Duloxetine: A Dual Action Antidepressant

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Abstract— Duloxetine is an orally administered, selective norepinephrine and serotonin reuptake inhibitor (SNRI) class of antidepressant that has been approved for the treatment of major depressive disorder (MDD). Its chemical designation is (+)-(S)-N-methyl-(1-naphthyloxy)-2-thiophenepropylamine. Duloxetine acts through the inhibition of reuptake of serotonin (5-HT) and noradrenalin/norepinephrine (NE) at presynaptic sites. Preclinical and placebo controlled trials of duloxetine have proved that duloxetine is significantly more efficacious in the treatment of major depression. Comparative trials of duloxetine with paroxetine and venlafaxine have the almost same efficacy. Similarly, with comparison of SSRI, duloxetine has shown similarity or noninferiority as compare to esitalopram in randomized trials. It is also efficacious in painful physical symptoms associated with depression at dose used for MDD during trials. Duloxetine is generally well-tolerated drug and it has already concluded that incidence of adverse events and drug interactions are less as compare to TCAs, SSRIs and other SNRIs. Duloxetine should be considered as a potential antidepressant effective in short- and long-term treatment of MDD. © 2011 IGJPS. All rights reserved

Keywords: Depression, Antidepressant, Duloxetine, Norepinephrine, Serotonin Reuptake Inhibitor
INTRODUCTION

Depression is a common psychological illness characterized by the complex symptoms like sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, poor concentration and possible suicidal ideation. It is also known as unipolar depression. It can be classified as mild, moderate and severe. There are several forms of depression. It is classified into Major Depressive Disorders (MDD), Dysthymic disorder, Psychotic depression, Postpartum depression, Seasonal Affective Disorder (SAD) and Bipolar depression. From all amongst the types of depression MDD and Dysthymic disorder are most common.

Depression disorders constitute a large proportion in the global burden of disease, both in developed and developing countries. According to WHO, the average age of onset of major depression is between 20 to 40 years and its occurrence in women are higher than men. Persons under 45 years are much more likely to suffer from depression than persons 45 years or older. MDD is less common in elderly people than in the adult population. According to NIMH, about 6.7% of U.S. population is affected by MDD.

According to initial Global Burden of Disease study found that depression was fourth leading cause of disease burden and according to that 3.7% total disability adjusted life years (DALYs) in the world in 1990. As per WHO survey, it was estimated that prevalence of depression in 2000 was 8.0%, 6.1%, 4.7% leading cause of disability adjusted life-years (DALYs) in America, Europe and south-east Asia respectively. By 2020, depression will become the second largest cause of suffering next only to ischemic heart disease.

Studies suggested that more than 65% of the depressive patients do not seek the treatment. Proper diagnosis of the disorder is very necessary. Only small number of total population is going to consult the physicians and undergo proper treatment. Also the cost effectiveness of treatment is necessary because the remission of disorder takes few months to years. Now a days, there are many potent and effective antidepressant drugs available which help to improve the quality of the life in patients and also reduces the cost of the treatment. Development of an antidepressant having a faster onset of action and improved tolerability and efficacy might enhance treatment adherence and in turn improve patient outcome.

The underlying pathophysiology of major depressive disorder (MDD) has not been clearly defined. Clinical and preclinical trials suggest a disturbance in CNS serotonin (5-HT) and Norepinephrine (NE) neurotransmission causes the depression. Antidepressants that combine noradrenergic and serotonergic mechanisms might also be more rapidly effective. Other neurotransmitter implicated includes dopamine (DA), γ-Amino butyric acid (GABA), peptide transmitters or trophic factors such as Brain Derived Neurotrophic Factor (BDNF), Somatostatin and Thyroid related hormone. Amongst that serotonin plays major role in depression.

Studies show that complex interaction between neurotransmitter availability, receptor regulation and sensitivity, and affective symptoms in major depressive disorder. Drugs that produce only an acute rise in neurotransmitter availability, such as cocaine, do not have the efficacy over time that antidepressants do. Furthermore, an exposure of several weeks' duration to an antidepressant is usually necessary to produce a change in symptoms.

All available antidepressants appear to work via one or more of the following mechanisms: (1) presynaptic inhibition of uptake of 5-HT or NE; (2) antagonist activity at presynaptic inhibitory 5-HT or NE receptor sites, thereby enhancing neurotransmitter release; or (3) inhibition of monoamine oxidase, thereby reducing neurotransmitter breakdown.

Most of the antidepressants act by working on the more than one neurotransmitter. Drug treatment of depression is majorly depending on the several factors including the efficacy, treatment resistant and tolerability of antidepressants. Only half of the population will respond to the initial treatment with pharmacotherapy, but patients who do not respond to the medication may respond to another-even one in the same therapeutic class. Generally, antidepressant medications are thought to have similar effectiveness between and within medication classes. It has been recommended that selective drug therapy targeted at multiple neurotransmitter systems. Thus, there is continued need for new antidepressants with novel mechanism of action.
**TREATMENT OF MDD**

The three main types of treatment for depression are pharmacotherapy, psychotherapy and supportive measures. Pharmacotherapy includes Antidepressants, Phytotherapy (St. John’s wart), Neuroleptics and Lithium. Psychotherapy for depression includes Cognitive behavioral therapy (CBT), Deep psychology-based and psychoanalytic psychotherapy, Interpersonal psychotherapy (IPT). Supportive therapy comprises light therapy, aerobic and endurance training, Electroconvulsive therapy (ECT).

The firstly discovered class of drug for the treatment of depression is Tricyclic antidepressants (TCAs). It is mainly act by the inhibiting uptake of serotonin and norepinephrine and lesser extant to dopamine reuptake. Also block the mascarinic, H₁ and α₁ receptors. The major drawback associated with the TCAs is large number of side effects which will lead to the discontinuation of treatment. The side effects associated with the TCAs is due to the non-selective binding to the various receptors which are mention above. Also the overdose may lead to severe cardiac conduction abnormalities or arrhythmias. Due to mention reasons, the uses of TCAs are restricted now days. Amitryptyline, clomipramine, desipramine, doxepine are the examples of TCAs.

The large fractions of side effects of TCAs propose the searching of newer selective antidepressants. Another class of antidepressant is (Selective Serotonin Reuptake Inhibitor) SSRI. It is particularly selective towards serotonin reuptake inhibition. These classes of antidepressant drugs are more effective and tolerable than the TCAs. Also having the better patient compliance and treatment adherence. SSRI having severe adverse effect like sexual dysfunction and sleep disturbance. Along with that fluoxetine, paroxetine and fluvoxamine have major risk of drug interaction because of inhibition of cytochrome P450 isoenzyme.

MAO inhibitors like tranylcypromine and moclobemide are also used in treatment of depression. Both act by inhibiting the catalytic enzyme Monoamine Oxidase A and B, which is responsible for the metabolic degradation of catecholamine in body. MAO inhibitors thus act by inhibiting the catecholamine metabolism and the availability of neurotransmitter increase at the nerve endings. MAO inhibitors are also less preferred because of side effects like severe serotonin syndrome if combined with another serotonergic medication, hypertensive crises and drug-food interaction.

Autoreceptor blocker like mianserine and mirtazapine used as antidepressants act by blockadge of presynaptic autoreceptors and thus inhibition of negative feedback mechanism.

Selective norepinephrine reuptake inhibitors (NERIs) like atomoxetine and reboxetine which are particularly selective to the norepinephrine reuptke, also used for the treatment of MDD.

Duloxetine, venlafexine and milnacipran are belonging too the newer class of antidepressant known as Serotonin Noradrenaline Reuptake Inhibitor (SNRI). This class of agent is mainly act by inhibition the uptake of noradrenalin and serotonin neurotransmitters and allows more effective control of emotional and physical symptoms of depression. Now a day, SNRIs are drug of choice for the treatment of depression because higher efficacy, less number of side effects and good tolerability as compare to the other classes of antidepressants.

**DULOXETINE**

Duloxetine is an orally administered, selective serotonin and noradrenaline reuptake inhibitor approved by FDA for the treatment of MDD. Its effective dose for MDD therapy is ranging from 40 to 120 mg/day in generally two divided dose and available in the form of hard gastroresistant and delayed release capsule. The maintenance dose of duloxetine is 60 mg/day for MDD. Preclinical studies proved that it binds to the both serotonin transporter (SERT) and noradrenaline (NAT) transporters with greater affinity and in balanced manner. Thus it is dual mechanistic antidepressant. As like to TCAs, no affinity for dopamine transporter (DAT) and no significant binding affinity for dopamine, serotonin, adrenergic, histaminic and opioid receptors. Also not affect the activity of GABA transporter and MAO activity. So as compare to the TCAs, it is highly effective, well tolerable and having less side effects.
effects. Unlike to venlafexine, the another SNRI requires higher dose (>150 mg) for binding to noradrenergic transporter. The remission rate in depression along with duloxetine is similar to the other existing SSRIs also simultaneously it proves its effectiveness in stress urinary incontinence (SUI) and diabetic peripheral neuropathic pain (DPNP) in same doses but not the first line treatment for both disorder. Based on the outcome of the various trials, the adverse event profile of the duloxetine was similar to the traditional SSRIs and generally well tolerated in depressed patients.

**CHEMISTRY, SYNTHESIS AND SAR**

Duloxetine is a thiophenepropylamine derivative with a secondary amino group to which naphthaline is linked via an ether bond. Chemically it is (+)-(S)-N-methyl-3-(1-napthalenyloxy)-2-thiophenepropanamine, its molecular weight is 297.4 and its empirical formula is C_{18}H_{19}NOS. It is positive isomer of the recemic compound. In market, it is available in the form of hydrochloride salt. The complete synthesis of duloxetine is quite complex but try to simplify in following manner.

Stating material for the synthesis of duloxetine is 2-acetylthiophene (A) which reacts under specified conditions in presence of mixture of reagents I (dimethylamine hydrochloride, paraformaldehyde, concentrated hydrochloric acid in isopropanol) gives 2-thienyl 2-dimethylaminoethylketone hydrochloride (B) in form of white solid. The reduction of intermediate B is done by reagents II (sodium borohydride, acetone, methyl t-butyl ether) under controlled condition finally the pH of mixture around 12. Further the aqueous phase is separated and the organic phase is concentrated by evaporation. In another vessel, the solution of (S)-(+) mandelic acid in ethanol is prepared and slowly add to the previous mixture at controlled temperature gives intermediate C ((S)-(+)N, N-dimethyl-3-hydroxy-3-(2-thienyl)-propanamine) in form of mandelic acid salt which is recovered by the washing with methyl t-butyl ether. Amine form of Intermediate C is obtained by dissolving in water at alkaline pH, extracted in to organic solvent and finally evaporates to remove the solvent. Intermediate C is dissolved in dimethylsulfoxide (DMSO) and poured in the reagent mixture IV (sodium hydride in mineral oil) with vigorous stirring. Then potassium benzoate and 1-fluoronaphthalene is added to the mixture in sequential manner with continuous stirring at controlled condition. After that doing phase separation with different organic solvent and filtration, phosphoric acid is added to the mixture dropwise and cool the mixture which gives the slurry of intermediate D in form of white solid. Finally duloxetine (Product E) is obtained from intermediate D.

**PHARMACODYNAMICS**

Action of duloxetine is mediated by the inhibition of the neuronal reuptake of 5-HT and NE. Several in vivo data from preclinical and clinical studies support that duloxetine has higher affinity for both the 5-HT and NE reuptake transporters (SERT and NET correspondingly). Studies shown that binding affinity of duloxetine is dose dependant. Binding affinity has inverse relation with the inhibition constant (K_i). Duloxetine was evaluated for its ability to displace [^3H]cyanoimipramine or [^3H]nisoxetine from the 5-HT and norepinephrine transporters, respectively with compared to other antidepressants. Following table shows the inhibition constant (K_i) for various antidepressants evaluated preclinically.

<table>
<thead>
<tr>
<th>Monoamine reuptake inhibitors</th>
<th>K_i (nM)</th>
<th>Selectivity ratio (5-HT/NE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[^3H]cyanoimipramine</td>
<td>[^3H]nisoxetine</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>1.8 ±0.1</td>
<td>3±0.3</td>
</tr>
<tr>
<td>Venlafexine</td>
<td>74±1.9</td>
<td>1260±144</td>
</tr>
</tbody>
</table>
Selectivity data reveals that duloxetine is a balanced inhibitor of 5-HT and NE, as the ratio is 1.7 between [3H]cynoimipramine and [3H]nisoxetine. While fluvoxamine and paroxetine have high selectivity ratio proves them Selective Norepinephrine Reuptake Inhibitor (SNRI).

In randomized, double-blind trials in healthy volunteers (n=6 and n=27) were reported that duloxetine 120 mg/day significantly reduced the whole blood 5-HT concentration also significantly decreased in urine excretion of NE metabolite. In addition, the effect of duloxetine on tyramine pressure response was variable and significant suppression was seen ≥ 120mg/day dose of duloxetine. The cardiovascular effects like Heart rate (HR) and/or Systolic Blood Pressure (SBP) had been increased in volunteers who were receiving the dose of duloxetine 60-240 mg/day.

**PHARMACOKINETICS**

Pharmacokinetics of duloxetine for single and multiple doses ranging from 20-80 mg/daily were evaluated in various studies are mentioned in the following tabulated form.

**Table 2:** Pharmacokinetic parameters of duloxetine

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Average values (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µg/L)</td>
<td>27.5</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (hr)</td>
<td>~ 6 (4-16)</td>
</tr>
<tr>
<td>V&lt;sub&gt;d/F&lt;/sub&gt; (L)</td>
<td>1943 (803-3531)</td>
</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>114 (44-218)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (hr)</td>
<td>12 (9.2-19.1)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (µg · hr/L)</td>
<td>464.3</td>
</tr>
<tr>
<td>Oral bioavailability (%)</td>
<td>50 (30-80)</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Steady state</td>
<td>3-5 days</td>
</tr>
<tr>
<td>Non-linear kinetics</td>
<td>Not at therapeutic doses</td>
</tr>
</tbody>
</table>

V<sub>d/F</sub> = Oral volume of distribution; CL/F = Oral systemic clearance; t<sub>max</sub> = time to reach C<sub>max</sub>; C<sub>max</sub> = Peak plasma concentration; AUC<sub>0-∞</sub> = area under the plasma concentration-time curve from time zero to infinity; t<sub>1/2</sub> = plasma elimination half-life.

Duloxetine Hydrochloride is rapidly absorbed orally. T<sub>lag</sub> (lag period for absorption) for duloxetine is around 2 hrs. Effect of food does not affect the C<sub>max</sub>, but delays to the time to reach the peak plasma concentration from 6 to 10 hours and slightly decreases the AUC. Administration of evening dose of duloxetine delays the absorption about 3 hours as compared to morning dose and increase clearance by 33% approximately.

As mentioned earlier, Duloxetine is highly plasma protein bound drug primarily albumin and α<sub>1</sub>-acid glycoprotein. Renal and hepatic impairment does not affect the plasma protein binding of duloxetine. Clinical trials based on effect of renal impairment on pharmacokinetic of duloxetine suggest that dose adjustment is not necessary in patients with mild (Creatinine clearance (CL<sub>CR</sub>) >60-90mL/min) to moderate (CL<sub>CR</sub> >30–60mL/min) impairment but patients with severe renal impairment or End Stage Renal Disease...
ESRD) \((CL_{CR} < 30mL/min)\), duloxetine is not generally not recommended because \(C_{max}\) and \(AUC\) is \(~ 2\) fold higher than in healthy subjects and decreased clearance of metabolites.\(^{36}\)

Cytochrome P450 (CYP) isoenzyme CYP1A2 and CYP2D6 is responsible for the metabolism of duloxetine.\(^{17,19,37,48}\) The major metabolite of duloxetine in plasma was the glucuronide conjugate of 4-hydroxyduloxetine and the second most abundant metabolite in plasma was the sulfate conjugate of 5-hydroxy-6-methoxyduloxetine in reported study. It was also suggested that intermediate unconjugated metabolites of duloxetine were not remain in plasma to an appreciable extant.\(^{17}\) Major route of excretion of duloxetine is urine (about 72%). It is also excreted in feces (20%). Very few amount of duloxetine is excreted in unchanged form in urine (1%).\(^{19,37,48}\) Metabolites of duloxetine have lack of activity because metabolite have been reported to lack significant affinity for 5-HT, NE and dopamine.\(^{19,38}\) Amongst all the SNRIs, duloxetine has long plasma elimination half life as compared to milnacipran and venlafaxine having elimination half life 8 and 4 hours respectively.\(^{22}\)

Population pharmacokinetic study of orally administered duloxetine in 594 patients had shown that the interpatient variability in apparent oral clearance (\(CL/F\)) was 59% and the interpatient variability in the apparent volume of distribution after oral administration (\(V_d/F\)) was 97%. Sex, smoking status, age and dose had a statistically significant effect on \(CL/F\), whereas the \(V_d/F\) was influenced by ethnicity. \(CL/F\) was 40% lower in females than in males and 30% lower in nonsmokers than in smokers. \(CL/F\) decreased with increasing dose and age.\(^{39}\)

**DRUG INTERACTION**

Duloxetine is both an inhibitor and a substrate of cytochrome CYP2D6 isoenzyme. Study was carried out on \(N = 14\) (7 men, 7 women) subjects shown that duloxetine increased the maximum plasma concentration of desipramine 1.7-fold and the area under the concentration-time curve 2.9-fold. In another study, Paroxetine increased the maximum plasma concentration of duloxetine and the area under the concentration-time curve at steady state 1.6-fold. Both studies concluded that Duloxetine 60mg twice daily is a moderately potent CYP2D6 inhibitor, intermediate between paroxetine and sertraline. The potent CYP2D6 inhibitor paroxetine has a moderate effect on duloxetine concentrations.\(^{40}\) In another comparative study of drug-drug interaction shown that duloxetine was effectively inhibit CYP2D6 isoenzyme than the desvenlafaxine.\(^{41}\) Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (\(n=14\)) resulted in a 6-fold increase in duloxetine AUC and \(C_{max}\). In vitro drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Activity of CYP2C9, CYP3A and CYP2C19 does not inhibited by the duloxetine.\(^{19,29}\)

**PRECLINICAL DEVELOPMENT**

Duloxetine was evaluated on several behavioral animal models which prove it is effective antidepressant in nature. Behavioral models like Forced Swim Test (FST) was evaluated on male Sprague-Dawley rats which revealed that duloxetine was produced a dose-dependent reduction in immobility that differed significantly from control values between 10 and 40mg/kg.\(^{42}\) In vivo, studies also reported that oral or subcutaneous administration of duloxetine increased in extracellular levels of both 5-HT and NA in the frontal cortex and hypothalamus of freely moving rats. Microdialysis studies in rats using 5-HT and NA neuron recordings also proved that duloxetine was founded to be the most potent SNRI and was five times more effective to inhibit the firing of 5-HT neurons than that of NA neurons and also potency of duloxetine to suppress NA neuronal firing was unaffected by a prior lesioning of 5-HT neurons. It was shown that among the SNRIs, only duloxetine desensitized the terminal \(\alpha_2\)-adrenergic autoreceptor.\(^{43}\)

In another behavioral and electroencephalographic studies in rats and mice shown that Duloxetine (3.13-50 mg/kg p.o.) significantly prevented tetrabenazine induced ptosis in mice and rats also inhibited reserpine induced hypothermia in mice. When duloxetine (12.5-100 mg/kg p.o.) and 5-hydroxytryptophan, a precursor of serotonin, were administered simultaneously to mice and
rats, head movement behavior and tremor were observed. In addition, duloxetine (25-100 mg/kg p.o.) significantly attenuated immobility in forced swimming in mice, as equally effective as commonly used antidepressant drugs. Duloxetine (1 2.5-25 mg/kg p.o.) significantly decreased rapid eye movement sleep and slow-wave deep sleep and increased the awake period, in the rat EEG. However, duloxetine (25-200 mg/kg p.o.) did not affect salivation and lacrimation induced by oxotremotide, a cholinergic agonist, whereas it (25-50 mg/kg) reduced the oxotremorine-induced tremor in part.44

Another in vivo blockade uptake study of 5-HT and NE using rat brain was shown that the uptake of both [3H]5-hydroxytryptamine (5-HT) and [3H]norepinephrine (NE) were equipotently inhibited in hippocampus slices prepared from rats treated for 2 days with different doses of duloxetine (5,10, 15 and 20 mg/kg/day s.c.). In the same study, electrophysiological experiments in hippocampus was revealed that five successive i.v. injections (2 mg/kg) significantly and dose-dependently prolonged the recovery time of the firing activity of hippocampus CA3 pyramidal neurons from the 5-HT applications and acute i.v. injections of duloxetine suppressed the spontaneous firing activity of dorsal raphe 5-HT and locus ceruleus NE neurons with ED50 values of 99 and 475 µg/kg, respectively. Subcutaneous administration of duloxetine (10, 15 and 20 mg/kg/day) increased the recovery time in a dose-dependent manner in hippocampus slices.45

Synaptosomal uptake inhibition studies in rats were shown that both enantiomers were equipotent at the NE transporters; however S-enantiomer was shown to be more active at the5-HT transporter. Simultaneously, comparison to the SSRI fluoxetine and the selective NE reuptake inhibitor atomoxetine was revealed that S-enantiomer of duloxetine was a potent dual inhibitor of 5-HT and NE.47

Comparative inhibition study of monoamine transporter between clomipramine, duloxetine, milnacipran and venlafaxine in rat was evaluated that duloxetine has higher 5-HT and NE transporter inhibition activity as compare to others. The rank order for 5-HT transporter inhibition potency was duloxetine > venlafaxine > chlorimipramine > milnacipran and for NE transporter inhibition potency, the rank order was duloxetine > chlorimipramine > milnacipran.46,48

The increase in extracellular concentration of 5-HT and NE at different doses was shown in the following table.

**Table 3:** Increase in extracellular concentration of 5-HT and NE in rats from baseline.46

<table>
<thead>
<tr>
<th>Drug</th>
<th>Extracellular conc. of 5-HT (%)</th>
<th>Extracellular conc. of NE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At 5 mg/kg i.p.</td>
<td>At 15 mg/kg i.p.</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>216 ± 35</td>
<td>217 ± 23</td>
</tr>
<tr>
<td>Chlorimipramine</td>
<td>191 ± 15</td>
<td>221 ± 44</td>
</tr>
<tr>
<td></td>
<td>5 mg/kg i.p.</td>
<td>40 mg/kg i.p.</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>120 ± 10</td>
<td>165 ± 21</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>176 ± 19</td>
<td>274 ± 34</td>
</tr>
</tbody>
</table>

The data was provided evidence that duloxetine had about equal affinity for 5-HT and NE transporters and increased 5-HT and NE extracellular concentrations approximately equally. Higher dose of duloxetine increased the concentration of NE more than the 5-HT.46,48

Studies in rats and dogs were shown that duloxetine was well absorbed, but extensively metabolized. The absolute bioavailability is estimated to be 21% in rats and 5% in dogs after single oral or intravenous 5 mg/kg doses. Peak plasma concentrations of duloxetine are 0.43 ng/mL in rats and 0.19 ng/mL in dogs. The plasma elimination half-life is about 2 hours in rats and about 3 hours in dogs. Metabolism of duloxetine constitutes the major route of clearance in both rats and dogs followed by excretion of the metabolites into bile (feces). Urinary excretion of metabolites accounts for about 22% of a duloxetine dose in rats and
about 29% in dogs. Duloxetine is highly bound to rat and dog plasma proteins. The mean percent bound at a duloxetine concentration of 150 ng/mL is 96% in rats and 97% in dogs. Duloxetine metabolism in rats includes oxidation in the naphthyl ring, followed by further oxidation and conjugation or formation of a dihydrodiol. The major biotransformation pathway is oxidation followed by glucuronidation. Duloxetine also undergoes extensive metabolism in dogs. The major biotransformation pathways lead to the formation of a des(aminomethyl) acid metabolite, cysteinyl hydroxy duloxetine, dihydrodiol duloxetine, desmethyl duloxetine, and a glucuronide conjugate of 5-hydroxy duloxetine. In dogs the 5-hydroxy related metabolites are predominant whereas, in the rat the 4-hydroxy related metabolites are predominant.\textsuperscript{48,49,50}

Also the preclinical profile of duloxetine, including its effects on persistent pain models, further makes it an ideal drug candidate to evaluate effects clinically both on the emotional/ psychological symptoms but also on painful physical symptoms.\textsuperscript{48}

**CLINICAL DEVELOPMENT**

**Placebo Controlled Trials**

Randomized, double-blind, evaluation of duloxetine at 40mg/day (20mg twice daily) and 80mg/day (40mg twice daily) versus placebo demonstrated that duloxetine 80mg/day was superior to placebo on mean 17-item Hamilton Depression Rating Scale total change by 3.62 points (95% CI 1.38, 5.86; P =0.002). Duloxetine at40mg/day was also significantly superior to placebo by 2.43 points (95% CI 0.19, 4.66; P =0.034) and Duloxetine 80mg/day was superior to placebo for most other measures, including overall pain severity.\textsuperscript{51}

In another randomized, double-blind, placebo-controlled trial meeting DSM-IV criteria for MDD received placebo (n =93), duloxetine 80mg/day (40 mg BID; n =95), duloxetine 120 mg/day (60 mg BID; n =93) versus placebo was shown that duloxetine 80 mg/day, duloxetine 120 mg/day, had significantly greater reductions in HAMD\textsubscript{17} total score compared with placebo and estimated probabilities of remission at week 8 for patients receiving duloxetine 80 mg/day (51%), duloxetine 120 mg/day (58%) were significantly greater compared with those receiving placebo (30%). The rate of discontinuation due to adverse events among duloxetine treated patients (80 and 120 mg/day) did not differ significantly from the rate in the placebo group.\textsuperscript{52}

9-week, multi-center, double-blind, parallel-group clinical trial of adult patient (N =267) with MDD were randomly assigned to receive duloxetine (60mg/day) or placebo. During study efficacy was evaluated using the17-item Hamilton Depression Rating Scale (HAMD17), Visual Analog Scales (VAS) for pain, Clinical Global Impression of Severity (CGI-S), Patient’s Global Impression of Improvement (PGI-I), and Quality of Life in Depression Scale (QLDS). Also, safety was evaluated by assessing discontinuation rates, adverse event rates, vital signs, and laboratory tests. Result from the trial was shown that Duloxetine (60mg QD) significantly reduced the HAMD17 total score compared with placebo at the end of 9-week therapy. Estimated probabilities of response and remission were 65 and 43%, respectively, for duloxetine compared with 42 and 28 % for placebo and concluded that duloxetine 60 mg administered once daily appeared to be a safe and effective treatment for MDD.\textsuperscript{54}

Onset of action for duloxetine 60 mg once daily was evaluated in two identical, but independent, randomized, double-blind, placebo-controlled, 9-week clinical trials of duloxetine (60mg QD). In trials, efficacy measures included the17-item Hamilton Rating Scale for Depression (HAMD17),

HAMD17 subscales (Maier, core, and anxiety), and the Clinical Global Impression of Severity (CGI-S) and Patient Global Impression of Improvement (PGI-I) scales. The probabilities of achieving a sustained 30% improvement (Maier subscale) at Week 1 for duloxetine and placebo-treated patients were 16.2% vs. 4.8%, respectively (P < 0:001). The corresponding probabilities of sustained improvement at weeks 2 and 3 for duloxetine were 32.5% and 45.4%, respectively, compared to 12.8% and 21.4% for placebo (P < 0:001 for both comparisons).\textsuperscript{55}

**Comparison with SSRIs**
Randomized, double-blind, evaluation of duloxetine at 40mg/day (20mg twice daily) and 80mg/day (40mg twice daily) versus paroxetine 20mg/day supported that the duloxetine 80mg/day group was superior to paroxetine 20mg/day at the last visit (8th week).\textsuperscript{51} Another comparison study with paroxetine (20 mg QD) was designed as randomized and double blind and proved that estimated remission rate was 47\% as compared to the 51\% and 58\% for duloxetine 80 mg/day and duloxetine 120 mg/day respectively. The incidence of acute treatment emergent sexual dysfunction in duloxetine and paroxetine-treated patients was 46.5\% and 62.8\%, respectively.\textsuperscript{52,64}

Comparative study with escitalopram was shown in randomized, double-blind and active comparator study for MDD in which duloxetine 60 mg/day (N=273) and escitalopram 10 mg QD (N=274) given for 8 week period. Outcome from the trail was that onset criteria for 2 weeks for duloxetine and escitalopram treated patient were 42.6\% and 35.2\% (treatment difference=7.4\%) and proven that duloxetine is as fast as an escitalopram in case of onset of efficacy.\textsuperscript{53}

Data were pooled from all Lilly-sponsored clinical trials where duloxetine was compared with placebo and an SSRI in patients with MDD: 7 randomized, double-blind, fixed-dose, 8-week studies of duloxetine (n = 1,133) versus SSRI (n = 689) versus placebo (n = 641). Duloxetine doses were 40, 60, 80 and 120 mg/day and SSRI doses were 10 mg/day (escitalopram) and 20 mg/day (fluoxetine and paroxetine). Results were demonstrated that compared to SSRI-treated patients, duloxetine-treated patients had a significantly greater ($p < 0.05$) reduction in the 17-item Hamilton Depression Rating Scale (HAMD\textsubscript{17}) total score and HAMD\textsubscript{17} items of work and activities, psychomotor retardation, genital symptoms and hypochondriasis.\textsuperscript{57}

Another double blind comparative study with escitalopram was designed 1-week, single-blind, placebo lead-in period followed by an 8-week, randomised, double-blind, multicentre, parallel-group comparison. A total of 278 outpatients of 382 patients screened with Diagnostic and Statistical Manual of Mental Disorders (4th edition) - diagnosed major depressive disorder (Montgomery- Asberg Depression Rating Scale [MADRS] total score $\geq 26$) were randomised to the two treatment groups. Patients were treated with either escitalopram 10–20 mg/day (fixed at 10 mg/day for the first 4 weeks) or duloxetine 60 mg/day. Results from trial shown that mean baseline MADRS total scores were 31.0 for the escitalopram group and 31.6 for the duloxetine group. Findings from trial was suggested that duloxetine is as effective as escitalopram in the treatment of major depressive disorder.\textsuperscript{58}

In controlled clinical trials for depressed patients associated with anxiety were treated with placebo, paroxetine, fluoxetine and duloxetine at therapeutic doses. Anxiety was assessed in all studies using the HAMD anxiety/somatization subfactor, the anxiety-psychic item (HAMD Item 10) and Hamilton Anxiety Rating Scale (HAMA). Results from the studies shown that the mean improvement for duloxetine was significantly greater than placebo, paroxetine or fluoxetine. Also revealed that duloxetine is efficacious in treating a broad spectrum of symptoms associated with depression, including mood, anxiety, and painful physical symptoms with remission rate about 43-57\%.\textsuperscript{62}

**Comparison with SNRIs**

All SNRIs have been compared to SSRIs, however and venlafaxine and milnacipran have been the subject of meta-analyses. Multicenter, randomized, double-blind, parallel group studies in which patients with major depressive disorder were randomized to either duloxetine 60mg/day or venlafaxine extended release (XR) 150mg/day (75mg/day for the first 2 weeks) for a 6-week fixed dosing period followed by an additional 6 weeks of treatment in which the dose could be increased up to 120 mg/day for duloxetine and 225 mg/day for venlafaxine. For the study, the primary outcome measure was the GBR comparison of duloxetine 60 mg/day and venlafaxine XR 150 mg/day after 6 weeks of treatment. In the GBR analysis, benefit was defined as remission at end point [17-item Hamilton Depression Rating Scale (HAMD\textsubscript{17}) $\leq 7$]. Results form the study was revealed that there were no significant differences between duloxetine 60 mg/day and venlafaxine 150 mg/day as measured by GBR assessment at the end of 6 weeks (-1.418 vs. -1.079, $P = 0.217$) or 12 weeks (-0.349 vs. -0.121, $P = 0.440$), nor were there significant differences between treatment groups on the majority
of efficacy measures and duloxetine 60mg/day and venlafaxine XR 150 mg/day have similar benefit–risk profiles on the basis of a comparison utilizing GBR assessment.\textsuperscript{56}

Another, recent open label, randomized, comparative, parallel group, multi-centric clinical trial was done to determine the safety and efficacy of duloxetine compared to venlafaxine in the treatment of major Depression. A total of 228 patients with diagnosis of major depression were randomized to duloxetine (n=117) and venlafaxine (n=111) treatment groups. Total 198 patients were evaluated for efficacy parameters using HAMD scores, MADRS total scores and CGI-S and CGI-I scales. Safety was assessed by Treatment-emergent adverse events. The results were comparable and there was no significant difference at the end of trial between duloxetine group and venlafaxine group. At the end of the trial concluded that duloxetine is an effective and safe antidepressant in Indian patients of Major Depressive Disorder. It is equally effective to the already marketed sustained release venlafaxine.\textsuperscript{66}

Also comparative studies reported that unlike venlafaxine, duloxetine does not causes the incidence of hypotension at the therapeutic doses.\textsuperscript{59}

**TOLERABILITY AND SIDE EFFECTS**

Treatment-emergent adverse events reported significantly more frequently by duloxetine-treated patients than by patients receiving placebo were constipation (80 and 120 mg/day), increased sweating (120mg/day), and somnolence (120mg/day).\textsuperscript{52}

Pooled data from two 9-week trials, which compared duloxetine 60-mg QD (n=251) with placebo (n=261) in the treatment of MDD revealed that individual symptoms showing the most rapid improvements (week 1) were depressed mood, guilt, suicidal ideation, work / activities, and psychic anxiety as well as back pain and shoulder pain. At subsequent visits, significant improvements were observed in retardation (week 2); hypochondriasis (week 3); general somatic symptoms (week 5); middle and late insomnia (week 7); and gastrointestinal (GI) symptoms, genital symptoms (level of sexual interest or ease of sexual arousal), insight, and early insomnia (week 9). Also proved that it is well tolerated amongst MDD patient.\textsuperscript{60}

Simultaneously the dose response relationship of duloxetine in controlled clinical trials shown that duloxetine 60 mg daily is the best effective dose.\textsuperscript{61} Adverse effects reported in association with duloxetine are diarrhea > asthenia > fatigue > insomnia > dizziness > nausea > constipation > somnolence > anorexia > nervousness > vomiting > dry mouth > sweating.\textsuperscript{62,63} Only dry mouth appears to be systematically more common with the SNRIs than the SSRIs. The dry mouth experienced with SNRIs is of noradrenergic origin and is similar to that encountered during stress. It is less severe and less long-lasting that the anticholinergic dry mouth experienced with TCAs.\textsuperscript{65} Trials revealed that the cardiovascular effects of duloxetine appear to be comparable with medications considered to be first-line options for depression.\textsuperscript{67,71} Case report studies were shown that hyponatremia is less common in MDD patient and elder patients should be closely monitored for clinical and laboratory evidence of hyponatremia.\textsuperscript{68,69} Results from open-label study of depressed patients aged 65 and older suggest that duloxetine is safe and well tolerated in long-term use. Furthermore, the efficacy and adverse event profile of duloxetine appears to be comparable in older (age \(\geq 65\)) and younger patients (age 18–64).\textsuperscript{74} Also it is effective, safe and tolerable in the prevention of relapse of MDD.\textsuperscript{75} Comparative trials of safety and efficacy with paroxetine and fluoxetine were shown that the incidence of duloxetine-induced nausea resembled that produced by paroxetine and fluoxetine.\textsuperscript{70} Duloxetine is less likely cause the sexual dysfunction. Among the newer antidepressants, venlafaxine is the most serotonergic agent, and was most likely to cause sexual dysfunction in all domains.\textsuperscript{73}

Another adverse drug reactions (ADRs) reported since market introduction that were temporally related to duloxetine therapy and not mentioned else where in the manufacturer labeling include : anaphylactic reaction, aggression and anger (particularly early in treatment or after treatment discontinuation), angioneurotic edema, erythema multiforme, extrapyramidal disorder, glaucoma, gynecological bleeding, hallucinations, hyperglycemia, hypersensitivity, hypertensive crisis, musclespasm, rash, supraventricular arrhythmia, tinnitus (upon treatment discontinuation), trismus and urticaria.\textsuperscript{72}
CONCLUSION

In SNRIs, duloxetine is the most balanced drug with high affinity at 5-HT and NA transporters as compared to other SNRIs. Duloxetine is superior in the treatment of moderate to severe depression as compare to TCAs and SSRIs. SSRIs have limited efficacy in major depression. Duloxetine has the low potential for the drug interaction. Also, duloxetine has the better efficacy and tolerability as compare to TCAs, SSRIs and other SNRIs like venlafaxine even in long term use also. Thus, duloxetine is the favorable option with improved efficacy and tolerability profile for the treatment in the patients with major depression.

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