

# Gut symptoms in the depressed elderly: The interactions between emotion and gastrointestinal neuroendocrinology

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Late-life depression (LLD) is a common but easily overwhelming psychiatric condition in the elderly. LLD has a complex pathogenesis that causes diagnostic difficulties, including emotion, response to stress, physical illness, and social support. Besides, psychiatric symptoms and consequences, depression in the elderly frequently associated with other medical conditions, including metabolic syndrome, diabetes, gastroesophageal reflux disease (GERD), osteoarthritis, malignancies, and multimorbidity.<sup>1</sup> Among the LLD-associated health problems, gastrointestinal (GI) discomfort is a prevalent phenomenon. Although there is already a wide discussion of the association between irritable bowel syndrome (IBS) and depression or anxiety in the general population,<sup>2</sup> LLD patients present different clinical manifestations from younger patients with major depression to late-life depression more commonly associated with somatic symptoms, especially GI symptoms.<sup>3</sup> A recent study illustrated the correlation between LLD and GI symptoms, and those with LLD manifest more reflux, abdominal pain, and dyspepsia.<sup>4</sup> The bidirectional interactions between the central nervous system and GI tract are complicated. There is no single theory to explain the association between depression and GI symptoms. Aging of the GI tract may increase susceptibility to stress-induced dysfunction. A previous study demonstrated that esophageal peristalsis contraction impairment showed increased prevalence with age, independent of GERD symptoms.<sup>5</sup> The elderly may be more easily affected by emotional stress due to their vulnerable GI status.

The gut–brain axis is the most crucial regulatory mechanism in normal physiology, as well as in neurologic, psychiatric, and GI disorders. The hypothalamic–pituitary–adrenal (HPA) axis is the most well-known mechanism for explaining the responses to stress. In animal studies, corticotropin-releasing hormone (CRH) administration delayed gastric emptying but increased

colonic motility and transit,<sup>6</sup> and aggravated visceral nociception,<sup>7</sup> which all supported the association between IBS-like symptoms and emotional disorders. The microenvironment of the GI tract, especially the microbiota, has been extensively discussed recently. The microbiota differences between depressed individuals and healthy subjects have been identified in a variety of animal models of depression, and in human studies,<sup>8</sup> with decreased diversity of the microbiota and increased richness of *Bacteroidetes* but decreased *Firmicutes* and *Lactobacillus*. The exact mechanism underlying the alteration of the microbiota is not fully understood. Emotional stress may also be bidirectionally associated with gut flora. Disturbance of normal gut microbiota increases the stress susceptibility and risk of depression.<sup>8</sup> Previous animal studies suggest that the potential mechanism may also include the HPA axis.<sup>9</sup> In addition, stress and CRH administration also affected intestinal motility and microbiota composition in a rat model.<sup>10</sup> Based on the current evidence, microbiota disturbance may lead to depressive mood disorders and somatic GI symptoms. Restoration of healthy gut microbiota with a healthy diet or probiotics may provide potential therapeutic effects in depressive patients with GI symptoms.

Nutrition and diet are also important factors in mental and physical health. In the elderly, malnutrition is often an under-recognized phenomenon that may cause morbidity and mortality. Poor nutritional status may be easily masked by other medical illnesses and may be ignored. Poor oral intake is common due to multiorgan degenerative processes, including the GI tract, decreased whole-body metabolism, and poor dentition. In developed countries, a western diet with high calories, carbohydrates, and lipids, but low fiber content may also exert detrimental effects. In a previous animal study, depression-like behavior was observed in high-fat diet (HFD)–fed mice. The hypothalamic fatty acid component is altered, and the cyclic AMP (cAMP)/protein kinase A (PKA) signaling pathway is suppressed by HFD.<sup>11</sup> Differences in diet may also contribute to LLD in humans. Skarupski et al<sup>12</sup> suggested that the Mediterranean diet has a protective effect on the development of depressive symptoms in older adults. The Mediterranean diet is rich in vegetables, fruits, fish, and olive oil, but low in red meat and saturated fat, and may have physical and mental benefits through different mechanisms, including maintaining the normal gut microbiota, reducing chronic inflammatory response, and providing sufficient vitamins and minerals. A recent systemic review study has also illustrated several crucial dietary components that

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can potentially reducing depressive symptoms in the elderly.<sup>13</sup> Vitamin deficiency, including B12 and B6, has been reported to be associated with low cognitive function and depressive mood. The other beneficial nutrient is  $\omega$ -3 polyunsaturated fatty acids, which are abundant in the Mediterranean diet. In addition, calorie restriction has also been reported to improve mood status in elderly individuals, despite the results based on a limited sample size.

It is noteworthy that LLD causes significant morbidity, as well as mental and somatic symptoms and consequences. Medical complaints may also be warning signs of depressive mood disorders. For clinicians, psychiatric conditions should be considered if organic disorders are excluded from older adults. Further investigation of the gut-brain axis, gut microbiota also provides new therapeutic strategies for treating LLD and functional GI disorders, such as probiotic supplements and healthy lifestyle modifications. In addition, gut hormones, such as ghrelin, have been demonstrated to modulate gut motility and feeding<sup>14</sup> and should be considered in future studies.<sup>15</sup>

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