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Abstract:

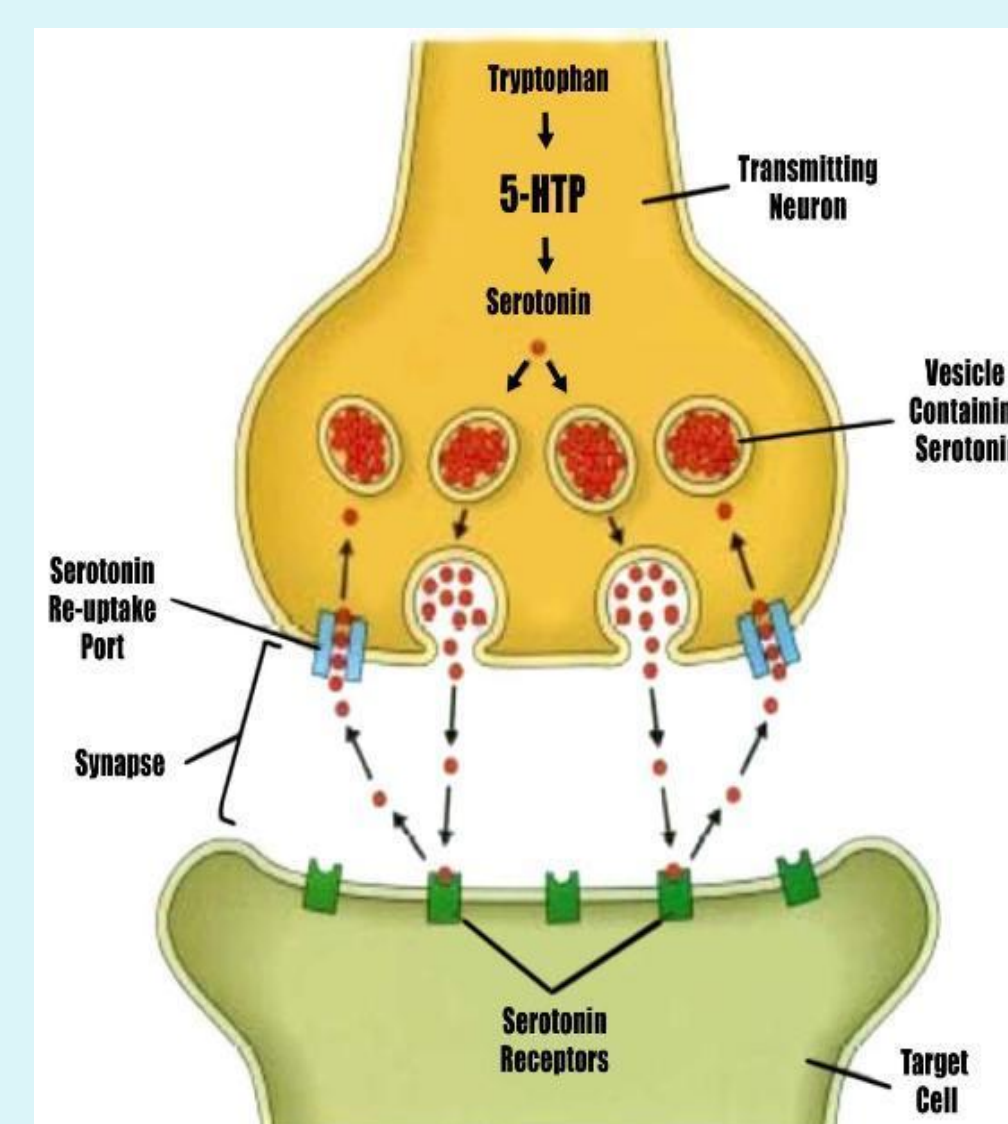
The antidepressant Sertraline is a Selective Serotonin Reuptake Inhibitor (SSRI), which works to increase concentrations of the neurotransmitter serotonin. The medication's function is in the synapse between two neurons, preventing serotonin recycling. Sertraline contains two chlorine molecules, which allow it to enter a specific binding pocket within Leu-T-type transporter proteins. This leucine transporter ultimately serves as a binding site for SSRIs, which allows for the prevention of serotonin recycling within the cleft. Sertraline, however, has the potential to cause Serotonin Syndrome, a fairly uncommon adverse effect of SSRIs, in which the neurons of the body become overloaded with serotonin. This potentially fatal condition can be difficult to diagnose due to its nonspecific symptoms, and is most common when medications that work to increase the activity of serotonin by different mechanisms are used in combination.

Introduction:

- Psychiatric and neurological disorders are some of the most debilitating diseases that affect the human population. Some of these disorders include: depression, attention deficit disorder (ADD), obsessive compulsive disorder (OCD), Parkinson's disease, anxiety disorders, and schizophrenia.
- The mechanism behind these disorders is the lack, or excess amount of, monoamine neurotransmitters within the brain.
- Serotonin Syndrome is a condition that occurs when the neurons of the body become overloaded with the neurotransmitter serotonin.
- A clinical example involved a 66-year-old man presenting to the pharmacy for a one-week follow-up appointment after the initiation of sertraline for depression. He complained of agitation and palpitations.
- Six weeks later, the same patient was admitted to a psychiatric outpatient unit with agitation, palpitations, sweating, shivering, fever, flushing, fatigue, dry mouth, insomnia, loss of appetite, weight loss, and constipation.⁶ It was determined that this patient was not taking any additional drug therapies, and the addition of sertraline was most likely the cause of this case of Serotonin Syndrome.

Molecular Story:

- The control of the synaptic monoamine neurotransmitters like serotonin and norepinephrine is regulated by the membrane-associated monoamine transporters, serotonin reuptake inhibitor (SERT) and norepinephrine reuptake inhibitor (NERT).



<http://www.ssrireview.com>

- Sertraline is bound to the serotonin transporter by seven amino acids.
- It binds via hydrophobic interactions with Phe253, Leu400, Asp401, Ala319, Phe320, and Arg30.
- It also binds via hydrogen bonding with Asp404.
- A binding pocket is formed by the amino acid sequence Leu25, Gly26, Leu29, Arg30, Tyr108, Ile111, and Phe253.

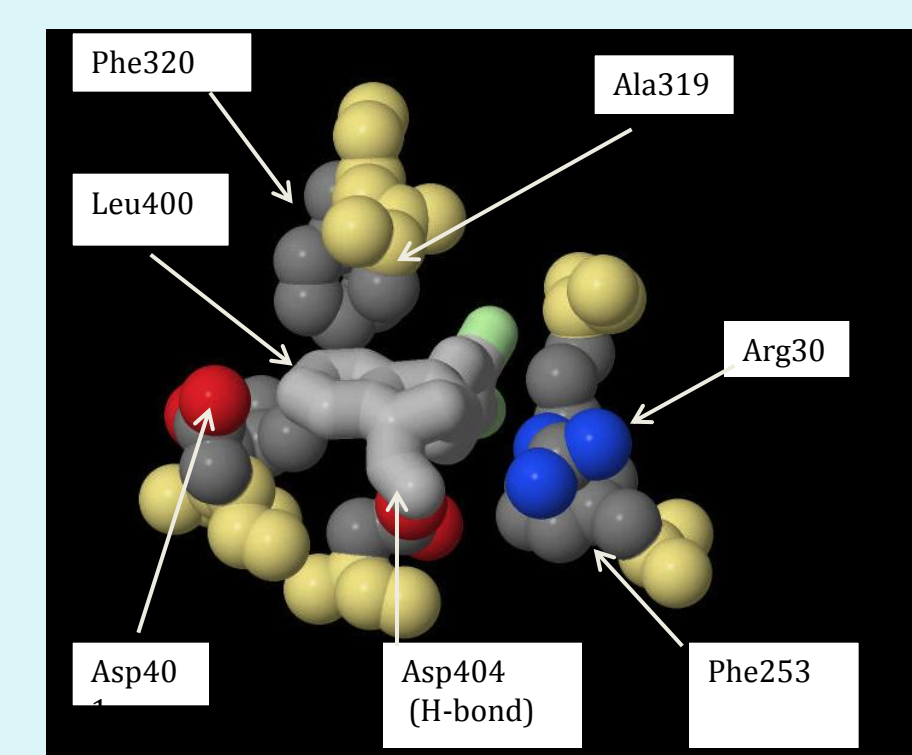


Figure 1: Sertraline in active site of leucine transporter

- Van der Waals forces are present in the interaction between the drug and Leu29, Tyr108, and Phe253, thus increasing the strength of the interaction.

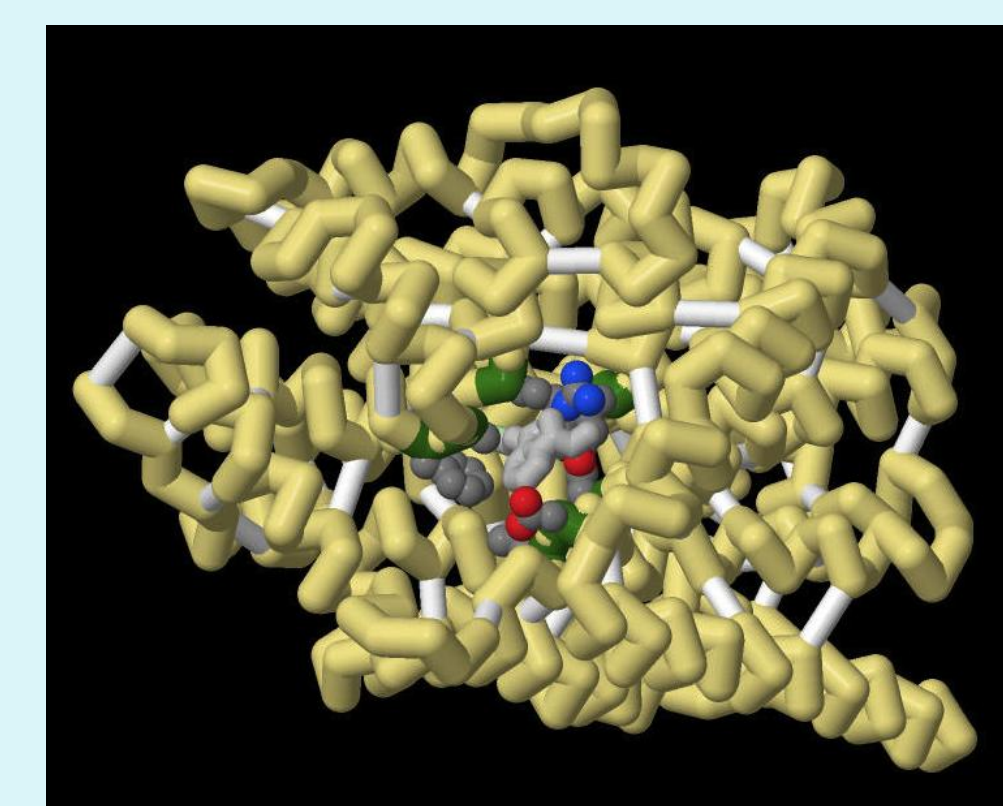
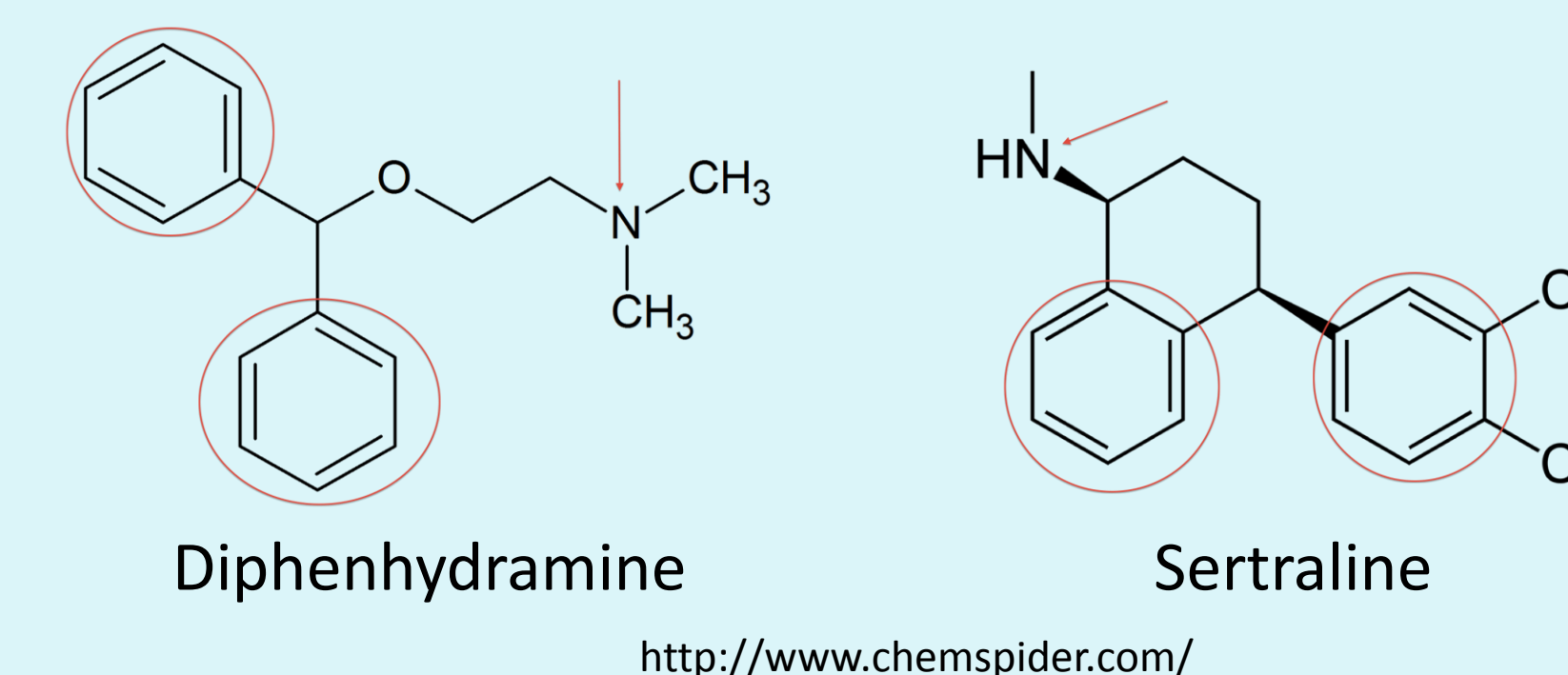


Figure 2: Leucine transporter showing sertraline in binding site

Figure 3: Pharmacophore-Derived from antihistamines



Unaddressed Clinical Issues:

- In order to prevent Serotonin Syndrome, dosing needs to be monitored, and medication histories need to be obtained to identify other serotonergic medications.
- Start low-dose and titrate up
- Educate the patient on side effects for monitoring at home
- From a future drug development standpoint, avoid inserting polar substituents (Ex: -OH) around the binding pocket, as that would disrupt the hydrophobic interactions and van der Waals forces at work. Though this would decrease the potential chances of Serotonin Syndrome, it may also decrease the therapeutic effects.

Summary:

Sertraline is bound to the serotonin transporter by seven amino acids. A binding pocket is formed, and van der Waals forces are present in the interaction between the polar amino acids, thus increasing the strength of the interaction. Because of these interactions, Sertraline does its job well in regards to treating psychiatric and neurological disorders. Serotonin Syndrome is a rare, but serious adverse effect of Sertraline but because of the effectiveness of Sertraline, the possibility of Serotonin Syndrome should not be a reason to avoid use of this valuable medication.

Selected References:

- Boyer, E. <http://www.nejm.org/doi/full/10.1056/NEJMra041867>
Manepalli, S. <http://www.dug.edu/chronic-pain-research/publications.cfm>
Preskorn, S. http://www.preskorn.com/books/ssri_s3.html