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An analysis of the Genetics Polymorphisms of the Serotonin (5-H T) Receptor (Article Review)

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ABSTRACT

Background: *Serotonin, also known as 5-hydroxytryptamine or 5-HT, is a crucial neurotransmitter in the human body, responsible for regulating various biological functions. It is often referred to as the "happy chemical" due to its role in promoting well-being and happiness. The body synthesizes 5-HT from the essential amino acid L-tryptophan, which is obtained from dietary protein. Serotonin receptors are divided into seven families, numbered 5-HT1 through 5-HT7. Certain families, such as 5-HT1A, 5-HT1B, 5-HT1C, 5-HT1D, 5-HT1E, and 5-HT1F, have multiple members. When taking antidepressants, there is a risk of developing the serotonin syndrome, which is a medication-induced condition resulting from serotonergic hyperactivity. As the number of patients with medically-treated major depressive disorder increases, so does the likelihood of experiencing serotonin syndrome. The serotonin transporter (also known as SLC6A4) and monoamine oxidase A (MAOA) are two molecules responsible for regulating serotonin levels in the brain. Genetic polymorphisms in the promoter regions of the genes encoding these proteins have been shown to affect their transcriptional activity in vitro. HTR2A has been identified as a gene that may increase susceptibility to rheumatoid arthritis (RA). In this study, we conducted an analysis to investigate the association between DNA methylation of HTR2A and RA using samples of peripheral blood.*

Keywords: Serotonin , (5-H T) Receptor, Genetics Polymorphisms

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INTRODUCTION

The chemical serotonin has a wide range of functions within the human body, often referred to as the "happy chemical" due to its contribution to overall well-being and happiness (McIntosh,J 2020). Its scientific name is 5-hydroxytryptamine (5-HT), and it is primarily found in the brain, bowels, and blood platelets. Serotonin is believed to play a role in mood, emotions, appetite, and digestion. Additionally, it is the precursor to melatonin, which helps regulate sleep-wake cycles and the body clock. Serotonin is produced when a component of proteins called tryptophan combines with tryptophan hydroxylase, a chemical reactor.

The intestines and brain both produce serotonin, and it is present in blood platelets, playing a role in the central nervous system. It influences a range of physical and psychological functions and can be found in animals, plants, and fungi. Some individuals have looked to food as a possible source of serotonin (McIntosh, 2020). Serotonin is

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unable to cross the blood-brain barrier, meaning it must be produced by the brain itself. Treatments for depression and other mental health issues do not provide serotonin directly but can trigger reactions that can boost serotonin levels in the brain(McIntosh, 2020). As a neurotransmitter, serotonin relays signals between nerve cells and regulates their intensity. Scientists believe it plays a role in mood and the CNS and can affect functions throughout the body, including bone metabolism, cardiovascular health, eye health, blood clotting, and neurological disorders. However, the relationship between serotonin and many bodily functions remains unclear.

Through the use of gene expression analysis and receptor antagonists, we have discovered that the activity of 5-HT2A receptors is crucial in the early stages of differentiation. This activity is responsible for the expression of adipogenic genes, including ppar-γ, aP2, adiponectin, and sgk1. This is the first time it has been demonstrated that 5-HT2A receptor activity is necessary for the differentiation of human primary subcutaneous preadipocytes to adipocytes, and that it plays a key role in the genes related to adipogenesis during this process. This finding is important in improving our understanding of the adipocyte differentiation process and the role of 5-HT2A receptors in peripheral tissues. It can also be relevant in developing new therapeutic strategies that target this receptor to treat obesity-related diseases. Studies have shown that genetic mutations in serotonin receptor genes are associated with obesity and cardiovascular disease (Gibson, W. T. *et al*,2004; Kring, S. I. *et al.*,2009). Among the serotonin receptors, the 5-HT2A receptor has been the most connected to behaviors and CNS function and is the most widely expressed serotonin receptor throughout the body (Choi, M. J. *et al.*,2004; Sorli, J. V. *et al.*,2008).Studies have established its role in the CNS, where it participates in processes such as cognition and working memory. Additionally, 5-HT2A receptor function has been linked to affective disorders like schizophrenia and is responsible for the primary effects of psychedelic drugs (Nichols, D. and Psychedelics, E. 2016). Serotonin 5-HT2A receptors are also expressed in many peripheral tissues (Watts, S. W. *et al*., 2009). They are known to modulate vasoconstriction and inflammation within the vasculature (Diaz, J. *et al.*2008). Genetic mutations in this receptor have been reported to be linked to cardiovascular diseases such as hypertension in both Caucasians and Asians (Yu, B. N. *et al.*2004). While research has implicated 5-HT2A receptor activity in metabolic processes, its function in many other peripheral tissues remains unclear. However, previous research has found that activation of peripheral and vascular 5-HT2A receptor produces potent anti-inflammatory effects, including the prevention of vascular inflammation and asthma (Nau, F. Jr. *et al.*,2015). There is also evidence suggesting that 5-HT2A receptor activity is involved in metabolic processes, such as increasing plasma glucagon levels in rats when activated with the agonist DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane)(Sugimoto, Y. and Yamada, J., 2000). HTR2A is a serotonin receptor called 5-hydroxytryptamine 2A, located on human chromosome 13q14-q21. It is comprised of three exons and several variants, including five non-synonymous variants, two synonymous variants, and over 200 known variants located in two introns (Seddighzadeh, M. *et al*., 2010).

The role of Serotonin in human physiology and related to food consumption

serotonin foods have been linked to the production of serotonin, which plays an important role in human physiology and is frequently studied for its potential to improve mental health and happiness. If an individual is lacking in serotonin, they can increase its

production through the consumption of specific foods (Jenkins *et al* ,.2016).

These foods, listed below, contain tryptophan, an amino acid that aids in serotonin production such as:

A. Salmon: Rich in tryptophan and omega-3 fatty acids, salmon is a beneficial food for the heart, bones, and skin. It also contains Vitamin D, which helps with serotonin production.

B. Nuts and Seeds: A natural source of tryptophan and protein, nuts and seeds are a great snacking option or addition to meals. Many whole grain breads now include them as well.

C. Turkey and Poultry: These meats are full of tryptophan and protein, which can contribute to feelings of well-being. They are often associated with Thanksgiving due to the large meals consumed during the holiday.

D. Eggs: A favorite among athletes and bodybuilders for their protein content, eggs should be prepared in a healthy manner such as boiled or poached.

E. Tofu and Soy: Tofu, made from soy, is an excellent source of tryptophan. Soy products are also popular among vegans and vegetarians.

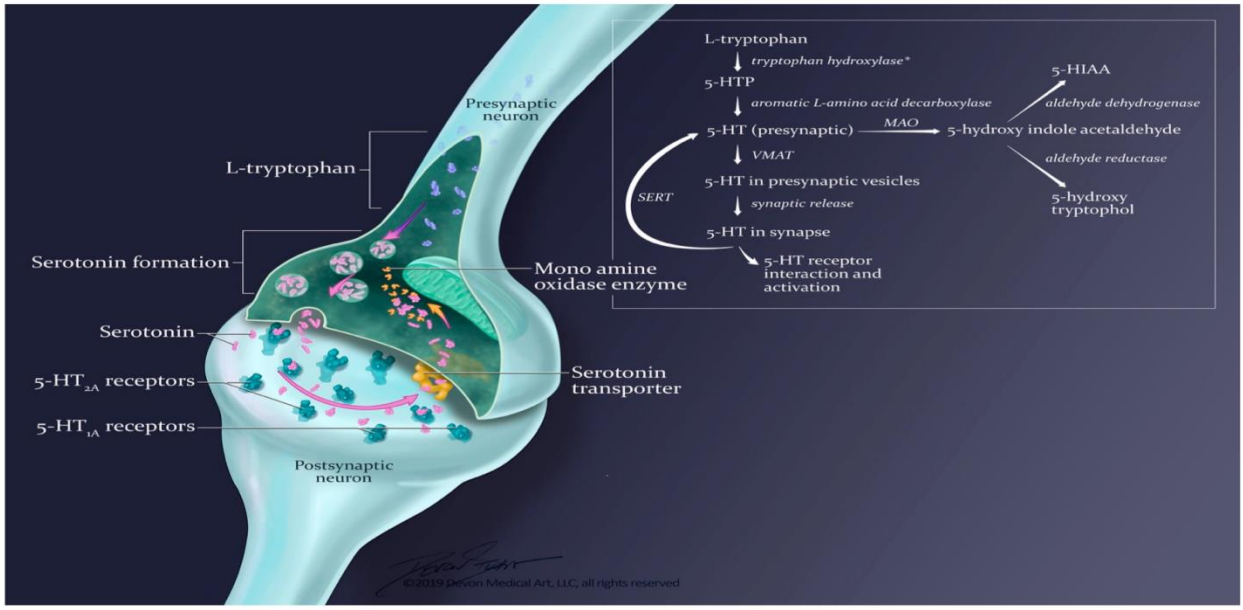
F. Milk and Cheese: Rich in tryptophan and calcium for healthy bones and teeth, low-fat varieties are a good option to avoid weight gain.

I. Pineapple: This fruit contains tryptophan to help boost serotonin levels in the brain.

It is important to avoid foods and drinks that may lower serotonin levels, such as alcohol and artificial sweeteners. Diet sodas and excessive caffeine can also reduce serotonin levels (Sanchez *et al*., 2015; Jenkins *et al*,. 2016).

The synthesis and release of serotonin

The synthesis and release of serotonin involves the conversion of the essential amino acid L-tryptophan, which is obtained from dietary protein [figure,1], [table,1]. In the brain, L-tryptophan is transported along with other neutral amino acids like phenylalanine, leucine, and methionine, by the same carrier (Frazer and Hensler, 1999). Therefore, the entry of tryptophan into the brain depends not only on its concentration in the blood, but also on its concentration relative to that of these other amino acids (Fernstrom, 2012; Francescangeli, J. *et al*,. 2019).



[Figure, 1]: At normal serotonergic neurons, the concentration of serotonin at a synapse is determined by several processes, including synthesis, controlled release from the presynaptic neuron, reuptake, and metabolism. 5-HTP = 5-hydroxytryptophan; 5-HT = 5-hydroxytryptamine (serotonin); VMAT = vesicular monoamine transporter; SERT= serotonin reuptake transporter; 5-HIAA = 5-hydroxy indole acetic acid. Asterisk denotes the rate-limiting step in serotonin synthesis (Francescangeli, J. *et al*,. 2019).

The first step in the synthesis of serotonin involves converting L-tryptophan to 5-hydroxytryptophan using the enzyme tryptophan hydroxylase. If this reaction is inhibited, serotonin levels can significantly decrease. The 5-hydroxytryptophan is then converted into serotonin using the enzyme aromatic L-amino acid decarboxylase (Pithadia, A.B and Jain, S.M, 2009 ; Fidalgo, S. *et al*., 2013). Once synthesized, serotonin is stored in vesicles using a vesicular monoamine transporter. The transport of serotonin into vesicles requires energy from the electrochemical gradient produced by a vesicular H+-ATPase, which results in the coupling of serotonin uptake with the efflux of hydrogen cations. In the central nervous system, serotonin is released into the synaptic cleft through calcium-dependent exocytosis from the vesicles (Hensler, J.G, 2012). The rate of serotonin release depends on the firing rate of serotonergic neurons.

[Table, 1]: Drugs associated with development of serotonin syndrome, classified according to their mechanism of action.

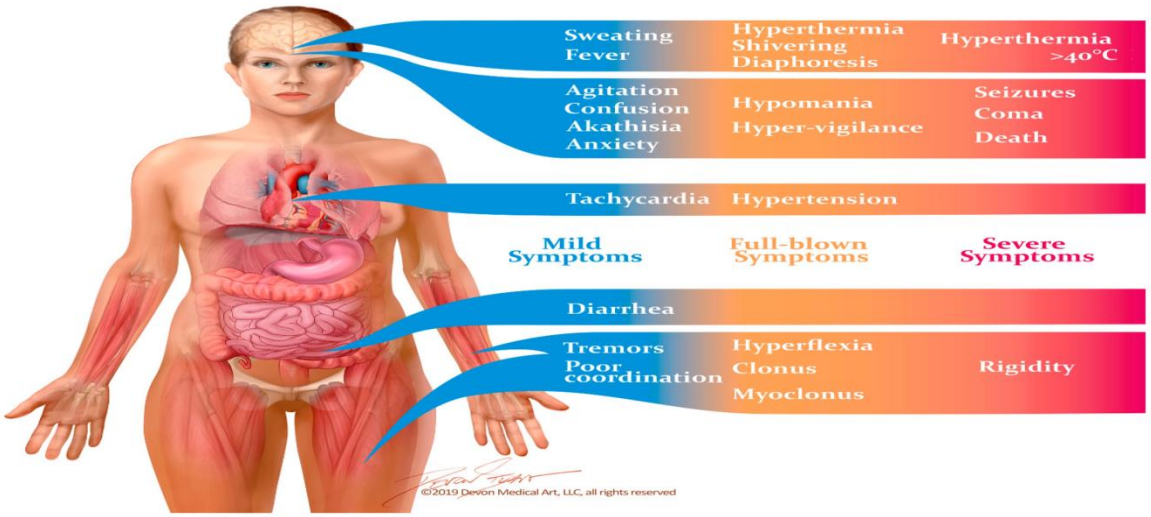
Synthesis and Release			
Increase Serotonin Synthesis	Dietary supplements: L-tryptophan		
Increase Serotonin Release	Psychostimulants: Amphetamines, phentermine, MDMA Antidepressants: mirtazapine Opioids: meperidine, oxycodone, tramadol Cough suppressants: dextromethorphan		
Metabolism			
Inhibit Serotonin Uptake	Psychostimulants: Amphetamines, MDMA, cocaine Antidepressants: trazodone SNRI: desvenlafaxine, duloxetine, venlafaxine SSRI: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline TCA: amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine Opioids: meperidine, methadone, tramadol Cough suppressants: dextromethorphan		
Inhibit Serotonin Metabolism	Anxiolytics: buspirone MAOI: furazolidone, isocarboxazid, linezolid, methylene blue, phenelzine, selegiline, tranylcypromine		
Inhibit Cytochrome P450 Microsomal Oxidases	**CYP2D6**	**CYP3A4**	**CYP2C19**
	Inhibitors: fluoxetine, sertraline Substrates: dextromethorphan, oxycodone, risperidone, tramadol	Inhibitors: ciprofloxacin, ritonavir Substrates: methadone, oxycodone, venlafaxine	Inhibitors: fluconazole Substrates: citalopram
Receptor Activation			
Activate Serotonin Receptors	Hallucinogen: LSD Anxiolytics: buspirone Antidepressants: trazodone Opioids*: fentanyl, meperidine Mood stabilizers: lithium		

* opioids most likely activate serotonergic receptors through a combination of postsynaptic 5-HT receptor stimulation as well as synergistic _-opioid and 5-HT receptor presynaptic inhibition of GABA release (Baldo, B.A, 2018). Adapted from (Volpi-Abadie, J. *et al*., 2013).

The Serotonin Syndrome

The serotonin syndrome (SS) is a medical condition caused by excessive activity of the serotonergic system, typically due to antidepressant medication. As more people receive treatment for major depressive disorder, the risk of serotonin syndrome increases. Overstimulation of 5-HT2A receptors can lead to serious autonomic and neuromuscular issues. The molecular basis of the condition and how common medications can interfere with normal serotonergic pathways, potentially resulting in fatal consequences. Mild cases may present as little more than flu-like symptoms, while severe cases may progress rapidly to cardiovascular collapse and death [figure, 2] (Francescangeli, J. *et al*,. 2019). Since serotonin syndrome can mimic other illnesses, it is important to understand its molecular context in order to identify and prevent rapid clinical decline.

Serotonin syndrome is a clinical condition that occurs when the serotonergic system is overactive in the central and peripheral nervous systems. The true prevalence of the condition is unknown, as its severity varies and many of its symptoms can be mistaken for other conditions. The condition is triggered by common therapeutic drugs, which are being used more frequently (Mason, P.J *et al*., 2000). Antidepressants are the most common triggers and their use in adults in the United States has increased from 6% in 1999 to 10.4% in 2010 (Mojtabai, R. and Olfson, M. 2014). Ingestion of selective serotonin reuptake inhibitors (SSRIs) has also increased in recent years almost 15% from 2002 to 2005 (Uddin, M.F. *et al*., 2017). The clinical pathophysiology of serotonin syndrome and present the leading molecular theories underlying the disease. Since the condition presents with a wide variety of symptoms, it is important to understand how it manifests in order to diagnose it accurately. This review will also explain how certain genetic polymorphisms can contribute to the development of serotonin syndrome in predisposed individuals. This information will help readers to understand how certain medications can trigger the syndrome, especially in high-risk patients. The review will also discuss current treatment strategies and future research directions.



[Figure, 2]: Signs and symptoms of the serotonin syndrome occur along a spectrum of severity. Mild symptoms may easily be overlooked, and may manifest as little more than diarrhea and flu-like symptoms. Unless the disease is recognized and the causative drugs are discontinued, it can rapidly progress to muscle rigidity, severe hyperthermia and death (Francescangeli, J. *et al*,. 2019).

Serotonin Receptors

The process of serotonin synthesis occurs in two locations: the gut neurons in the periphery and the neurons of the raphe in the brain stem in the central nervous system. Peripheral serotonin production can be affected by tryptophan depletion. However, for central serotonin production to happen, tryptophan must first cross the blood-brain barrier. This can be challenging as tryptophan competes with other amino acids essential for brain function to gain access to the central nervous system(Sanchez *etal*., 2015). Serotonin receptors are grouped into seven families, each with a numerical name from 5-HT1 to 5-HT7. Some of these families have multiple members with different names, such as 5-HT1A, 5-HT1B, 5-HT1C, 5-HT1D, 5-HT1E, and 5-HT1F. This classification is based on both the pharmacologic properties of each receptor and their secondary messenger systems (Fidalgo *et al.,* 2013)**.**

Receptor-Targeted Therapy for Serotonin Syndrome

Clinicians can prevent Serotonin Syndrome (SS) by being vigilant of patients taking high-risk medications. They should reassess the need for serotonergic medications yearly, use the lowest effective dose, take an accurate medical history with an emphasis on illicit drug use, closely monitor patients during medication dose increases and hospital encounters, and educate patients to recognize early symptoms of SS (Foong, A.L. *et al*., 2018). For patients experiencing SS, toxicity typically resolves after discontinuing serotonergic medications. Seventy percent of patients recover completely within 24 hours, 40% of patients require ICU admission, and only 25% of patients require endotracheal intubation (Mills, K.C, 1995). Supportive care, including benzodiazepines, is the primary treatment for SS in humans (Francescangeli, J. *et al*., 2016). Stimulation of 5-HT2A receptors causes life-threatening manifestations of SS such as rigidity and hyperthermia (Buckley, N.A *et al*., 2014). Targeted therapy for SS should focus on blocking this receptor. While 5-HT2A blockers ritanserin and piperine have been successful in animal studies, there are no specific 5-HT2A receptor antagonists approved for human use, nor are there medications capable of increasing the body's clearance of serotonin.

Genetic variability affecting serotonin levels

The brain's serotonin levels are regulated by two important molecules, namely the serotonin transporter (also known as SLC6A4) and monoamine oxidase A (MAOA). These proteins have genetic polymorphisms in their promoter regions that can affect their transcriptional activity, as found in vitro studies (Guo *et al*., 2008).

The genetic variants of these genes have been researched to understand their potential involvement in psychiatric conditions and behavioral traits (Hu *et al*., 2006). The serotonin transporter polymorphism (5HTTLPR) and monoamine oxidase A polymorphism (MAOA-LPR) have been linked to conditions and behaviors such as depression, anxiety, aggression, alcoholism, autism, suicidality, and impulsiveness (Lau *et al*., 2009). However, the relationship between these traits and genetic variability in these genes has not been consistent. In fact, these genes have demonstrated interactions with environmental factors and different effects in males and females. The 5HTTLPR is a region with a complex structured length polymorphism (Lau *et al*., 2009).

Genetic Polymorphisms of Serotonin Receptor

It seems that individuals with certain genetic variations of at the T102C site of the

5-HT2A receptor gene may have a higher risk of developing SS (Buckley, N.A. *et al*.,2014; Cooper, J. *et al.*, 2014). In recent years, genetic variations affecting the 5-HT2A receptor have been linked to antidepressant treatment failure and various neuropsychiatric disorders, including schizophrenia and mood disorders (Norton, N. *et al*.,2005). In a randomized pharmacogenetic study, patients with different T/C single nucleotide polymorphisms affecting the 5-HT2A receptor were given either the SSRI paroxetine or the non-SSRI antidepressant mirtazapine to compare treatment outcomes (Murphy, G.M. *et al*., 2003). The study found that patients who were homozygous for polymorphisms at the HTR2A locus (C/C) were more likely to stop taking paroxetine due to severe side effects. Mirtazapine has a unique mechanism of enhancing serotonergic and noradrenergic pathways in the central nervous system, inhibiting presynaptic inhibitory receptors on noradrenergic and serotonergic neurons, and blocking 5-HT2 and 5-HT3 receptors, only serotonergic transmission via 5-HT1A is enhanced(Kasper, S. *et al*.,1997). A case report described a patient taking the MAOI phenelzine, who developed SS without being exposed to other serotonergic agents, and was subsequently found to be a homozygous carrier for T102C allele (i.e., C/C)(Lattanzi, L. *et al*., 2008). However, Cooper et al. presented contrary evidence, failing to find a significant increase in clinically significant cases of SS in individuals with polymorphisms at the T102C locus(Cooper, J. *et al*., 2014). It has also been proposed that individual variations in serotonin metabolism by CYPs may contribute to SS susceptibility (Hegazi, A. *et al*., 2012; Piatkov, I. *et al*., 2017). One case report described an individual who developed SS while taking the SSRI paroxetine without other known serotonergic medications. This patient was found to have a polymorphism for the CYP2D6 allele, which may have impaired the metabolism of paroxetine and contributed to the development of SS (Kaneda, Y.*et al*., 2002). Another similar case report suggested that altered drug pharmacokinetics may have played a role in the development of SS in a patient taking fluoxetine, who was found to have a nonfunctioning CYP2D6 genotype and was heterozygous for an allele of CYP2C19 that results in poor metabolizing ability (Piatkov, I. *et al*., 2017).

CONCLUSION

This review discusses the functions of serotonin in the human body and its syndrome, which is a condition caused by serotonergic hyperactivity resulting from medication, particularly antidepressants:

1- Serotonin plays a crucial role in regulating the neuro-development of brain regions responsible for emotional processing. It also regulates different physiological processes like pain perception, digestion, and energy balance through various opposing mechanisms.

2- The understanding of serotonin receptors' specific role in human physiology is evolving. Depression is projected to be the second leading cause of death and disability by 2020, but up to 70% of patients do not respond to or tolerate their prescribed antidepressant therapy.

3- Personalized medicine using pharmacogenetic tools can address this issue by better understanding an individual's transporter, enzyme, and receptor profile to tailor medication therapy accordingly.

4- Epidrugs can alter the individual's epigenome to lessen the disease burden of depression or increase their

tolerance to existing antidepressant therapies.

5- The FDA has already approved several genetically prescreened drugs in psychiatry, and the development of such tools can help combat SS in the face of an increasing epidemic of major depressive disorder. The most commonly prescribed medications for depression are also the ones most likely to cause SS, making the ongoing development of these tools our best defense.

6- Future studies on the causal mechanisms behind the role of serotonin during brain development will provide us with valuable knowledge. It's important to continue to explore the functions of serotonin in the human body, especially in relation to emotional processing and other physiological processes. By gaining a better understanding of how serotonin works, we may be able to develop more effective treatments for conditions like depression and serotonin syndrome.

ABBREVIATIONS

5-HT	5-Hydroxytryptamine
CYP	Cytochromes p450
MAO-A subtype A	Monoamine Oxidase Inhibitor
MAO-B subtype B	Monoamine Oxidase Inhibitor
MAOI	Monoamine Oxidase Inhibitor
NMDA	N-methyl-D-aspartate
SS	Serotonin Syndrome
SSRI SNRI Reuptake Inhibitor	Serotonin Norepinephrine
TCA	Tricyclic Antidepressant

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