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Duloxetine: Review of Its Pharmacology, and Therapeutic Use in Depression and Other Psychiatric Disorders

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Background. *The discovery of antidepressant medications has revolutionized the treatment of depression and other psychiatric illnesses. The coming of the selective serotonin (5-HT) reuptake inhibitors (SSRIs) marked a new era in the treatment of depression. These therapies frequently fall short of getting the patient to remission. Agents with a dual action have subsequently been developed which inhibit the reuptake of both 5-HT and NE, getting more patients to remission. Physical symptoms are associated with depression, preventing the patient from obtaining complete recovery. This article provides an overview of the pharmacology, efficacy, and techniques for the clinical use of duloxetine, a dual reuptake inhibitor, which has recently become available.*

Methods. *The English literature has been reviewed including both controlled and uncontrolled studies.*

Results. *Duloxetine is a dual reuptake inhibitor with actions on serotonin as well as norepinephrine. It has been shown to have efficacy in treating depressive symptoms including those with painful physical symptoms. Common side effects include nausea, insomnia, and dizziness.*

Conclusions. *The article has been written with clinicians as the target audience, the data suggesting it can be used as a first line agent.*

Keywords Depression, Duloxetine, Antidepressants, Pain symptoms

INTRODUCTION

The World Health Organization (WHO) report indicates that depression will be the medical disease with the greatest burden worldwide within the next decade and will be second only to ischemic heart disease by the year 2020 with regard to disability adjusted life years (1–3). Hence there is an ongoing need to develop newer and more effective treatments for depression, which is often under recognized (4). Depression is often accompanied by physical symptoms such as headaches, abdominal and musculoskeletal pains in the lower back and joints (5). Often these symptoms prolong morbidity and prevent patients from getting to remission (5). Treating the physical symptoms may also be important in helping the depressed patients achieving remission. As 50%–80% of patients with depression may present with the physical symptoms (5–7) there is likelihood that depression may be missed resulting in expensive physical work ups for medical problems. Depression is commonly associated with increased levels of anxiety, which can also increase suicide risk (8,9). There is some evidence that

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dual reuptake inhibitors specifically those with actions on the noradrenergic and serotonergic systems are more effective in treating such depressions (10–13). Duloxetine is one such agent recently developed and approved by the US Food and Drug Administration in August of 2004 for the treatment of depression and diabetic peripheral neuropathic pain (DPNP).

This article will review the pharmacological profile, clinical trials, and guidelines for the prescription of duloxetine, developed by Eli Lilly and Company.

Overview of Pharmacodynamic Properties

Effects on Central Neurotransmitter Systems

Duloxetine hydrochloride {LY248686, (+)-N-methy-3-(1-naphthalenyloxy)-(2-thiophene)-propanamine} is a potent dual reuptake inhibitor of both 5-HT and NE. It lacks significant affinity for histamine H1, alpha1-adrenergic, dopamine D2, 5-HT1A, 5-HT1B, 5-HT ID, 5-HT2A, 5-HT2C, and opioid receptors (14–16). Studies indicate that duloxetine has about an equal affinity for binding to both the 5-HT and NE reuptake transporters (14–16). In vitro studies reveal a Ki (reflects the potency of inhibition at the transporter level, lower values reflect greater potency of inhibition) of 0.8 nM for NE and 7.5 nM for 5-HT for duloxetine (14–17). Citalopram which is a potent serotonin reuptake inhibitor has a Ki of 9.5 Nm for 5-HT and a Ki > 10000 Nm for NE (refer to Table 1 for comparison of other agents). As a comparison the Ki for venlafaxine for NE was 2480 Nm and that for 5-HT was 82 Nm. Duloxetine is a weak inhibitor of dopamine reuptake and has a low affinity for adrenergic, histaminic, and muscarinic receptors (14).

Behavioral Effects in Animals

In animal studies, duloxetine increases cerebrospinal fluid (CSF) levels of 5-HT and NE. Studies using microdialysis reveal duloxetine increases levels of 5-HT and NE in rat brain to a greater extent than venlafaxine dose by dose. The increase in 5-HT and NE in the rat brain was noted to be dose dependent. Duloxetine inhibited ex vivo binding to rat 5-HT transporters and NE transporters with ED50 values of 0.03 and 0.7 mg/kg, respectively whereas venlafaxine had ED50 values of 2 and 54 mg/kg respectively (14). Depletion of rat brain 5-HT by p-chloramphetamine and depletion of rat hypothalamic NE by 6-hydroxydopamine was blocked by duloxetine with ED50 values of 2.3 and 12 mg/kg respectively. Venlafaxine had ED50 values of 5.9 and 94 mg/kg for blocking p-chloramphetamine- and 6-hydroxydopamine-induced monoamine depletion, respectively. These experiments suggest that duloxetine more potently blocks 5-HT and NE transporters in vitro and vivo than venlafaxine (14). It should be noted that animal doses and human doses are not comparable.

Effects on Pain Models in Animals

Duloxetine has been studied in experiments with regard to its effects on pain. In the formalin model of persistent pain duloxetine was compared with venlafaxine, amitriptyline, and gabapentin using in vivo microdialysis studies in rats. Intrathecal, intracisternal or intraperitoneal administration of duloxetine significantly attenuated formalin-induced late phase paw-licking behavior in a dose-dependent manner. Duloxetine was noted to be more potent than velafaxine which is another dual 5HT/NE reuptake inhibitor in its ability to reverse formalin-induced late phase paw licking behavior (18).

In other experiments on pain the data using tests such as the hot plate test in mice, writhing test in mice, carrageenan-induced hyperalgesia in rats, capsaicin-induced hyperalgesia in rats, and tail flick test in mice suggest that duloxetine is efficacious in the treatment of persistent and/or inflammatory pain states in dosages that have little effect on acute nociception. The preclinical data indicate that duloxetine has a beneficial effect on chronic pain states (data on file, Eli Lilly and Company).

Pharmacokinetic Properties

Absorption and Plasma Concentrations

Duloxetine is rapidly absorbed following oral administration. There is a median two-hour lag until absorption begins, the maximal plasma concentration of duloxetine occurs six hours after the medication is taken. The presence of food tends to reduce the rate of absorption by about 10 percent, which has no significant clinical relevance. The volume of distribution of duloxetine is an average of 1,640 L. Duloxetine is highly plasma protein bound (96%), primarily to albumin and alpha1-acid glycoprotein. The plasma protein binding of duloxetine is unaffected by renal or hepatic impairment. As the drug is highly bound to plasma proteins, interactions with certain drugs (e.g., warfarin, carbamazapine) that are also highly bound are possible. Higher free plasma levels of the drug occur in patients with hepatic disease because of reduced albumin, requiring lower starting dosages. In patients on warfarin the PT, PTT, and INR may need monitoring for dosage adjustment while in patients on carbamezapine blood level monitoring may be useful (19).

Metabolism and Excretion

Duloxetine is metabolized in the liver by cytochrome P450 IID6 and 1A2 isoenzymes to inactive metabolites. Metabolites found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6 methoxy duloxetine sulphate are largely excreted in the urine. Duloxetine does have an inhibitory effect on the 2-D6 isoenzyme which is somewhere in between sertraline and fluoxetine/paroxetine. Duloxetine has clinically insignificant

inhibition of 1A2 and has no effect on 3A4,2C9, and 2C19 isoenzymes. The 2-D6 drug interactions include mostly psychotropic agents such as the tricyclic antidepressants, phenothiazines, Type 1C antiarrhythmics (flecainide and propafenone) as well as pain medications such as codeine and dextromethorphan. No clinically significant interactions are noted between duloxetine and caffeine or theophylline (19).

Caution needs to be exercised when duloxetine is used in conjunction with potent inhibitors of CYP2D6 pathway (paroxetine, fluoxetine) as significantly high concentrations of duloxetine may result (19). The use of duloxetine with drugs such as fluvoxamine and certain quinolone antibiotics (CYP1A2 inhibitors) should be avoided (19). It should be noted that duloxetine does not have any active metabolites. In smokers there is a one third reduction in duloxetine bioavailability versus nonsmokers due to an effect on CYP1A2. No dosage change is suggested for smokers (19). No dosage adjustment is recommended for gender or age (19).

Duloxetine has a mean plasma half-life of 12 hours. There is evidence to suggest that the drug can be dosed once daily, the thought being that the CNS half life may be very different from the plasma half life. In patients with endstage renal disease (ESRD) the limited data suggest that Cmax and AUC concentrations are 100% greater. Mild renal dysfunction does not appear to any significant effect on duloxetine clearance. Duloxetine is not recommended for patients with End Stage Renal Disease (ESRD) (requiring dialysis or Creatnine clearance < 30 ml/min) (19). Patients with hepatic insufficiency have decreased duloxetine metabolism as well as excretion, raising plasma levels. In a series of six cirrhotic patients compared with age matched healthy subjects the half life was (34 hours) three times longer than normal. It is suggested that duloxetine not be administered to patients with hepatic insufficiency (19).

Therapeutic Use in Major Depression

Comparisons with Placebo and Other Antidepressants

The double-blind studies of duloxetine have used placebo or an active comparator. There were of six major original trials in depressed patients and one in stress urinary incontinence (SUI) (20–27). Additional reviews of these trials have also been published (28,29). All except the SUI study were efficacy as well as safety studies while the SUI study was a safety only study. There were two pivotal randomized double-blind placebo-controlled studies, which have demonstrated the efficacy of duloxetine in DSM-IV major depression (20,21). In one of these pivotal studies, duloxetine (N = 123) was studied using 60 mg/day dosage for nine weeks (20). In addition to assessing depression using the HAMD17 painful symptoms of depression were assessed using the visual analog scale. Duloxetine was significantly superior to placebo (N = 122) ($p < .001$) in reducing the HAMD17 total scores. Forty-four percent of the duloxetine treated patients went into remission versus 16% of the placebo treated patients. Discontinuation due to adverse events was 13.8% the common ones being as nausea, dry mouth, somnolence. No incidence of hypertension was noted (20). The nausea reports were in the first week and were in the mild to moderate range. In the pooled data from the two pivotal studies duloxetine had a 22% incidence of nausea compared to 31% for venlafaxineXR, 26% for both sertraline and paroxetine, and 21% for both fluoxetine and citalopram (data on file, Eli Lilly and Company). The pivotal trials excluded treatment refractory patients.

In another trial, which was of eight weeks duration, two different dosages (20 mg bid, N=84 and 40 mg bid, N=86) of duloxetine were compared with paroxetine (N=84) 20 mg per day (active comparator) and placebo (N=88) to prove non-inferiority. The 80 mg/day arm revealed significant improvement compared to the duloxetine 40 mg/day and placebo by week two and the effect was maintained throughout the study (25). The Hamilton Anxiety Scale also showed a statistically significant improvement in the anxiety symptoms (25). There were two eight week trials comparing duloxetine with fluoxetine and placebo in which the duloxetine dosage was increased to 120 mg/day as against 20 mg daily of fluoxetine. In this study the remission rate was 56% (data on file, Eli Lilly and Company).

Use in Treatment-Resistant Depression

The role of duloxetine in treatment-resistant depression needs to be established, because it has not been specifically studied in this group. The clinical trials excluded treatment refractory patients. The clinical trials do show the drug to be effective for hard to treat depression especially patients with multiple physical symptoms especially aches and pains.

Adverse Effects

Nausea is one of the more common adverse events, though the incidence is less than with venlafaxine as well as other SSRIs. Common side effects include insomnia and nausea. Specifically a comparison of the nausea rates using information from the Physicians' Desk Reference (PDR) revealed a nausea rate of 31% with venlafaxine XR (75–225 mg) compared to 22% for duloxetine (40–120 mg). In the pivotal trials where duloxetine 60 mg was the starting dose the pooled data from the trials revealed the discontinuation rate was rather low 0.8%. Nausea if experienced was mild and transient usually in the first week. After the first week the nausea rates were no different than placebo. Only two patients discontinued duloxetine at the 60 mg dose while one discontinued on placebo due to nausea (19).

No hematological effects or damage to other organ systems have been observed (20–27). There are no clinically significant effects on vital signs (20–27). Clinically insignificant instances of nonicteric transaminase elevations (e.g.,

ALT) have been observed in a small number of patients; on follow-up they either decline with cessation of dosing or continued dosing (data on file, Eli Lilly and Company). In some patients with a history of elevated liver functions such as with hepatitis C and severe alcoholism the use of duloxetine may exacerbate abnormal liver functions. We suggest that the drug not be used in those with a history of severe liver problems or alcoholism. No effects were observed on the QT interval in the trials (20–27,30). In the clinical trials urinary hesitancy and/or retention was a rare event. In over a 1000 patients duloxetine did not result in urinary retention or hesitation (<2% in clinical trials) and no patients needed to be catherized (data on file, Eli Lilly and Company).

The clinical trials revealed a weight loss of 1.1 pounds in 8–9 weeks of duloxetine treatment vs. one-half pound weight gain with placebo treatment (20–27). The one-year data revealed an average weight gain of 2.46 pounds in duloxetine patients (data on file). This study did not have a placebo arm. In a recent review antidepressants have been reported to have a 7–9 Ib weight increase after 6–12 months of therapy (31). No significant effects on glucose were reported in the trials. Spontaneously reported sexual side-effects were reported more frequently with duloxetine than with placebo. Sexual functioning was prospectively assessed in the trials using the Arizona Sexual Experience Scale (ASEX) at study entry, 8 weeks, and 8 months. In the short-term trials there was a statistical difference in the duloxetine group vs. placebo (p=0.007) (20–25). The inability of males to achieve an orgasm contributed to this. At six months there was no statistical difference between duloxetine and placebo (p=0.677) (data on file, Eli Lilly and Company). Pooled analyses have revealed that acute treatment emergent sexual dysfunction with duloxetine (p=0.007) and paroxetine (p=0.001) was significantly higher than placebo (p=0.007). Sexual dysfunction was significantly lower for duloxetine compared with paroxetine (p=0.015). The long-term incidence of sexual dysfunction did not differ significantly between duloxetine, paroxetine, and placebo (32).

The clinical trials data have shown the drug to be safe in overdose (defined as > 240 mg) (20–25). There were four cases of acute overdose up to a maximum of 1400 mg and no fatalities (data on file, Eli Lilly and Company).

Due to the short half-life of duloxetine it is recommended that the medication be tapered rather than being discontinued suddenly. In a one-year trial of duloxetine, abrupt discontinuation resulted in adverse events of dizziness (8.3%), anxiety (4.3%), nausea (4.2%), and headache (3.1%) which were statistically significant compared to placebo (data on file).

There were no reports of mania (0/755) patients receiving duloxetine in the clinical trials compared to placebo of 0.2% (1/585) (19). It is recommended that duloxetine be used cautiously in patients with a history of mania or family history of bipolar disorder. It should not be used without concurrent administration of a mood stabilizing medication in such patients.

Pregnancy and Nursing Mothers

Animal data suggests that duloxetine and its metabolites cross the placenta and are excreted in breast milk. No teratogenacity was noted in rats or rabbits. The effect of duloxetine on labor and delivery in humans is unknown, however once used widely in clinical practice such information will become available. Nursing while on duloxetine is not recommended. Duloxetine is pregnancy category C that is consistent with other antidepressants. In treating pregnant patients it is important to do a risk benefit analysis, have a detailed discussion with the patient as well as the father of the child and document in the medical record (19).

Contraindications for Duloxetine

This medication is contraindicated in patients with known hypersensitivity to the drug and concomitant therapy with monoamine oxidase inhibitors is also contraindicated. Duloxetine should not be prescribed in patients with uncontrolled narrow angle glaucoma. Suicidal ideation may result from worsening depression in both adult as well as pediatric patients. There is concern that antidepressants may worsen depression as well as result in suicidality, such a link has not been established. It is important to monitor for worsening depression as well as emergence of suicidal ideation (19). Severe liver problems such as hepatitis C and alcohol related hepatitis are contraindications for the prescription of duloxetine.

Informed Consent

The decision to use duloxetine should be discussed with the patient. Side effects, potential benefits, other treatment options, and reasons for its selection should be explored. The physician should ensure that the patient understands the implications of treatment with duloxetine and is legally competent to give consent. Family involvement is important and, if available, spouses or other close relatives should participate in discussions. Informed consent should be documented in the medical record.

Treatment Implementation

Duloxetine can be used as a first-line drug in treating depression. Before initiating treatment with duloxetine, the patient should have an assessment, especially to differentiate unipolar depression from bipolar illness. This diagnostic evaluation is best done by a good history from the patients as well as a collateral source such as a spouse or significant other who knows the patient well. A complete medical history including the assessment of thyroid status should be conducted. Family history of psychiatric illness in blood relatives should be

explored. A pregnancy test should be performed in women of child bearing potential.

Antidepressant efficacy for duloxetine has been shown for dosages between 60 mg /day and 120 mg/ day (60 mg/day being the optimal dosage). Higher dosages may result in an increase in side-effects. The safety of dosages above 120 mg/ day has not been evaluated. The drug is administered using a once daily schedule, the suggested starting dose being 30 mg daily and increasing to 60 mg per day after a week to lower the incidence of side-effects (19), although in clinical practice and in the trials a 60 mg/day starting dose has been used successfully. If starting at 60 mg/day taken after breakfast and not on an empty stomach the nausea rate is low. As with other new antidepressants the therapeutic dosage will be determined by clinical experience with this drug after it is widely prescribed to a large number of patients.

Side Effect Monitoring and Management

No fatalities have been reported from overdose. The signs and symptoms reported were those resulting from exaggeration of drug induced-side effects. The management of overdose is the same as for other antidepressants, i.e., maintaining patency of the airway, gastric lavage, and the use of activated charcoal in addition to other life support measures (19).

Utility of Drug Plasma Concentrations

Plasma concentrations of duloxetine have not been shown correlation with clinical response. At the present, plasma levels do not have clinical value. Additional studies are needed to investigate the utility of plasma levels.

Maintenance Treatment

The guidelines for maintenance treatment are similar to those for the treatment of depression with other antidepressants. The therapeutic dose is usually also the maintenance dosage. The elderly patients, those with onset of depression at an early age, and those with risk factors such as family history need treatment for an extended duration of time possibly lifelong similar to the treatment of hypertension or diabetes to prevent recurrence (33).

Place of Duloxetine in Therapy

Duloxetine is a dual action agent inhibiting the reuptake of both serotonin as well as norepinephrine. This agent is efficacious and well tolerated. It has the potential for a significant role in the current treatment of major depression especially in patients with physical symptoms such as aches and pains. Duloxetine is a first-line drug because of the low frequency of side-effects, as well as an alternative agent for patients unable to tolerate standard antidepressants.

The dual action agents and duloxetine in particular have ushered in an exciting new era in the treatment of depression as they get more patients to achieve remission. The concept of treating to remission has become a benchmark for antidepressant drug development (34,35).

As with any new medication, time and experience will be needed for us to learn what its final role will be. However, with duloxetine, it appears that psychiatrists have a broader armamentarium of effective and well-tolerated antidepressant agents to choose from.

Duloxetine is currently the only FDA approved antidepressant studied prospectively in clinical trials with the concept of getting patients to remission (HAMD <7). Nevertheless there are studies of other antidepressants looking at their ability to get patients to remission. Venalfaxine was studied using a pooled analysis. In one study remission data from eight randomized, double-blind studies was examined. This large study compared patients on venlafaxine (N=851), SSRIs such as fluoxetine, paroxetine, fluvoxamine (N=748), and placebo (N=446). The remission rates were obtained using pooled analysis, which revealed a 45% remission (382/851) for venlafaxine, 35% SSRIs (260/748), and 25% for placebo (110/446) (36).

In another study sustained remission data was obtained from four clinical trials of citalopram (N=810 patients with major depression) the treatment duration being of at least 20 weeks. The sustained remission rates ranged from 53–72%. In these trials at least 230 patients were over 65 years of age suggesting applicability to geriatric depression (37). It should be noted that the venlafaxine and citalopram studies were not designed a priori to test remission.

To get patients to remission from depression core emotional symptoms, painful physical symptoms, and anxiety needs to improve. A secondary analysis of placebo-controlled duloxetine trials in major depression, which included placebo, fluoxetine and paroxetine revealed statistically significant improvement in anxious symptoms compared to placebo, fluoxetine, and paroxetine with duloxetine. Efficacy in symptoms domains of core depression symptoms, painful physical, symptoms, and anxious symptoms may explain the high remission rate (43–57%) across studies (38).

Special Populations

Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder. The use of antidepressants including duloxetine in this population needs careful assessment of suicide risk as well as close observation for clinical worsening of suicidal ideation. Families and caregivers need to be advised about these issues. There is a black-boxed

warning from the FDA for duloxetine as well as other antidepressants (19). It should also be noted that it is important to screen depressed patients including children and adolescents for bipolar disorder prior to treating them for an episode of major depression as the prescription of antidepressant to bipolar patients may promote cycling of the illness which may lead to increased in suicidality. Hence a thorough diagnostic evaluation is essential. Inaccurate diagnosis may promote suicide attempts.

Older Adults

An initial open label trial revealed duloxetine to be helpful in treating depression in adults 65 years and older (39). Duloxetine was studied in older adults (minimum age 55 years) in two identical trials starting at a dosage of 60 mg daily, the HAMD 17 being the efficacy measure. Pain was also evaluated at this time. The combined result indicated that duloxetine was significantly better than placebo in treating depression as well as reduction in overall pain including back pain. Remission was achieved in 44% of the medication group while it occurred in 16.1% of the placebo group. Rate of discontinuation was 21% fro the medication group due to adverse events while it was 6.7% for the placebo group. There are no published studies in children and adolescents as of the writing of this review paper (40).

Pain Patients

There are now several studies providing data that duloxetine helps improve painful physical symptoms along with depression. In addition to the pivotal trials this finding has borne out in subsequent studies. Painful physical symptoms such as headaches, backaches, and arthralgias associated with depression have been noted to improve with duloxetine (41–43).

In addition, duloxetine is FDA indicated in the treatment of diabetic peripheral neuropathic pain (DPNP). In the clinical trials two dosages (60 mg daily and 60 mg twice a day) have been tested. In the multicenter randomized placebo-controlled trial (N=348) patients were assigned to placebo, duloxetine 60 mg daily, and duloxetine 60 mg bid for 12 weeks (44). Both dosages of duloxetine separated from placebo, however, there were more discontinuations in the 60 mg bid group without a report of added efficacy for the higher dosage. In another trial (N=457) DPNP patients were assigned to either duloxetine 20 mg daily, duloxetine 60 mg daily, Duloxetine 60 mg bid, and placebo (45). The two groups 60 mg daily and the 60 mg bid group separated from placebo on the 24 hour average pain score beginning week one after randomization. The drug was well tolerated with less than 20 percent discontinuation due to adverse events.

In an open-label study, the safety of duloxetine dosage of 60 mg bid was compared to routine clinical care which consisted of the prescription of gabapentin, venlafaxine, and amitriptyline (46). A higher percentage of the routine group experienced one or more serious adverse events. The treatment emergent adverse events reported by 10 percent or more of the duloxetine patients were nausea while the routine group reported peripheral edema, pain in extremety, somnolence, and dizziness. Duloxetine did not affect glycemic control, lipid profiles, nerve function or the course of DPNP.

Off Label Uses of Duloxetine

Duloxetine being a dual acting agent may be prescribed for other conditions such as obsessive-compulsive disorder for which clomipramine with a low margin of safety is prescribed. This drug may also be tried in conditions such as generalized anxiety disorder, fibromyalgia and chronic fatigue syndrome (47). Another potential use of duloxetine may be in patients with chronic pain. Duloxetine may also play a beneficial role in generalized anxiety disorder and panic disorder, illnesses where the SSRIs and venlafaxine have been used. Duloxetine may be tried for patients with attention deficit hyperactivity disorder (ADHD) as a second or third line agent especially in those with substance abuse issues just as other antidepressants such as buproprion and venlafaxine have been tried. No formal studies are available in this area.

The use of duloxetine in stress urinary incontinence is off-label despite the fact there are studies done in this area. Although statistically superior to placebo in these efficacy trials the clinical effects are small suggesting modest benefit to the patient and this should be weighed against the drug's adverse event profile (27). When using a drug off-label it is important to inform the patient during the consent process and document.

CONCLUSIONS

Duloxetine is a promising antidepressant, which has been prospectively studied using the remission concept (getting the patient asymptomatic) as against response (getting the patient 50% better). Five out of the six initial duloxetine efficacy studies have demonstrated clinical benefit in the treatment of DSM-IV major depression as well as diabetic peripheral neuropathic pain. The emerging data suggests that dual action agents may have greater efficacy in getting the patients to remission. Finally the real test will come once this drug is widely prescribed and used in the community by clinicians. The use of duloxetine will also depend on its acceptance by formularies, which will probably occur if this agent differentiates from others in its class, not only in cost but also, onset of action, and in getting patients to a sustained level of remission as suggested by the clinical trials (48,49). Widespread use of the drug will also provide us with the real dose range unlike the dosage from the clinical trials, which would only be a guideline.

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REFERENCES

1. Adapted from the World Health Organization: World health report, 1999
2. Murray CJL, Lopez AD: Global mortality, disability, and the contribution of risk factors: The Global Burden of Disease Study. *Lancet* 1997; 349(9063):1463–1472
3. Michaud CM, Murray CJ, Bloom BR.: Burden of disease—implications for research. *JAMA* 2001; 285:535–539
4. Davidson JRT, Meltzer-Brody SE: The under-recognition and under-treatment of depression: what is the breadth and depth of the problem? *J Clin Psychiatry* 1999; 60(suppl 7):4–9
5. Fava M: Somatic symptoms, depression, and antidepressant treatment. *J Clin Psychiatry* 2002; 63:305–307
6. Von Korff M, Simon G: The relationship between pain and depression. *Br J Psychiatry* 1996; 30:101–108
7. Hotopf M, Mayou R, Wadsworth M, Wesseley S: Temporal relationship between physical symptoms and psychiatric disorder: Results from a national birth cohort. *Br J Psych* 1998; 173:255–261
8. Sareen J, Houlahan T, Cox BJ, Asmundson GJ: Anxiety disorders associated with suicidal ideation and suicide attempts in the National Comorbidity Survey. *J Nerv Ment Dis*. 2005 Jul; 1993:450–454
9. Bush KA, Fawcett J, Jacobs DG: Clinical correlates of inpatient suicide. *J Clin Psychiatry* 2003 Jan; 64:14–19
10. Thase ME, Entsuah R, Rudolph RL: Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psych* 2001;178:234–241
11. Wong DT and Bymaster FP: Dual serotonin and noradrenaline uptake inhibitor class of antidepressants-potential for greater efficacy or just hype? *Prog Drug Res* 2002; 58:169–222
12. Danish University Antidepressant Group: Paroxetine: A selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. *J Affect Disord* 1990; 18:289–299
13. Tran PV, Bymaster FP, McNamara RK, Potter WZ: Dual monoamine modulation for improved treatment of major depressive disorder. *J Clin Psychopharmacol* 2003; 23:78–86
14. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG et al.: Compare the affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro, human serotonin receptor subtypes, and other neuronal receptors. *Neuropsychopharmacology* 2001; 25:871–880
15. Nemeroff CB, Schatzberg AF, Goldstein DJ, Detke MJ, Mallinckrodt C, Lu Y, Tran PV: Duloxetine for the treatment of major depressive disorder. *Psychopharmacol Bull*. 2002; 36:106–132
16. Kihara T, Ikeda M: Duloxetine-induced dose dependent increase of extracellular monoamine in frontal cortex. *J Pharmacol Exp Ther* 1995; 272:1–183
17. Karpa KD, Cavanaugh JE, Lakoski JM: Duloxetine pharmacology: Profile of a dual monoamine modulator. *CNS Drug Rev* 2002; 8:361–376
18. Iyengar S, Bymaster F, Wong D, Ahmad L: Efficacy of the serotonin and norepinephrine reuptake inhibitor, duloxetine, in the formalin model of persistent pain. Annual Meeting of the European College of Neuropsychopharmacology 2002
19. Cymbalta product monograph. Indianapolis, Ind: Eli Lilly and Company; 2004
20. Detke MJ, Lu Y, Goldstein DJ, Hayes JR, Demitrack MA: Duloxetine 60 mg once daily, for major depressive disorder: A randomized double-blind placebo-controlled trial. *J Clin Psychiatry* 2002;63:308–315
21. Detke MJ, Lu Y, Goldstein DJ, McNamara RK, Demitrack MA: Duloxetine 60 mg daily dosing versus placebo in acute treatment of major depression. *J of Psychiatric Res.* 2002; 36:383–390
22. Goldstein DJ, Mallinckrodt C, Lu Y, Demitrack MA: Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. *J Clin Psychiatry* 2002; 63:225–231
23. Mallinckrodt CH, Watkin JG, Liu C, Wohlreich MM, Raskin J: Duloxetine in the treatment of Major Depressive Disorder: A comparison of efficacy in patients with and without melancholic features. *BMC Psychiatry*. 2005; 5:1
24. Mallinckrodt CH, Goldstein DJ, Detke MJ, Lu Y, Watkin JG, Tran PV: Duloxetine: A new treatment for the emotional and physical symptoms of depression. *Prim Care Companion J Clin Psychiatry*. 2003; 5:19–28
25. Detke MJ, Wiltse CG, Mallinckrodt CH, McNamara RK, Demitrack MA, Bitter I: Duloxetine in the acute and long-term treatment of major depressive disorder: A placebo- and paroxetine-controlled trial. *Eur Neuropsychopharmacol*. 2004; 14(6):457–470
26. Norton PA, Zinner NR, Yalcin I, Bump RC: Duloxetine versus placebo in the treatment of stress urinary incontinence. *Am J Obstet Gynecol* 2002; 187:40–48
27. Guy DR: Duloxetine for the management of stress urinary incontinence. *Am J Geriatr Pharmacother* 2005; 3:25–28
28. Mallincrokdt CH, Goldstein DJ, Detke MJ, Lu Y, Watkin JG, Tran PV: Duloxetine: A new treatment for the emotional and physical symptoms of depression. *Primary Care Companion J Clin Psychiatry* 2003; 5:19–28
29. Nemeroff CB, Goldstein DJ, Detke MJ, Mallinckrodt C, Lu Y, Tran PV: Duloxetine for the treatment of major depressive disorder. *Psychopharmacol Bull* 2002; 36:06–132
30. Thase ME, Tran PV, Wiltse C, Pangallo BA, Mallinekrodt C: Cardiovascular profile of duloxetine, a dual reuptake inhibitor of serotonin and norepinephrine. *J Clin Psychopharmacol*. 2005; 25:132–140
31. Masand PS, Gupta S: Long-term of new generation antidepressants: SSRIs, venlafaxine, nefazodone, buproprion, mirtazapine. *Ann Clin Psychiatry* 2002; 14:175–182
32. Delgado PL, Brannan SK, Mallinekrodt CH, Tran PV, Mc Namara RK, Wang F, Watkin JG, Detke MJ: Sexual functioning assessed in 4 double-blind placebo- and paroxetine-controlled trials of duloxetine for major depressive disorder. *J Clin Psychiatry* 2005; 66:686–692
33. Raskin J, Goldstein DJ, Mallinckrodt CH, Ferguson MB: Duloxetine in the long-term treatment of major depressive disorder. *J Clin Psychiatry*. 2003; 64:1237–1244
34. Nirenberg AA, Wright EC: Evolution of remission as the new standard in the treatment of depression. J Clin Psychiatry. 1999; 60 (Suppl) 22:7–11
35. Rush A, Trivedi M.:Treating depression to remission. Psychiatr Ann. 1995; 25:704–710

36. Thase ME, Entsuah A, Rudolph RL: Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry* 2001; 178:234–241
37. Thase ME: Full-sustained remission rates among citalopram-treated patients. Annual Meeting of the American Psychiatric Association, May 5–10, 2001, New Orleans, LA.
38. Dunner DL, Goldstein DJ, Mallinckrodt C, Lu Y, Detke MJ: Duloxetine in treatment of anxiety symptoms associated with depression. *Depress Anxiety* 2003; 18:53–61
39. Wohlreich MM, Mallinckrodt CH, Watkin JG, Hay DP: Duloxetine for the long-term treatment of Major Depressive Disorder in patients aged 65 and older: An open-label study. *BMC Geriatr*. 2004; 4:11
40. Nelson JC, Wohlreich MM, Mallinckrodt CH, Detke MJ, Watkin JG, Kennedy JS: Duloxetine for the treatment of major depressive disorder in older patients. *Am J Geriatr Psychiatry* 2005; 13:227–235
41. Wohlreich MM, Watkin JG: Role of duloxetine in the treatement of depression and associated painful symptoms. *Primary Care Companion J Clin Psychiatry* 2003; 5:286–287
42. Goldstein DJ, Lu Y, Detke MJ, Hudson J, Iyengar S, Demitrack MA: Effects of duloxetine on painful physical symptoms associated with depression. *Psychosomatics* 2004; 45:17–28
43. Fava M, Mallinckrodt CH, Detke MJ, Watkin JG, Wohlreich MM: The effect of duloxetine on painful physical symptoms in depressed patients: Do improvements in these symptoms result in higher remission rates? *J Clin Psychiatry*. 2004; 65:521–530
44. Raskin J, Pritchett YL, Wang F, D'Souza DN, Waninger AL, Iyengar S, Wernicke JF: A double-blind, randomized multi-center trial comparing duloxetine with placebo in the management of peripheral neuropathic pain. *Pain Med.* 2005; 5:6346–6356
45. Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S: Duloxetine vs. placebo in patients with painful diabetic neuropathy. *Pain.* 2005; 6:109–118
46. Raskin J, Smith TR, Wong K, Pritchett YL, D'Souza DN, Iyengar S, Wernicke JF: *J Palliat Med.* 2006; 9:29–40
47. Arnold LM, Lu Y, Crofford LJ, Wohlreich M, Detke MJ, Iyengar S, Goldstein DJ: A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis Rheum*. 2004; 50: 2974–2984
48. Brannan SK, Mallinckrodt CH, Detke MJ, Watkin JG, Tollefson GD: Onset of action for duloxetine 60 mg once daily: double-blind, placebo-controlled studies. *J Psychiatr Res.* 2005; 39:161–167
49. Goldstein DJ, Lu Y, Detke MJ, Wiltse C, Mallinckrodt C, Demitrack MA: Duloxetine in the treatment of depression: A double-blind placebo-controlled trial. *J Clin Psychopharmacol*. 2004; 24:389–399