The discovery of Fluroxene in depression treatment

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Abstract. Depression, particularly major depressive disorder (MDD), has become the world's most frequent mental illness. As the demand for antidepressant medication expanded, monoamine-oxidase inhibitors (MAOIs) were explored first, followed by selective serotonin reuptake inhibitors (SSRIs). One of the most widely recommended SSRIs for the treatment of major depression is fluoxetine (MDD). Fluoxetine has recently been in marketing and therapy, and it has already gone through multiple stages. This document provides an overview of fluoxetine, including its mechanism of action and typical adverse effects. Furthermore, the purpose of this work is to suggest the discovery method (phases I, II, and III), as well as to finish the processes involving sample size, type, and designation. The comparison experiments were taken to suggest how effective the fluoxetine was with the addition of other pharmacies. This review focused on the discovery of Fluroxene in depression treatment.

Keywords: Fluroxene, Clinical, Depression, Treatment.

1. Introduction

Depression has ranked second among all diseases, which is a common illness worldwide now. According to Global Health Data Exchange (GHDx), approximately there are 280 million depression patients all over the world. It is usual but severe due to the limitation of efficient therapies, especially for those who live in poor countries and regions, as there's no professional diagnosis provided. People who suffer from depression normally feel sad or other depressed moods, containing empty and irritable). Even though they have slept a lot, their daily functions are still missed during school or work [1]. The more serious symbol includes the thought of death or suicide. Depression can be divided into different types, and major depressive disorder (MDD) is the most common. Common symbols occurred are stressfulness, lack of energy, anxiety, weight loss, and weight gain. Usually, in children and young adults, they will feel worried and painful, resulting in refusing to school, and some will use recreational drugs or alcohol. Orderly adults are more likely to show suicidal thinking and often choose to stay at home instead of outgoing, and usually, the depression shown in the elderly people is likely confusion or dementia. People are diagnosed with MDD when they have over five symbols for over two weeks.

Serotonin antagonist and reuptake inhibitors (SARIs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and other therapeutic approaches have been explored to expiry [2], depending on the demand for a healthy psychological state. Various sorts of medications are used to treat patients of all ages and health issues. The surge in evidence presented has spurred a recent debate concerning the safety and effectiveness of antidepressants, particularly SSRIs (fluoxetine, citalopram, and sertraline) and SNRIs (mirtazapine and venlafaxine).

However, depression therapy continues to create certain issues. Despite the fact that several novel therapy modifications have been created throughout the years, their efficacy has not improved [3]. Furthermore, determining and predicting which sort of patient is more likely to benefit from a given drug is difficult, as individuals are frequently subjected to a variety of treatments before finding the one that works is difficult. The mechanics behind how different therapies operate are still largely unknown [4]. Some of this is due to a lack of understanding regarding what depression is, what its borders are, whether or not that is heterogeneous [5].

The mechanism and discovery process of fluoxetine, a common antidepressant used in many therapies, were the subject of this research. Premature ejaculation can also be treated with it. It's also

used in conjunction with olanzapine to treat bipolar depression. Fluoxetine is an orally administered depression medicine for adolescents and children aged 8 and higher.

2. The identification of Fluoxetine

Depression was originally identified as 'melancholia,' and it was largely medicated with barbiturates as well as amphetamines [6]. Monoamine oxidase inhibitors (MAOI) and tricyclic antidepressants were the first antidepressants developed in the 1950s (TCA). The monoaminergic theory of depression was proposed in 1965 [7], which linked depression to noradrenergic and serotoninergic dysfunction. As a result, several pharmaceutical companies have concentrated their research on finding novel medications that target 5-HT reuptake specifically [6]. As a starting point, Molloy created a sequence of hundreds of derivatives of 3-phenoxy-3-phenylpropanolamine, a structurally related molecule to diphenhydramine. David T. Wong, an Eli Lilly scientist, initiated an investigation and proposed retesting the series for serotonin, norepinephrine, and dopamine in vitro reuptake in order to find a derivative inhibiting just serotonin reuptake. In May 1972, Jong-Sir Horng[8] performed this test and determined that the chemical afterwards dubbed fluoxetine was the most potent and selective inhibitor of serotonin reuptake in the series[9]. After a year, Eli Lilly and Company assigned it the scientific chemical name fluoxetine and the commercial name Prozac. In February 1977, one company filed an Investigational New Drug Application (IND) for fluoxetine with the US FDA. In 1986, fluoxetine was first offered in Belgium [11]. In the United States, the FDA granted final clearance in December 1987.

3. The structure and mechanism of Fluoxetine

Fluoxetine is a phenylpropyl amide derivative with the formula 3-(p-trifluoromethyl phenoxy)-N-methyl-3-phenylpropanolamine that is often taken as a chloride salt. Fluoxetine combined with olanzapine can be used to treat panic disorder, premenstrual stress disorder, bipolar depression, etc. Common fluoxetine side effects include irritability, anxiety, insomnia and vomiting.

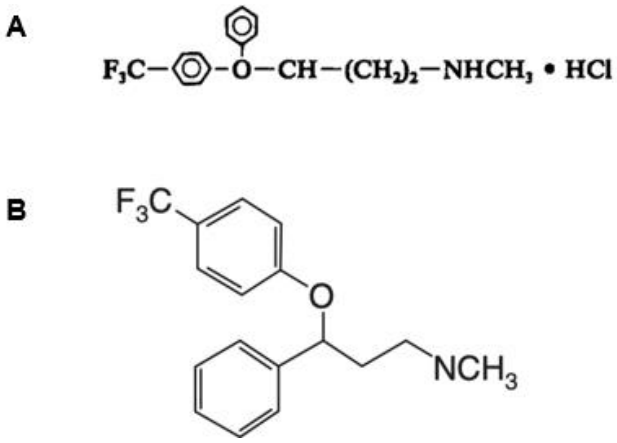

Figure 1. The molecular structure of fluoxetine

Fluoxetine is a mood stabilizer. Regularly prescribed antidepressants are known as SSRIs. Depending on their safety, effectiveness, and tolerance, they are used as pharmacology for depression and other mental diseases. They have been authorized for adult, as well as kid usages [14]. In the United States, the most often prescribed SSRIs are Fluoxetine, Sertraline, Paroxetine, and Fluvoxamine. Other off-indications mainly include abnormal eating, abnormal changes and entering menopause [15]. Oral dosage forms of SSRIs mainly include decoction pieces, capsules and suspensions. Currently, there are no other dosage forms such as injection. SSRIs patients take it daily, morning and evening. With the exception of verazoldone, SSRIs can be taken with or without meals. Velazodone should be taken with meals whenever possible [16]. By inhibiting the reuptake shuttle at the neuromuscular junction, fluoxetine enhances neurotransmission and increases serotonin

availability [10]. limiting serotonin reuptake into presynaptic serotonin neurons and so delivering antidepressant effects. The 5HT2A and 5HT2C receptors are only slightly affected by fluoxetine.

The 5-HT2 receptors 5HT2A and 5HT2C are members of the 5-HT2 receptor family. The 5-HT2A receptor is a G protein-coupled receptor (GPCR) that is one of the serotonin receptors, and a subtype of the 5-HT2 receptor. 5-HT stands for 5-hydroxy-tryptamine, which is a serotonin derivative. 5-HT2A is the most excitatory serotonin GPCR subtype, despite being an inhibitory receptor. Emotion, anxiousness, appetite, and hormonal activity are all linked to 5-HT2C receptors [20]. Phospholipase C (PLC) hydrolyzes phosphatidylinositol 4,5-bisphosphate to create diacylglycerol (DAG) and inositol 1, 4, 5-triphosphate (IP3) when 5-HT2 receptors are activated (PIP2). A rise in cytosolic calcium concentration ([Ca2+] I) is the result of this intracellular cascade. The 5-HT2 receptor was activated by fluoxetine [21] in primary cultures of cortical astrocytes, resulting in an increase in [Ca2+] I.

The metabolites of fluoxetine, which are also serotonin reuptake inhibitors, DE fluoxetine and Dem fluoxetine prolong the duration of the drug's effects [22]. Fluoxetine inhibits noradrenergic reuptake to a small extent. Because of its serotonin reuptake, fluoxetine has an activating impact, and it takes two to four weeks for depressive efficiency to manifest. The active metabolite of fluoxetine, norfluoxetine, is generated by the cytochrome P450 enzyme (CYP2D6) [13]. It's crucial to note that because fluoxetine is converted by the CYP2D6 isoenzyme, it has a majority of medical interactions. Norfluoxetine has been shown to inhibit CYP3A4[23, 24].

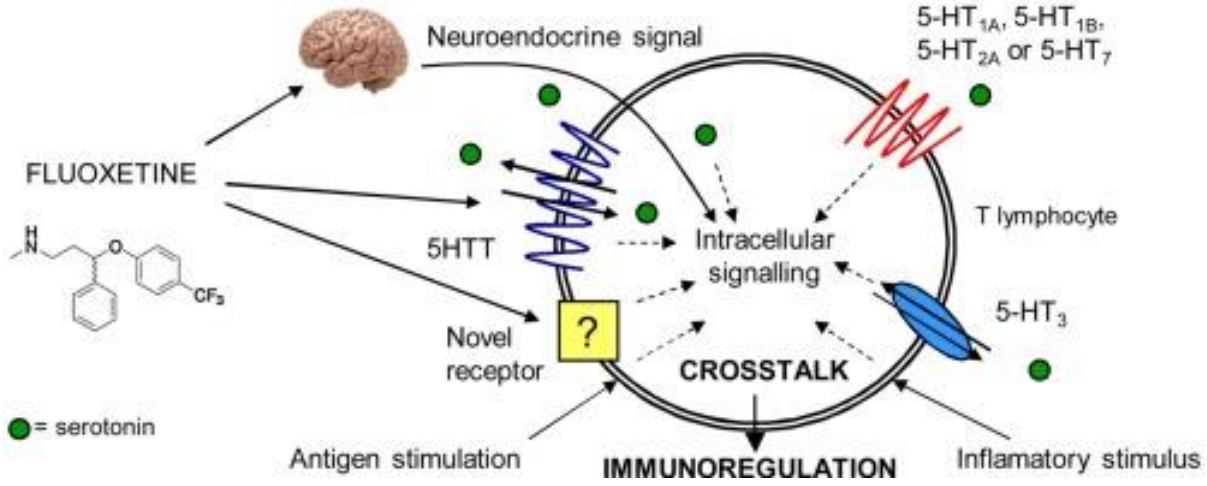

Figure 2. Mechanism of fluoxetine in depression therapy [25].

4. The study on Fluoxetine dosage

According to WebMD, the average cost for 30 capsules, 20mg each of the fluoxetine is $26.59 [1]. Fluoxetine is an oral medication that can be used for therapies on various diseases, including major depression disorder (MDD), resistant depression, depression associated with bipolar I disorder, obsessive-compulsive disorder, etc. For MDD treatment, initially, 20mg per day is suitable, which then may consider increasing gradually dose after several weeks. However, the highest dosage cannot be over 80mg each day. Moreover, resistant depression patients take fluoxetine which is indicated in combination with olanzapine. The initial dosage is 20mg fluoxetine as well as 5mg olanzapine by mouth at bedtime. According to efficiency and tolerability, the dose range of fluoxetine is 20-50mg for resistance depression, and olanzapine doesn't exceed 20mg. Similarly, the therapy for depression associated with bipolar I disorder is indicated to combine fluoxetine and olanzapine with both the same dosages as 20mg fluoxetine plus 5mg olanzapine orally per day. The excessive dose of fluoxetine is 50, while olanzapine to treat depression associated with bipolar I disorder isn't over 12.5mg.

Patients in different age groups require different dosages of fluoxetine. For depression, adults should take 20mg once a day in the morning, while children aged eight years and older take 0.01 or

0.02 g once in the morning. Moreover, the therapy for depression associated with bipolar disorder taken in adults is 20mg of fluoxetine and 5 mg of olanzapine, while the amount of olanzapine taken by children is 2.5mg. Adults who suffer from resistant depression take 20mg of fluoxetine as well as 5mg of olanzapine once per day at first, however, the dosages of fluoxetine and olanzapine are needed to be determined by doctors after diagnosis.

5. The clinical trials of Fluoxetine

5.1. phase I

5.1.1. Effects on Unipolar Depression of Imaging Antidepressants vs. Cognitive Behavior Therapy

This study began in June 2008, with 98 adult individuals taking part. This study will use functional magnetic resonance imaging to evaluate multiple proven Cognitive Therapy (CT) and antidepressant SSRI treatments (fMRI). For 14 weeks, 25 people were randomly administered the FDA-approved SSRIs Lexapro, fluoxetine, and Zoloft. After an initial 30–45-minute session, patients will be seen for 16-20 sessions [lasting 15-30 minutes] over 14 weeks. By week 6, if the patient has not achieved a minimum degree of response (i.e., a CGI of 2) and tolerability is acceptable, the medicine will be increased to 30 mg per day (or its equivalent). The drug will be changed or augmented if you do not react by week 10 (CGI 2).

In contrast, 40 patients were given 60 sessions of procedurally determined CT over the course of 14 weeks. Patients will start with fllowing two weekly sessions, that might be reduced to one weekly in the latter stages of the study if the treatment is effective. Patients with remitting depression following CT should have lower pre-treatment activity but higher post-treatment activation with in subgenual anterior cingulate cortex (sgACC), according to research [26]. Unfortunately, the conclusions of the investigation were never made public.

5.1.2. An investigation when both Fluoxetine and LY2216684 are given together to see whether there is any difference in how the body breaks down or inactivates them

The goal of this research aimed to investigate whether there was a distinction for how the system collapsed or immobilized prozac or LY2216684 when taken together. The goal of this research is to examine how fluoxetine affects LY2216684 as well as how providing LY2216684 influences prozac inside the body. The project started in October of 2010 and ended in January of 2011. Twenty adult patients were administered 18 mg orally once on Days 1, 2, 3, and 25-27. Between days 4 and 10, they were administered 60 mg of fluoxetine, followed by 20 mg for 17 days (Day 11-27).

Both two medicine did not cause any serious side effects in this study. Comparingly, fluoxetine can cause more adverse effects than LY2216684. Parts of the result were shown in the table below.

5.2. phase II

The purpose of this research was to see if the rate of fluoxetine might be enhanced by using DU125530, a comprehensive 5-HT1A antagonism. This study was started in May 2004 and ended in November 2007. 50 adult participants attended this study, with two comparators examined for the difference.

This was an experiment to test the efficiency of fluoxetine plus DU125530, compared with the group of fluoxetine plus placebo as a control group. During the research, the active comparator group took 20 mg fluoxetine + DU twice a day, which was the same dosage taken in the placebo comparator. However, there's not any result posted.

The molecular formula of DU125530 is C23H26ClN3O5S, which is a competitive 5-HT1A adrenergic receptor. In rats and the human brain, DU-125530 was shown to be equally effective in dislodging both agonist and antagonist adherence to pre- and post-synaptic 5-HT1A receptors. It has the capability to be used to treat anxiety, depression, and mood disturbances.

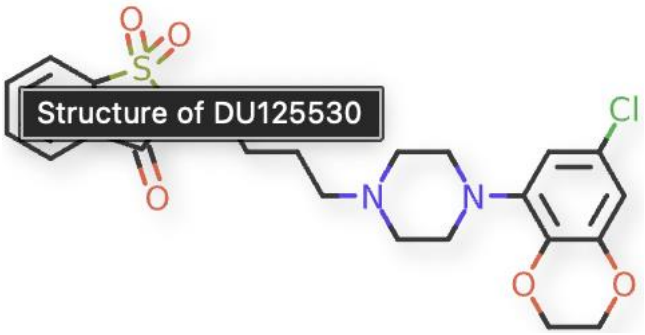

Figure 3. Chemical structure of DU125530

5.3. phase III

Eli Lilly and Company began phase 3 of the fluoxetine trial in March 2014, with 513 patients participating in three arms: 20 mg Fluoxetine, 40 mg Fluoxetine, and Placebo. This was a four-month period. This trial included three phases: a single-blind screening session including 7 days of placebo, a short-term double blind therapy period involving 7 days of placebo accompanied via a random allocation of the ratio 2:1:3 to 0.02 g fluoxetine, 0.04 g Prozac, or placebo for six weeks), as well as a single-blind withdrawal period (14 days of placebo). There were supposed to be 522 persons registered. Randomization of 2:1:3 was intended (20 mg fluoxetine:40 mg fluoxetine: placebo). The study showed 85 percent capacity to identify an effective dose of 0.33 (20 mg prozac versus placebo on HAMD21 overall points) depending on calculations with a 0.05 two-sided significance threshold, assuming 5% of patients had missing post-baseline data (Company, n.d.).

5.4. a comparison study between citalopram and fluoxetine

Patients suffering from unipolar major depressive illness were compared to two SSRIs, citalopram as well as Prozac, both at a concentration of 20 mg per day, in general practitioners. In France, a randomized, multicenter, double-blind experiment was conducted. The experiment's double-blind phase lasted eight weeks, and 357 people of both genders, ranging in age from 21 to 73, took part. Apart from internal discomfort, which was reported quite often in the citalopram group, there was no significant disparity in adverse events between these two experimental sample sets, and both citalopram and fluoxetine were deemed to be well tolerated. In the therapy of monopolar major depressive disorder, citalopram has been shown to be equally efficient as fluoxetine. In terms of recovery, citalopram appears to be more beneficial than fluoxetine [27].

6. Conclusion

Antidepressants are medications which are used to treat severe depression, anxiousness, as well as chronic pain, and addictions [28]. MAOIs, SSRIs, serotonin, and norepinephrine inhibitors (SNRIs) are all common forms of antidepressants According to the data, the highest rise was in anti-anxiety drugs, which increased by 34.1 percent during the month and 18 percent in the week of March 15. Antidepressant prescriptions grew by 18.6%, while anti-insomnia drugs increased by 14.8%. Fluoxetine is an SSRI drug that goes by the brand names Prozac and Sarafem. The goals of this study are to learn more about how fluoxetine works and to concentrate on fluoxetine's successful discovery timeframe. In December 1987, the FDA gave fluoxetine its final clearance. Scientists have been trying to identify new illness therapies for fluoxetine in recent years, as well as expanding the stages to maximize the effectiveness. For example, several studies have been conducted to see if fluoxetine may be used to treat the COVID-19 virus. Fluoxetine may be utilized in additional therapies in the future, not just for depression and anxiety.

References

[1] Myers, R. L., The 100 most important chemical compounds: a reference guide. 2007: ABC - CLIO.

[2] Cheung, A. H., G.J. Emslie, and T.L. Mayes, the use of antidepressants to treat depression in children and adolescents. Cmaj, 2006. 174 (2): p. 193 - 200.

[3] Holmes, E. A., et al., The Lancet Psychiatry Commission on psychological treatments research in tomorrow's science. The Lancet Psychiatry, 2018. 5(3): p. 237 - 286.

[4] Furukawa, T. A., et al., Placebo response rates in antidepressant trials: a systematic review of published and unpublished double-blind randomised controlled studies. The Lancet Psychiatry, 2016. 3 (11): p. 1059 - 1066.

[5] Cuijpers, P., A. Stringaris, and M. Wolpert, Treatment outcomes for depression: challenges and opportunities. The Lancet Psychiatry, 2020. 7 (11): p. 925 - 927.

[6] Perez-Caballero, L., et al., Fluoxetine: a case history of its discovery and preclinical development. Expert opinion on drug discovery, 2014. 9 (5): p. 567 - 578.

[7] Argyelan, M., et al., Dopamine transporter availability in medication free and in bupropion treated depression: a 99mTc-TRODAT-1 SPECT study. J Affect Disord, 2005. 89 (1-3): p. 115 - 23.

[8] Wong, D.T., F.P. Bymaster, and E.A. Engleman, Prozac (fluoxetine, Lilly 110140), the first selective serotonin uptake inhibitor and an antidepressant drug: twenty years since its first publication. Life sciences, 1995. 57 (5): p. 411 - 441.

[9] Wong, D. T., et al., A selective inhibitor of serotonin uptake: Lilly 110140, 3-(p-trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine. Life sciences, 1974. 15 (3): p. 471 - 479.

[10] Breggin, P.R. and G. R. Breggin, Talking Back to Prozac: What Doctors Aren't Telling You About Prozac and the Newer Antidepressants. 2014: Open Road Media.

[11] Swiatek, J., Prozac's profitable run coming to an end for Lilly. The Indianapolis Star, 2001.

[12] Messiha, F., Fluoxetine: a spectrum of clinical applications and postulates of underlying mechanisms. Neuroscience & Biobehavioral Reviews, 1993. 17 (4): p. 385 - 396.

[13] Sohel, A.J., M.C. Shutter, and M. Molla, Fluoxetine. StatPearls [Internet], 2020.

[14] DeLucia, V., G. Kelsberg, and S. Safranek, Which SSRIs most effectively treat depression in adolescents? 2016.

[15] Coleiro, B., et al., Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. Rheumatology, 2001. 40 (9): p. 1038 - 1043.

[16] Preskorn, S.H., Clinically relevant pharmacology of selective serotonin reuptake inhibitors. Clinical pharmacokinetics, 1997. 32 (1): p. 1 - 21.

[17] Cook Jr, E.H., et al., Primary structure of the human platelet serotonin 5-HT2A receptor: Identity with frontal cortex serotonin 5-HT2A receptor. Journal of neurochemistry, 1994. 63 (2): p. 465 - 469.

[18] Martin, P., et al., Rodent data and general hypothesis: antipsychotic action exerted through 5-HT2A receptor antagonism is dependent on increased serotonergic tone. Journal of neural transmission, 1998. 105 (4): p. 365 - 396.

[19] Alex, K.D., et al., Modulation of dopamine release by striatal 5-HT2C receptors. Synapse, 2005. 55 (4): p. 242 - 251.

[20] Heisler, L., et al., Serotonin 5-HT2C receptors regulate anxiety-like behavior. Genes, Brain and Behavior, 2007. 6(5): p. 491 - 496.

[21] Quesseveur, G., et al., 5-HT2 ligands in the treatment of anxiety and depression. Expert opinion on investigational drugs, 2012. 21 (11): p. 1701 - 1725.

[22] Benfield, P., R.C. Heel, and S. P. Lewis, Fluoxetine. Drugs, 1986. 32 (6): p. 481 - 508.

[23] Robertson, O. D., et al., Putative neuroprotective pharmacotherapies to target the staged progression of mental illness. Early intervention in psychiatry, 2019. 13 (5): p. 1032 - 1049.

[24] Cao, B., et al., Pharmacological interventions targeting anhedonia in patients with major depressive disorder: A systematic review. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2019. 92: p. 109 - 117.

[25] Di Rosso, M.E., M.L. Palumbo, and A. M. Genaro, Immunomodulatory effects of fluoxetine: A new potential pharmacological action for a classic antidepressant drug? Pharmacological Research, 2016. 109: p. 101 - 107.

[26] Siegle, G.J., et al., Toward clinically useful neuroimaging in depression treatment: prognostic utility of subgenual cingulate activity for determining depression outcome in cognitive therapy across studies, scanners, and patient characteristics. Archives of general psychiatry, 2012. 69 (9): p. 913 - 924.

[27] Patris, M., et al., Citalopram versus fluoxetine: a double-blind, controlled, multicentre, phase III trial in patients with unipolar major depression treated in general practice. International clinical psychopharmacology, 1996. 11 (2): p. 129 - 136.

[28] Kaulage, S.R., et al., Review on Antidepressant Medication. 2019.