.B. Clinical implications of the STAR*D trial. *Handb Exp Pharmacol.* **2019**, *250*, 51-99.
6. Zhou, X., Teng, T., Zhang, Y., Del Giovane, C., Furukawa, T.A, Weisz, J.R., Li, X., Cuijpers, P., Coghill, D., Xiang, Y., Hetrick, S.E., Leucht, S., Qin, M., Barth, J., Ravindran, A.V., Yang, L., Curry, J., Fan, L., Silva, S.G., Cipriani, A., Xie, P. Comparative efficacy and acceptability of antidepressants, psychotherapies, and their combination for acute treatment of children and adolescents with depressive disorder: a systematic review and network meta-analysis. *Lancet Psychiatry* **2020**, *7*, 581-601.
7. Krause, M., Gustmiedl, K., Bighelli, I., Schneider-Thoma, J., Chaimani, A., Leucht, S. Efficacy and tolerability of pharmacological and non-pharmacological interventions in older patients with major depressive disorder: a systematic review, pairwise and network meta-analysis. *Eur Neuropsychopharmacol*. **2019**, *29*, 1003-1022.
8. Santoft, F., Axelsson, E., Ost, L-G., Hedman-Lagerlof, M., Fust, J., Hedman-Lagerlof, E. Cognitive behaviour therapy for depression in primary care: systematic review and meta-analysis. *Psychol Med.* **2019**, *49*, 1266-1274.
9. Patel, V., Araya, R., Chatterjee, S., Chisholm, D., Cohen, A., De Silva, M., Hosman, C., McGuire, H., Rojas, G., van Ommeren, M. Treatment and prevention of mental disorders in low-income and middle-income countries. *Lancet* **2007**, *370*, 991-1005.
10. Boku, S., Nakagawa, S., Toda, H., Hishimoto, A. Neural basis of major depressive disorder: beyond monoamine hypothesis. *Psychiatry Clin Neurosci.* **2018**, *72*, 3-12.
11. Brunoni, A.R., Lopes, M., Fregni, F. A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. *Int J Neuropsychopharmacol.* **2008**, *11*, 1169-1180.
12. Kohler, C.A., Freitas, T.H., Maes, M., de Andrade, N.Q., Liu, C.S., Fernandes, B.S., Stubbs, B., Solmi, M., Veronese, N., Herrmann, N., Raison, C.L., Miller, B.J., Lanctot, K.L., Carvalho, A.F. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. *Acta Psychiatr Scand.* **2017**, *135*, 373-387.
13. Chavez-Castillo, M., Nunez, V., Nava, M., Ortega, A., Rojas, M., Bermudez, V., Rojas-Quintero, J. Depression as a neuroendocrine disorder: emerging neuropsychopharmacological approaches beyond monoamines. *Adv Pharmacol Sci.* **2019**, *2019*, 7943481.
14. Godfrey, K.E.M., Gardner, A.C., Kwon, S., Chea, W., Muthukumaraswamy, S.D. Differences in excitatory and inhibitory neurotransmitter levels between depressed patients and healthy controls: a systematic review and meta-analysis. *J Psychiatr Res.* **2018**, *105*, 33-44.
15. Pereira, V.S., Hiroaki-Sato, V.A. A brief history of antidepressant drug development: from tricyclics to beyond ketamine. *Acta Neuropsychiatr.* **2018**, *30*, 307-322.
16. An, D., Wei, C., Wang, J., Wu, A. Intranasal ketamine for depression in adults: a systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials. *Front Psychol.* **2021**, *12*, 648691.
17. Ali, M., Aamir, A., Diwan, M.N., Awan, H.A., Ullah, I., Irfan, M., De Berardis, D. Treating postpartum depression: what do we know about brexanolone? *Diseases* **2021**, *9*, 52.
18. Sylvia, K.E., Demas, G.E. A gut reaction: microbiome-brain-immune interactions modulate social and affective behaviors. *Horm Behav.* **2018**, *99*, 41-49.
19. Molina-Torres, G., Rodriguez-Arrastia, M., Roman, P., Sanchez-Labraca, N., Cardona, D. Stress and the gut microbiota-brain axis. *Behav Pharmacol.* **2019**, *30*, 187-200.
20. Generoso. J.S., Giridharan, V.V., Lee, J., Macedo, D., Barichello, T. The role of the microbiota-gut-brain axis in neuropsychiatric disorders. *Braz J Psychiatry* **2021**, *43*, 293-305.
21. Trzeciak, P., Herbet, M. Role of the intestinal microbiome, intestinal barrier and psychobiotics in depression. *Nutrients* **2021**, *13*, 927.
22. Huang, J., Cai, Y., Su, Y., Zhang, M., Shi, Y., Zhu, N., Jin, F., Peng, D., Fang, Y. Gastrointestinal symptoms during depressive episodes in 3256 patients with major depressive disorders: findings from the NSSD. *J Affect Disord.* **2021**, *286*, 27-32.
23. Zhang, W., Qu, W., Wang, H., Yan, H. Antidepressants fluoxetine and amitryptiline induce alterations in intestinal microbiota and gut microbiome function in rats exposed to chronic unpredictable mild stress. *Transl Psychiatr.* **2021,** *11*, 131.
24. Ciocan, D., Cassard, A-M., Becquemont, L., Verstuyft, C., Voican, C.S., El Asmar, K., Colle, R., David, D., Trabado, S., Feve, B., Chanson, P., Perlemuter, G., Corruble, E. Blood microbiota and metabolomic signature of major depression before and after antidepressant treatment: a prospective case-control study. *J Psychiatry Neurosci.* **2021**, *46*, E358-E368.
25. Tetel, M.J., de Vries, G.J., Melcangi, R.C., Panzica, G., O'Mahony, S.M. Steroids, stress and the gut microbiome-brain axis. *J Neuroendocrinol.* **2018**, *30*, e12548.
26. Lach, G., Schellekens, H., Dinan, T.G., Cryan, J.F. Anxiety, depression, and the microbiome: a role for gut peptides. *Neurotherapeutics* **2018**, *15*, 36-59.
27. Sun, L-J., Li, J-N., Nie, Y-Z. Gut hormones in microbiota-gut-brain cross-talk. *Chin Med J.* **2020**, *133*, 826-833.
28. Kojima, M., Hosoda, H., Date, Y., Nakazato, M., Matsuo, H., Kangawa, K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* **1999**, *402*, 656-660.
29. Stone, L.A., Harmatz, E.S., Goosens, K.A. Ghrelin as a stress hormone: implications for psychiatric illness. *Biol Psychiatry* **2020**, *88*, 531-540.
30. Huang, H-J., Zhu, X-C., Han, Q-Q., Wang, Y-L., Yue, N., Wang, J., Yu, R., Li, B., Wu, G-C., Liu, Q., Yu, J. Ghrelin alleviates anxiety- and depression-like behaviors induced by chronic unpredictable mild stress in rodents. *Behav Brain Res.* **2017**, *326*, 33-43.

31. Fan, J., Li, B.J., Wang, X.F., Zhong, L.L., Cui, R.J. Ghrelin produces antidepressant-like effect in the estrogen deficient mice. *Oncotarget* **2017**, *8*, 58964-58973.
32. Akter, S., Pham, N.M., Nanri, A., Kurotani, K., Kuwahara, K., Jacka, F.N., Yasuda, K., Sato, M., Mizoue, T. Association of serum leptin and ghrelin with depressive symptoms in a Japanese working population: a cross-sectional study. *BMC Psychiatry* **2014**, *14*, 203.
33. Algul, S., Ozcelik, O. Evaluating the levels of nesfatin-1 and ghrelin hormones in patients with moderate and severe major depressive disorders. *Psychiatry Investig.* **2018**, *15*, 214-218.
34. Mani, B.K., Zigman, J.M. Ghrelin as a survival hormone. *Trends Endocrinol Metab.* **2017**, *28*, 843-854.
35. Samson, W.K., Lumpkin, M.D., Nilaver, G., McCann, S.M. Motilin: a novel growth hormone releasing agent. *Brain Res Bull.* **1984**, *12*, 57-62.
36. Peeters, T.L. Ghrelin and the gut. *Endocr Dev.* **2013**, *25*, 41-48.
37. Wierup, N., Bjorkqvist, M., Westrom, B., Pierzynowski, S., Sundler, F., Sjolund, K. Ghrelin and motilin are cosecreted from a prominent endocrine cell population in the small intestine. *J Clin Endocrinol Metab.* **2007**, *92*, 3573-81.
38. Loh, H.H., Lim, L.L., Yee, A., Loh, H.S. Association between subclinical hypothyroidism and depression: an updated systematic review and meta-analysis. *BMC Psychiatry* **2019**, *19*, 12.
39. Peet, M. International variations in the outcome of schizophrenia and the prevalence of depression in relation to national dietary practices: an ecological analysis. *Br J Psychiatry* **2004**, *184*, 404-408.
40. Way, B.M., Lieberman, M.D. Is there a genetic contribution to cultural differences? Collectivism, individualism and genetic markers of social sensitivity. *Soc Cogn Affect Neurosci.* **2010**, *5*, 203-211.
41. Chiao, J.Y., Blizinsky, K.D. Culture-gene coevolution of individualism-collectivism and the serotonin transporter gene. *Proc R Soc B.* **2010**, *277*, 529-537.
42. Gressier, F., Calati, R., Serretti, A. 5-HTTLPR and gender in affective disorders: a systematic review. *J Affect Disord.* **2016**, *190*, 193-207.
43. Melas, P.A., Wei, Y., Wong, C.C.Y., Sjoholm, L.K., Aberg, E., Mill, J., Schalling, M., Forsell, Y., Lavebratt, C. Genetic and epigenetic associations of MAOA and NR3C1 with depression and childhood adversities. *Int J Neuropsychopharmacol.* **2013**, *16*, 1513-1528.
44. Slavich, G.M., Tartter, M.A., Brennan, P.A., Hammen, C. Endogenous opioid system influences depressive reactions to socially painful targeted rejection life events. *Psychoneuroendocrinology* **2014**, *49*, 141-149.
45. Xu, H-L., Hsing, A.W., Koshiol, J., Chu, L.W., Cheng, J-R., Gao, J., Tan, Y-T., Wang, B-S., Shen, M-C., Gao, Y-T. Variants in motilin, somatostatin and their receptor genes and risk of biliary tract cancers and stones in Shanghai, China. *Meta Gene* **2014**, *2*, 418-426.
46. Rajeevan, H., Osier, M.V., Cheug, K-H., Deng, H., Druskin, L., Heinzen, R., Kidd, J.R., Stein, S., Pakstis, A.J., Tosches, N.P., Yeh, C-C., Miller, P.L., Kidd, K.K. ALFRED: the ALlele FREquency Database. Update. *Nucleic Acids Res.* **2003**, *31*, 270-271.
47. ALFRED: The ALlele FREquency Database. Available online: http://alfred.med.yale.edu (accessed on 26/7/2021).
48. World Health Organization. Depression and other common mental disorders: global health estimates. Geneva: World Health Organization, 2017.
49. Kessler, R.C., Bromet, E.J. The epidemiology of depression across cultures. *Annu Rev Public Health* **2013**, *34*, 119-138.
50. Marqueze, E.C., Vasconcelos, S., Garefelt, J., Skene, D.J., Moreno, C.R., Lowden, A. Natural light exposure, sleep and depression among day workers and shiftworkers at arctic and equatorial latitudes. *PLoS One* **2015**, *10*, e0122078.
51. GNI per capita, Atlas method. Available online: https://data.worldbank.org/indicator/NY.GNP.PCAP.CD (accessed on 29/7/2021)
52. FAOSTAT. Available online: http://www.fao.org/faostat/en/#home (accessed on 29/7/2021)
53. Parker, G., Hadzi-Pavlovic, D., Hickie, I., Mitchell, P., Wilhelm, K., Brodaty, H., Boyce, P., Eyers, K., Pedic, F. Psychotic depression: a review and clinical experience. *Aust N Z J Psychiatry* **1991**, *25*, 169-180.
54. Ruhland, C., Koschke, M., Greiner, W., Peupelmann, J., Pietsch, U., Hocke, M., Yeragani, V.K., Bar, K-J. Gastric dysmotility in patients with major depression. *J Affect Disord.* **2008**, *110*, 185-190.
55. Quick, C., Kliem, A., Berger, S., Hocke, M., Tancer, M., Juckel, G., Yeragani, V.K., Bar, K-J. Gastric dysmotility in major depression. *Prog Neuropsychopharmacol Biol Psychiatry* **2010**, *34*, 92-97.
56. Sanger, G.J., Wang, Y., Hobson, A., Broad, J. Motilin: towards a new understanding of the gastrointestinal neuropharmacology and therapeutic use of motilin receptor agonists. *Br J Pharmacol.* **2013**, *170*, 1323-1332.
57. Esterita, T., Dewi, S., Suryatenggara, F.G., Glenardi, G. Association of functional dyspepsia with depression and anxiety: a systematic review. *J Gastrointest Liver Dis.* **2021**, *30*, 259-266.
58. Zamani, M., Alizadeh-Tabari, S., Zamani, V. Systematic review with meta-analysis: the prevalence of anxiety and depression in patients with irritable bowel syndrome. *Aliment Pharmacol Ther.* **2019**, *50*, 132-143.
59. Fond, G., Loundou, A., Hamdani, N., Boukouaci, W., Dargel, A., Oliveira, J., Roger, M., Tamouza, R., Leboyer, M., Boyer, L. Anxiety and depression comorbidities in irritable bowel syndrome: a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci.* **2014**, *264*, 651-660.
60. Sibelli, A., Chalder, T., Everitt, H., Workman, P., Windgassen, S., Moss-Morris, R. A systematic review with meta-analysis of the role of anxiety and depression in irritable bowel syndrome onset. *Psychol Med.* **2016**, *46*, 3065-3080.
61. Van den Houte, K., Scarpellini, E., Verbeure, W., Mori, H., Schol, J., Masuy, I., Carbone, F., Tack, J. The role of GI peptides in functional dyspepsia and gastroparesis: a systematic review. *Front Psychiatry* **2020**, *11*, 172.

62. Sjolund, K., Ekman, R., Lindgren, S., Rehfeld, J.F. Disturbed motilin and cholecystokinin release in the irritable bowel syndrome. *Scand J Gastroenterol.* **1996**, *31*, 1110-1114.
63. Van Der Veek, P.P.J., Biemond, I., Masclee, A.A.M. Proximal and distal gut hormone secretion in irritable bowel syndrome. *Scand J Gastroenterol.* **2006**, *41*, 170-177.
64. Sjolund, K., Ekman, R., Wierup, N. Covariation of plasma ghrelin and motilin in irritable bowel syndrome. *Peptides* **2010**, *31*, 1109-1112.
65. Fukudo, S., Suzuki, J. Colonic motility, autonomic function, and gastrointestinal hormones under psychological stress on irritable bowel syndrome. *Tohoko J Exp Med.* **1987**, *151*, 373-385.
66. Jonsson, B.H., Hellstrom, P.M. Motilin- and neuropeptide Y-like immunoreactivity in a psychophysiological stress experiment on patients with functional dyspepsia. *Integr Physiol Behav Sci.* **2000**, *35*, 256-265.
67. Jiang, S-M., Jia, L., Liu, J., Shi, M-M., Xu, M-Z. Beneficial effects of antidepressant mirtazapine in functional dyspepsia patients with weight loss. *World J Gastroenterol.* **2016**, *22*, 5260-5266.
68. Du, H-G., Ming, L., Chen, S-J., Li, C-D. Xiaoyao pill for treatment of functional dyspepsia in perimenopausal women with depression. *World J Gastroenterol.* **2014**, *20*, 16739-16744.
69. Ko, S-J., Park, J., Kim, M-J., Kim, J., Park, J-W. Effects of the herbal medicine Rikkunshito, for functional dyspepsia: a systematic review and meta-analysis. *J Gastroenterol Hepatol.* **2021**, *36*, 64-74.
70. Zhou, H., Yao, M., Cheng, G-Y., Chen, Y-P., Li, D-G. Prevalence and associated factors of functional gastrointestinal disorders and bowel habits in Chinese adolescents: a school-based study. *J Pediatr Gastroenterol Nutr.* **2011**, *53*, 168-173.
71. Ulusoy, E., Arslan, N., Kume, T., Ulgenalp, A., Cirah, C., Bozkaya, O., Ercal, D. Serum motilin levels and motilin gene polymorphisms in children with functional constipation. *Minerva Pediatr.* **2016** Oct 5.
72. Sakkas, P.N., Soldatos, C.R., Bergiannaki, J.D., Paparrigopoulous, T.J., Stefanis, C.N. Growth hormone secretion during sleep in male depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry* **1998**, *22*, 467-483.
73. Naughton, M., Dinan, T.G., Scott, L.V. Corticotropin-releasing hormone and the hypothalamic-pituitary-adrenal axis in psychiatric disease. *Handb Clin Neurol.* **2014**, *124*, 69-91.
74. Bueno, L., Fargeas, M.J., Gue, M., Peeters, T.L., Bormans, V., Fioramonti, J. Effects of cotricotropin-releasing factor on plasma motilin and somatostatin levels and gastrointestinal motility in dogs. *Gastroenterology* **1986**, *91*, 884-889.
75. Zhang, L., Gong, J.T., Song, Q.H., Xu, G.H., Cai, L., Tang, X.D., Zhang, H.F., Liu, F-E., Jia, Z.S., Zhang, H.W. Melatonin attenuates noise stress-induced gastrointestinal motility disorder and gastric stress ulcer: role of gastrointestinal hormones and oxidative stress in rats. *J Neurogastroenterol Motil.* **2015**, *21*, 189-199.
76. Guo, F., Xu, L., Sun, X., Gao, S., Zhu, H. The paraventricular nucleus modulates thyroidal motilin release and rat gastric motility. *J Neuroendocrinol.* **2011**, *23*, 767-777.
77. Cosci, F., Fava, G.A., Sonino, N. Mood and anxiety disorders as early manifestations of medical illness: a systematic review. *Psychother Psychosom.* **2015**, *84*, 22-29.
78. Aoyagi, K., Mishima, Y., Murakami, S., Ito, K. Serum gastrin and motilin in treated and untreated hypothyroidism. *Bull Tokyo Med Dent Univ.* **1982**, *29*, 153-159.
79. Krysiak, R., Kowalcze, K., Okopien, B. Sexual functioning and depressive symptoms in young women with overt hypothyroidism. *Eur J Obstet Gynecol Reprod Biol.* **2019**, *234*, 43-48.
80. Krysiak, R., Marek, B., Okopien, B. Sexual function and depressive symptoms in men with overt hyperthyroidism. *Endokrynol Pol.* **2019**, *70*, 64-71.
81. Tsukamura, H., Tsukahara, S., Maekawa, T., Moriyama, R., Reyes, B.A.S., Sakai, T., Niwa, Y., Foster, D.L., Maeda, K-I. Peripheral or central administration of motilin suppresses LH release in female rats: a novel role for motilin. *J Neuroendocrinol.* **2000**, *12*, 403-408.
82. Holst, N., Jennsen, T.G., Burhol, P.G., Haug, E., Forsdahl, F. Plasma gastrointestinal hormones during spontaneous and induced menstrual cycles. *J Clin Endocrin Metab.* **1989**, *68*, 1160-1166.
83. Rapkin, A.J., Akopians, A.L. Pathophysiology of premenstrual syndrome and premenstrual dysphoric disorder. *Menopause Int.* **2012**, *18*, 52-59.
84. Kornstein, S.G., Harvey, A.T., Rush, A.J., Wisniewski, S.R., Trivedi, M.H., Svikis, D.S., McKenzie, N.D., Bryan, C., Harley, R. Self-reported premenstrual exacerbation of depressive symptoms in patients seeking treatment for major depression. *Psychol Med.* **2005**, *35*, 683-692.
85. Dennis, C-L., Ross, L.E., Herxheimer, A. Oestrogens and progestins for preventing and treating postpartum depression. *Cochrane Database Syst Rev.* **2008**, *2008*, CD001690.
86. Pae, C-U., Mandelli, L., Kim, T-S., Han, C., Masand, P.S., Marks, D.M., Patkar, A.A., Steffens, D.C., De Ronchi, D., Serretti, A. Effectiveness of antidepressant treatments in pre-menopausal versus post-menopausal women: a pilot study on differential effects of sex hormones on antidepressant effects. *Biomed Pharmacother.* **2009**, *63*, 228-235.
87. Pillai, R.R., Sharon, L., Premkumar, N.C., Kattimani, S., Sagili, H., Rajendiran, S. Luteinizing hormone-follicle stimulating hormone ratio as biological predictor of post-partum depression. *Compr Psychiatry* **2017**, *72*, 25-33.
88. Ansseau, M., Von Frenckell, R., Cerfontaine, J.L., Papart, P., Franck, G., Timsit-Berthier, M, Geenen, V., Legros, J.J. Blunted response of growth hormone to clonidine and apomorphine in endogenous depression. *Br J Psychiatry* **1988,** *153*, 65-71.
89. Krogh, J., Nordentoft, M., Mohammad-Nezhad, M., Westrin, A. Growth hormone, prolactin and cortisol response to exercise in patients with depression. *J Affect Disord.* **2010**, *125*, 189-197.
90. Birmaher, B., Heydl, P. Biological studies in depressed children and adolescents. *Int J Neuropsychopharmacol.* **2001**, *4*, 149-157.

91. Samson, W.K., Lumpkin, M.D., Nilaver, G., McCann, S.M. Motilin: a novel growth hormone releasing agent. *Brain Res Bull.* **1984**, *12*, 57-62.
92. Bhagwagar, Z., Hafizi, S., Cowen, P.J. Cortisol modulation of 5-HT-mediated growth hormone release in recovered depressed patients. *J Affect Disord.* **2002**, *72*, 249-255.
93. Thakore, J.H., Dinan, T.G. Effect of fluoxetine on dexamethasone-induced growth hormone release in depression: a double-blind, placebo-controlled study. *Am J Psychiatry* **1995**, *152*, 616-618.
94. Kluge, M., Schussler, P., Dresler, M., Schmidt, D., Yassouridis, A., Uhr, M., Steiger, A. Effects of ghrelin on psychopathology, sleep and secretion of cortisol and growth hormone in patients with major depression. *J Psychiatr Res.* **2011**, *45*, 421-426.
95. Liang, C., Luo, H., Liu, Y., Cao, J., Xia, H. Plasma hormones facilitated the hypermotility of the colon in a chronic stress rat model. *PLoS ONE* **2012,** *7*, e31774.
96. Cai, G-X., Liu, B-Y., Yi, J., Chen, X-M., Liu, F-L. Simotang enhances gastrointestinal motility, motilin and cholecystokin expression in chronically stressed mice. *World J Gastroenterol.* **2011**, *17*, 1594-1599.
97. Cohen, S., Janicki-Deverts, D., Doyle, W.J., Miller, G.E., Frank, E., Rabin, B.S., Turner, R.B. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proc Natl Acad Sci U S A* **2012**, *109*, 5995-5999.
98. Zhu, G., Kang, Z., Chen, Y., Zeng, J., Su, C., Li, S. Ultrasound-guided stellate ganglion block alleviates stress responses and promotes recovery of gastrointestinal function in patients. *Dig Liver Dis.* **2021**, *53*, 581-586.
99. Mu, D-Z., Xue, M., Xu, J-J., Hu, Y., Chen, Y., Ren, P., Huang, X. Antidepression and prokinetic effects of paeoniflorin on rats in the forced swimming test via polypharmacology. *Evid Based Complement Altern Med.* **2020**, *2153571*, 2153571.
100. Marzio, L., Neri, M., Pieramico, O., Delle Donne, M., Peeters, T.L., Cuccurullo, F. Dopamine interrupts gastrointestinal fed motility patterns in humans. Effect on motilin and somatostatin blood levels. *Dig Dis Sci.* **1990**, *35*, 327-332.
101. Funakoshi, A., Matsumoto, M., Sekiya, K., Nakano, I., Shinozaki, H., Ibayashi, H. Cholinergic independent dopaminergic regulation of motilin release in man. *Gastroenterol Jpn.* **1983**, *18*, 525-529.
102. Itoh, H., Katagiri, F., Ikawa, K., Takeyama, M. Effects of domperidone on human plasma levels of motilin, somatostatin, gastrin, adrenocorticotropic hormone and cortisol. *Biol Pharm Bull.* **2005**, *28*, 1752-1756.
103. Takahashi, T. Mechanism of interdigestive migrating motor complex. *J Neurogastroenterol Motil.* **2012**, *18*, 246-257.
104. Koutsoumbi, P., Epanomeritakis, E., Tsiaoussis, J., Athanasakis, H., Chrysos, E., Zoras, O., Vassilakis, J.S., Xynos, E. The effect of erythromycin on human esophageal motility is mediated by serotonin receptors. *Am J Gastroenterol.* **2000**, *95*, 3388-3392.
105. Tack, J. Georges Brohee Prize 1994. Motilin and the enteric nervous system in the control of interdigestive and postprandial gastric motility. *Acta Gastroenterol Belg.* **1995**, *58*, 21-30.
106. Chan-Palay, V., Ito, M., Tongroach, P., Sakurai, M., Palay, S. Inhibitory effects of motilin, somatostatin, [leu]enkephalin, [met]enkephalin, and taurine on neurons of the lateral vestibular nucleus: interactions with γ-aminobutyric acid. *Proc Natl Acad Sci USA* **1982**, *79*, 3355-3359.
107. Feng, B., Liu, J-C., Zhang, J., Ozaki, K-I., Guo, Y-Y., Yi, D-H., Li, X-Q., Zhao, M-G. Anxiolytic actions of motilin in the basolateral amygdala. *Mol Neurobiol.* **2013**, *47*, 892-902.
108. Yao, Z., Fu, Y., Wu, J., Zhang, W., Yu, Y., Zhang, Z., Wu, X., Wang, Y., Hu, B. Morphological changes in subregions of hippocampus and amygdala in major depressive disorder patients. *Brain Imaging Behav.* **2020**, *14*, 653-667.
109. Tang, S., Li, H., Lu, L., Wang, Y., Zhang, L., Hu, X., Bu, X., Hu, X., Gao, Y., Gong, Q., Huang, X. Anomalous functional connectivity of amygdala subregional networks in major depressive disorder. *Depress Anxiety* **2019**, *36*, 712-722.
110. Price, J.L., Drevets, W.C. Neural circuits underlying the pathophysiology of mood disorders. *Trends Cogn Sci.* **2012**, *16*, 61-71.
111. Guan, Y., Tang, M., Jiang, Z., Peeters, T.L. Excitatory effects of motilin in the hippocampus on gastric motility in rats. *Brain Res.* **2003**, *984*, 33-41.
112. Wu, M., Tang, M., Adriaensen, D., Depoortere, I., Peeters, T.L., Timmermans, J-P. Central, but not peripheral application of motilin increases c-Fos expression in hypothalamic nuclei in the rat brain. *Histochem Cell Biol.* **2005**, *123*, 139-145.
113. Sanger, G.J. Motilin receptor neuropharmacology: revised understanding. *Curr Opin Pharmacol.* **2012**, *12*, 641-646.
114. Bottomley, J.M., LeReun, C., Diamantopoulos, A., Mitchell, S., Gaynes, B.N. Vagus nerve stimulation (VNS) therapy in patients with treatment resistant depression: a systematic review and meta-analysis. *Compr Psychiatry* **2019**, *98*, 152156.
115. Zhao, D., Meyer-Gerspach, A.C., Deloose, E., Iven, J., Weltens, N., Depoortere, I., O'Daly, O., Tack, J., Van Oudenhove, L. The motilin agonist erythromycin increases hunger by modulating homeostatic and hedonic brain circuits in healthy women: a randomized, placebo-controlled study. *Sci Rep.* **2018**, *8*, 1819.
116. Depoortere, I., Thijs, T., Keith, J. Jr., Peeters, T.L. Treatment with interleukin-11 affects plasma leptin levels in inflamed and non-inflamed rabbits. *Regul Pept.* **2004**, *122*, 149-156.
117. Powell, T.R., Smith, R.G., Hackinger, S., Schalkwyk, L.C., Uher, R., McGuffin, P., Mill, J., Tansey, K.E. DNA methylation in interleukin-11 predicts clinical response to antidepressants in GENDEP. *Transl Psychiatry* **2013**, *3*, e300.
118. Liu, W., Ge, T., Leng, Y., Pan, Z., Fan, J., Yang, W., Cui, R. The role of neural plasticity in depression: from hippocampus to prefrontal cortex. *Neural Plast.* **2017**, *2017*, 6871089.
119. Zhao, M., Chen, L., Yang, J., Han, D., Fang, D., Qiu, X., Yang, X., Qiao, Z., Ma, J., Wang, L., Jiang, S., Song, X., Zhou, Z., Zhang, J., Chen, M., Qi, D., Yang, Y., Pan, H. BDNF Val66Met polymorphism, life stress and depression: a meta-analysis of gene-environment interaction. *J Affect Disord.* **2018**, *227*, 226-235.
120. Molendijk, M.L., Spinhoven, P., Polak, M., Bus, B.A.A., Penninx, B.W.J.H., Elzinga, B.M. Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analysis on 179 associations (n = 9484). *Mol Psychiatry* **2014**, *19*, 791-800.

121. Cryan, J.F., Slattery, D.A. GABAB receptors and depression. Current status. *Adv Pharmacol.* **2010**, *58*, 427-451.
122. Westover, A.N., Marangell, L.B. A cross-national relationship between sugar consumption and major depression? *Depress Anxiety* **2002**, *16*, 118-120.
123. Rajkumar, R.P. Cross-national variations in COVID-19 mortality: the role of diet, obesity and depression. *Diseases* **2021**, *9*, 36.
124. Wu, H., Xia, F-Z., Xu, H., Zhai, H-L., Zhang, M-F., Zhang, H-X., Li, Y-X., Li, Y., Gu, T., Ma, L-M., Lu, Y-L. Acute effects of different glycemic index diets on serum motilin, orexin and neuropeptide Y concentrations in healthy individuals. *Neuropeptides* **2012**, *46*, 113-118.
125. Kay, R.G., Foreman, R.E., Roberts, G.P., Hardwick, R., Reimann, F., Gribble, F.M. Mass spectrometric characterisation of the circulating peptidome following oral glucose ingestion in control and gastrectomised patients. *Rapid Commun Mass Spectrom.* **2020,** June 1.
126. Lan, J., Wang, K., Chen, G., Cao, G., Yang, C. Effects of inulin and isomalto-oligosaccharide on diphenoxylate-induced constipation, gastrointestinal motility-related hormones, short-chain fatty acids, and the intestinal flora in rats. *Food Funct.* **2020**, *11*, 9216-9225.
127. Huang, W., Jiang, S-M., Jia, L., You, L-Q., Huang, Y-X., Gong, Y-M., Wang, G-Q. Effect of amitryptiline on gastrointestinal function and brain-gut peptides: a double-blind trial. *World J Gastroenterol.* **2013**, *19*, 4214-4220.
128. Allen, J.M., Christofides, N.D., Cramer, P.A., Steinert, J., Bloom, S.R. Elevated motilin levels in patients treated with antidepressant and neuroleptic drugs. *Br J Psychiatry* **1982**, *141*, 27-29.
129. Wang, T., Yan, Y-F., Yang, L., Huang, Y-Z., Duan, X-H., Su, K-H., Liu, W-L. Effects of Zuojin pill on depressive behavior and gastrointestinal function in rats with chronic unpredictable mild stress: role of the brain-gut axis. *J Ethnopharmacol.* **2020**, *254*, 112713.
130. Abouesh, A., Hobbs, W.R. Clarithromycin-induced mania. *Am J Psychiatry* **1998**, *155*, 1626.
131. Kwan, B.Y.M., Rabheru, K. Manic episode associated with clarithromycin in a patient with medically treated depression. *Prim Care Companion CNS Disord.* **2012**, *14(2)*, e01285.
132. Goldberg, J.F., Truman, C.J. Antidepressant-induced mania: an overview of current controversies. *Bipolar Disord.* **2003**, *5*, 407-420.
133. Hu, B., Kuang, Y., Jing, Y., Li, Y., Zhao, H., Ouyang, H. Pediatric allergic rhinitis with functional gastrointestinal disease: associations with the intestinal microbiota and gastrointestinal peptides and therapeutic effects of interventions. *Hum Exp Toxicol.* **2021**, *May 21*, 9603271211017325.
134. Domin, H. Neuropeptide Y Y2 and Y5 receptors as potential targets for neuroprotective and antidepressant therapies: evidence from preclinical studies. *Prog Neuropsychopharmacol Biol Psychiatry* **2021**, *111*, 110349.
135. Raison, C.L., Miller, A.H. The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). *Mol Psychiatry* **2013**, *18*, 15-37.
136. Scott, K.M., Zhang, Y., Chardoul, S., Ghimire, D.J., Smoller, J.W., Axinn, W.G. Resilience to mental disorders in a low-income, non-Westernized setting. *Psychol Med.* **2020**, *May 5*, 1-10.
137. Miller, R., Kirschbaum, C. Cultures under stress: a cross-national meta-analysis of cortisol responses to the Trier Social Stress Test and their association with anxiety-related value orientations and internalizing mental disorders. *Psychoneuroendocrinology* **2019**, *105*, 147-154.
138. Xue, Z., Wum C., Wei, J., Xian, M., Wang, T., Yang, B., Chen, M. An orally administered magnosolide A ameliorates functional dyspepsia by modulating brain-gut peptides and gut microbiota. *Life Sci.* **2019**, *233*, 116749.
139. Raison, C.L., Lowry, C.A., Rook, G.A.W. Inflammation, sanitation and consternation: loss of contact with coevolved, tolerogenic microorganisms and the pathophysiology and treatment of major depression. *Arch Gen Psychiatry* **2010**, *67*, 1211-1224.
140. Pasricha, P.J., Yates, K.P., Nguyen, L., Clarke, J., Abell, T.L., Farrugia, G., Hasler, W.L., Koch, K.L., Snape, W.J., McCallum, R.W., Sarosiek, I., Tonascia, J., Miriel, L.A., Lee, L., Hamilton, F., Parkman, H.P. Outcome and factors associated with reduced symptoms in patients with gastroparesis. *Gastroenterology* **2015**, *149*, 1762-1774.
141. Liu, X., Zhang, J., Sang, Y., Liu, K., Zhu, Y., Yang, L., Wang, S., Sheng, J., Wang, Q., Zhang, D., Cao, H., Tao, F. Antibiotic exposure and potential risk of depression in the Chinese elderly: a biomonitoring-based population study. *Environ Sci Pollut Res Int.* **2021**, *28*, 26794-26806.
142. Tsai, C-F., Chen, M-H., Wang, W-P., Liu, P-Y., Hou, M-C., Lee, F-Y., Lu, C-L. Increased risk of short-term depressive disorder after Helicobacter pylori eradication: a population-based nested cohort study. *Helicobacter* **2021**, *26*, e12824.
143. Doan, T., Hinterwirth, A., Worden, L., Arzika, A.M., Maliki, R., Abdou, A., Kane, S., Zhong, L., Cummings, S.L., Sakar, S., Chen, C., Cook, C., Lebas, E., Chow, E.D., Nachamkin, I., Porco, T.C., Keenan, J.D., Lietman, T.M. Gut microbiome alteration in MORDOR I: a community-randomized trial of mass azithromycin distribution. *Nat Med.* **2019**, *25*, 1370-1376.
144. Neufeld, N.H., Mohamed, N.S., Grujich, N., Shulman, K. Acute neuropsychiatric symptoms associated with antibiotic treatment of Helicobacter pylori infections: a review. *J Psychiatr Pract.* **2017**, *23*, 25-35.
145. Lally, L., Mannion, L. The potential for antimicrobials to adversely affect mental state. *BMJ Case Rep.* **2013**, *2013*, bcr2013009659.
146. Ueno, N., Uemoto, M., Komatsu, Y., Sato, Y., Inui, A. A motilin agonist, erythromycin, decreases circulating growth hormone levels in normal subjects but not in diabetic subjects. *J Diabetes Complications* **2006**, *20*, 380-383.
147. Hao, K., Qi, Q., Hao, H., Wang, G., Chen, Y., Liang, Y., Xie, L. The pharmacokinetic-pharmacodynamic model of azithromycin for lipopolysaccharide-induced depressive-like behavior in mice. *PLoS One* **2013**, *8*, e54981.

148. Heightman, T.D., Conway, E., Corbett, D.F., Macdonald, G.J., Stemp, G., Westaway, S.M., Celestini, P., Gagliardi, S., Riccaboni, M., Ronzoni, S., Vaidya, K., Butler, S., McKay, F., Muir, A., Powney, B., Winborn, K., Wise, A., Jarvie, E.M., Sanger, G.J. Identification of small molecule agonists of the motilin receptor. *Bioorg Med Chem Lett.* **2008**, *18*, 6423-6428.
149. Steiger, A. Sleep and endocrinology. *J Intern Med.* **2003**, *254*, 13-22.
150. Eisenbeg, D.T.A., Hayes, M.G. Testing the null hypothesis: comments on 'Culture-gene coevolution of individualism-collectivism and the serotonin transporter gene'. *Proc Biol Sci.* **2011**, *278*, 329-332.