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Studies on Second Generation Anti-Depressants: SSRIs

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Introduction:

Depression affects nearly 350 million people yearly. That translated to 1 in 20 people of the 17 countries studied. Depression can lead to suicide and there are over a million suicide deaths happening yearly. This is what the WHO says. (1) But what is depression, in fact what is a mental disorder? The book which is used by clinicians and researchers to diagnose a mental illness is the Diagnostic and Statistical Manual of Mental Disorders.(DSM) And it defines mental illness as the following.

"A mental disorder is a syndrome characterized by clinically significant disturbance in an individual's cognition, emotion regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning. Mental disorders are usually associated with significant distress or disability in social, occupational, or other important activities."(2) There are many types of depression but I'll be focusing on Major Depressive Disorder.(MDD) So the question is how do you identify a person with depression. If that person exhibits some of these symptoms then he/she can be diagnosed with MDD.

"DSM-IV Criteria for Major Depressive Disorder

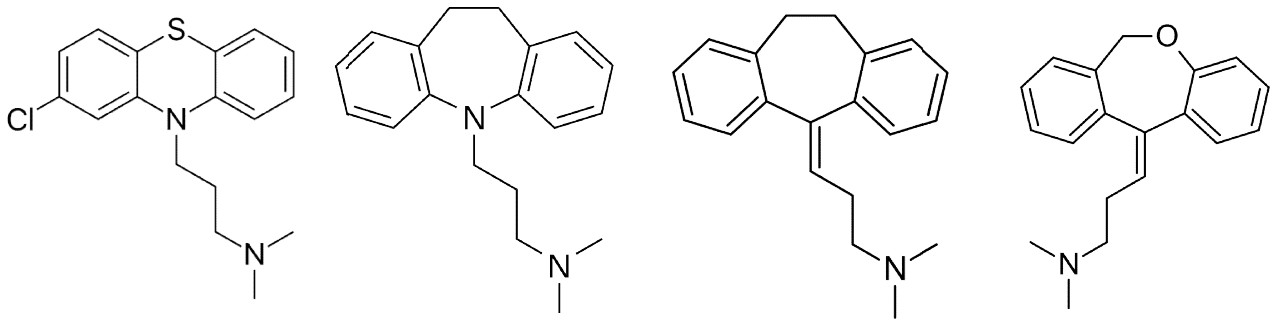
- Depressed mood or a loss of interest or pleasure in daily activities for more than two weeks.
- Mood represents a change from the person's baseline.
- Impaired function: social, occupational, educational.
- Specific symptoms, at least 5 of these 9, present nearly every day.

1. Depressed mood or irritable most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
2. Decreased interest or pleasure in most activities, most of each day.
3. Significant weight change (5%) or change in appetite.
4. Change in sleep: Insomnia or hypersomnia.
5. Change in activity: Psychomotor agitation or retardation.
6. Fatigue or loss of energy.
7. Guilt/worthlessness:Feelings of worthlessness or excessive or inappropriate guilt.
8. Concentration: diminished ability to think or concentrate, or more indecisiveness.
9. Suicidality:Thoughts of death or suicide, or has suicide plan."(2)

So what to do?

There are mainly two types of treatment one is using drugs and another is by therapy which includes behavioral changes, exercise etc., The primary idea for making of anti-depressants came from looking at pain pathways. Serotonin and noradrenaline are the major neurotransmitters which are involved in passing on the pain signals from the brain to the body. Dysfunction in these pathways due to imbalance of these neurotransmitters is a possible explanation for depression in some people. (3)

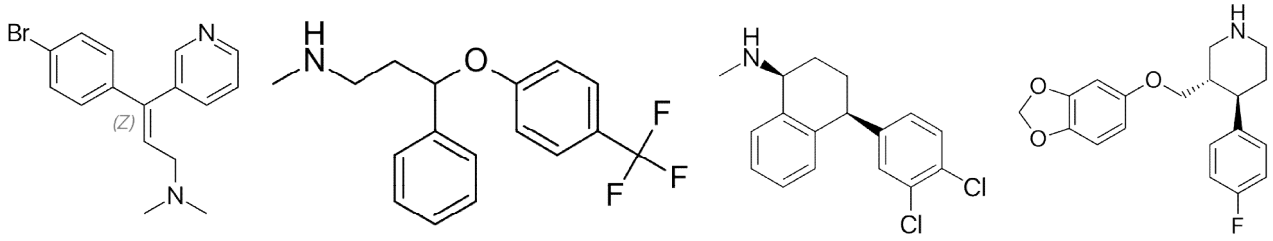
Tricyclic anti-depressants were discovered in the 1950s and consequently introduced into the market. Paul Charpentier discovered chlorpromazine (Thorazine, Largactil) a derivative from a synthetic derivative of antihistamine developed by Rhône-Poulenc in the 1940's. It was used as an anti-psychotic. For depression the first drug approved was Imipramine (Tofranil) which is a TCA of the diabenzazepine group. It was tested on patients and its anti-depressant effects were reported by Roland Kuhn in 1957.Other popular TCAs include Amitriptyline (Elavil) and Doxepin (Deptran). These work by binding to the 5-hydroxytryptamine (5-HT) receptors which are seratonin receptors of GPCR type and also inducing Norepinephrine reuptake inhibition.(4)



chlorpromazine(5) imipramine(6) Amitryptiline(7) Doxepin(8)

But there were many side-effects associated with this such as dry mouth, constipation, ocular side-effects and urinary retention. This was happening primarily because these drugs were not selective and had an affinity to bind to Muscarinic Acetylcholine Receptors. (9) There were other serious side-effects such as cardiac conduction abnormalities with overdoses and sometimes had the tendency to cause seizures.(10)

There were efforts made to selectively target the serotonin re-uptake inhibitor (SERT) which led to the development of second generation anti-depressants. The first SSRI to be designed was Zimelidine which was derived from brompheniramine an anti histamine.(11) It showed selective inhibition of SERT 5-HT re-uptake. Also it did not have the adverse effects shown by TCAs. (12) But there was a serious problem. Many patients administered with this drug developed Guillain–Barré syndrome a muscle weakness syndrome.(13) So its production was discontinued in 1983.

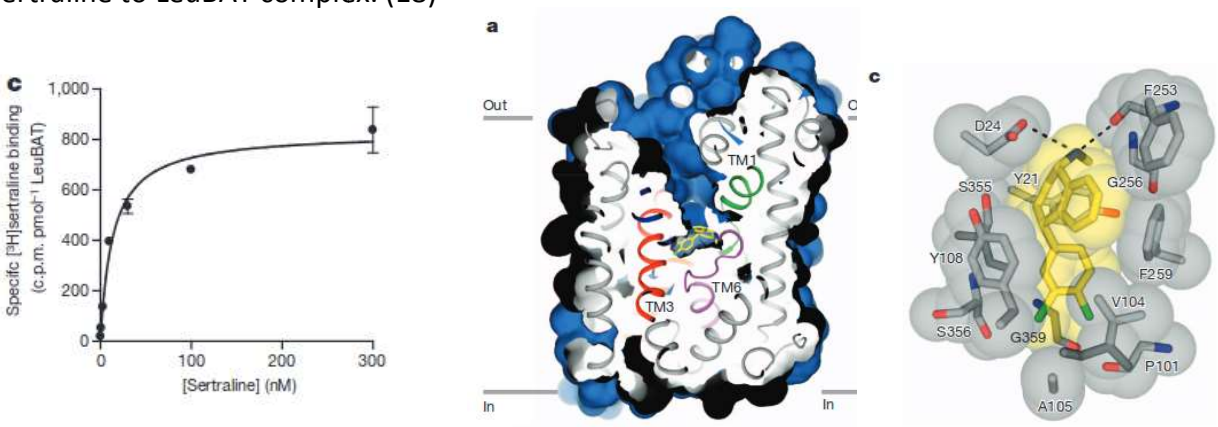


Zimeldine (14) Fluoxetine(15) Sertraline(16) Paroxetine(17)

Zimeldine served as a template for development of SSRI's. Next came Fluoxetine (Prozac), Sertraline (Zoloft), Paroxetine (Paxil) and others.

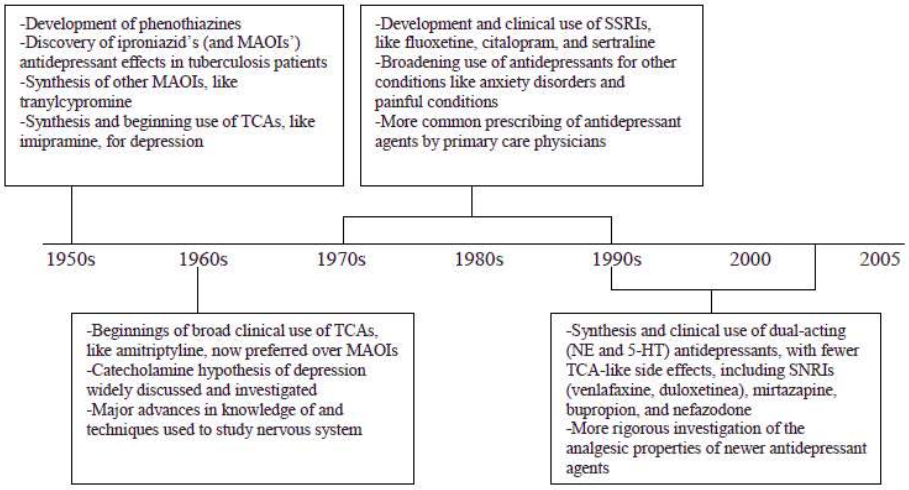
Mechanism of action of SSRIs

Biogenic amine transporters (BATs) are regulators of neurotransmitter levels in eukaryotic organisms. They serve as targets for SSRIs, TCAs and other anti depressants. Crystallizing BATs is very difficult and this limits our understanding of the mechanism of SSRIs binding to these receptors. LeuT a homologue of BATs is found in bacteria has helped us to understand the mechanism. But LeuT is only 25% similar to BATs with respect to amino acid sequence. So LeuBAT a human analog was engineered by changing key amino acid sequences to make it similar to BAT and its properties were studied. SSRIs act as competitive inhibitors by binding to the primary binding site. (18) The figures below show the binding of Sertraline to LeuBAT complex. (18)



More recent studies have contested this and have shown that all though fluoxetine binds to the central substrate in the LeuBAT structures as in SERT. Its orientation is reversed and induces allosteric modifications due to interaction with the chloride group. And that LeuBAT structures cannot be taken as direct evidence of the nature of binding.(19)

Side-effects associated with SSRI are nausea, sleep disturbances, sexual dysfunction, appetite changes, headache, dry mouth. The possible cause for this is interaction with nitric oxide in the 5-HT2 receptor. (10)



After SSRI's came Serotonin Norepinephrine Re-uptake Inhibitors (SNRI's) venlafaxine, reboxetine and mirtazepine but they have not shown any significant improvement with respect to efficacy over SSRI's and safety is the same. (20,21). Timeline given below. (22)

Future Prospects

Loss of ability to grow new neurons lends anti-depressants ineffective. So adult neurogenesis may ease depression.(23) Stress seems to be a major risk factor effecting MDD. In light of this ketamine which is primarily used as an anesthetic is undergoing clinical trials. Ketamine primarily acts as an antagonist of the N-Methyl D-Aspartate (NMDA) receptor for glutamate. Ketamine can induce stress resilience and may be used for treating stress related depression.(24,25)

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