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A potential impact of Fluoxetine in Neurological Pain: A review

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Abstract: **Fluoxetine is the first major drug for treating up the neurological pain associated with depression since the evolution of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) nearly 3 decades earlier. It was the one and only of its kind because of its activity along the selective serotonin reuptake inhibitor (SSRI) which was sanctioned by the United States Food and Drug Administration, offering a good efficacy and a decreased side effects comparatively to TCAs and MAOIs. However, a debate remains active regarding the true mechanism of the drug by which the medical efficacy of fluoxetine is observed, the value of fluoxetine and its related SSRIs to the profession is unquestionable. Prozac has permeated popular culture, helping to raise awareness of depression and to diminish the prevalence of long-standing stigmas associated with this illness. In this Review, we will showcase the history and importance of fluoxetine to neuroscience in general, as well as for the treatment of depression, and review the nature, pharmacology, preclinical reports, and adverse effects of fluoxetine.**

Keywords: **central nervous system, peripheral nervous system, tricyclic anti-depressants, serotonin-norepinephrine reuptake inhibitors.**

I. INTRODUCTION

According to recent researches in pain management, the brain plays a key role in chronic pain management. So, any injury in the brain can cause chronic neurological pain disease [1, 2]. Neurological pain is an ailment of the central nervous system (CNS) which occurs due to primary lesions or any disturbance in the peripheral nervous system (PNS) or central nervous system and it is also because of rupture of somatosensory nervous system [3-6]. Diabetic neuropathy, post-operative neurological pain, post-treated shingles pain are examples of peripheral neurological pain, and spinal cord affliction, multiple sclerosis, or post-treated stroke pain are examples of central neurological pain [7-9]. Anti-convulsants, tricyclic anti-depressants (TCAs), and selective inhibition of serotonin-norepinephrine reuptake are the first-line treatment for neurological pain. Anticonvulsants like, gabapentin or pregabalin are the GABAergic drugs which act by blockage of calcium-channel as well as TCAs act on sodium channel and shows significant effect [10, 11]. Lidocaine, capsaicin in high dose patches, or tramadol are the second-line treatment and strong opioids are the third-line treatment for neurological pain [12]. But these medications also causes some of the side effects to the body, like the use of TCAs may also cause cardiac blockage, anticholinergic effects (dryness in the oral cavity, constipation, blurred vision), gain in weight, sedation, etc and use of serotonin-norepinephrine reuptake inhibitors (SNRIs) can cause anxiety, hypertension, loss of appetite, mouth dryness, insomnia, etc and use of anticonvulsants can cause edema, dizziness, blurred vision, weight gain, etc [13]. But fluoxetine was the first SNRIs drug, which is having high efficacy and fewer side effects than other TCAs and anti-convulsant drugs. Fluoxetine act by blocking the reuptake of serotonin by transporter protein of reuptake situated on the presynaptic terminal of the presynaptic neuron of serotonin. Fluoxetine also shows activity on 5-HT receptors [14]. Preclinical evidences of fluoxetine to establish its efficacy is explained in the present review.

A. Definition of neurological Pain

According to the International Association for the Study of Pain, Neurological pain is pain "initiated or caused by a primary lesion or dysfunction in the nervous system". It may occur due to injury in nerve-fiber or damage in a single

nerve or multiple nerves. Neurological pain may occur from weeks to months whenever the pain is initiated. Loss of tendon reflexes, weakness, and numbness may be the initial signs of neurological pain [15-17]. Neuropathic pain/Neurological pain (NP) affects both central and peripheral nervous system [18]. It is a severe chronic condition of neural system which damages the DNA, cellular protein, lipid by the direct injury and damage of signaling pathway, oxidative stress pathway by the injury known as indirect injury [19]. Further, the neuropathic pain is ostentatious which act on the body function like increasing the cGMP followed by increasing the GABA receptor, also changes in peripheral and central pain pathways. In addition, it also affects the BDNF and TrkB signaling [20].

B. Charecteristics and causes of neurological pain

Five subgroups of neurological pain i.e. neuropathic pain are made by Neuropathic Pain Symptom Inventory (NPSI) which include burning (superficial) pain, pressing pain, paroxysmal pain, evoked pain and paresthesia/dysesthesia. Burning and pressing pains are spontaneous in nature (Fig.1.) [21-26]. NP causes changes in the vascular function in the body, decreases the conduction of velocity of the nerve as well as it also decreased the neural function which leads to major cause of NP. Hyperalgesia isextreme pain intensity felt upon noxious stimulation, allodynia can be explained as sensation of pain elicited by stimuli that are normally below pain threshold and paraesthesia is stimulation of the sensory endings in the tissue pain [27, 28]. Several factors have been figured for the painful neuropathy in which the threshold time, withdrawal time, flicking, and liking behavior [4, 7] these are not only the observation of pain they can be felt by electrical or burning by touching the skin [29, 30].

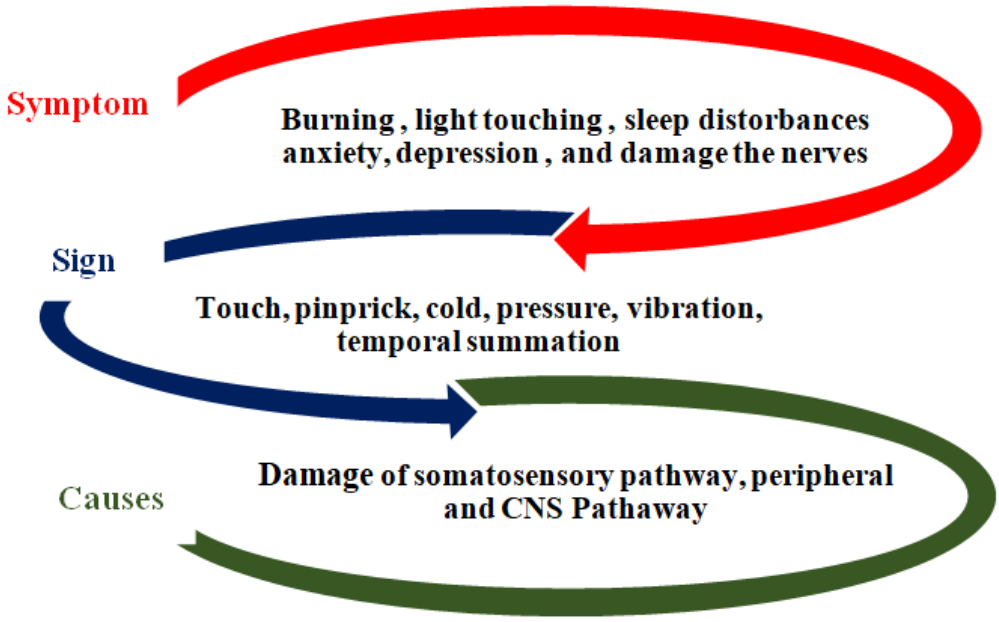


Figure 1: Symptom, sign, and causes of NP

The occurrence of NP effects the Neuroendocrine dysregulation, fatigue, dysphoria, impaired physical and even though it affects the mental performance of the patient [31]. The pathological states and the conditions that describe the origin of neurological pain are majorly neuropathies initiated with viral viruses (like, HIV, leprosy, postherpetic neuralgia), metabolic disorders (like, diabetic neuropathy), autoimmune disorders of CNS (like, multiple sclerosis), induced-chemotherapy of peripheral neuropathies, injury to the traumatic origin of the nervous system (like, amputation, spinal cord injury), channelopathies, inflammation diseases, hereditary neuropathies [7, 32-40].

C. Drug treatment of neurological pain and its failure

To treat this severe painful condition there are various drug treatment available in market. These available drugs can be classified as 1st, 2nd and 3rd line drug treatment. These drug treatments are highly recommended by the physician according to different clinical state of the patients. But these drugs are known to cause various side effects and sometimes it is not tolerated to the patients. These drugs are given in table I, II and III.

TABLE I. THE FIRST-LINE TREATMENT OF NEUROLOGICAL PAIN

TYPES OF DRUG	DRUGS	ADVERSE EFFECTS	RELATIVE CONTRAINDICATION	MAIN INDICATION	References
Tricyclic antidepressants (TCAs)	Amitriptyline	Sedation, cardiac arrhythmia, urinary retention, dry mouth, drowsiness, weight gain	Suicide risk, epilepsy, heart disease, myocardial infarction, glaucoma	Diabetic peripheral neuropathy, post-stroke pain, postherpetic neuralgia	[11, 41-43]
	Nortriptyline				
	Imipramine				
	Desipramine				
Serotonin-norepinephrine reuptake inhibitors (SSNRI)	Venlafaxine	Nausea, dizziness, diarrhea, constipation, anorexia	Alcohol abuse, liver damage, concomitant use of MAO inhibitors, seizures	Diabetic peripheral neuropathy	
	Duloxetine				
Anti-convulsants	Gabapentin	Dizziness, peripheral edema, leucopenia, blurred vision, weight gain, hyponatremia	Renal inadequacy, use with cautions in a patient with leucopenia, hyponatremia, thrombocytopenia	Diabetic peripheral neuropathy, post-herpetic neuralgia, phantom pain, small fiber sensory neuropathy	
	Pregabalin				
	Phenytoin				
	Oxcarbazepine				
	Carbamazepine				

The anti-convulsants, TCAs, and SNRIs drugs are used to be the first choice of treating the NP. These drugs are given to patients in the required dose, the maximum dose for (TCAs is 150mg/day, SNRIs is 225mg/day, anti-convulsants is 3600mg/day in divided dosing) [44].

TABLE II. THE SECOND-LINE TREATMENT OF NEUROLOGICAL PAIN

TYPE OF DRUG	ADVERSE EFFECTS	CONTRAINDICATION	ANOTHER BENEFITS	References
Tramadol	Nausea, constipation, dizziness, drowsiness, vomiting, epilepsy	Suicide risk, drug abuse, used with TCAs, SNRIs	Shows immediate action	[13, 17, 40, 42, 43, 45]
Opioids				
Capsaicin 8% patches				
Lidocaine patches				

Opioid, tramadol are the drugs which are used as a second-line treatment for neurological pain. These drugs cannot be used directly because of their adverse effects. These drugs are used with first-line drugs in the required dose when they failed to give the therapeutic response. But for injury of the musculoskeletal system, the opioids are prescribed in large doses and stronger potencies [46]. According to literature, these drugs are not having good pharmacokinetic status but tramadol exhibits good analgesic agent that is used to treat the pain syndromes in patients [47]. The remaining information on second-line drugs is added in Table II.

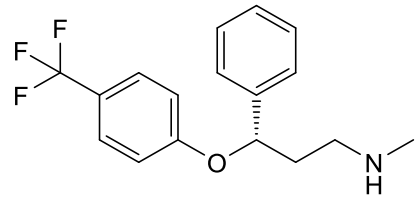
Table III. Third line treatment of neurological pain

TYPE OF DRUG	DRUGS	ADVERSE EFFECTS	CONTRAINDICATION	References
Strong opioids	Morphine	Nausea, vomiting, constipation, epilepsy, dizziness, drowsiness, addiction to body	Heart attack, drug abuse, suicidal risk, used with TCAs, SNRIs	[48]
	Hydromorphone			
	Oxycodone			

Morphine, hydromorphone, and oxycodone are strong opioids, which are used as a third-line treatment for neurological pain. These drugs show similar action as antidepressants but these drugs are not given much to patients due to their severe side effects of drug abuse, addiction, and diversion [17, 48]

D. Chemical nature of Fluoxetine (FLX)

Fluoxetine is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) type. It is used to treat major depressive disorder, obsessive-compulsive disorder (OCD), anxious bulimia, panic disorder, and dysphoric premenstrual disorder. Fluoxetine is taken by orally route. Fluoxetine is a low molecular weight compound and racemic phenoxyphenylpropylamine (MW = 309.3) contain lone hydrogen bond donor. It is designated chemically as (R, S)-N-methyl-3-phenyl-3-(4-(trifluoromethyl) phenoxy) propan-1-amine, **(Fig.1). Its** LogP value is 4.2. As per Lipinski's rules it exhibits excellent DMPK parameters and CNS penetration [49].



(R, S)-N-methyl-3-phenyl-3-(4-(trifluoromethyl) phenoxy) propan-1-amine

Figure 1: Chemical structure of fluoxetine

E. Mechanism of action of FLX

FLX is a kind of antidepressant which shows its therapeutic effect by increasing serotoninergic neurotransmission through potent and selective inhibition of neuronal reuptake of serotonin. Its metabolism occur by N-desmethylation which produces desmethylfluoxetine, which is also known to inhibits serotonin reuptake [50]. It act on GABA as an inhibitory action to the muscles relaxation by increasing GABA signaling and directly targets G-protein– coupled 5-HT receptors [51]. It produces a nociceptive effect by the Descending inhibitory systems [52, 53]. It stimulates the 5-HT2B receptor (Chung et al., 2015), with the effects of acute administration of antibody towards the TRPC1 channel or effects occurring in cells treated with siRNA towards TRPC1, which caused a large knock-down of TRPC1 mRNA Expression TRPC1 inactivation altered [54].

F. Pharmacokinetics of FLX

It is well absorbed after oral administration, from the GI tract. It is estimated that oral bioavailability is at least 60-80 percent. Its Peak plasma concentrations occur within 6-8 hours. 94.5 percent, including albumin and alpha-1-glycoprotein, are bound to human serum proteins. FLX tends to be widely metabolised into norfluoxetine (active metabolites) and other metabolites, which are likely to occur throughout the liver. Hepatic metabolism occur to give inactive metabolites excreted by the kidney tends to be the main route of removal [55].

G. Pharmacodynamic

A functional decrease in the activity of amines, such as serotonin and norepinephrine, would result in depression, according to the amine hypothesis; a functional increase in the activity of these amines would result in mood elevation. The effects of fluoxetine are believed to be associated with 5HT receptor inhibition, which leads to an increase in the level of serotonin. Fluoxetine binds to these and other brain tissue membrane receptors much less strongly in vitro than tricyclic drugs do [56-58]. Modulation of immune system is observed by the administration of fluoxetine and thus it reduces

lymphocyte activity on the time of high basal immune function, and on the other hand it also improves the deficient function of the immune system (Fig.2.). There is a conflicted verification/proof about the mechanism of action of fluoxetine on immune system. Because of the decrease in mitogen induced T cell lymphocyte multiplication before chronic fluoxetine therapy/or after acute. Summing up, the subchronic fluoxetine administration in ailments associated to depression in patients shows a regularized increase of pro inflammatory cytokine cells in the plasma. Effect of fluoxetine is shown in 3 pathological conditions

1. Increase in INF and TNF – INFLAMMATION
2. Decrease in phagocytosis- STRESS

Response of T-cell get decreased TNF and INF- production get decreased

3. In orders related to depressiveness in immune system, normalization occurs in the stimulated proliferation and both basal.

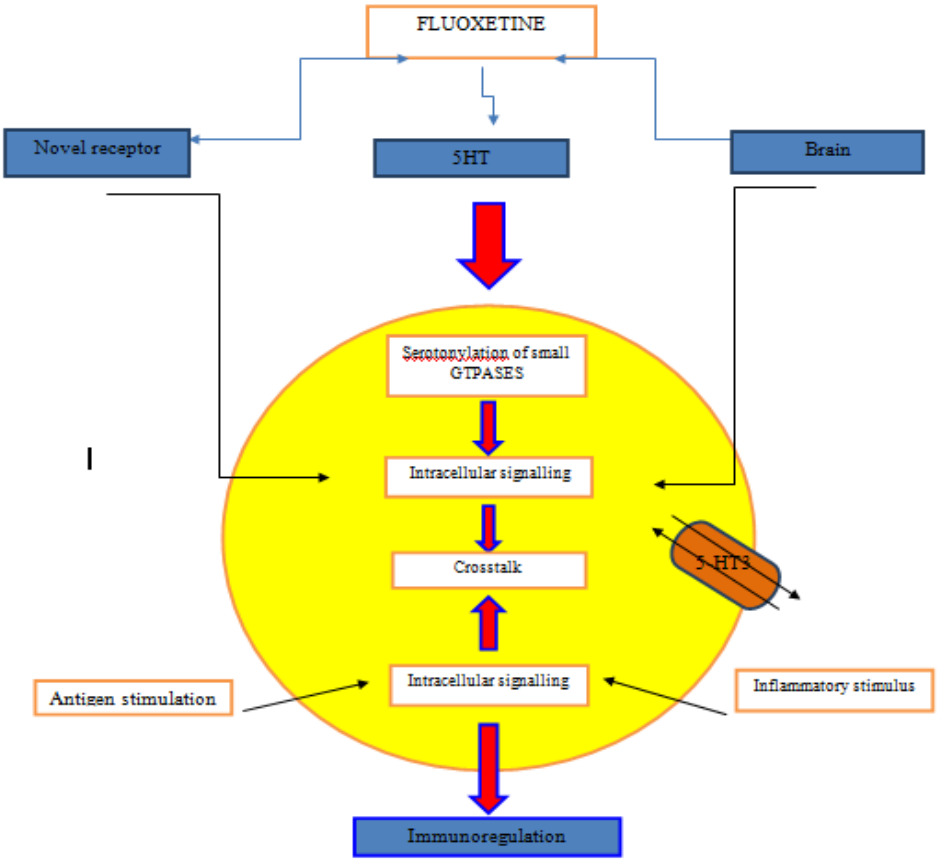


Figure 2: Immunomodulatory effects pathways shown by FLX

Effect of fluoxetine is shown in both indirect and direct mechanism systems, indirect systems involve both 5ht dependent and independent receptors. It is important to consider that high level of the drug in-vitro studies can cause apoptotic &cytotoxic which don't occur necessarily when administered in-vivo which shows the importance of the drug molecule as an immunomodulatory useful in treating several pathologies that occur due to immune system deficiency or deregulation of immune system [59]. Immunomodulatory effects of fluoxetine are seen due to its action on the neurons(serotonergic) in the central nervous system regulating the signals of the neuroendocrine signals moreover, fluoxetine can also act directly on the proliferating t-lymphocytes on cellular activation in a dual manner. The mechanism of action can include:

a) Action is done through a novel intracellular mechanism which is coupled to a 5-HT transport or by a novel receptor

b) Activation of intracellular signalling because of the bonding at the serotogenergic receptor by the increase in the concentration of 5-HT in lymphocyte milieu

c) Serotonylation of minute GTPases because of the intracellular increase of 5-HT.

All these affect combinely shows the immune-regulatory effect in inflammatory stimulus & presence of antigen. These all results show that the direct action of the drug are shown by in-vitro studies, the antidepressant volume used is very important due to the apoptotic/cytotoxic phenomena which may be only due to the large size of doses but not necessary if effect occurs in vivo [60].

H. Preclinical evidences of FLX

FLX and its combination	Dose	NP model	MOA	Remarks	References
FLX, ondansetron, pindolol, Ritanserin	(5, 10 and 20 mg/kg), (1 and 2 mg/kg), (5 and 10 mg/kg), (1 and 2 mg/kg)	Streptozotocin-induced diabetic neuropathy	It is SSRI also modulate the serotonins pathway through 5-HT1 and 5-HT2 receptors, but not through 5-HT3 receptors.	FLX given Intraperitoneal increase synaptic 5-HT levels and generally delay the antinociceptive.	**[61]**
FLX HCL, Morphine sulphate, naloxone hydrochloride, and naltrexone hydrochloride	(5, 10 and 20 mg/ kg i.p.)	acetic acid-induced writhing model	Involve in reuptake of monoamines and also involve of voltage-sensitive calcium	FLX produced dose dependent action on the dose of 5–20 mg kg, i.p. effect against acetic acid-induced in mice. In 20mg/kg dose of fluoxetine showed effect on tail flick and produced significant antinociceptive effect. It does not produce any significant effect on the dose of (1 mg/10 ml / rat, i.c.v.) further the combination was introduced (pindolol and fluoxetine) and effect was increased antinociceptive activity.	**[62]**
FLX and clonidine	30 nmol	Pre-injury administration of morphine model	FLX reduced neuronal hyperactivity markers such as c-Fos and protein kinase C (PKC) in the spinal dorsal horn.	Activation of descending monoaminergic system in spinal cord by systemic morphine might have prevented the development of central sensitization. FLX activates monoaminergic system in spinal cord by systemic morphine might have prevented the development of central sensitization.	[63]
FLX and reboxetine, bupropion, venlafaxine	(3–30 mg/kg)	CCI and SNL models	Combination of 5-HT and NA re-uptake inhibition produced anti-nociception in this model. After nerve injury, inhibition of NA re-uptake appeared to preferentially mediate anti-	FLX showed flinching behavior in formalin test and significant result with allodynia test also with hyperalgesia test but the Reboxetine and venlafaxine showed second-phase flinching in the formalin test, i.e. Drugs such as (bupropion) which do not show effect in formalin test	[64]

			nociception in response to noxious thermal but not innocuous mechanical stimulation	but show response in allodynia test.	
Streptozotocin, atropine, naloxone and yohimbine, FLX	10 and 20 mg/kg)		FLX increases 5-HT levels, also causes modulation of cholinergic system, opioidergic system. Act on 5HT $_{2A}$ receptor and NK_1may cause release of P and acetylcholine	20 mg/ kg of Fluoxetine showed significant result in diabetic neuropathy observing by tail-immersion and hotplate systems. Pretreatment with yohimbine (2 and 5 mg/kg) did not affect FLX in diabetic mice in both the tail-immersion and hot-plate.	[65]
Desipramine, paroxetine, and ketorolac, FLX, Reboxetine, *S*,*S*-reboxetine, duloxetine, and gabapentin	(10, 30, and 56 mg/kg s.c.)	Rodent model of pain	It is selective NE and 5-HT reuptake inhibitors, selective serotonin reuptake inhibitor, antagonist nor-BNI can acutely block the antiallodynic effect of chronic TCA treatment.	Relative potency and efficacy are evaluated in models of neuropathic and visceral (acute inflammatory) pain greater NRI activity should be more effective for the treatment of pain than compounds having only SRI activity Evaluated potentially the synergistic effects between NRIs and SRI compounds in the visceral pain model.	[66]
FLX, Nortriptyline, amitriptyline	(5 or 10 mg/kg), (0.5, 2.5 or 5 mg/kg, (5 mg/kg)	sciatic nerve cuffing in mice model	Blockage of noradrenaline and/or serotonin uptake for the chronic treatment, FLX was described as a SSRI, opioid receptor antagonist naloxone, the delta-opioid receptor antagonist naltrindole and the kappa-opioid receptor antagonist nor-BNI.	A chronic (but not acute) treatment with the TCAs nortriptyline or amitriptyline is necessary to suppress the cuff-induced allodynia. On the contrary side, the specific-serotonin reuptake inhibitor (SSRI) FLX remained ineffective. Demonstrated pharmacologically that both delta-opioid receptors and kappa-opioid receptors are recruited in the therapeutic effect of chronic TCA treatment.	[67]
Bis selenide, FLX, amitriptyline, and bupropion	(1 and 5 mg/kg, p.o.), and (10 or 30 mg/kg, p.o.),	CCI model	Mechanism by descending inhibitory pain pathways in the brain and spinal cord. Increasing the 5-HT, DA, and NA neurotransmitter level for the control of chronic pain	Depression like behavior is generated by the CCI; the entire drug was showed antiallodynic effects. NP is demonstrated by the fluoxetine and buproprione.	[68]

FLX	5–25 mg/kg, ip)	CCI model	Underlying mechanisms are not known, the data suggest that the endogenous CART might modulate the anti-hyperalgesic effect of fluoxetine like VLPAG, DRD and LC showed significant increase in the population of CART fibers following neuropathic pain.	Involvement of CART in mediating the anti-hyperalgesia effect of FLX in neuropathic rats. While the sciatic nerve was ligated to induce the neuropathic pain, hyperalgesic response was tested using paw withdrawal latency in the Hargreaves apparatus. FLX treatment in neuropathic animals might bring about the release of CART at synaptic level, eventually contributing to the antihyperalgesic effect.	[69]
FLX	20 mg/kg/ i.p.	Oxaliplatine induced model	FLX blocked 5-HT_{2C} receptor in brain areas and increase in PAG and amygdala region	FLX stimulate the descending inhibitory pathway also reduce the 5-HT2C receptor in the area of PAG region. Other hand the FLX increases the level of 5-HT2C receptor in Amygdala region.	[70]
FLX	20 mg/kg, p.o.	Diabetes-induced Neuropathic Pain	Fluoxetine increases the licking time and withdrawal latency in hot plate and tail flick test respectively	Chronic treatment of fluoxetine significantly decreases the glycemic level	[71]
FLX		Sciatic nerve injury (CCI) in rats	Western blot analysis showed the upregulation of the IBA-1 in the lumbar spinal cord while after fluoxetine the downregulation was observed	CCI is related with the activation of microglia, which is diminished by fluoxetine	[72]
Sildenafil (SD), fluoxetine (FLX) and its co-administration	5 mg/kg	Chronic constriction injury induced neuropathic pain in rats	SD produces an additive effect when given with FLX in attenuation of NP may be due to elevation of intracellular concentrations of cyclic GMP which further causes downregulation of calcium channel.	Co-administration of SD + FLX + CCI gave the pronounced effect that was superior over individual responses of SD and FLX in all behavioral as well as biochemical parameters	[4]

III. CONCLUSION

The action mechanism of neurological pain is complicated. Till date we haven't found a single method which is able to relief the pain immediately. Fluoxetine is inexpensive and appears to be effective and associated with few adverse effects when administered once or twice daily, compared with several other treatment options. Fluoxetine is equally effective as, and has a distinctly more benign side-effect profile and lower rates of discontinuation than the TCAs, is safer in overdose and easier and simpler for patients to use and physicians to prescribe.

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