# Is Depression Linked to Inflammation and the Gut? An invitation to challenge the methodology of depression therapy through medication in Japan and refocusing the strategy for treatment by including inflammation treatment and incorporating gut flora management

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# Is Depression Linked to Inflammation and the Gut? An invitation to challenge the methodology of depression therapy through medication in Japan and refocusing the strategy for treatment by including inflammation treatment and incorporating gut flora management

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**Abstract**

In this paper I want to challenge the effectiveness of the present drugs used for the treatment of depression by challenging the concept that depression is only centered in the brain: treating neurotransmitters such as serotonin, norepinephrine, and dopamine. By neglecting other factors that might have even more weight in the cause of depression such as inflammation and the influence of the human gut we are taking away valuable tools away from psychiatrists. Not only should we challenge the way present treatment of depression should be performed using more cognitive and behavioral therapies such as CBT, which operates on the basic principle that a person's moods and sense of self are intimately linked with their thoughts, and that recognizing dysfunctional thought patterns and replacing them with healthier ones can lead to improvements in mood, but by also giving psychiatrists a different group of medication that might be a more effective tool to help their suffering patients.

**Key words :** Depression, Inflammation, Gut Flora

## 1. Introduction

50 years ago the first drug to help people to fight their depression was released to the market and since then many more medications have been appearing after that. Most of these medications seem to work on the same parts of the brain biology: The neurotransmitters serotonin, norepinephrine, and dopamine. They seem to work for some people but the results confirm that at least one third of the patients that show major depressive symptoms have not found any relief despite the promise of being able to escape this unbearable suffering. Now come new discoveries that might give us some hope: Inflammation and the knowledge of the importance of the gut.[8-11,14,16]

## 2. Inflammation and Depression

The study of inflammation as a cause of depression began in the early 1990's but was not able to provide with any strong evidence that it should be pursued. Finally though, this is changing and for the last five years, research on inflammation and depression[1,3-7,9-19,21-24,26-33] has been accelerating and is finally becoming mainstream. Even though there is no strong path to show how the two conditions are linked, there is growing evidence that inflammation has a significant role in depression.[3-4,8-10,14,16,18,20-22,24,26-27,29,31,33] This evidence is like the sun rising again after a long journey through a dark tunnel to give hope to those who have not found peace of mind in taking all those medications and have on the contrary, being left to suffer terribly.[6-7,13,15]

Physiologically, inflammation seems an unlikely link to depression and mental problems. Inflammation, after all, originates from the need of the body to defend itself against infection and injury through the process of white blood cells releasing some chemical compounds that bring blood cells to the location of injury or infection and also immobilizes the affected area and finally raises the temperature to kill invading microbes. These same chemicals induce the body to modify the total behavior of the body to conserve energy for healing but at the same time this process can go wrong and these chemicals can attack the body's own tissues in autoimmune diseases such as rheumatoid arthritis and ulcerative colitis. Inflammation has already being linked to other illnesses such as diabetes, heart diseases and even Alzheimer's.[2,8-9]

Doctors have become more aware of the link between depression and inflammation by observing patients with prominent inflammation also having high depression rates. This has been also corroborated by studies where healthy people were injected with messenger chemicals such as cytokines, which caused them to have depressive symptoms. At the same time, depressed individuals tend to have elevated blood levels of the proteins that signal chronic inflammation.[8-9,17,21-22]

## 3. Research Question: Is inflammation the cause or the effect of depression or is it irrelevant?

This question will only be answered if people get relief of their depression after their inflammation is blocked. So far no definitive studies have proven this. Some drug trials have not being conclusive and even thought some chemical elements such as Curcumin seem promising, they are still in the trial phase.[2-3]

One of the reasons of the lack of success in this search could be the fact that the research did not factor in the fact that inflammation is likely only one part of equation: The Gut, stress, a person's moods and sense of self which are intimately linked to dysfunctional thought pattern could also have a large say in the mental condition.

We are in need of a novel treatment and this can only occur if we refocus our attention to these different causes, not one, but a combination of them. According to data from a ten-year

study by Avon Longitudinal Study of parents and children monitoring the health of 14,500 families in Bristol, England since 1991, shows that excessive inflammatory response makes depression more likely to occur. Children who at age 9 had high levels of the cytokine interleukin-6 or IL-6 were 50 percent more likely to be depressed when they were 18-and the higher their IL-6 level, the greater the depression risk. These results do not necessarily mean that chronic inflammation caused depression in these young children but that it certainly has shown that it is an important risk factor and this study highlights inflammation as an important piece in the larger puzzle of depression.[34-37]

## 4. Another piece of the puzzle: The link between stress, inflammation and depression.

A study at Mt. Sinai School of Medicine, the link between stress, inflammation and depression was highlighted.[38] In this experiment, a population of mice had their levels of IL-6 determined. They were then put in a highly stressful environment. The mice with higher levels of IL-6, and therefore higher predisposition to inflammation, were found to be also much more stress-sensitive to the stressful environment by entering into a depression-like state of avoidance versus the rats with lower levels of IL-6 levels. This study showed that as with the Avon Study, a naturally elevated inflammatory response of the white cells also indicated that there is a predisposition to depression versus those mice that do not have an elevated inflammatory response.

It has been the general belief that inflammatory biomarkers in the blood reflect something occurring in the brain but the above experiment is showing that inflammatory factors in the peripheral circulation could be the actual cause of brain pathology and depression.

Further study to understand the mechanism of the above is needed. One part of this future study should focus on Cytokines like IL-6 than can squeeze through the blood-brain barrier after being carried there by the peripheral leukocytes (white cells). Within the brain, cytokines may interfere with basic communication processes, such as neurotransmitter release and reception and with connections between brain regions.

In a recent study published by Jeffrey Meyer et. al. of the University of Toronto for the first time actual evidence of inflammation within the brain was found using positron emission tomography (PET) scans that showed higher concentrations of translocator protein in the brains of depressed individuals compared to controls. This protein, he proposed, reflects the activation of microglia, which release inflammatory chemicals. Increased activity was especially marked in brain regions linked to depression symptoms but the correlation was not complete: Translocator protein was elevated in about half of the patients and in 15 percent of the non-depressed controls which could mean that it takes several biological and psychological changes to push someone into a depressive state.

The way to proceed studying the influence of inflammation in depression could be to first identify the subgroup of depression sufferers that actually show certain levels of inflammation before treating them. This distinction in future studies could indicate the difference between success and failure.

## 5. The Gut: Does it dictate your mental health, thoughts and moods?

About half of neurochemicals are actually engaged in gut function, thus regulating appetite, digestive rate, and metabolism. These neurochemicals include a significant amount of the dopamine and serotonin in our bodies, which are not produced in the brain although used in the brain itself. In truth, most of those neurochemicals are directly managed and produced in the gut.

Initial research has begun to confirm that bacteria can modulate the levels of stress hormones in the body. A preliminary study has showed that having higher levels of two particular strains of bacteria, bifid bacteria and lactobacillus, are linked to a reduced release of stress hormones into the bloodstream. This test has its basis in lab rats, but the early human experiments with these two strains of bacteria have produced similarly low levels of anxiety in response to typically anxiety-inducing activities.

Ongoing research related to gastroenterology and psychiatric conditions seems to indicate the relationship between elevated levels of a particular chemical, 4-ethylphenylsulphate, also known as 4EPS, which seems to be produced by gut bacteria, and autism. Children with autism demonstrate statistically higher levels of 4EPS than those without, and lab studies have shown that mice injected with concentrated doses of this chemical also began exhibiting autistic symptoms.

The reason that this gut-brain connection matters so much is that for many neurological conditions, no cure is known, but that may be because researchers have been looking in the wrong place. Neurotransmitters, as the name implies, are largely thought of as being in the brain, but as it turns out, the gut also produces important neurotransmitters that can affect social behavior and brain chemistry. By narrowing down the candidates for a link between gut bacteria and autism, researchers could theoretically eliminate those bacteria, and the chemical that they produce, thus minimizing or even reversing the symptoms of autism.

Other research has even linked our psychological response to emotional stimuli to the presence or absence of gut bacteria. In a controlled study, two groups were given a probiotic and a placebo, respectively. When later shown images of people with emotional facial expressions, those who had been given_the probiotic were more aware and responsive to emotions, something that people with an autism spectrum disorder often struggle with.[9-10,18]

That being said, the exact mechanisms behind much of this gut-brain interaction are not understood. Theories include a key connection between bacteria and the vagus nerve (control-

ling digestive contraction and sensory input to the brain), but this has yet to be proven. The most recent research has focused on the wide range of metabolites, the drug-like chemicals that are produced by microflora that could potentially mimic, counter or complement the traditional neurotransmitters.

It is important to remember that evolution is typically extremely efficient - over a long enough timescale. Therefore, to improve its ability to reproduce, spread and survive, bacteria has likely altered our brain chemistry in myriad ways over time, perhaps even driving our social behavior to form communities and settle in close proximity to other potential hosts.

## 6. Proposal for a possible research approach

Chart 1 is an Observational/Prospective approach research setup that could be used as a base to investigate further the outcome of 2 different therapy treatments based on DNA blood samples with similar markers for inflammation and gut flora contents.

## Conclusion

What Does This All Mean?

If we can understand which types of gut bacteria control what moods, emotions and chemical signals within the body that affect brain function, we could theoretically tailor a healthy bacterial balance in the stomach. Essentially, it could be possible to reverse or even inhibit certain chronic psychological or mental disorders. If inflammation does play a role in depression as the nascent research seems to indicate, professionals in Japan would be able to count with one more tool to alleviate this pain-

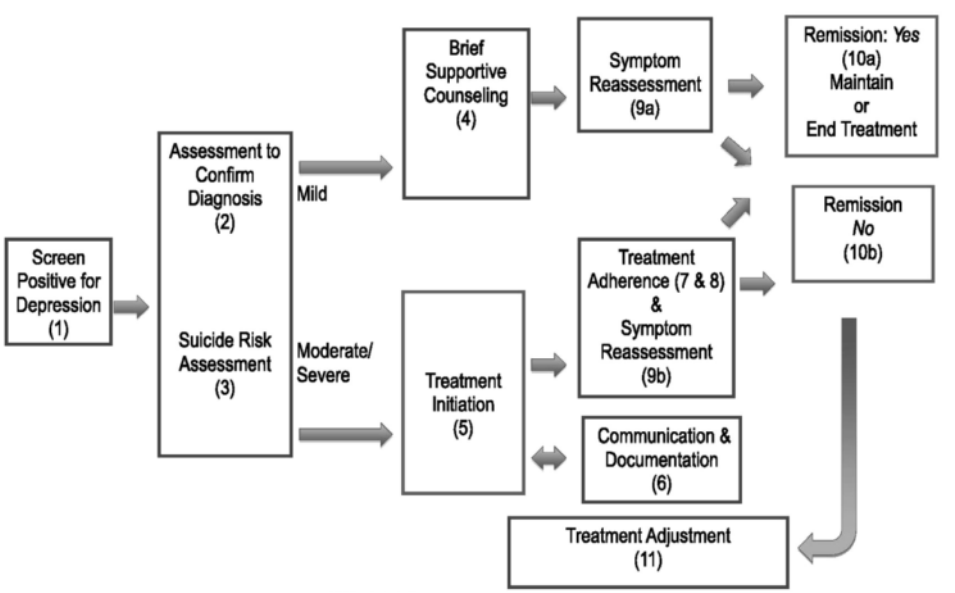


CHART 1

ful disease instead of to prescribing into the dark and hoping that the medication they are handing out will solve the patient's depression. The more we learn about inflammation and bacteria, the more we realize that it does far more than digest our food – it dictates the way we experience, think about and approach the world around us.

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