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Lettre to the Editor

Potential Antidepressant Effects of Omeprazole Introduced through Network Analysis and Systems Biology Should Be Interpreted with Caution in the Clinical Environment

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Dear Editor,

I am writing about an article published in the Iran J Psychiatry 2024; 19: 4: 367-383 titled "Identifying Key Genes and Approved Medications Associated with Major Depressive Disorder Using Network Analysis and Systems Biology" (1). The authors presented important findings about potential therapeutic candidates for Major Depressive Disorder (MDD) using Network Analysis and Systems Biology. One of the medications introduced as a candidate to have potential antidepressant effects was Omeprazole, based on its association with key genes identified in the pathogenesis of MDD. The authors have introduced the Omeprazole's association with Tumor Necrosis Factor-α (TNF), and Interleukin-1β (IL-1 β) genes as the underlying mechanism for this proposal. Although I do appreciate the innovation with which the authors were able to use network analysis and systems biology to identify these potential relationships, I felt quite urged to present a more critical perspective before interpreting the findings of network analysis and systems biology into clinical practice.

New investigations explore the role of long-term administration of proton pump inhibitors (PPIs), including Omeprazole, and their potential link to mood disorders, major depressive disorder, and even suicidal ideation. Pedro Fong *et al*. (2) in a cross-sectional study of more than sixteen thousand adults found that PPIs are associated with suicidal ideation OR = 2.34 (95% CI 1.66–3.31). Another large-scale cohort study on elderlies revealed that PPIs could increase the risk of dementia (hazard ratio: 1.44; 95% CI 1.36–1.52) (3). Still another study on elderlies associated the PPI intake with the Geriatric Depression Scale (OR: 2.38; 95% CI 1.02–5.58) (4).

Recently, a case report study presented a 34-year-old female patient with a history of gastroesophageal reflux disease (GERD) treated with PPIs, who developed significant symptoms of depression without any distinguishable history of mental disorders (5). Further evaluation suggested that she had a profound deficiency of tyrosine, which is an amino acid necessary for the production of neurotransmitters such as dopamine and norepinephrine which play consequential roles in mood. Subsequently, withdrawing PPIs along with amino acid supplementation led to the disappearance of depressive symptoms within several months.

While the authors identified various medications as well as Omeprazole that potentially interact with genes related to MDD including IL-1β and TNF, it seems that the link between chronic use of Omeprazole and amino acid deficiencies, which are the precursors of anti-depressant neurotransmitters, is stronger than the link between olanzapine, IL-1β, TNF and MDD. While the authors of the study targeted certain genes and medicine interactions for proposing new antidepressant agents and suggesting potential beneficial medications, talking of Omeprazole as a therapeutic agent for depression might be overemphasized without considering the complications it logically comes with.

The effect of Omeprazole on depression can be more explained by the gut-brain axis. Even though Omeprazole treats GERD, there are possibilities of changing the gastric PH and the gut microbiota. Chronic Omeprazole consumption may lead to overgrowth of

Streptococcaceae and decrease of the Lactobacillus family in the patient's gut (6). These alterations could affect protein/amino acid malnutrition and eventually lead to increased signs of depression. Furthermore, malabsorption of magnesium, calcium, and B vitamins may occur, which are all important in maintaining optimal brain function and mood stability. Literature has shown that a deficiency in B vitamins could be a possible cause of depressive symptoms (7). This emphasizes the controversy on long-term prescription of PPIs without proper concern on micronutrient malabsorption and the resulting chronic impact on patients' mood.

Hence, the hypothetical identification of medications like Omeprazole to treat MDD is indeed a progression; however, it is important to take a more careful analysis of such results and findings, and translate such findings into clinics when it is possible. The likely side effects of long-term PPI administration, especially on micronutrient absorption and patients' mood and depressive symptoms, should be discussed when we are outlining the association of Omeprazole with MDD. Therefore, since long-term administration of Omeprazole might have a link with depression among its side effects, this creates some worry over suggesting Omeprazole for the treatment of MDD.

In conclusion, the methodology for the identification of the link between genetic markers and medications initially proposed in this paper provides a strong groundwork for subsequent research; while also pointing at the need to pay sufficient care to the side effects of medications like Omeprazole on the patient's mental state. Subsequent clinical investigations must critically look at the consequences of long-term administration of PPIs. They should focus on the biopsychosocial model of depression and hence need a multi-disciplinary approach.

I appreciate your time and patience in considering this critical topic concerning the impact of Omeprazole and its suitability in MDD treatment. I hope that the gut-brain axis and the complexity of the effects of pharmacological treatments and their interaction with nutrients in the patients gastro intestinal system would be taken into account when suggesting anti-depressant agents; noting that sufficient clinical research is needed before interpreting the effects of therapeutic agents in the clinical environment.

Conflict of Interest

None.

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