2. REVIEW OF LITERATURE

3.1 Milnacipran

3.1.1 Pharmacodynamic Properties
Depression is thought to be caused by a functional deficit in noradrenergic and/or serotonergic central neurotransmission. Most antidepressants are assumed to act by increasing synaptic levels of one or both of these neurotransmitters via inhibition of their metabolism or neuronal reuptake. Down-regulation of \( \alpha \)-adrenergic receptors has also been postulated as a possible mechanism by which antidepressant agents exert their effect, but recent evidence shows that some agents, such as milnacipran, citalopram and paroxetine, do not modify these receptors. 

Like the tricyclic antidepressants, milnacipran inhibits uptake of noradrenaline and serotonin. The inhibitory capacity of milnacipran was of approximately the same order as that of imipramine for noradrenaline and serotonin uptake in vitro. Neither agent significantly inhibited dopamine uptake. Hyperthermic tests conducted in rats confirmed that milnacipran and imipramine produce approximately equipotent inhibition of both noradrenaline and serotonin uptake. Plasma from 12 healthy male volunteers who received milnacipran 25 to 400mg dose-dependently inhibited serotonin and noradrenaline uptake by human platelet rich plasma and rat brain homogenate, respectively, ex vivo. Inhibition of up-take of the 2 monoamines correlated with each other at all measured times and this inhibition was correlated with unchanged plasma milnacipran concentrations.

In agreement with this decrease in monoamine uptake, cerebral extracellular levels of noradrenaline and serotonin were increased and levels of their metabolites were decreased in freely moving guinea-pigs given intraperitoneal milnacipran 10 or 40 mg/kg (906% and 3094% increase, respectively, for noradrenaline and 635% and 2437% increase for serotonin). Recent in vivo data suggest that milnacipran may exert its suppressant effect on serotonergic neurons via inhibition of noradrenaline uptake. However, an in vitro investigation of the distribution of radiolabelled milnacipran binding sites showed that the
drug binds to the serotonin transporter, and perhaps some other unidentified sites in the rat brain, but it does not bind to noradrenergic or dopaminergic neurons. Binding sites for the radiolabelled drug correlated with areas dense in serotonergic innervation, and binding density correlated with serotonin levels in each region. Competitive inhibition experiments and analysis of the effect of lesion of serotonergic or noradrenergic neurons confirmed the binding of milnacipran to serotonergic terminals.[59]

As well as inhibiting monoamine reuptake, tricyclic antidepressants also interact with neurotransmitter receptors such as adrenergic, muscarinic and histaminic receptors. In addition, in common with selective serotonin reuptake inhibitors (SSRIs), they induce down-regulation of 5-HT₂ receptor negative feedback mechanisms, resulting in increased serotonergic neurotransmission. [55]

In contrast, milnacipran, at a peritoneal dosage of 10 mg/kg twice daily or a continuous subcutaneous dosage of 20 mg/kg/day for 3 weeks, had no effect on α -adrenergic or postsynaptic 5-HT₂ receptor numbers or cyclic AMP levels following stimulation with isoprenaline (a measure of adenyl-cyclase activity) in rats. In addition, α-adrenergic receptor density, function and affinity were unaffected by oral milnacipran 15 mg/kg/day for 6 weeks, intraperitoneal milnacipran 3 to 30 mg/kg/day for 21 days or administration by mini-pump of milnacipran 30 mg/kg/day for 27 days in rats. In 3 of these studies, imipramine reduced some or all of the measured parameters [60] and in the remaining study, oral citalopram had no effect and oral desipramine reduced α -adrenergic receptor numbers. Oral milnacipran 50 mg/kg/day for 21 days did not hyposensitise 5-HT receptors in rats and the negative feedback system continued to function. The same regimen of milnacipran did not alter noradrenergic neurotransmission in rats, which suggests that the noradrenergic α₂ - autoreceptor is also insensitive to the drug.[61]

Indeed, milnacipran had little or no affinity for any postsynaptic receptor (α₁, α₂ or α-adrenergic, muscarinic, histamine H₁, dopamine D₂, 5-HT₁, 5-HT₂ or benzodiazepine) or effect on monoamine A or B activity in vitro. In rats, it had no effect on α₁ or α₂ adrenergic, 5-HT₁, 5-HT₂ or benzodiazepine receptors or monoamine A or B activity. Similarly, neither
citalopram nor desipramine altered α-adrenergic or 5-HT receptors in vivo. Therefore, milnacipran appears to act exclusively at presynaptic sites to inhibit noradrenaline and serotonin uptake. It does not appear to act at any postsynaptic receptor and thus would be expected to cause fewer anticholinergic, sedative or adverse cardiovascular effects than tricyclic anti-depressants.\(^{[55]}\)

### 3.1.1.1 Behavioural Effects

Behavioural tests in animals assessing interactions with the noradrenergic or serotonergic system showed milnacipran to be very active. The effective oral dose in 50% of mice (ED\(_{50}\)) for antagonism of tetrabenazine-induced ptosis was 0.5 or 1 mg/kg; for potentiation of yohimbine induced toxicity it was 0.5 mg/kg, and for antagonism of oxotremorine or apomorphine induced hypothermia, 0.7 and 0.2 mg/kg, respectively.\(^{[62]}\)

Respective values for imipramine were 5, 7, 1 and 4 mg/kg (last 2 values are minimal significantly active dose), for clomipramine 9, 5, >1 and 6 mg/kg, and for desipramine 2.5, 1.5, 0.3 and 5 mg/kg. Compared with a single 15 mg/kg dose, long term oral administration (10 to 15 mg/kg/day for 6 weeks) of milnacipran or imipramine did not result in a significantly different ED\(_{50}\) value for yohimbine-induced toxicity. However, long term treatment did cause the ED\(_{50}\) value for tetrabenazine induced ptosis to be reduced compared with the value after a single dose in mice given imipramine (1 vs 5 mg/kg) but not in those given milnacipran. This could have occurred because of imipramine induced up-regulation of the α\(_1\) -adrenergic receptor.\(^{[62]}\)

In rats, the ED\(_{50}\) for death caused by yohimbine-induced toxicity was 7.5 mg/kg for milnacipran, 87.5 mg/kg for imipramine and 89.5 mg/kg for mianserin. Head twitching after 5-hydroxy-L-tryptophan dose-dependently increased in mice given milnacipran 3 to 30 mg/kg (p < 0.05 at the highest dose). Significant inhibition of reserpine induced hypothermia was noted with milnacipran 3 to 30 mg/kg. However, the drug did not alter the effects of subsequent levodopa administration.\(^{[62]}\)
Notably, anticholinergic activity (mydriasis) was not significant with milnacipran, but 61% and 38% increases in pupil diameter occurred with imipramine and clomipramine, respectively. In general, milnacipran did not alter the cholinergic effects (including salivation) of oxotremorine or pilocarpine, whereas imipramine and desipramine both inhibited these effects. When given to 8 healthy volunteers, oral milnacipran 50mg did not significantly alter salivation (4% increase) when compared with placebo. In contrast, amitriptyline 75mg caused a 30% decrease in saliva secretion relative to placebo. \[62\]

### 3.1.1.2 Antidepressant Activity

Milnacipran demonstrated antidepressant activity in a number of experimental tests conducted in rats and/or mice. Single or multiple (daily for 7 days) doses of oral milnacipran 10, 30 or 60 mg/kg dose-dependently decreased the duration of immobility in the forced swimming test in mice and rats. This inhibition was significant for the 2 highest drug doses. Similarly, milnacipran 3 to 60 mg/kg dose-dependently inhibited freezing behaviour of rats in the conditioned fear stress test [significant for the highest tested drug dose (30 and 60 mg/kg)]. However, this latter experiment has also been suggested as a test for anxiolytic activity. Reductions in immobility time during the forced swimming test were associated with increases in interstitial serotonin levels and decreased serotonin metabolite levels in rats. Milnacipran pretreatment also tended to suppress forced swimming induced increases in dopamine turnover. 14 days’ administration of milnacipran 30 mg/kg once daily by injection reduced hyperactivity of olfactory bulbectomised rats in the ‘open field’ test. Lower doses of the drug (1 to 10 mg/kg) did not significantly decrease hyperactivity in this test. \[63\]

The behavioural deficit caused by exposure to an uncontrollable aversion situation was also significantly attenuated by 4 days of oral milnacipran 2, 5 and 10 mg/kg in rats. The effect of milnacipran 20 mg/kg was not significant. Long term administration of milnacipran or maprotiline (doses and duration not specified) restored spontaneous running in rats exposed to forced walking stress. \[63\]
3.1.2 Pharmacokinetic Properties

The pharmacokinetics of single oral doses of milnacipran has been investigated in 2 groups of 12 healthy volunteers. Milnacipran 50mg had a bioavailability of 85%. Maximum plasma drug concentrations ($C_{max}$) were dose-proportional for milnacipran 25 to 200mg, but above this dose (300 and 400mg) no such relationship was observed; time to $C_{max}$ ($t_{max}$) and elimination half-life ($t_{1/2}$) appeared to be independent of dose over the range 25 to 400mg. Volume of distribution was 5.3 L/kg after a 50mg dose, $C_{max}$ was 134 µg/L at 2 hours, area under the plasma concentration-time curve (AUC) was 1833 µg/L • h, $t_{1/2}$ or terminal $t_{1/2}$ ($t_{1/2\beta}$) was 8.1 or 6.1 hours, respectively, and total clearance was 37.6 L/h/1.73m$^2$.\[^{64}\]

Interindividual variation in pharmacokinetic parameters was low (except for $t_{max}$) and good correlation was demonstrated between single-dose and steady-state pharmacokinetics, suggesting that steady-state values may be predicted from single-dose data.\[^{64}\]

In 17 patients with major depressive disorder, oral milnacipran 50 or 100mg twice daily for 28 days had linear pharmacokinetics. $C_{max}$ values of D- and L-milnacipran were 223 to 419 nmol/L 2 hours after a 50mg dose and 381 to 690 nmol/L 2 hours after a 100mg dose. AUC values were larger and $t_{1/2}$ values longer (8 to 9 vs 5 to 6 hours) for D- than for L-milnacipran; $t_{1/2}$ values appeared to be independent of dose and time.\[^{64}\]

Administration of multiple doses of milnacipran 25 to 200mg twice daily for 14 days to 10 healthy volunteers resulted in rapid achievement of steady-state concentrations (after 2 to 3 days with twice daily dosing). Although mean pharmacokinetic values were slightly higher than on day 1, repeated drug administration did not significantly alter the pharmacokinetics of milnacipran. Milnacipran does not accumulate after multiple dose administration. Serotonin uptake inhibition paralleled blood drug concentrations, was maximal from day 1 and remained constant over the 14-day period. Although plasma milnacipran concentrations were not correlated with clinical efficacy or adverse events in patients, they do appear to relate to inhibition of serotonin reuptake.\[^{64}\]
The $C_{\text{max}}$ of oral milnacipran was slightly increased by concomitant food intake (39 µg/L after a meal vs 32 µg/L in fasting state for milnacipran 15mg) in Japanese volunteers, but other parameters such as $t_{\text{max}}$, $t_{1/2\beta}$, AUC and urinary excretion were not affected.\[^{[64]}\]

Milnacipran is poorly bound to plasma proteins (13%); this binding is nonsaturable. First-pass metabolism is low, with the predominant metabolite being the glucuronide conjugate of the parent drug. Metabolism also appears to be nonsaturable. No active metabolites have been identified in humans. 50% to 60% of the drug is excreted unchanged, 20% to 30% as glucuronon conjugated milnacipran and <20% as glucuronon conjugated phase I metabolites (including N-dealkylated milnacipran).\[^{[65]}\]

Milnacipran crossed the placental barrier in rats, rabbits and monkeys.\[^{[64]}\]

### 3.1.2.1 Patients with Hepatic or Renal Impairment and the Elderly

The pharmacokinetics of milnacipran is not significantly affected by hepatic impairment. In 8 patients with renal impairment [glomerular filtration rate of 9 to 85 ml/min (0.54 to 5.1 L/h)], the pharmacokinetics of a single oral dose of milnacipran 50mg were significantly different from those of a group of 6 healthy volunteers. $C_{\text{max}}$, AUC and $t_{1/2}$ values were significantly increased in patients with renal impairment because of significant reductions in apparent total and renal clearance of the drug. Changes in total clearance paralleled those in renal clearance and both parameters were correlated with the decrease in glomerular function.\[^{[66]}\]

Similarly, comparison with historical controls (young adults) showed that $C_{\text{max}}$ values for milnacipran are higher and elimination is prolonged in the elderly (mean age 80 years). After a single 50mg oral dose of milnacipran, the mean $C_{\text{max}}$ value was 219 µg/L at 1.8 hours, the mean $t_{1/2}$ value was 11 hours and the mean AUC value was 2335 µg/L • h in 20 fasting elderly volunteers.\[^{[66]}\]
3.1.3 Therapeutic Efficacy

3.1.3.1 Placebo-Controlled Trials

Milnacipran has been evaluated in 3 double-blind multicentre placebo-controlled trials. All enrolled patients had major depressive disorder as assessed by DSM-III criteria. Overall, milnacipran 50mg twice daily was significantly more effective than placebo in these trials, 2 of which included hospitalised patients. In the trial for which these data were available, improvement was noted within 7 days and was significantly greater than that produced by placebo after 14 days.

Analysis of pooled results of these studies confirms that milnacipran 50mg twice daily is clinically and statistically superior to placebo.

The largest and longest trial compared 3 dosages of milnacipran (25, 50 and 100mg twice daily) with placebo in 412 outpatients with moderate or severe major depression. After 8 weeks, milnacipran 50mg twice daily was significantly superior to placebo as shown by all 3 efficacy measures. In addition, the proportion of responders (>50% decrease in HDRS total score from base-line) was significantly larger in this treatment group than in the placebo group (65% vs 44%). The 200 mg/day dosage also reduced MADRS scores more than placebo (p < 0.01), but it did not produce significantly different changes in HDRS scores or in the proportion of responders according to the CGI rating. Milnacipran 25mg twice daily was less effective than the other 2 drug dosages (p < 0.05) and its effects were not significantly different from those of placebo.

165 patients from the above study received treatment for more than 8 weeks (for a mean of 21 weeks). Limited evidence suggests that milnacipran could prevent relapse (18% of placebo recipients withdrew because of clinical deterioration vs 6% of those taking milnacipran 50mg twice daily).
Patients with melancholia appeared to be particularly responsive to milnacipran 50mg twice daily (73% of these patients responded to milnacipran and 39% to placebo in the largest trial). [46]

3.1.3.2 Comparisons with Other Active Agents
Milnacipran has been compared with the tricyclic antidepressants amitriptyline, imipramine and clomipramine, the SSRIs fluoxetine and fluvoxamine, and mianserin. Patients enrolled in these trials met DSM-III [56, 68] or DSM-III-R [69],[51] criteria or Research Diagnostic Criteria for major depressive disorder. Patients usually had a MADRS score of ≥25, HDRS score ≥18 and CGI severity of illness score of ≥4 or ≥5. [70]

3.1.3.2.1 Comparisons with Tricyclic Antidepressants
When compared with amitriptyline 150 mg/day in two 4-week, multicentre double-blind trials which enrolled treatment groups of 40 to 45 inpatients, the efficacy of milnacipran was dependent on the dosage administered and appeared to be optimal at a dosage of 100mg twice daily. Drug dosages were titrated to the levels specified over 5 days. This was apparently performed to maintain blinding, as milnacipran does not require dose titration. It should be noted that the dose-finding study (which enrolled outpatients) and dosage recommendations suggest that the optimal dosage of milnacipran is 50mg twice daily. [71]

In the first of these trials, milnacipran 50 or 100 mg/day (administered as 2 doses) had a significantly slower onset of action than amitriptyline in inpatients with major depressive disorder (of various subtypes). Reductions in MADRS and HDRS scores were greater in amitriptyline than in milnacipran recipients at 2 weeks (p = 0.03), but after 4 weeks there was no significant difference between the amitriptyline and milnacipran 100 mg/day groups. Similarly, CGI severity of illness and global improvement scores improved more with amitriptyline than milnacipran at 2 weeks (p ≤0.03), but no significant differences between treatments were noted at 4 weeks. CGI efficacy index scores (measure of benefit to risk ratios) did not differ significantly between treatments at either time. Milnacipran 50 mg/day was inferior to both milnacipran 100 mg/day and amitriptyline. [71]
The investigators of the above study postulated that a higher dosage of milnacipran (200 mg/day) would overcome the slow onset of action observed with the titrated 100 mg/day dosage. Results of another trial, conducted to test this hypothesis, showed no significant between-treatment differences over time in total MADRS, HDRS, CGI severity of illness or global improvement scores in patients meeting the same criteria for depression as those in the earlier trial (although not all patients had depression of the endogenous subtype in the first trial) and receiving milnacipran 200 mg/day or amitriptyline 150 mg/day. Improvements in CGI efficacy index scores were significantly greater in milnacipran recipients than in amitriptyline-treated patients at 7 and 28 days. Amitriptyline appeared to have better efficacy for treatment of sleep disorders, whereas milnacipran reduced concentration difficulties and retardation to a greater extent.\[^{71}\]

Milnacipran has also been compared with imipramine or clomipramine in a number of double-blind randomised trials.\[^{68}\]

In these 7 trials, 842 patients with major depressive disorder (64 to 221 patients per study) were randomised to twice daily treatment with milnacipran 50mg or with imipramine 75mg (50mg in elderly patients) or clomipramine 75mg for 4 to 12 weeks. Most patients were hospitalised at the beginning of treatment. Individual results of each study (2 of which are available as unpublished reports and pooled data from all the trials showed no significant differences between milnacipran and these 2 tricyclic antidepressants as measured using HDRS and/or MADRS scores. Overall, 64% of milnacipran, and 67% of tricyclic antidepressant, recipients achieved a ≥50% decrease in HDRS score, with 39% and 42% of patients, respectively, achieving remission.\[^{68}\]

Similarly, moderate to marked improvement was noted after 4 weeks in 58% of 62 milnacipran 50 to 150 mg/day and 56% of 65 imipramine 50 to 150 mg/day recipients meeting DSM-III criteria for major depressive disorder in a Japanese trial. Milnacipran produced significantly greater improvement than imipramine after 1 week of treatment.\[^{68}\]
The comparative efficacy of milnacipran and clomipramine was similar or favoured clomipramine in 3 published trials. No significant between-treatment differences were noted at any time in a 3-month trial comparing milnacipran 100 mg/day with clomipramine 150 mg/day in 111 patients with major depressive disorder (patients were hospitalised for 3 weeks then were followed as outpatients). Patients with melancholia tended to respond to either treatment better than those without melancholia. However, CGI efficacy index scores, an indicator of the therapeutic benefit to tolerability ratio, favoured milnacipran at 2, 3, 4, 8 and 10 weeks (p ≤0.04) [but not at 12 weeks]. These findings indicate the importance of the preferred acceptability (tolerability) of milnacipran over clomipramine. [68]

Results of another trial, in which 62 patients were enrolled, failed to demonstrate clinically relevant efficacy over 26 weeks with either milnacipran (200 mg/day for 10 weeks then a titrated dosage of 100, 150 or 200 mg/day) or clomipramine (150 mg/day for 10 weeks then a titrated dosage of 75, 100 or 150 mg/day). A total of 64.5% of patients failed to complete the 26 weeks of treatment. Enrolment of a large proportion of treatment resistant patients was offered by investigators as a possible explanation for these findings. A similar design was used in another 26-week double-blind randomised multicenter trial which was conducted in 93 evaluable in- or outpatients with a 17-item HDRS score of ≥18. In this trial, clomipramine was significantly more effective than milnacipran when administered according to the regimen used in the latter study. The primary endpoint (change in HDRS) significantly favoured clomipramine (a mean decrease of 65 vs 49% at last visit; p = 0.01), as did the number of responders according to HDRS scores (72 vs 58% of patients with a reduction of ≥50%), the time to onset of action (mean time to a 50% decrease in HDRS score of 29 vs 43 days) and the response in patients severe depression (baseline HDRS score of ≥24). Changes in MADRS scores and CGI scores tended to favour clomipramine, but differences were not significant. 50% of patients withdrew from treatment before the end of 26 weeks; however, adverse events were the predominant cause of withdrawal in clomipramine recipients (21% of milnacipran- vs 38% of clomipramine-treated patients stopped treatment for this reason) whereas milnacipran recipients were more likely to withdraw from treatment because of lack of efficacy (19% vs 7%). [51]
One of the trials included in the pooled comparisons between milnacipran and tricyclic anti-depressants included elderly (65 to 90 years) patients only. Of a total of 219 patients included in an intent-to-treat analysis, 60% responded to milnacipran (50mg twice daily or 50mg plus 25mg daily; n = 112) and 60% responded to imipramine 75 or 100 mg/day for 8 weeks according to HDRS scores, indicating no significant between-treatment differences in this population. There was also no significant difference in the number of responders in each group as measured by MADRS. ⁶⁸

After 8 weeks, HDRS and MADRS scores decreased by 62% and 66%, respectively, in milnacipran recipients and by 66.5% and 71% in imipramine recipients according to intent-to-treat analysis. Other assessments, including CGI severity of illness, global impression of change and therapeutic effect indices and quality-of-life analyses, also showed no significant differences between treatments at 8 weeks. ⁶⁸

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₃.₃.₃.₂.₂ Comparisons with Selective Serotonin Reuptake Inhibitors

In a multicentre double-blind randomised trial, currently published only as part of a review, changes in HDRS and MADRS scores after 12 weeks were not significantly different in 93 in patients with severe major depressive disorder treated with milnacipran 50mg twice daily (73% and 75% decrease, respectively), in 96 who received milnacipran 100mg twice daily (70% and 72% decrease) and in 100 who were given fluoxetine 20mg once daily (67% and 68.5% decrease). According to HDRS scores, 62% of milnacipran 50mg twice daily, 54% of milnacipran 100mg twice daily and 51% of fluoxetine recipients responded to treatment. ≥50% of patients in each group did not complete 12 weeks of therapy (no significant between-treatment difference in the reasons for withdrawal), but endpoint analysis also showed no significant between-treatment differences in efficacy. Changes in CGI scores also indicated no between-treatment differences. Milnacipran recipients responded sooner than fluoxetine-treated patients, with milnacipran recipients having significantly lower HDRS and MADRS scores at 4 weeks according to the per protocol analysis (but not intent-to-treat analysis for change in HDRS score). ⁷²
However, milnacipran 100 mg/day, given as a single dose each evening, (n = 97) was not as effective as fluoxetine 20 mg/day (n = 93) after 6 weeks in outpatients with major depressive disorder enrolled in another double-blind multicentre comparison. Indeed, MADRS, HDRS, CGI severity of illness and efficacy index scores were all improved to a significantly greater extent with fluoxetine than with milnacipran (p ≤0.01) and more fluoxetine recipients responded to treatment (≥50% decrease in MADRS score; p = 0.03 at 2 weeks and p = 0.009 at 6 weeks). However, the proportion of milnacipran-treated patients who responded to treatment (40%) was lower than that seen in several other trials of the drug, possibly because the unusual dosage regimen was suboptimal [milnacipran has a short half-life and no active metabolites. A 4-week trial comparing milnacipran with fluvoxamine in inpatients with major depressive disorder also evaluated an uncommon dosage regimen for the drug. 41 patients received a loading dosage of milnacipran 150mg twice daily for 2 weeks then 75mg twice daily, 42 patients received milnacipran 100mg twice daily and 37 received fluvoxamine 100mg twice daily. No significant differences in MADRS, HDRS or CGI scores or in the number of patients who responded to therapy were noted at any time between the 2 milnacipran regimens or between milnacipran and fluvoxamine therapy. These results suggest that a loading dose of milnacipran is not required. Milnacipran 50mg twice daily (n = 57) produced a greater reduction in MADRS scores than fluvoxamine 100mg twice daily (n = 56) [64% vs 46% reduction; p < 0.01] in another trial, although the difference in changes in HDRS scores was not significant (62% vs 50% reduction). 68% of milnacipran and 52% of fluvoxamine recipients responded to therapy according to changes in MADRS score (it was not specified whether in- or outpatients were enrolled). [72]

Analysis of pooled data from the 2 studies comparing milnacipran 50mg twice daily (n = 150) with fluoxetine 20 mg/day or fluvoxamine twice daily (total n = 156) indicated that milnacipran results were significantly better than those for the 2 SSRIs: pooled decreases in HDRS (15 vs 12 points) and MADRS (19 vs 15 points) scores and pooled responder numbers (64% vs 50% HDRS responders and 67% vs 51% MADRS responders) were significantly greater with milnacipran. [72]
3.2 Duloxetine

Duloxetine [LY248686, (+)-N-methyl-γ-(1-naphthalenyl-oxy)-3(2-thiopene)-propanamine] is a new antidepressant drug.\(^{[73]}\)

3.2.1 Pharmacodynamic Properties

Duloxetine is an inhibitor of neuronal reuptake of both serotonin (5-HT) and norepinephrine (NE). Other antidepressants (eg, tertiary amine tricyclic agents such as imipramine, amitriptyline, and venlafaxine) are also considered dual reuptake inhibitors. These drugs, in this regard, differ from SSRIs. Tertiary amine TCAs, such as amitriptyline and imipramine, however, are metabolized to secondary amines that are much more selective as NE reuptake inhibitors. Therefore, in practice, the TCAs exert actions more consistent with drugs that are predominantly inhibitors of NE reuptake.\(^{[73]}\)

The potency of duloxetine as a 5-HT and NE reuptake inhibitor has been assessed in vivo, ex vivo, and in vitro and compared with the potency of venlafaxine. Both drugs inhibit binding of radio ligands to transporters for these monoamines in a dose-dependent fashion. Duloxetine has a higher affinity than venlafaxine for human and rat 5-HT and NE transporters in vitro. In vivo, using rat models of toxin induced depletion of monoamines, duloxetine was 2.5 and 7.8 times more potent than venlafaxine at preventing depletion of 5-HT and NE, respectively. The 5-HT/NE selectivity ratio for duloxetine inhibition of human transporters in vitro is 9.4, while the ratio is 30 for venlafaxine. This ratio for ex vivo transporter binding is 23 with duloxetine and 27 with venlafaxine; for in vivo prevention of toxin-induced monoamine depletion, duloxetine is 5 times more selective for 5-HT than for NE and venlafaxine is 16 times more selective.\(^{[73]}\)

Selectivity of antidepressant drugs for monoamine reuptake has been defined as a ten-fold difference in potency based on Ki’s. In comparison, SSRIs such as sertraline and fluoxetine have 5-HT/NE selectivity ratios of greater than 10. Therefore, duloxetine can be considered a relatively non-selective inhibitor of the reuptake of both 5-HT and NE (ie, a dual reuptake inhibitor).\(^{[74]}\)
Duloxetine, like venlafaxine and SSRIs, has a low affinity for muscarinic, dopamine D₂, α₁-adrenergic, α₂-adrenergic, and histamine H₁/H₂ receptors. Both duloxetine and venlafaxine also have low affinities for various adenosine, α-adrenergic, β-adrenergic, GABA, glutamate, calcium channel, choline, cholecystokinin, neurokinin, melatonin, nicotinic, sigma, and opiate transporters or receptors. Neither duloxetine nor venlafaxine inhibits monoamine oxidase type A or B. These low affinities predict that duloxetine is unlikely to cause anticholinergic side effects (eg, dry mouth, constipation secondary to muscarinic receptor antagonism), antihistaminic side effects (eg, sedation and weight gain secondary to H₁ receptor antagonism), and orthostasis (secondary to α₁-adrenergic antagonism) that commonly occur with tricyclic antidepressants. [73]

Studies of duloxetine in normal human volunteers assessed 5-HT and NE reuptake blockade. Whole blood 5-HT concentrations were measured to evaluate 5-HT reuptake blockade. Urinary excretion of NE and its metabolites and presser responses to intravenous tyramine infusion were used to assess NE reuptake blockade. One study compared the effects of duloxetine 80 mg/day and 120 mg/day with the NE reuptake inhibitor, desipramine 100 mg/day, and placebo. Duloxetine at both doses decreased whole blood 5-HT concentrations, indicating inhibition of 5-HT reuptake; desipramine did not deplete whole blood 5-HT. [75]

No data is available to determine whether there was a dose relationship with respect to 5-HT reuptake blockade. Both duloxetine and desipramine decreased urinary excretion of NE and its metabolites, but only desipramine significantly increased the dose of tyramine needed to increase systolic blood pressure by 30 mmHg. Another study compared duloxetine 20 mg/day, 40 mg/day, and 60 mg/day with placebo and the relatively non-selective NE and 5-HT reuptake inhibitor, clomipramine 100 mg/day. Duloxetine, at all doses, and clomipramine significantly decreased whole blood 5-HT concentrations. Only clomipramine significantly reduced the presser response to intravenous administration of either 4 mg or 6 mg of tyramine. [75]

Urinary excretion of NE and its metabolites was not assessed in this study. However, supine and standing plasma concentrations of NE were measured, as well as systolic and diastolic
blood pressures and pulse rates. Neither drug increased NE plasma concentrations on standing. High dose duloxetine (60 mg/day) did increase supine systolic blood pressure by 7 mmHg, but there was no significant change in pulse rates with any duloxetine dose. The reason for the lack of interference with the tyramine presser response by duloxetine in these studies is unclear, although the authors of the second study hypothesized that 60 mg/day of duloxetine may represent a threshold dose at which NE reuptake blockade begins. The authors in both of these studies also pointed out the possibility that interference with the presser response to tyramine may not be a valid test of NE reuptake blockade.[75]

On the basis of these studies in animal preparations and in human volunteers, it appears that duloxetine potentially has significant potency as a reuptake blocker for both 5-HT and NE. Its effects on NE reuptake, however, may be less prominent and may not appear until doses of approximately 60 mg/day. This pattern of effects may be consistent with receptor affinity data indicating an approximately 5 to 10-fold greater potency for 5-HT reuptake blockade.[75]

3.2.2 Pharmacokinetic Properties

The pharmacokinetics of duloxetine has been evaluated in human volunteers. Pharmacokinetic parameters are best characterized by a one compartment open model with plasma concentrations changing in a linear fashion with respect to dose. [76]

The pharmacokinetics of a multiple-dose regimen of orally administered duloxetine were evaluated in a study in 12 healthy men, 8 receiving duloxetine and 4 receiving placebo. Subjects had a mean age of 39.3 years (range, 22-53 years) and a mean weight of 74.3 kg (range, 61.7-88.9 kg). The active-treatment group received duloxetine at escalating doses of 20 mg BID for 7 days, 30 mg BID for 7 days, and finally 40 mg BID for 7 days. Duloxetine displayed linear kinetics across the studied dosage range and was characterized by a one compartment model with a first-order elimination rate constant. [77]
Duloxetine is acid labile at pH below 2. For this reason, investigational dosage forms have been enteric-coated formulations. The time ($T_{\text{max}}$) to achieve maximum plasma concentrations is 4 to 6 hours. Administration with food or at bed-time delays $T_{\text{max}}$ by 4 hours. Food does not affect ultimate peak plasma concentrations ($C_{\text{max}}$) of duloxetine, but bedtime administration decreases $C_{\text{max}}$ by 28.7%. Bedtime administration also results in a 17.8% reduction in area-under-the-curve. Administration of the enteric-coated dosage form of duloxetine with either an antacid or a histamine-2 ($H_2$) antagonist had no effect on the pharmacokinetics of the drug. Administration of 50 Gm of activated charcoal 2 hours after duloxetine dosing reduced $C_{\text{max}}$ by approximately 33% and area-under-the-curve by approximately 35%. [76]

Duloxetine is highly protein bound (> 95%). The drug is extensively metabolized. It is at least partly demethylated to an active metabolite. There is considerable interindividual variability in the pharmacokinetic parameters for duloxetine, probably because of its extensive biotransformation. [76]

The mean oral clearance of duloxetine is 114 L/h (range: 44 to 218 L/h), the mean apparent volume of distribution is 1943 L (range: 803 to 3531 L), and the mean half-life is 12.5 hours (range: 9.2 to 19.1 hours). Steady-state plasma concentrations are achieved within 3 to 5 days. [76]

Plasma concentrations of duloxetine do not correlate well with the degree of 5-HT reuptake blockade. This may occur because the reuptake blockade produced by the drug is long lasting and does not acutely fluctuate with plasma concentration. It does appear that maintenance of trough plasma concentrations of duloxetine above 5 ng/mL predicts sustained inhibition of 5-HT reuptake. [76]

The pharmacokinetic and metabolite profiles of duloxetine were assessed in 4 fasted, healthy subjects who were administered a single 20-mg oral dose of radiolabeled duloxetine. Subjects were primarily male (n = 3) and ranged in age from 44 to 48 years. Duloxetine was found to undergo phase I metabolic oxidation, with subsequent phase
II glucuronidation and sulfonation. Phase I oxidation of duloxetine is carried out by the cytochrome P450 (CYP) enzyme system, with CYP2D6 and CYP1A2 identified as the primary CYP isozymes responsible for the oxidation of duloxetine to its major metabolites. The primary metabolite observed in plasma was the glucuronide conjugate of 4-hydroxy duloxetine. Conjugated forms of 4,6-dihydroxy duloxetine, 5-hydroxy-6-methoxy duloxetine and 6-hydroxy-5-methoxy duloxetine were also identified in plasma. The intermediate unconjugated metabolites were not present in plasma to an appreciable extent, leading to the conclusion that conjugation of oxidized duloxetine metabolites occurs rapidly.\(^{[77]}\)

The conjugated metabolites of duloxetine have been reported to lack significant affinity for the 5-HT, NE, or dopamine transporter and are considered in-active metabolites. Elimination is primarily renal, with 72% excreted in the urine and 19% excreted in the feces. Biliary excretion is thought to be the main cause for the proportion of drug eliminated in the feces.\(^{[78]}\)

### 3.2.2.1 Special Populations

Skinner et al conducted 2 studies in women to evaluate the effects of age and sex on the pharmacokinetics of duloxetine. In the first study, 12 healthy women aged 32 to 50 years and 12 healthy women aged 65 to 77 years were administered a single dose of duloxetine 40 mg. No statistically significant differences in Cmax, AUC, or apparent clearance were observed between the 2 groups. The older women did show a statistically significant decrease in the elimination rate constant, but there was no significant difference in clearance. The second study involved pooled data from 2 Phase II trials of duloxetine in the treatment of stress urinary incontinence. The pooled analysis included 821 plasma samples from 198 women aged between 24 and 77 years. Population pharmacokinetic analyses were performed to assess the effects of a variety of covariates. Age was found to be a statistically significant covariate affecting apparent clearance; however, this effect was found to account for only -3% of the interindividual variability in apparent clearance. These investigators concluded that dose adjustment was not necessary based on age when using duloxetine in an elderly female population.\(^{[79]}\)
An open-label study compared the pharmacokinetic parameters of duloxetine in 6 patients having Child-Pugh class B hepatic cirrhosis with those in age- and sex-matched healthy subjects. The cirrhotic patients had a lower apparent clearance compared with the healthy patients (24 vs 160 L/h) and an increased elimination $t_{1/2}$ (47.8 vs 13.5 hours). Use of duloxetine in patients with hepatic insufficiency is not recommended. \[80\]

3.2.3 Therapeutic Efficacy

3.2.3.1 Double-blind placebo-controlled studies

The efficacy of duloxetine in the treatment of major depressive disorder was evaluated in a multicenter, double-blind, placebo-controlled study of 173 patients. Inclusion criteria for this study were: age 18 to 65 years; a diagnosis of nonpsychotic major depressive disorder based on DSM-IV criteria; a rating of 4 or greater (moderate) on the Clinical Global Impression-Severity of Illness (CGI-S) scale; and a score of 15 or greater on the 17-item Hamilton Depression Rating Scale (HAM-D-17). Patients were excluded from the study if they had an Axis I diagnosis other than major depressive disorder or any anxiety disorder (other than phobias) within the past year, had a history of substance abuse or dependence within the past year, had a positive urine screen for drugs of abuse, or had failed two or more previous courses of adequate antidepressant therapy for the current episode of depression. At the beginning of the study there was a double blind placebo lead in where neither investigators nor patients knew when randomization occurred or when active study drug was first administered. The study also included a double-blind placebo lead-out and a 1-week follow-up period while patients were off all study medications to assess potential discontinuation-emergent events. Patients were randomly assigned to 8 weeks of treatment with duloxetine, fluoxetine, or placebo in a 2:1:2 ratio. The fluoxetine arm was intended to be an internal control rather than an active drug comparator. The initial dose of duloxetine was 20 mg daily (10 mg twice daily). There was forced titration of the duloxetine doses at weekly intervals up to 120 mg/day (60 mg twice daily) at 3 weeks. The dose of fluoxetine was 20 mg once daily. All patients received four capsules every morning and three capsules every evening in order to maintain blinding. The primary efficacy endpoint for the study was improvement in the HAM-D-17 score. Secondary endpoints were improvements in scores on
At the end of 8 weeks, the mean change in HAMD-17 scores for all patients was significantly greater (P = 0.009) for the duloxetine group (−9.73) than for the placebo group (−6.61). Analysis of the results after excluding eight patients who discontinued treatment within the first week following randomization indicated that the significant difference between duloxetine (−8.58) and placebo (−6.20) remained (P = 0.012). Improvement with duloxetine also differed significantly from that with placebo at week 4 (P = 0.049). When mean changes in HAMD-17 total scores at 8 weeks were compared for patients with a baseline score of less than 19 those with baseline scores of 19 or greater indicating more severe depression, there was a numerically greater decrease for all treatments, but this difference was not statistically significant. Response rates, calculated using the last observation carried forward (LOCF), were 49% with duloxetine (P = 0.167 vs placebo), 45% with fluoxetine (P = 0.393 vs placebo), and 36% with placebo after 8 weeks of therapy. Remission rates, using LOCF analysis, were 43% (P = 0.072 vs placebo), 30% (P = 0.815 vs placebo), and 27% for duloxetine, fluoxetine and placebo respectively. The estimated probability of remission was 56% (P = 0.02 vs placebo) with duloxetine, 30% with fluoxetine, and 32% with placebo. Duloxetine therapy produced improvements in most secondary endpoints (MADRS, CGI-S, CGI-I, PGI, and HAMD-17 subscales for Anxiety, Core Factor, Retardation, and Maier) over placebo therapy. Duloxetine did not produce changes significantly different from placebo on the HAM-A or on the HAM-D-17 sleep subscale. On the HAM-D-17 anxiety subscale, improvement with duloxetine was greater than with fluoxetine (P = 0.041). When changes with duloxetine and fluoxetine treatment were compared on other primary and secondary endpoints, duloxetine was numerically superior, although differences did not reach statistical significance. Importantly, this study was statistically powered at 65% for detection of a difference between duloxetine and placebo in changes on HAMD-17 and it was
underpowered with respect to differences attributable to fluoxetine. Therefore, firm conclusions cannot be drawn regarding comparisons between fluoxetine and duloxetine.\cite{82}

Another multicenter randomized, double-blind, parallel-group, placebo-controlled study enrolling 245 patients with major depressive disorder used similar inclusion and exclusion criteria. Patients in this study, however, could be older than 65 years of age; patients with psychotic major depressive disorder were not specifically excluded; patients’ CGI-S scores were required to be 4 or above on the first two visits in this study (as opposed to only the first visit in the first trial); patients with any anxiety disorder as a primary diagnosis during the preceding year were excluded from this trial (the previously described study permitted patients to have specific phobias); and this study specifically excluded patients with serious medical illness or those who had started or stopped psychotherapy within 6 weeks before enrollment or who initiated psychotherapy during the study (these criteria were not specifically addressed in the first study). All patients received a placebo lead-in prior to starting the active drug portion of the study and a placebo lead-out period after the active treatment phase. Placebo periods were of variable length in order to blind patients and investigators to the beginning and end of active treatment. Patients who completed this phase of the study were randomly assigned to treatment with duloxetine 60 mg or placebo at a 1:1 ratio. The study medication was given as three capsules (placebo or duloxetine 20 mg per capsule) once daily in the morning for 9 weeks. During the first few weeks, the dose could be decreased by one capsule if necessary, but was escalated back to three capsules after three weeks on study drug. Doses of either placebo or duloxetine were required to remain at 3 capsules daily for the majority of the study. Patients were allowed to use chloral hydrate (up to 1000 mg/day) or zolpidem (up to 10 mg) for insomnia for no more than 6 nights during the study. The primary end-point was an improvement in the HAM-D-17 total score and the secondary endpoints were improvements in the CGI-S, visual analog scales for pain (VAS), PGI-I, and Quality of Life in Depression Scale (QLDS). The safety analysis was based on the intent-to-treat cohort (n = 245) and the efficacy analysis was based on those patients with at least one post-randomization visit (n = 236; 115 patients treated with placebo and 121 patients treated with duloxetine).\cite{82}
At week 2, duloxetine treatment produced significantly greater improvement in HAM-D-17 total scores compared to placebo (P < 0.001); this significant difference was maintained through week 9. The response rates, calculated using LOCF analysis, were 45% with duloxetine therapy and 23% with placebo therapy (P < 0.001) after 9 weeks of therapy. Rates of remission, using LOCF analysis, were 31% with duloxetine and 15% with placebo (P < 0.003). The estimated probability of remission with duloxetine was 44% compared to 16% with placebo (P < 0.001), while the estimated probabilities of response were 62% with duloxetine and 29% with placebo (P < 0.001). In addition, improvements in all secondary endpoints were observed with duloxetine therapy, and these improvements were significantly greater than those observed in placebo-treated patients. This study was statistically powered at approximately 80%. [82]

Thus, the results do appear to demonstrate a significant difference between placebo treatment and duloxetine treatment. [82]

Onset of antidepressant effects with duloxetine treatment has been reported to occur as early as 1 week following initiation of therapy. Analysis of data pooled from two 9-week, double-blind, placebo-controlled, randomized studies that evaluated 512 patients with major depressive disorder showed that depressed mood and psychic anxiety (items 1 and 10 on the HAM-D-17) were significantly improved after 1 week of treatment at 60 mg/day. Other items on the HAM-D-17 were improved by week 2. Improvement in symptoms at week 1 was also noted on the CGI-S scale and on the PGI-I scale. This preliminary finding of a potential early onset of antidepressant effect, if confirmed by other studies, may represent a potential advantage of duloxetine over other current antidepressant drugs. [82]

### 3.2.3.2 Open-Label Studies

A multicenter open-labeled study was conducted in Belgium, France, the Netherlands, South Africa, and the United Kingdom. Patients met criteria for major depressive disorder according to DSM-III-R, had HAM-D-17 scores of 18 or greater, and were between 18 and 65 years of age. Both inpatients and outpatients were included. Patients were excluded from the study if they were a serious suicidal risk; had a clinically important physical illness,
schizophrenia, or other psychotic disorders; or had electroconvulsive therapy within 3 months before enrollment were also excluded. All patients received placebo during a single-blind treatment phase (n = 93). If the HAM-D-17 total score was improved by more than 20% during this phase, the patient was excluded from the study. Eighty patients entered the second phase of the study where patients were treated with duloxetine 20 mg once daily for 6 weeks. Concurrent use of other psychotropic agents (antidepressants, lithium, carbamazepine, or L-tryptophan) or adrenergic receptor agonists or antagonists (other than inhaled-beta-1 agonists for asthma) was not allowed. Short-acting benzodiazepines were allowed for the treatment of anxiety or agitation during the study. Chloral hydrate or temazepam could be used for the treatment of insomnia. If patients experienced pronounced side effects during the duloxetine therapy, the dose could be decreased to 10 mg/day. Only four patients (5%) required a reduction in dose. Clinical response was classified as a 50% or greater reduction in the HAM-D-17 score and remission was defined as a HAM-D-17 score of 6 or below. Sixty-five patients (81.3%) completed the entire study. Fifteen patients discontinued the study due to lack of efficacy (five patients), adverse effects (four patients), lost to follow-up (three patients), or for other reasons (three patients). Two patients who began the second phase of the study had no post-baseline data recorded. Therefore seventy-eight patients were included in the LOCF analysis and 65 patients included in the analysis of only those patients who completed 6 weeks of therapy. The mean HAM-D-17 score at baseline was 24.9. The mean HAM-D-17 score decreased to 7 in those patients completing 6 weeks of therapy and 8.5 in the LOCF analysis. The mean MADRS score at baseline was 32.7. It decreased to 9.7 in those patients completing 6 weeks of therapy and 11.3 in the LOCF analysis. The mean CGI-S score decreased from 4.6 to 1.9 in those patients completing 6 weeks of therapy and 2.1 in the LOCF analysis. Response occurred in 78.2% of the patients and remission occurred in 60.3%. [83]

An additional open-label, multinational study evaluated duloxetine therapy for 1 year in 1,279 patients with major depressive disorder. At doses of either 80 mg/day or 120 mg/day, 79% of patients achieved response and 69% achieved remission of their depressive symptoms. [83]
3.2.3.3 Comparisons with SSRIs

3.2.3.3.1 Paroxetine, Fluoxetine

The primary aim of the eight acute-phase registration studies was to compare the efficacy of duloxetine with that of placebo; individually, none of the six trials that included an SSRI treatment arm (paroxetine or fluoxetine) were designed or powered to detect a difference between (or compare) the active treatments. \[81, 82, 84-87\]

No significant between-group differences were reported with regard to the effects of duloxetine 40–120 mg/day and paroxetine 20mg once daily on the primary efficacy measure in three of the four studies. In the fourth trial, paroxetine, unlike duloxetine, was only transiently effective and no longer differed significantly from placebo at week 8, when the improvement on the HAM-D-17 total score was significantly less than that observed with duloxetine at a dosage of 80 mg/day. \[87\]

No significant between-group differences were reported with respect to the effects of duloxetine 40–120 mg/day and fluoxetine 20mg once daily on HAM-D-17 total score in two trials. In pre-planned analyses, the results of paired identical studies were pooled to provide sufficient statistical power to test the non-inferiority of duloxetine at the higher than recommended dosages of 80 and 120 mg/day compared with paroxetine 20mg once daily, using a one-sided 97.5% CI and a non-inferiority margin of $-2.2$ for mean HAM-D-17 total scores. \[87\]

Both duloxetine dosages met the criteria for non-inferiority to paroxetine (on both an ITT and per-protocol basis), using either MMRM or mean change analysis. \[87\]

A similar non-inferiority analysis using data pooled from the two fluoxetine-controlled trials has not been performed. \[87\]

Two paroxetine-controlled trials, incorporated a 26-week continuation phase following the 8-week acute treatment phase. The increase in the time to loss of antidepressant response (median time from the end of acute phase until the first visit [during the continuation
phase] at which the HAM- D-17 total score no longer showed a ≥30% reduction from the acute phase baseline score) in the duloxetine and paroxetine treatment groups relative to that in the placebo group reached statistical significance (p ≤0.018) in one of these studies, but not in the other. This between-study difference in continuation phase outcome may reflect variation in the size of the placebo response; only two (HAM-A total score and PGI-I score) of five (HAM-D-17 total score, MADRS total score, HAM-A total score, CGI-S score and PGI-I score) measures of emotional symptoms and global functioning significantly (p ≤0.05) improved on placebo during the continuation phase (i.e. relative to the last observation in the acute phase) in the former study, compared with all five measures in the latter trial. Duloxetine, like paroxetine, significantly (p ≤0.05) improved all five measures during the continuation phase in both studies. [86, 87]

3.2.3.3.2 Escitalopram

The results of three studies comparing duloxetine administered at fixed or flexible dosages between 60 and 120 mg/day with escitalopram administered at dosages between 10 and 20mg once daily have, in general, been inconsistent. [88-90]

Based on primary endpoint analyses, fixed- dose age duloxetine 60 mg/day was non-inferior to fixed- dosage escitalopram 10 mg/day with respect to onset of antidepressant response in one study, inferior to flexible-dosage escitalopram 10–20 mg/day with respect to short-term antidepressant efficacy in a second trial, and no different to fixed-dosage escitalopram 20 mg/day with respect to long-term antidepressant efficacy in a third investigation. [88-90]

In two instances, the result on the primary out-come was varied depending on the type of efficacy analysis used. Thus, duloxetine 60 mg/day was inferior to escitalopram 10–20 mg/day with regard to the change from baseline to week 8 in MADRS total score when an LOCF analysis was used, but not when an MMRM approach was used (post hoc analysis). Conversely, duloxetine 60 mg/day did not differ from escitalopram 20 mg/day with regard to the change from baseline to week 24 in MADRS total score when an LOCF analysis was used, but escitalopram was superior when an MMRM approach was used (post hoc analysis). [88-90]
Similar to the above, duloxetine 60 mg/day was non-inferior to escitalopram 10 mg/day when onset of antidepressant response was assessed as the primary endpoint using the MMRM approach, but inferior to escitalopram 10 mg/day when this parameter was assessed as a secondary efficacy measure in a post hoc analysis using the LOCF approach.\[88-90\]

Short-term (8 weeks) treatment with escitalopram also demonstrated superiority to duloxetine on other secondary efficacy measures in two trials; these included the MADRS total score, MADRS responder rate and HAM-D 17 total score. In the remaining study, which may have enrolled less severely ill patients, duloxetine demonstrated superiority over escitalopram on the HAM-D-17 Maier subscale at weeks 3 ($p \leq 0.05$) and 6 ($p \leq 0.05$), but not at week 8.\[88-90\]

According to a preliminary report, flexible-dosage duloxetine 60–120 mg/day demonstrated similar antidepressant efficacy to flexible dosage escitalopram 10–20 mg/day during an 8-month treatment period that consisted of an 8-week acute phase and a 6-month extension. Of the 273 (274) patients randomised to fixed-dosage duloxetine 60 mg/day (escitalopram 10 mg/day) at the start of the acute phase, 180 (195) entered the extension. Fifty-nine patients randomised to placebo at the start of the acute phase who met pre-defined rescue criteria were re-allocated to flexible-dose duloxetine ($n = 28$) or escitalopram ($n = 31$) at the start of the extension phase. No further details are available from the abstract report.\[89\]
3.3 Venlafaxine

3.3.1 Pharmacodynamic Properties
Venlafaxine is a phenethylamine bicyclic compound (chemical name: 1-[2-(dimethyl-amino)-1- (4-methoxyphenyl)-ethyl]cyclohexanol hydrochloride). The molecule exists as a racemic mixture of R (+) and S (-) enantiomers in approximately equal proportions. [91, 92]

A series of in vivo and in vitro animal studies provided preclinical evidence that venlafaxine had potential antidepressant properties. In common with classical antidepressants, it suppresses histamine induced ACTH release in rats, and antagonises reserpine-induced hypothermia suggesting an ability to block noradrenaline uptake at sympathetic nerve terminals. It also reduces noradrenergic neuronal firing rates in the rat locus coeruleus. [93]

Many effective antidepressant treatments cause desensitization and down-regulation of β-adrenergic receptors in rodents after repeated administration and this has been correlated with the onset of anti-depressant effect. Venlafaxine causes a reduction of the cyclic AMP response to isoproterenol (2µmol/kg) in the rat pineal gland, an effect that is mediated by the activation of β-adrenergic receptors. The response was reduced by 51 percent after a single injection of venlafaxine (10 mg/kg i.p.), and by 43 per cent after repeated injections (10 mg/kg i.p. twice daily for 5 days). This contrasts with the delayed onset of this effect observed with other antidepressants. Desipramine, which was used as the standard in this study, reduced cAMP responsiveness by 81 percent, but only after repeated administration. The unusual property of venlafaxine to reduce noradrenergic responsiveness after a single dose led to the suggestion that it might have a more rapid onset of clinical effects than other antidepressants. [94, 95]

The antidepressant effects of venlafaxine were studied in animal models of depression. In the behavioral despair (forced swim model), venlafaxine significantly lengthened the time of activity exhibited by mice treated with both 15 and 30 mg/kg s.c. without producing stimulation or sedation. Chronic treatment with venlafaxine markedly increased the aggressive behavior of resident rats that were confronted with an intruder rat, and increased the flight time of the residents. [96, 97]
The ability of a drug to displace $[3^H]$ imipramine from rat brain cortical binding sites \textit{in vitro} has been correlated with its potency to inhibit 5HT reuptake. Although this property is not universal amongst the new generation of antidepressant, it is used as a screening test for the antidepressant potential of a drug. \cite{96, 97} Venlafaxine inhibits $[3^H]$ imipramine noradrenaline and, to a lesser extent, dopamine at the presynaptic membrane. Both the enantiomers of venlafaxine inhibit uptake of noradrenaline and 5HT, but the S enantiomer is relatively more selective for 5HT reuptake inhibition. \cite{98, 99}

Venlafaxine block $[3^H]$ noradrenaline, $[3^H]$ serotonin, and $[3^H]$ dopamine into rat brain synaptosomes by various anti-depressants using the measurement of the inhibitor constants (Ki). Venlafaxine has approximately five times greater potency to inhibit the reuptake of serotonin than noradrenaline. \cite{98, 99}

Venlafaxine has no significant affinity for the rat brain muscarinic cholinergic, $\alpha_1$, $\alpha_2$ or $\beta$-adrenergic receptors, nor does it have appreciable effects at serotonin-1, serotonin-2, dopamine-2, histamine or benzodiazepine or $\mu$-opiate receptors. Venlafaxine is not a monoamine oxidase A or B inhibitor because it does not inhibit the oxidation of $[14^C]$ tryptamine, a non-specific monoamine oxidase substrate. \cite{98, 99}

The potency of an antidepressant to block specific human brain receptors is predictive of certain side effects and drug interactions. The equilibrium dissociation constant ($K_d$) measures the potency of a drug for a specific receptor using radio ligand binding assays and post mortem human brain tissue. In a study designed to compare the binding potencies of 17 antidepressants, including fluoxetine, sertraline and paroxetine, at seven different receptors (muscarinic, histamine $H_1$, $\alpha_1$-adrenergic, $\alpha_2$-adrenergic, $D_2$, 5HT$_{1A}$, 5HT$_2$), most of the newer compounds were shown to have only weak ability to block neurotransmitter receptors. Venlafaxine produced the least blockade of all the drugs tested, with essentially no activity at any of the receptor sites. \cite{100}
3.3.2 Pharmacokinetic Properties

The pharmacokinetic properties of venlafaxine in healthy volunteers and in patients with renal or hepatic dysfunction have been comprehensively reviewed recently.\[^{[101]}\]

3.3.2.1 Absorption and Distribution

The pharmacokinetics of venlafaxine after administration of single or multiple doses of venlafaxine XR 75 and 150mg have been studied in healthy volunteers.\[^{[102]}\]

Venlafaxine XR provides a prolonged duration of absorption compared with the IR formulation, yet with a similar extent of absorption of the drug.\[^{[102]}\]

The absolute bioavailability of venlafaxine XR is approximately 45% in healthy volunteers, and it is not affected by food or the time of administration. Maximum plasma concentrations (C\(_{\text{max}}\)) of venlafaxine and ODV occurred approximately 5.5 and 9 hours (t\(_{\text{max}}\)), respectively, after administration of venlafaxine XR. Venlafaxine IR, on the other hand, has a t\(_{\text{max}}\) of about 2 hours. Steady-state concentrations are reached within 3 days with ongoing administration.\[^{[103, 104]}\]

Proportionality between the dosage of the drug and plasma concentrations of venlafaxine and ODV has previously been demonstrated. Venlafaxine and ODV are minimally bound to plasma proteins (27 and 30%, respectively).\[^{[105]}\]

Both venlafaxine and ODV are excreted in breast milk; the areas under the concentration-time curve (AUCs) were approximately 3- to 5-fold greater in breast milk than those in maternal plasma. Plasma concentrations of the drug are not affected by gender or age.\[^{[106]}\]

3.3.2.2 Metabolism and Elimination

Once absorbed from the gastrointestinal tract, venlafaxine undergoes extensive cytochrome P450 (CYP) 2D6–mediated oxidative metabolism to form the major active metabolite ODV.\[^{[107, 108]}\] In most individuals, plasma concentrations of ODV are approximately 2- to 3- fold higher than those of the parent drug. However, because CYP2D6 metabolism is subject to
genetic polymorphism, venlafaxine concentrations are higher than ODV concentrations in poor metabolisers. \(^{[109,110]}\)

Nevertheless, this phenomenon does not affect therapeutic efficacy as venlafaxine and ODV have similar pharmacological activities. N-desmethyl and N,O-didesmethylvenlafaxine are minor metabolites of venlafaxine with limited pharmacological activity and are generated predominantly by CYP3A3/4 metabolism of venlafaxine. \(^{[92,107]}\)

However, there have been studies that suggest the N-demethylation of venlafaxine could be affected by both CYP3A3/4 and CYP2C19. \(^{[108,109]}\)

The majority (87%) of the administered dose of venlafaxine is eliminated by renal excretion within 48 hours, primarily as unconjugated (29%) or conjugated (26%) ODV or inactive metabolites (27%). \(^{[109]}\)

Only 5 to 7% of the dose is excreted as unchanged parent drug. The terminal elimination half-lives \(t_{1/2}\) of venlafaxine and ODV were 5 and 11 hours, respectively, and plasma clearance values at steady state were 1.3 and 0.4 L/h/kg, respectively. \(^{[111]}\)

**3.3.2.3 In Patients with Renal or Hepatic Dysfunction**

Dosage adjustments are recommended in patients with renal or hepatic dysfunction. \(^{[111]}\)

The \(t_{1/2}\) of venlafaxine was prolonged by approximately 50% and plasma clearance was reduced by 24% in patients with mild to moderate renal dysfunction [estimated creatinine clearance \(CL_{CR}\) 10 to 70 ml/min (0.6 to 4.2 L/h)]. In patients undergoing haemodialysis the \(t_{1/2}\) was 2.8-fold greater and clearance was 57% lower than in individuals with normal organ function. \(^{[111]}\)
In patients with hepatic cirrhosis, venlafaxine and ODV $t_{1/2}$ values were prolonged by 30 and 60%, respectively, and plasma clearance of these 2 entities decreased by 50 and 30% compared with individuals with normal hepatic function.\[111\]

### 3.3.3 Therapeutic Efficacy

The therapeutic efficacy of venlafaxine XR in the management of major depression, as defined by DSM-IV or DSM-III-R criteria, has been evaluated in 5 randomised, double-blind, multicenter studies.\[112-114\] In addition, a randomised, double-blind, multicentre study examined the effects of venlafaxine XR on symptoms of anxiety in depressed patients. There has also been a subanalysis of 2 of the trials\[112, 113\] involving patients with major depression, in which the efficacy of venlafaxine XR on symptoms of anxiety was examined.\[115\]

Five of the trials included a placebo group, and the drug’s efficacy was compared with that of venlafaxine IR,\[112\] fluoxetine, and paroxetine.\[114\]

Venlafaxine XR was given once daily at dosages ranging from 75 to 225 mg/day for up to 8 to 24 weeks in flexible dose studies. In these studies, all patients received placebo during a 4- to 10-day lead-in period before double-blind treatment began. A dosage of 75 mg/day was evaluated in a single 12-week fixed dose study.\[112-114\]

In the studies that evaluated the effects of study medication on symptoms of depression, primary outcome measures were the change in scores between baseline and end-point on the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), the Clinical Global Impression Severity of Illness (CGI-S) and Clinical Global Impression Global Improvement (CGI-I) scales, as well as the reduction from baseline in the HAM-D depressed mood item. In the studies investigating symptoms of anxiety in patients with depression, primary outcome measures were changes from baseline scores in the Hamilton Rating Scale for Anxiety (HAM-A), HAM-D psychic anxiety item and the CGI-I scale. All studies enrolled elderly patients (aged $\geq$ 65 years); the age range across the trials was between 18 and 83 years. In all studies, efficacy analyses were performed on a modified
intent-to- treat basis. This included all randomised patients who received ≥ 1 dose of study medication, had ≥ 1 baseline evaluation of one primary efficacy variable, and had ≥ 1 primary efficacy evaluation while receiving treatment. The last observation was carried forward for patients who discontinued treatment prematurely.\textsuperscript{[112-114]}

### 3.3.3.1 Comparisons with Placebo

Venlafaxine XR produced consistent and significant reductions in all primary outcome measures compared with placebo during an 8-week flexible dose study. Treatment was initiated at 5 mg/day and, if the response was inadequate, the dosage could be increased in increments of 75 mg/day every 2 weeks to a maximum of 225 mg/day. The mean dosage from days 29 to 56 ranged from 172 to 177 mg/day. A significant reduction in the CGI-S score was evident after 2 weeks of treatment with venlafaxine XR 75 mg/day, and the HAM-D depressed mood item score was significantly reduced by the beginning of week 3 (p < 0.05 vs placebo). By week 4, venlafaxine XR was significantly more effective than placebo (p < 0.05) at reducing the HAM-D and MADRS total scores.\textsuperscript{[113]}

The greater therapeutic effect of venlafaxine XR compared with placebo was maintained throughout the remainder of the study. By week 8, the change in baseline scores for all primary outcome measures was approximately twice as large in the venlafaxine XR group as in the placebo group.\textsuperscript{[113]}

The HAM-D, MADRS and CGI-I therapeutic response rates, defined as a ≥ 50% reduction in HAM-D and MADRS total scores or a score of 1 or 2 on the CGI-I rating, were significantly greater in recipients of venlafaxine XR than those in the placebo group (p ≤ 0.005) at week 8. Moreover, the HAM-D and CGI-I therapeutic response rates to venlafaxine XR were significantly greater than those to placebo by week 6 (p < 0.05). Sustained response rates, as determined by an improvement in the HAM-D, MADRS and CGI-I scales that, once observed, persisted until the end of treatment, were significantly higher (p < 0.05) with venlafaxine XR (37.2, 34.1 and 40.0%, respectively) than with placebo (18.8, 16.5 and 24.0%).\textsuperscript{[113]}
Remission (defined as a HAM-D score of ≤ 8) was achieved in 35% of patients given venlafaxine XR and 19% of placebo recipients. Furthermore, significantly fewer venlafaxine XR – treated patients than placebo recipients discontinued treatment because of unsatisfactory clinical response (5 vs 22%; p ≤ 0.001). In a second flexible dose study which examined relapse prevention and was reported, 328 patients with major depressive disorder who responded to venlafaxine XR 75 to 225 mg/day during an 8-week, nonblind lead-in period were randomised to continue receiving venlafaxine XR or to be switched to placebo for up to 6 months under double-blind conditions. Cumulative relapse rates ( CGI-S score ≥ 4) were lower for venlafaxine XR–treated patients than for placebo recipients after 3 and 6 months (18.5 and 28.0% vs 43.2 and 52.4%, respectively; p < 0.001 vs placebo). Furthermore, significantly fewer patients treated with venlafaxine XR discontinued treatment because of lack of therapeutic response (24 vs 42%; p < 0.001 vs placebo).[113]

3.3.3.2 Comparisons with Venlafaxine Immediate-Release and Placebo

Venlafaxine XR was significantly more effective than venlafaxine IR or placebo in a 12-week randomised, double-blind, multicentre study.[112]

Among patients randomised to receive venlafaxine XR 75 to 150 mg/day (mean dosage from week 3 to 12 was 124 to 140 mg/day) or venlafaxine IR 75 to 150 mg/day (mean = 115 to 125 mg/day), mean reductions in all primary efficacy variables (HAM-D and MADRS total scores, HAM-D depressed mood item and the CGI-S rating) were significantly greater than those in placebo recipients at week 12. Reductions from baseline in HAM-D total and CGI-S scores were significantly higher among patients treated with venlafaxine XR than venlafaxine IR at week 8 (–13.7 and –1.86 vs –11.1 and –1.38, respectively; p < 0.05). Furthermore, reductions from baseline were significantly greater among recipients of venlafaxine XR for all 4 efficacy variables at week 12 (p < 0.05 vs venlafaxine IR). The mean percentage reduction from baseline at week 12 of the HAM-D, MADRS and CGI-S scores (baseline values for the HAM-D depressed mood item were not reported). Venlafaxine XR and IR both significantly reduced the HAM-D depressed mood item score compared with placebo from week 2 (p < 0.01) to week 12 (p < 0.001). Similarly, reductions in HAM-D total scores were significantly greater among venlafaxine XR- or venlafaxine IR–treated patients
than placebo recipients at week 2 and from week 4 to 12 (p < 0.001 and 0.05 vs placebo, respectively). Reductions in MADRS scores were significantly higher in the active treatment groups than in placebo recipients from weeks 3 to 12 (p < .05).\[112]\n
Response rates based on the HAM-D and MADRS scales were significantly higher in patients treated with venlafaxine XR than in patients treated with venlafaxine IR (p < 0.05) or placebo (p < 0.001) at week 12. Response rates based on CGI-I criteria were significantly higher among recipients of venlafaxine XR than placebo during weeks 3 to 12 (p < 0.01; actual values not reported). Sustained response rates based on the HAM-D and MADRS total scores and the CGI-I scale were significantly higher with venlafaxine XR and venlafaxine IR than with placebo (p < 0.05). [112]\n
Discontinuations because of an unsatisfactory clinical response were significantly higher (p = 0.01) among patients given placebo (12%) than patients given venlafaxine XR (2%) or venlafaxine IR (4%).[112]\n
### 3.3.3.3 Effects on Symptoms of Anxiety in Patients with Depression

The effects of venlafaxine XR on symptoms of anxiety in patients with major depression have been evaluated in a separate analysis [115] of 2 of the trials. [112, 113] Venlafaxine XR was significantly more effective than placebo at reducing symptoms of anxiety in 2 randomised, double-blind, multicentre studies that enrolled patients with depression and associated anxiety.[115] In 1 study, among patients randomised to venlafaxine XR 75 to 150 mg/day or venlafaxine IR 75 to 150 mg/day, mean reductions in the HAM-D psychic anxiety score were significantly greater than those in placebo recipients at week 12. Similarly, in the other study, venlafaxine XR 75 to 225 mg/day produced significant reductions in anxiety in patients with moderate (HAM-D psychic anxiety score ≥ 2 and ≤ 3) or severe (HAM-D psychic anxiety score ≥ 3) anxiety compared with placebo. [115]\n
Response rates in both studies, defined as a reduction in the HAM-D psychic anxiety score to < 2 in patients who had a baseline score ≥ 2, were significantly higher with venlafaxine XR than with placebo. Anxiety developed in 7% of patients who received venlafaxine XR
compared with 19 and 22% of patients given venlafaxine IR or placebo, respectively. There was no significant difference between response rates (based on the HAM-D psychic anxiety item) in patients receiving venlafaxine XR or venlafaxine IR (i.e. 74 vs 67%).[115]

Among patients with severe anxiety, a reduction in anxiety was reported in 88% of patients receiving venlafaxine XR, 78% of patients given venlafaxine IR and 69% of placebo recipients.[115]

A pooled analysis of both studies involving the HAM-D item scores from the anxiety somatisation cluster (psychic anxiety, somatic anxiety, somatic gastrointestinal and somatic general items) showed mean score reductions in patients who received venlafaxine XR were significantly higher than in those receiving placebo (p < 0.001) or venlafaxine IR (p < 0.05) at week 12.[115]

While this sub analysis suggests that venlafaxine XR reduces symptoms of anxiety in depressed patients, well designed trials using symptom-specific instruments, such as the HAM-A, are needed to support these findings.[115]

3.3.3.4 Comparisons with Fluoxetine and Placebo

Venlafaxine XR has been compared with fluoxetine and placebo in patients with major depression in 2 randomised, double-blind, placebo-controlled, multicentre studies.[114,116]

There were no significant differences in mean reductions in HAM-D or HAM-A total scores at end-point (using a last observation carried forward analysis) among patients randomised to venlafaxine XR 75 to 225 mg/day, fluoxetine 20 to 60 mg/day or placebo for 8 weeks. However, whereas venlafaxine XR significantly reduced the MADRS (p = 0.013), CGI-S (p = 0.01) and HAM-D depressed mood (p = 0.002) scores compared with placebo, fluoxetine significantly reduced only the HAM-D depressed mood item compared with placebo (p = 0.044). Significantly more patients treated with venlafaxine XR achieved full remission based on a HAM-D total score of ≤ 7 at end-point p ≤ 0.05 vs fluoxetine or placebo). 37, 22 and
18% of patients treated with venlafaxine XR, fluoxetine or placebo, respectively, achieved full remission. [114]

Venlafaxine XR and fluoxetine demonstrated similar efficacy in reducing symptoms of depression and anxiety in a 12-week randomised, double-blind, multicentre study that enrolled patients with major depression and associated anxiety (patients with a score of ≥ 8 on the Covi scale). Among patients randomised to venlafaxine XR 75 to 225 mg/day or fluoxetine 20 to 60 mg/day, mean reductions in HAM-D total scores were significantly greater than those in placebo recipients from week 2 to week 12. Reductions in HAM-A total scores in patients given venlafaxine XR were significantly greater than those in placebo recipients after 8 weeks (p < 0.05). Among fluoxetine recipients, HAM-A total score reductions were significantly higher than those of patients given placebo at only the final on-therapy evaluation (week 12). [116]

There were also statistically significant improvements in some secondary efficacy parameters. Among patients receiving active treatment, improvements in the anxiety and depression items of the Hospital Anxiety and Depression Scale and the Covi scale were significant (p < 0.05) compared with those in placebo recipients from week 8. Remission rates (based on a HAM-D total score of < 8 at end-point) among patients treated with venlafaxine XR or fluoxetine were similar (46.0 and 45.2%, respectively) and significantly higher than placebo treated patients (24.4%; p < 0.001). However, remission rates among venlafaxine-treated patients were significantly higher than those of placebo recipients from week 3, compared with week 8 among recipients of fluoxetine. The HAM-A response rate to venlafaxine XR, defined as a ≥ 50% reduction in HAM-A total scores, was significantly higher than that to placebo at weeks 3, 8, 12 and the final on-therapy evaluation (p < 0.05). Furthermore, the HAM-A response rate was also significantly higher (p < 0.05) among recipients of venlafaxine XR than fluoxetine at week 12, but not at the final on-therapy evaluation. Discontinuation of venlafaxine XR (5%) or fluoxetine (5%) because of unsatisfactory clinical response occurred significantly less often than that of placebo (24%) throughout the trial. [116]
3.3.3.5 Comparison With Paroxetine

Venlafaxine XR 75 mg/day or paroxetine 20 mg/day demonstrated similar efficacy in patients with major depression. Reductions from baseline in HAM-D and MADRS total scores among patients receiving venlafaxine XR or paroxetine for 12 weeks were significant \( (p \leq 0.05) \), but there were no significant differences between the 2 treatment groups in any of the outcome measures. \[113\]

Similarly, there were no significant between-group differences in response rates based on the HAM-D, MADRS or CGI-I scales, although the proportion of responders was higher among patients receiving venlafaxine XR. \[113\]

Remission (defined as a HAM-D score of < 7) was achieved in 53.7% of patients given venlafaxine XR and 52.2% of paroxetine recipients. \[113\]
3.4 Mirtazapine

Mirtazapine is a racemic mixture of 1,2,3,4,10,14b-hexahydro-2-methylpyrazino-[2,1-a]-pyrido[2,3-c][2]benzazepine, which belongs to the chemical class of compounds known as piperazinoazepines. \[117\]

3.4.1 Pharmacodynamic Properties

The clinical relevance of receptor pharmacology is readily apparent when considering the pharmacodynamic effects of a number of the newer psychotropic drugs. Newer antidepressants with prominent 5-HT₂ receptor antagonist properties demonstrate both anxiolytic and antidepressant activity in animal and clinical studies. \[118\] In addition, the contribution of the postsynaptic 5-HT₃ receptor in the limbic system may be important in states where abnormal dopaminergic tone has been thought to play a role, such as, schizophrenia, mania, substance abuse and emesis. Several newer generation neuroleptics antagonize 5-HT₂ receptors, and newer antiemetics, such as ondansetron, dolasetron and granisetron, block the 5-HT₃ receptor. The clinical implication is that the 5-HT₂ and 5-HT₃ receptor blocking activity of mirtazapine causes a unique therapeutic effect profile when compared with the SSRIs, due to its receptor pharmacology. \[119\]

Mirtazapine has a relatively low affinity for muscarinic and dopaminergic receptors but has a high affinity for histamine- H1 receptors, and 5-HT₂AC and 5-HT₃ receptors. The relatively low affinity of mirtazapine for central post-synaptic and peripheral presynaptic alpha 2-autoreceptors adrenergic and muscarinic receptors, as well as its selective affinity for specific postsynaptic 5-HT₂ and 5-HT₃ serotonergic receptors, may explain its favorable adverse experience profile compared with the TCAs or the SSRIs. Mirtazapine shows rapid improvement in the symptoms of depression, with minimal anticholinergic adverse effects and is not associated with serotonin-related adverse effects, such as nausea, headache, anxiety, agitation, jitteriness or sexual dysfunction. Antagonism of 5-HT₃ receptors provides antiemetic benefit in the management of neuropathic pain and in selected cancer patients. \[120\]
Mirtazapine is a centrally active presynaptic $\alpha_2$ receptor antagonist, with postsynaptic 5-HT$_2$A, C and 5-HT$_3$ antagonist specificity. It preferentially blocks presynaptic $\alpha_2$-auto and heteroreceptors, controlling norepinephrine and serotonin release, respectively. The affinity of mirtazapine for central presynaptic $\alpha_2$-autoreceptors is about ten-fold higher than for central postsynaptic and peripheral presynaptic autoreceptors. Mirtazapine also has a 30-fold higher affinity for central pre-synaptic $\alpha_2$ -autoreceptors compared to central and peripheral $\alpha_1$ adrenoceptors. \[120\]

Mirtazapine enhances norepinephrine release by presynaptic $\alpha_2$ -autoreceptor antagonism of noradrenergic neurons. This inhibits negative feedback on these neurons and facilitates the release of synaptic norepinephrine. \[120\]

Norepinephrine acts on serotonergic cell bodies in a dual manner by increasing the serotonergic dorsal raphe cell firing via $\alpha_1$ -mediated effect, and by inhibiting hippocampal serotonin release via $\alpha_2$mediated effect. Because mirtazapine blocks $\alpha_2$ -heteroreceptors located on the serotonergic neuron terminals, it prevents the inhibitory effect of norepinephrine on serotonin release. \[120\]

Consequently, the activity of serotonin in the central nervous system is enhanced by indirect ($\alpha_1$) adrenoceptor mediated enhancement of serotonergic cell firing, and by direct ($\alpha_2$) blockade of inhibitory $\alpha_2$ heteroreceptors located on serotonergic nerve terminals. The pharmacodynamic effect of serotonin release is specifically mediated postsynaptically via 5-HT$_3$ subtype receptors, because mirtazapine specifically blocks the 5-HT$_2$ and 5-HT$_3$ type receptors, allowing released serotonin to stimulate 5-HT$_3$ receptors.

The $\alpha_2$ auto and $\alpha_2$ heteroreceptor blocking properties and the 5-HT$_2$ type receptor antagonistic effects are present primarily in the (+)-enantiomer of mirtazapine, whereas the $\alpha_2$ heteroreceptor and 5-HT$_3$ type receptor antagonistic activities reside predominantly in the (-)-enantiomer. \[120\]
3.4.1.1 Neurotransmitter studies

Mirtazapine is a very weak inhibitor of the neuronal uptake of norepinephrine, and has no effect on the uptake of dopamine or serotonin. Mirtazapine was about 1000-fold less active than desipramine and 100-fold less active than imipramine in the inhibition of in vitro uptake of norepinephrine. Neurotransmitter studies of serotonergic receptor interactions show that mirtazapine has a relatively selective affinity for serotonergic receptors. Mirtazapine has a relatively low affinity for receptor subtypes 5-HT_{1A,B,D} (pKi≈5.0), and a relatively high affinity for 5-HT_{2A,B,C} (pKi≈8.0) and 5-HT_3 (pKi≈58.0). This reflects approximately a 1000-fold difference in the binding of mirtazapine to the 5-HT receptor subtypes.\(^{120}\)

3.4.2 Pharmacokinetic Properties

3.4.2.1 Absorption

Mirtazapine is well absorbed from the gastrointestinal tract following oral administration, and the bioavailability of mirtazapine does not appear to be affected by the presence of food in the stomach. The absolute bioavailability of mirtazapine was assessed in eight healthy male volunteers. An intravenous 3.5 mg \([^{13}\text{C}]\)-mirtazapine dose was administered as an infusion at a constant rate over 1 h concomitantly with a single 15 mg, non-labeled, oral dose. The absolute bioavailability (F) upon single dosing was 49.7±9.8%, which was similar to the steady-state oral bioavailability (47.8±6.9%) during the administration of multiple oral 15-mg doses for seven days. Mean (±SD) peak plasma levels were reached in 1.86±0.7 h after a single oral dose and 1.5±0.7 h at steady state. Peak plasma concentrations were 31.6±12.8 and 41.8±7.7 ng / ml after single and multiple oral doses, respectively. The mean steady-state trough concentration was 4.2±1.5 ng / ml, and the peak-to-trough ratio was 10.6±5.2. The half-life of mirtazapine was 16.3±4.6 h following a single dose, and 16.7±5.0 h following multiple dosing. Area-under-the-concentration-curve (AUC) was 215.8±46.5 ng/ml*h after a single dose and 252.3±48.2 ng/ml*h after multiple dosing.\(^{121}\)

The dose-proportionality of mirtazapine at steady state was studied in 27 healthy, young male subjects administered single, daily oral doses of 15, 30, 45, 60 and 75 mg. Serial blood
samples were taken on the fifth day of dosing at each dosage level. Steady state was achieved on the fifth day of each treatment period, and the pharmacokinetics of mirtazapine after the oral administration of mirtazapine tablets were found to be linear within the dose range studied.\textsuperscript{[121]}

Mirtazapine showed dose-proportionality over the range of 15 to 75 mg and the mean (±SD) Cmax values were 39±12 and 181±44 ng / ml, respectively.\textsuperscript{[121]}

### 3.4.2.2 Distribution
Mirtazapine is approximately 85% bound to plasma proteins over a concentration range of 0.01 to 10 mcg / ml. The central volume of distribution was 107±42 l during 11 days of multiple dosing and the steady-state total volume of distribution was 339±125 l / kg, or an average of 4.5 l / kg of body weight.\textsuperscript{[121]}

### 3.4.2.3 Metabolism
Mirtazapine is extensively metabolized in the liver. Major pathways of biotransformation are demethylation and hydroxylation, followed by glucuronide conjugation. The main unconjugated metabolites are the demethylated and the oxygenated products (N-desmethylmirtazapine and 8-hydroxy-mirtazapine, respectively. The unconjugated dimethyl metabolite is pharmacologically less active than the parent compound, and it is present in lower serum concentrations in depressed patients than the parent compound. Mirtazapine lacks both auto-induction and auto-inhibition of hepatic isoenzymes (cytochrome P450). Mirtazapine is a substrate for the P450 isoenzymes 1A2, 2D6 and 3A4, but \textit{in vitro} studies show that it is not a potent inhibitor of any of these enzymes. It is a competitive inhibitor of CYP2D6, but to a much lesser extent than fluoxetine. \textsuperscript{[122]}

### 3.4.2.4 Elimination and clearance
Mirtazapine and its metabolites are eliminated predominantly in the urine (up to 75%) and feces (up to 15%), with 90% to 100% of the elimination occurring within the first three to four days. The elimination half-life of mirtazapine after oral administration ranges from 20 to 40 h, and women of all ages exhibited significantly longer elimination half-lives than men.
(37 h, women vs. 26 h, men). The mean $C_{\text{max}}$ was found to be slightly lower in young males than in young females or in elderly patients of either gender. However, the observed pharmacokinetic differences do not justify a dosage adjustment based on gender.\textsuperscript{[121]}

There was no change in the plasma clearance of mirtazapine between Day 1 and Day 12 during multiple oral dosing, and the mean (±SD) plasma clearance of mirtazapine was $38.3±4.8$ l / h after Day 1 and $31.2±4.3$ l / h after Day 12.\textsuperscript{[121]}

Preliminary data suggest that mirtazapine clearance may be altered in the presence of hepatic or renal impairment. The elimination half-life of mirtazapine was found to be increased by 40% in hepatically impaired subjects compared to patients with normal hepatic function. This effect on elimination resulted in a 57% increase in AUC and a 33% decrease in clearance. Subjects with moderate (GFR 11–39 ml / min / l.73 m$^2$) to severe (GFR ≤ 10 ml / min / l.73 m$^2$) renal impairment showed a significant increase in AUC and consequent decrease in the clearance of mirtazapine ($≈30$ to $50\%$, respectively). However, renal impairment has not been shown to have a significant effect on the elimination half-life of this drug. Elderly subjects had a significantly larger AUC than younger subjects, however, there were no differences in efficacy or incidence of adverse experiences between elderly and younger adult populations.\textsuperscript{[121]}
3.4.3 Therapeutic Efficacy

The efficacy of oral mirtazapine in adults with major depression has been demonstrated in a number of randomized, double-blind, placebo or active-controlled trials of 4-8 weeks' duration, enrolling >100 patients. Patients meeting DSM-III, DSM-III-R or DSM-IV criteria for major depression were included. Patients had depression that was moderate (e.g. Hamilton Depression Rating Scale [HAM-D] score 18-24) or severe (e.g. HAM-D score >25). Most studies included a 3- to 7-day placebo washout period and patients who had a >25% decrease in HAM-D score during this period were excluded.\[123\]

In most trials, the dosage of mirtazapine was titrated according to response; initial dosages were 5-20 mg/day and maximum dosages were 35-80 mg/day (except for one trial that used dosages of 40-100 mg/day). Mirtazapine was taken orally once daily at night-time.\[123\]

The primary efficacy measure was generally the 17-item HAM-D or the Montgomery-Asberg Depression Rating Scale (MADRS). Response was usually defined as a >50% decrease from baseline in HAM-D (or MADRS) score; remission was defined as HAM-D score <7 (or MADRS score <12) at study end; and in long term studies, relapse was defined as HAM-D score >16. Most analyses were performed on an intent-to-treat (ITT) basis and included all randomized patients who received > 1 dose of study medication and had >1 post-baseline assessment. Most trials indicated that the last observation carried forward (LOCF) method was used for the endpoint analysis.\[123\]

3.4.3.1 Comparisons with Placebo

Mirtazapine was significantly more effective than placebo at treating moderate to severe major depression in a number of trials of 5-6 weeks' duration. Meta-analyses that included published and unpublished placebo-controlled trials have confirmed the antidepressant efficacy of mirtazapine. In the largest analysis (n = 495), mirtazapine was associated with significantly (p< 0.0001) greater improvements in HAM-D score than placebo from week 1 through to study end, and a significantly higher proportion of responders at study end (62% vs 45%; p<0.05).\[118, 124-126\]
One meta-analysis focused on depression specific terms within HAM-D, and found that mirtazapine had a significantly greater effect than placebo on the HAM-D 6-item depression factor (as well as the full 17-item HAM-D), and that significant between-group differences were apparent in the HAM-D item of depressed mood from week 1 onwards (p<0.05).[126]

In addition, another meta-analysis (n=1853) demonstrated that, including patients who were a suicide risk at baseline, treatment with mirtazapine significantly reduced the risk of suicide compared with placebo, as assessed by a surrogate endpoint, the combined suicide item scores from HAM-D and MADRS (odds ratio [OR] 0.68; 95% CI 0.52, 0.88). Patients who were not a suicide risk at baseline, mirtazapine significantly reduced the HAM-D suicide item score (OR 0.38; 95% CI 0.21, 0.66), with the difference apparent from week 2 of treatment; however, there was no significant reduction in risk when assessed using the MADRS suicide item score.[127]

A 1-year study showed that mirtazapine was effective at preventing relapse during long-term treatment. In this trial, patients who were in remission (defined as HAM-D score <7 and Clinical Global Impression [CGI] scale scored as 'much' or 'very much' improved, sustained for >2 weeks) after 8-12 weeks' treatment with mirtazapine were randomly assigned to receive mirtazapine (n = 76) or placebo (n = 80) in double-blind fashion for 40 weeks. The relapse rate (based on the physician's assessment of the need for alternative treatment) was significantly lower in the mirtazapine group than the placebo group (19.7% vs 43.8%; p=0.001). The outcome was similar if relapse was defined as HAM-D score >18, HAM-D score >15 on two consecutive visits or the occurrence of suicide/suicide attempt. [128]

The efficacy of mirtazapine has been evaluated in Japanese patients with depression in short- and long-term studies. In a 6-week, randomized, double-blind, placebo-controlled trial (reported as an abstract), mirtazapine 30 mg/day was associated with a significantly greater improvement' from baseline to week 6 in total HAM-D score than placebo (-13.8 vs -10.4; p<0.01). Improvement in HAM-D scores was significantly greater with mirtazapine than placebo at all-time points form week 1 to 6, indicating a rapid and stable response.
Mirtazapine dosages of 15, 30 and 45 mg/day were evaluated in the study and the dose-response curve was deemed to be flat. In the fully published long-term study, patients who had completed a 6-week double-blind, placebo-controlled trial of mirtazapine and who had shown improvement in CGI continued receiving open-label mirtazapine for a total of 52 weeks.\textsuperscript{[128]}

Among 107 patients who were evaluable for efficacy, mean HAM-D scores were consistently <7 from week 8 to week 52, approximately 8% of patients discontinued mirtazapine because of worsening symptoms during this period. Among 72 patients who completed the 1-year study, the HAM-D remission rate was 85%.\textsuperscript{[128]}

3.4.3.2 Comparisons with Tricyclic Antidepressants

In short-term trials in patients with moderate to severe major depression, mirtazapine generally showed similar antidepressant efficacy to TCAs and trazodone when assessed using HAM-D or MADRS. The proportion of patients classified as HAM-D responders in comparisons with amitriptyline ranged from 53% to 72% with mirtazapine and from 48% to 72% with amitriptyline. In comparisons with trazodone, HAM-D response rates were 51-61% with mirtazapine and 41-51% with trazodone.\textsuperscript{[129]}

Meta-analyses confirmed that the efficacy of mirtazapine was similar to that of amitriptyline in the short term, In a long-term, double-blind continuation study, in which patients who had responded to treatment in a 6-week study continued on the same treatment for up to 2 years. The sustained remission rate at endpoint was significantly higher among recipients of mirtazapine <3 5 mg/day (n = 74) than patients treated with amitriptyline <280 mg/day (n = 86) \[77\% vs 57\%;p = 0.008\]. Both mirtazapine and amitriptyline were significantly more effective than placebo at reducing the rate of relapse during the first 20 weeks of the continuation phase and also at endpoint \(p<0.01\), but the time to relapse was significantly longer with mirtazapine than amitriptyline during the first 20 weeks \(p = 0.037\).\textsuperscript{[130]}

In one of the two comparisons with trazodone, mirtazapine led to a significantly greater reduction in HAM-D score and higher responder rate than trazodone at the weekly
assessment on day 42 (18 vs 16 points and 78% vs 61%; both p<0.05), although the between-group differences at endpoint (using LOCF) did not reach statistical significance. [129]

In a follow-on phase of the comparative fixed-blood concentration trial with imipramine 57 nonresponders had lithium added to ongoing double-blind treatment with mirtazapine or imipramine, and efficacy was assessed 2 weeks after target blood lithium concentration (0.5-1.0 mmol/L) was achieved. Based on data from both phases of the study, the proportion of patients achieving a MADRS response (primary variable for this analysis) was lower among those treated with mirtazapine ± lithium than those who received imipramine ± lithium (48% vs 64%; p-value not stated), with survival analysis confirming the between-group difference (p = 0.04). The efficacy of the combination strategies was not assessed separately.[131]

3.4.3.3 Comparisons with Selective Serotonin Reuptake Inhibitors
Mirtazapine showed similar antidepressant efficacy to citalopram (single study) [132], fluoxetine [133-135], paroxetine [136, 137] and sertraline after 6-24 weeks' treatment in patients with moderate to severe major depression. Overall, the proportion of patients classified as HAM-D responders at endpoint in these trials was 50-73% for mirtazapine, 45-71% for fluoxetine, 50-56% for paroxetine and 52% for sertraline. [132]

Two of these studies showed that the efficacy of mirtazapine was maintained to 24 weeks at a similar level to that seen with SSRIs. [136] One trial was in a primary care setting. This study also reported relapse rates, with two patients in both the mirtazapine and the paroxetine groups relapsing during the study period. [137] In the other study, in elderly patients, those classified as responders after 8 weeks were able to continue treatment under double-blind conditions for a further 16 weeks. [136] Among these patients, mean reductions in HAM-D at the end of the initial 8-week period and the end of the overall 24-week study were 6.9 and 8.2 points (from a baseline of 21.6) for mirtazapine and 6.8 and 7.8 points (baseline 22.7) for paroxetine. [136] During the initial 8-week period, mirtazapine was associated with a more rapid onset of beneficial effects than paroxetine, with significantly greater reductions in
mean HAM-D scores at days 7, 14, 21 and 42. Some of the studies also evaluated patient quality of life using instruments such as the Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ), the Leeds Sleep Evaluation Questionnaire (LSEQ) or the St Mary’s Sleep Questionnaire. In general, mirtazapine and comparators showed significant improvements from baseline in QLESQ and sleep evaluation scores, with no statistically significant differences between groups for most parameter’s. However, mirtazapine was associated with faster or greater improvement of sleep and/or quality of sleep compared with citalopram, fluoxetine or paroxetine.

In a recently published meta-analysis of 12 new-generation antidepressants, mirtazapirie emerged as one of four agents deemed to have superior efficacy in the acute-phase treatment of major depression. The multiple-treatments meta-analysis, which accounted for both direct and indirect comparisons, included 25,928 patients from 117 randomized controlled studies that compared any of the following 12 agents when used as monotherapy: the NaSSA mirtazapine; SSRIs citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline; the dopamine/noradrenaline reuptake inhibitor bupropion; the noradrenaline reuptake inhibitor reboxetine; and SNRIs venlafaxine, duloxetine and milnacipran. Response was the primary efficacy outcome and was defined as the proportion of patients who had a reduction of >50% from baseline on the HAM-D or MADRS scales or who scored ‘much improved’ or ‘very much improved’ on the CGI at 8 weeks. Mirtazapine had significantly greater efficacy than duloxetine (OR 1.39), fluoxetine (OR 1.37), fluvoxamine (OR 1.41), paroxetine (OR 1.35) and reboxetine (OR 2.03). Escitalopram, venlafaxine and sertraline were also significantly more efficacious than these agents.

Data from a number of clinical trials suggest that mirtazapine may have a more rapid onset of action than various SSRIs, with significant differences in favour of mirtazapine being seen for some variables at time points during the first 4 weeks. Meta-analyses of double-blind trials in patients with depression have also suggested an earlier onset of efficacy with mirtazapine than with SSRIs. In a pooled analysis of three studies with fluoxetine, paroxetine and citalopram as the comparators, there was no difference between mirtazapine and the
SSRIs for the number of responders at study end, but the proportion of responders with onset of persistent improvement in week 1 was significantly higher in the mirtazapine group than the combined SSRI group (13% vs 6%; p = 0.008). Persistent responders were patients who were assessed as 'much' or 'very much' improved on the CGI scale and maintained that response throughout the study.\[^{139}\]

Mirtazapine was also shown to have a more rapid onset of action than SSRIs in a meta-analysis of 25 randomized controlled trials, with a relative risk of response of 1.36 (99% CI 1.13, 1.64; p< 0.0001) and a relative risk of remission of 1.68 (99% CI 1.20, 2.36; p< 0.0001) after 2 weeks.\[^{140}\] A meta-analysis of 12 double-blind trials involving a total of >2500 patients found that the probability of achieving response and sustained response during the first 3 weeks of treatment was significantly greater with mirtazapine than with SSRIs (p<0.001). It also found that the probability of achieving first remission and sustained remission at time t was significantly greater with mirtazapine than with SSRIs (both p< 0.001), when results from the first 3 weeks of therapy were taken into account. Meta-analysis of data from 11 trials showed significant differences in favour of mirtazapine over SSRIs for change from baseline in HAM-D Bech depression factor at week 2, HAM-D factor I (anxiety/somatization) at weeks 1, 2 and 4 and factor V/VI (retardation/sleep disturbance) up to week 6 The onset of antidepressant activity was also faster during treatment with mirtazapine ODT 30-45 mg/day than with sertraline 50-150 mg/day in a randomized, double-blind trial in 345 patients with moderate to severe major depression. The primary endpoint was change from baseline in HAM-D score during the first 2 weeks of treatment (with assessments on days 4, 7, 10 and 14 after starting treatment), although treatment continued for a total of 6 weeks.\[^{141}\]