Article ID: WMC001800 ISSN 2046-1690

Fluoxetine: Pharmacological and Computational Study

Author(s):Prof. Nadeem Siddiqui, Mr. M Shamsher Alam, Dr. Ozair Alam, Ms. Andalip , Mr. Bishmillah Azad

Corresponding Author:
Prof. Nadeem Siddiqui,
Prof & Head, Department of Pharmaceutical Chemistry, Jamia Hamdard, INDIA, 110062 - India

Submitting Author:
Prof. Nadeem . Siddiqui,
Prof & Head, Department of Pharmaceutical Chemistry, Jamia Hamdard, INDIA, 110062 - India

Article ID: WMC001800

Article Type: Review articles

Submitted on:23-Mar-2011, 11:10:27 AM GMT **Published on:** 24-Mar-2011, 08:37:53 PM GMT

Article URL: http://www.webmedcentral.com/article_view/1800

Subject Categories:PHARMACEUTICAL SCIENCES

Keywords: Fluoxetine, Molecular Modelling, Mode of Action

How to cite the article: Siddiqui N , Alam M , Alam O , A , Azad B . Fluoxetine: Pharmacological and Computational Study . WebmedCentral PHARMACEUTICAL SCIENCES 2011;2(3):WMC001800

Competing Interests:

Authors have no any conflict of interest in the given study.

Fluoxetine: Pharmacological and Computational Study

Abstract

Major depressive disorder is currently the fourth leading cause of disease or disability worldwide. Fluoxetine is approved for the treatment of major depression (including paediatric depression), obsessive-compulsive disorder (in both adult and paediatric populations), bulimia nervosa, panic disorder and premenstrual dysphoric disorder. Compared to other popular Selective Serotonin Reuptake Inhibitors (SSRIs), fluoxetine has a strong energizing effect. The study shows fluoxetine is effective in the treatment of depression. The pharmacological and computational studies have been presented.

Introduction

Depression is a chronic, recurring and potentially life threatening illness that affects up to 20% of the population worldwide. It is a state of low mood and aversion to activity that can affect a person's thoughts, behaviour, feelings and physical well-being1. The report summarizes the results of that analysis, which indicated that, among 235,067 adults (in 45 states, the District of Columbia [DC], Puerto Rico, and the U.S. Virgin Islands), 9.0% met the criteria for current depression, including 3.4% who met the criteria for major depression. By state, age-standardized estimates for current depression ranged from 4.8% in North Dakota to 14.8% in Mississippi.2 A review of all studies of anti-depressants ever submitted to the U.S. Food and Drug Administration (FDA), published and unpublished, was submitted to the FDA in 2004. In the published literature, anti-depressants had 94% success in treating depression.3,4 Recent advancement in antidepressant therapeutics included the monoamine oxidase inhibitors (MAOIs, e.g. Nardil) tricyclic antidepressants (TCAs, e.g. Elavil), serotonin selective reuptake inhibitor (SSRI) (Prozac), inhibition of serotonin reuptake transporter (SERT), norepinephrine reuptake inhibitors (NRIs). Anxiety disorders, such as post–traumatic stress disorder (PTSD), obsessive–compulsive disorder, panic disorder, social phobia and generalized anxiety disorder, often accompany depression.5,6 In a National Institute of Mental Health (NIMH)–funded study, researchers found that more than 40 percent of people with PTSD also had depression at one-month and four-month intervals after the traumatic event.7 Alcohol and other substance abuse or dependence may also co–occur with depression. The higher doses of fluoxetine appeared to result in better response, while the reverse relationship was observed in the treatment of depression.8 Fluoxetine has been approved by the FDA for the treatment of major depression, obsessive compulsive disorder, bulimia nervosa and panic disorder.8

In fact, research has indicated that the co–existence of mood disorders and substance abuse is pervasive among the U.S. population.9 Fluoxetine is Over 22.2 million prescriptions for generic formulations of fluoxetine were filled in the United States, making it the third most prescribed antidepressant after sertraline (SSRI that became generic in 2006) and escitalopram (non-generic SSRI).Consequently, there is still a great need for faster acting, safer, and more effective treatments for depression. The present review focuses on the pharmacological and computational approach to establish fluoxetine is good candidate for antidepressant treatment.

Mode of Action

Fluoxetine is selective serotonin reuptake inhibitor; it worked by inhibiting the uptake of serotonin by the neurons in the brain and enhances serotonin neurotransmission through action on 5HT2ain particular 5HT2c receptors. It has longest half-life in all the selective serotonin reuptake inhibitors (SSRIs); it may also produce some of its effects through 5-HT2C antagonism10. Fluoxetine does not significantly inhibit nor epinephrine and dopamine reuptake.

Pharmacokinetics

The bioavailability of fluoxetine is relatively high (72%), and peak plasma concentrations are reached in 6 to 8 hours. It is highly bound to plasma proteins, mostly

albumin. Fluoxetine is well absorbed from the gastrointestinal tract. After oral administration peak plasma concentration occurs between 4-8 or 6-12 h and maximal cerebral effect reported between 8-10 h. Fluoxetine undergoes hepatic metabolism and CYP2D6 isoenzyme convert fluoxetine to pharmacologically active metabolite norfluoxetine by demethylation, norfluoxetine is also serotonin reuptake blocker.11 Fluoxetine has a long Tl/2 of 1-3 days after a single dose or 2-7 days after repeated administration, while norfluoxetine has a TI/2 of approximately 7-15 days. Fluoxetine's excreted through urine and faeces. Fluoxetine is highly bound to plasma protein, with no displacement from plasma binding by lithium salts, warfarin, or digoxin, and little by ibuprofen.

Indication and Usage

The recent research suggests that a significant part of the resistance to the SSRIs paroxetine (Paxil) and citalopram (Celexa) can be explained by the genetic variation of Pgp transporter. Paroxetine and citalopram, which are Pgp substrates, are actively transported from the brain by this protein. Fluoxetine is not a substrate of Pgp, and thus a switch from paroxetine or citalopram to fluoxetine may be beneficial to the nonresponders.12, 13 Fluoxetine and its metabolite product norfluoxetine is used for treating depression (20-80 mg of fluoxetine daily), bulimia (60 mg of fluoxetine daily), obsessive-compulsive disorder (OCD) (20-60 mg daily), panic disorder (10-60 mg daily), and premenstrual dysphoric disorder (PMDD) (20 mg administered every day of the menstrual cycle or daily for 14 days prior to the onset of menstruation through the first day of menses). Combination with olanzapine (Zyprexa) is used for resistant depression and treatment of depression associated with bipolar disorder (20-50 mg fluoxetine and 5-12.5 mg olanzapine once daily in the evening).

Adverse Effects

Among the common adverse effects associated with fluoxetine, the effects with the greatest difference from placebo are nausea, insomnia, somnolence, anorexia, anxiety, nervousness, asthenia and tremor Those that most often resulted in interruption of the treatment were anxiety, insomnia, and nervousness (1-2% each), and in pediatric trials—mania (2%).14 Similarly to other SSRIs, sexual side effects are common with fluoxetine; they include anorgasmia and reduced libido.

Computational analyses

Crystal data and physicochemical parameters of Fluoxetine have been presented in Table 1 and Table 2.

Conclusions

Fluoxetine has been approved by the FDA for the treatment of major depression, obsessive compulsive disorder, bulimia nervosa and panic disorder. The present study revealed that Fluoxetine with minimal side effects emerged as choice of drug among the antidepressants.

References

1. Salmans S. Depression: questions you have - answers you need. People's Medical Society. 1997, ISBN 9781882606146.
2. "Current Depression Among Adults --- United States, 2006 and 2008" Morbidity and Mortality Weekly Report (MMWR) October 1, 2010, 59(38): 1229-1235.
3. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. "Selective publication of antidepressant trials and its influence on apparent efficacy". N. Engl. J. Med. 2008, 358 (3): 252–260.
4. Joanna M, Simon W, Rebecca H, Joanna M. "Active placebos versus antidepressants for depression". Cochrane database of systematic reviews (Online) 2004, 1: CD003012. doi:10.1002/14651858.
5. Regier DA, Rae DS, Narrow WE, Kaebler CT, Schatzberg AF. Prevalence of anxiety disorders and their comorbidity with mood and addictive disorders. B. J. Psych. 1998, 173 (34): 24-28.
6. Devane CL, Chiao E, Franklin M, Kruep EJ. Anxiety disorders in the 21st century: status, challenges, opportunities, and comorbidity with depression. Am. J. Man. Care. 2005, 11 (12): S 344-353.
7. Shalev AY, Freedman S, Perry T, Brandes D, Sahar T, Orr SP, Pitman RK. Prospective study of posttraumatic stress disorder and depression following trauma. Am. J. Psych. 1998, 155(5): 630-637.
8. "Prozac prescribing information" (PDF). Eli Lilly. 2007-06-21. http://pi.lilly.com/us/prozac.pdf. Retrieved 2008-01-09.
9. Conway KP, ComptonW, Stinson FS, Grant BF. Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin. Psych. 2006, 67(2):

247-257.
10. Ni YG, Miledi R. Blockage of 5HT2C serotonin receptors by fluoxetine (Prozac). Proc. Natl. Acad. Sci. U S A 1997, 4, 94(5): 2036-2040.
11. Prozac Pharmacology, Pharmacokinetics,Studies, Metabolism". RxList.com. 2007. http://www.rxlist.com/cgi/generic/fluoxetine_cp.htm. Retrieved 2007-04-14.
12. Uhr M, Tontsch A, Namendorf C, Ripke S, Lucae S, Ising M, Dose T, Ebinger M, Rosenhagen M, Kohli M, Kloiber S, Salyakina D, Bettecken T, Specht M, Pütz B, Binder EB, Müller-Myhsok B, Holsboer F. "Polymorphisms in the Drug Transporter Gene ABCB1 Predict Antidepressant Treatment Response in Depression". Neuron. 2008, 57(2):203–209.
13. Kato M, Fukuda T, Serretti A, Wakeno M, Okugawa G, Ikenaga Y, Hosoi Y, Takekita Y, Mandelli L, Azuma J, Kinoshita T (). "ABCB1 (MDR1) gene polymorphisms are associated with the clinical response to paroxetine in patients with major depressive disorder". Prog. Neuropsychopharmacol. Biol. Psychiatry. 2008, 32(2): 398–404.
14. Settle EC, Settle GP. "A case of mania associated with fluoxetine". American Journal of Psychiatry 1984, 2: 141-144.

Illustrations

Illustration 1

Table 1

Crystal data of Fluoxetine

Space group	**Pcab**
a, A^o	10.457
b, A^o	10.387
c, A^o	32.345
V, A^{o3}	3513.1(1.4)
Z	8
Reflection measured	2394
Observed reflection	1759
Final R	0.074

Illustration 2

Table 2 Physicochemical parameters of Fluoxetine

Properties	Value
Molecular Formula	$C_{17}H_{18}F_3NO.HCl$
Molecular Weight	345.8
Boiling point	713.63[K]
Melting point	410.29[K]
Critical temp.	803.42[K]
Critical pres	18.66[Bar]
Critical vol.	861.5[cm^3/mol]
Gibbs energy	-292.19[KJ/mol]
Henrys Law	4.27
Heat of form	81.04[cm^3/mol]
MR	5.44
CLogP	4.566

Disclaimer