Duloxetine Pharmacology: Profile of a Dual Monoamine Modulator

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ABSTRACT

Dysregulation within central monoaminergic systems is believed to underlie the pathology of depression. Drugs that selectively inhibit the reuptake of central monoamines have been used clinically to alleviate symptoms of depressive illnesses. Duloxetine, a novel compound currently under investigation for the treatment of depression, binds selectively with high affinity to both norepinephrine (NE) and serotonin (5-HT) transporters and lacks affinity for monoamine receptors within the central nervous system. It has been suggested that dual inhibition of monoamine reuptake processes may offer advantages over other antidepressants currently in use.

In preclinical studies, duloxetine mimics many physiologic effects of antidepressants. Consistent with other antidepressants, duloxetine, by acute administration, elevates extracellular monoamine levels, while by chronic administration it does not alter basal monoamine levels. Like the selective serotonin reuptake inhibitor, fluoxetine, by microiontophoretic application, duloxetine inhibits neuronal cell firing. However, in comparison with fluoxetine, duloxetine is a more potent serotonin reuptake inhibitor. Furthermore, in behavioral experiments, duloxetine attenuates immobility in forced swim tests in animal models of depression to a greater extent than several other commonly used antidepressants.

In a six-week open label uncontrolled study, duloxetine was evaluated in patients with a history of depression. Duloxetine was effective in treating depression as determined by marked reduction in Hamilton Depression Rating scores. Adverse effects reported during

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duloxetine treatment were minor and similar to those of other antidepressants. In an eight-week multicenter, double-blind, placebo-controlled study in patients with a major depressive disorder, duloxetine was effective as an antidepressant, particularly in patients with greater symptom severity. Only limited data are available regarding the pharmacokinetic profile of duloxetine in humans, although a half-life of 10 to 15 h has been reported. Studies conducted in healthy human subjects confirm the preclinical profile of duloxetine as an inhibitor of 5-HT and NE reuptake. Taken together, existing data suggest that duloxetine is a novel and effective antidepressant.

INTRODUCTION

Depression is characterized by a discouraged mood, diminished interest in activities usually found pleasurable, lack of energy, deflated self-worth, decreased ability to maintain concentration, aberrant sleep patterns, abnormal appetite, and alterations in psychomotor activity, with symptoms persisting for more than two weeks. While the true prevalence of depression is unknown, estimates suggest that over 15% of the population will suffer from a depressive episode at some point during their life (33).

As with many neuropsychiatric disorders, the etiology underlying depressive illness is too complex to be explained by a single factor and likely involves several components. Several lines of evidence support the involvement of both noradrenergic and serotonergic neurotransmitter systems in the pathogenesis of depression. As a result, compounds that modulate both of these monoaminergic systems are under investigation for potential utility as antidepressants. In this review, the pharmacologic effects of duloxetine, an investigational agent that inhibits the activity of noradrenergic and serotonergic transporters, will be discussed. Due to simultaneous inhibition of both noradrenergic and serotonergic monoamine systems, duloxetine may prove to be an efficacious alternative in the treatment of depression.

EVOLVING MONOAMINE THEORIES OF DEPRESSION

The initial hypothesis of major depression was based upon the relatively high incidence of depression experienced by patients receiving the antihypertensive agent, reserpine. Reserpine was known to deplete catecholamine stores both centrally and peripherally (27). This led to the suggestion that inadequate norepinephrine (NE) concentrations in synaptic regions contribute to the clinical symptoms of depression (38). Centrally, NE is synthesized predominantly in the brain stem nuclei, locus coeruleus and subcoeruleus, which together with the A1 and A2 medullary cell groups project rostrally to nearly every mid- and forebrain region, dorsoventrally to the cerebellum, and caudally to the spinal cord (41). This extensive pattern of central innervation suggests that NE serves as a regulator and/or modulator of neurotransmission. Within the central nervous system, NE has been implicated in mood stabilization, sleep regulation, expression of aggression, and overall alertness and arousal (14,19,29,32).

A subsequent hypothesis to explain the etiology of depression was introduced in the early 1970s. Based upon studies with L-tryptophan, a precursor to 5-hydroxytryptamine (5-HT), Prange and colleagues suggested the involvement of the serotonergic system in the pathology of major depression (49). Prange et al. put forth the “permissive hypothesis of affective illness” asserting that decreased levels of 5-HT may *permit* an affective state (resultant from decreased NE) to be displayed. According to this hypothesis, correction of a 5-HT deficit should ameliorate the underlying affective disease. Numerous investigations have substantiated this hypothesis. For example, when individuals prone to depressive episodes are placed on diets low in tryptophan or on tryptophan-depleting diets, depressive episodes are precipitated since tryptophan is a necessary precursor to 5-HT synthesis (15). Alternatively, L-tryptophan replacement may ameliorate symptoms of depression (57). Centrally, the serotonergic system originates with 5-HT-containing cell bodies in the dorsal raphe and median raphe nuclei, which project to innervate the forebrain. Within the central nervous system, 5-HT has an established role in the integration of emotional, cognitive, and motor functions (4).

One currently accepted hypothesis regarding depression might be described as the “5-HT/NE link hypothesis” (24). This hypothesis asserts that both, noradrenergic and serotonergic systems, must be functional for antidepressant drug therapy to be effective. In support of this hypothesis, pharmacologic agents that modulate both noradrenergic and serotonergic systems have been found useful in alleviating depressive episodes (9).

Antidepressant Mechanisms

Early antidepressants were derived largely from two classes of compounds: monoamine oxidase inhibitors and tricyclic antidepressants. Monoamine oxidase inhibitors, such as phenelzine, prevent the degradation of NE. However, numerous food-drug interactions preclude its widespread use. Tricyclic antidepressants (TCAs), such as imipramine, are pharmacologically promiscuous in binding to serotonin transporters (SERT), norepinephrine transporters (NET), histamine, α_1 -adrenergic, and muscarinic receptors. The high affinity with which TCAs bind to numerous neurotransmitter receptors correlates well with their side effect profile of sedation, orthostatic hypotension, dry mouth, constipation, and tachycardia.

More recently, drugs that selectively modulate the serotonergic system have become recognized as first-line agents for the management of depressive illnesses and other affective disorders, including anxiety. While some antidepressants modulate serotonergic activity by actions on specific 5-HT receptors, the therapeutic efficacy of most newer agents is thought to derive from their ability to selectively inhibit SERT. Once SERT are inhibited, a cascade of adaptive responses produces a gradual upregulation of central serotonergic function (18). Drugs such as fluoxetine, which selectively inhibit SERT, are no more efficacious than TCAs in the treatment of depression and may even have a slightly slower onset of action. However, fluoxetine and its congeners lack adverse sedative, anticholinergic, hypotensive, and cardiac effects characteristic of TCAs.

Monoamine Transporters

Evaluation of cloned neurotransmitter transporters has led to the prediction that monoamine transporters are structurally comprised of 12 transmembrane domains with amino-

and carboxy-termini located intracellularly. Located in the presynaptic terminal region, transporters are necessary for maintaining homeostasis, termination of neurotransmitter activities, and reuptake of signalling molecules into presynaptic terminals. Endogenous transporter function is likely to be regulated through a variety of mechanisms including multiple phosphorylation sites (6), alternative splicing mechanisms (11,36), and oligomerization (35). Antidepressants that modulate noradrenergic and serotonergic activity by binding to either NET or SERT have been demonstrated to inhibit neurotransmitter reuptake, thus altering neurotransmitter clearance and homeostasis.

In the early 1990s, it was postulated that simultaneous inhibition of both NET and SERT may offer additional benefits over the earlier generation of antidepressants. Nelson et al. suggested that dual inhibition of NE and 5-HT may result in faster onset of antidepressant activity compared to standard antidepressants (44). Furthermore, it was hypothesized that NE and 5-HT dual reuptake inhibitors may display enhanced efficacy in treatment-resistant depression (45,55). Theoretically, a pharmacological agent capable of dual inhibition of NET and SERT, without binding promiscuously to multiple neurotransmitter receptors, should result in an effective antidepressant void of many bothersome adverse effects.

To date, two FDA approved antidepressants, venlafaxine and nefazodone, and one investigational compound, duloxetine, purportedly bind to monoamine transporters and inhibit the reuptake of NE and 5-HT. However, *in vitro* radioligand binding assays examining the affinity of venlafaxine for NET and SERT found that venlafaxine displayed only moderate affinity for SERT and very low affinity for NET (2,46). Therefore, modulation of noradrenergic and serotonergic activity may stem from other mechanisms that are independent of monoamine transporter modulation. Additionally, nefazodone was found to be a relatively weak inhibitor of both NET and SERT but binds with moderate to high affinity to histamine, α_1 -, and α_2 -adrenergic, and 5-HT_{2A} receptors (46). These results suggest that, while they are effective antidepressants, neither venlafaxine nor nefazodone is explicitly a dual inhibitor of NET and SERT. Table 1 depicts putative transporter and receptor-binding profiles for venlafaxine, nefazodone, and other commonly prescribed antidepressants. In comparison to venlafaxine and nefazodone, duloxetine displays a high affinity for both NET and SERT and lacks significant affinity for neurotransmitter receptors (65). As a result, duloxetine may be the only pharmacologic compound that truly represents a dual selective NET and 5-HT reuptake inhibitor.

DULOXETINE

Binding Profile

Mechanistically, duloxetine (previously known as LY248686) is a potent inhibitor of NET and SERT (65). In radioligand binding assays utilizing rat cerebral cortex synaptosomes, duloxetine possesses high affinity for both norepinephrine and 5-HT uptake carriers with K_i values of 2.1 and 0.53 nM, respectively. In contrast to its effects on noradrenergic and serotonergic systems, duloxetine does not appear to directly modulate dopaminergic function. This is demonstrated by its inability to inhibit synaptosomal reuptake of [³H]dopamine (65), failure to protect against MPTP-induced depletion of striatal do-

pamine (25), and lack of alteration in dopamine or 3,4-dihydroxyphenylacetic acid (DOPAC) levels following duloxetine administration (21). Furthermore, duloxetine lacks appreciable affinity for muscarinic, histamine, α_1 -adrenergic, serotonin, dopamine, and opioid receptors (65).

Inhibition of NE and 5-HT Reuptake

Numerous investigations have extended and provided evidence that duloxetine inhibits the reuptake of norepinephrine and serotonin. The neurochemical actions of duloxetine on monoamine concentrations have been studied in a variety of tissues using different animal models. Table 2 summarizes the preclinical experimental paradigms that have been used in either *in vivo*, *in vitro*, or *ex vivo* studies to assess the ability of duloxetine to inhibit the reuptake of monoamines. Fuller and colleagues examined the effects of duloxetine on monoamine levels in rats and mice using heart and brain tissue (25). When p-chloroamphetamine depleted 5-HT levels in mouse brain by 39%, pretreatment with duloxetine dose-dependently antagonized this depletion. Also consistent with the inhibition of serotonin reuptake is the increase in extracellular 5-HT-levels and lowering of 5-hydroxyindoleacetic acid (5-HIAA) levels in the rat brain by duloxetine (21).

Whether duloxetine preferentially and to greater extent inhibits reuptake of 5-HT than NE, or whether it inhibits reuptake of both monoamines equipotently, remains unclear. *In vitro* experiments using rat hippocampal slices demonstrated that duloxetine is twice as more potent at inhibiting [3 H]5-HT than [3 H]NE reuptake, while *ex vivo* uptake experiments utilizing hippocampal slices from rats treated continuously over a two-day period with duloxetine suggest that the drug equipotently inhibits the reuptake of [3 H]5-HT and [3 H]NE (31). The reason for these divergent results is unknown. It is conceivable, however, that these differences are due to various experimental paradigms and are determined by different concentrations of neurotransmitters in the incubation medium. Indeed, Pineyro et al. observed that *in vitro*, the apparent potency of selective serotonin reuptake

TABLE 1. Comparison of binding affinities of commonly prescribed antidepressants and duloxetine

Antidepressants	Transporters			Receptors					
	NET	SERT	DAT	D ₂	H ₁	Musc	5-HT _{2A}	5-HT _{2C}	NE α_1
Bupropion (53)	>700	>700	570	>700	ND	>700	>700	>700	>700
Citalopram (30)	>700	1.8	>700	>700	350	>700	>700	630	>700
Duloxetine (65)	2.1	0.53	ND	>700	>700	>700	>700 ^a	>700 ^a	>700
Fluoxetine (30,53)	370	6.8	>700	>700	>700	>700	>700	160	>700
Nefazadone (20,53)	110	68	470	180	370	>10	10	72	42
Paroxetine (30)	81	0.29	>700	>700	>700	210	>700	>700	>700
Sertraline (30)	160	0.19	48	>700	>700	>700	>700	ND	>700
Venlafaxine (42,48)	640	210	>700	>700	>700	>700	>700	>700	>700

Abbreviations: NET, norepinephrine transporter; SERT, serotonin transporter; DAT, dopamine transporter; D₂, dopamine₂ receptor; H₁, histamine₁ receptor; Musc, muscarinic receptor; 5-HT_{2A}, serotonin_{2A} receptor; 5-HT_{2C}, serotonin_{2C} receptor; NE α_1 , α_1 adrenergic receptor; ND, not determined.

^aAs determined by [3 H]ketanserin radioligand binding.

TABLE 2. Preclinical experimental paradigms assessing duloxetine inhibition of norepinephrine or serotonin reuptake

Parameters measured	Species	Reference
ED ₅₀ for antagonizing depletion of brain 5-HT by p-chloroamphetamine following i.p. duloxetine	Mice/rats	Fuller et al. (25)
ED ₅₀ for antagonizing depletion of heart NE by 6-hydroxydopamine following i.p. duloxetine	Mice	Fuller et al. (25)
ED ₅₀ for antagonizing depletion of hypothalamic 5-HT by p-chloroamphetamine and NE by 6-hydroxydopamine following i.c.v. duloxetine	Rats	Fuller et al. (25)
Blockade of cortical 5-HT depletion induced by p-chloroamphetamine following i.p. duloxetine	Rats	Wong et al. (65)
IC ₅₀ for inhibition of radiolabeled 5-HT and NE uptake from hippocampal slices	Rats	Kasamo et al. (31)
K _i for inhibition of 5-HT and NE uptake in hypothalamic/cortical synaptosomes and platelets <i>in vitro/ex vivo</i> following p.o. duloxetine	Rats	Engleman et al. (21)
% increase in cortical 5-HT and NE using microdialysis following s.c. duloxetine	Rats	Gobert et al. (26)
% increase in hypothalamic 5-HT and NE using microdialysis following i.p. duloxetine	Rats	Engleman et al. (21,22)
% inhibition of 5-HT and NE uptake in hypothalamus <i>ex vivo</i> following p.o. duloxetine	Rats	Wong et al. (65)
% inhibition of 5-HT and NE uptake in hypothalamic/cortical synaptosomes <i>in vitro</i> following p.o./i.p. duloxetine	Rats	Wong et al. (65)
Blockade of heart NE uptake following i.v. duloxetine	Rats	Wong et al. (65)
Increase in cortical 5-HT and NE using <i>in vivo</i> microdialysis following p.o. duloxetine	Rats	Kihara et al. (34)
Stimulation of contraversive circling following microinjection into substantia nigra compacta	Rats	Bata-Garcia et al. (1)
RT ₅₀ for hippocampal neuronal activity from microiontophoretically applied 5-HT and NE following i.v. duloxetine	Rats	Kasamo et al. (31)
RT ₅₀ for hippocampal neuronal activity following chronic i.p. duloxetine across ages	Rats	Smith and Lakoski (62)
ED ₅₀ for dorsal raphe neurons following i.v. duloxetine; RT ₅₀ of hippocampal neuronal activity following microiontophoretic application of duloxetine	Rats	Smith and Lakoski (60)
RT ₅₀ for hippocampal neuronal activity following microiontophoretic application of duloxetine across ages	Rats	Smith and Lakoski (61)

Abbreviations: i.p., intraperitoneally; i.c.v., intracerebroventricularly; i.v., intravenously; p.o., orally; s.c., subcutaneously; NE, norepinephrine; 5-HT, serotonin; RT₅₀, 50% recovery time.

inhibitors varies according to [^3H]5-HT concentrations (47), suggesting that different concentrations of neurotransmitters in the incubation medium may affect reuptake inhibition.

While the precise extent of NE reuptake inhibition vs. that of 5-HT remains unclear, neurochemical evaluation of duloxetine is consistent with a profile of potent inhibition of NET. For example, duloxetine pretreatment dose-dependently antagonizes NE depletion in cardiac tissues elicited by the selective neurotoxin, 6-hydroxydopamine (25). Consistent with inhibition of norepinephrine reuptake, a single intraperitoneal dose of duloxetine dose-dependently increases NE concentrations while decreasing 3-methoxy-4-hydroxy-phenylethyleneglycol (MHPG) levels in microdialysate taken from rat hypothalamus (21). In addition, continuous duloxetine delivery via osmotic minipumps over a 48-h period inhibits [^3H]NE uptake in hippocampal slices in a dose-dependent manner (31). These results confirm that by virtue of its high affinity for NET, duloxetine potentially inhibits the reuptake of NE.

While acute administration of duloxetine increases both, NE and 5-HT concentrations in identified rat brain regions, chronic administration of duloxetine over 14 days does not alter basal monoamine levels in rat frontal cortex and nucleus accumbens (34). However, chronic administration of this compound does augment subsequent duloxetine-induced increases in NE and 5-HT output (34). These results are consistent with those observed following acute vs. chronic administration of other antidepressants (54,58).

Electrophysiological Profile

It has been previously documented that recovery time (RT_{50}) after microiontophoretic application of NE or 5-HT reflects the *in vivo* activity of the NE and 5-HT reuptake process with suppression of neuronal firing indicative of inhibition of neurotransmitter reuptake (16,28,47). RT_{50} is defined as the time in seconds required for cells to return to 50% of their baseline firing rates. Therefore, RT_{50} provides a valuable index of the ability of a presynaptic transporter to remove its neurotransmitter from the synapse. As a result of the monoaminergic reuptake blocking mechanism by which antidepressants are presumed to derive their efficacy, RT_{50} values are an appropriate method to assess antidepressant activity within neuronal synapses.

When administered i.v. or by continuous infusion duloxetine significantly and dose-dependently delayed RT_{50} values in rat hippocampal CA3 pyramidal neurons subjected to extracellular recording of their responses to microiontophoretic application of 5-HT (31). The recovery time following NE application was also increased albeit only at higher doses (31). These electrophysiological results confirm the neurochemical profile of duloxetine as a dual reuptake inhibitor, although they suggest a preferential effect on SERT inhibition over NET inhibition.

Smith and Lakoski compared the effects of duloxetine with those of the selective serotonin reuptake inhibitor, fluoxetine (60). Both duloxetine and fluoxetine, administered intravenously, induce rapid and reversible inhibition of cell firing within the dorsal raphe nucleus in male rats in a dose-dependent manner. However, duloxetine is more potent than fluoxetine. Additionally, co-application of fluoxetine and 5-HT significantly enhances the recovery phase of hippocampal neurons following 5-HT application. In contrast to 5-HT co-application with fluoxetine, which increases RT_{50} values by 59%, duloxetine co-applied with 5-HT does not alter the recovery of pyramidal neurons produced by application of 5-HT alone. The difference in binding profiles between fluoxetine and duloxetine, se-

lective inhibition of 5-HT transport vs. dual inhibition of NE and 5-HT reuptake, may underlie this divergent physiologic response.

Interdependence of Monoamines

Inherent with the currently accepted hypothesis of depression is the notion that alterations in one monoamine may be reflected by changes in the activities of another. To investigate possible interactions between neurotransmitter systems further, duloxetine was co-administered with a 5-HT_{1A} receptor antagonist and an α_2 -adrenoceptor antagonist and changes in monoamine concentrations were observed (22,26). After concurrent administration of duloxetine and LY206130, a 5-HT_{1A} receptor antagonist, monoamine levels were elevated and significantly exceeded levels elicited by administration of either agent alone (22). Following coadministration of duloxetine and LY206130, extracellular hypothalamic 5-HT, NE, and dopamine concentrations increased 669, 579, and 404%, respectively, as measured by *in vivo* microdialysis techniques. Consistent with these results, Kihara and colleagues observed increases in dopamine output within the nucleus accumbens following chronic administration of duloxetine (34). As duloxetine is not a potent inhibitor of dopamine reuptake in striatal synaptosomes (65), it is likely that extracellular dopamine elevations may be a reflection of increased serotonin availability and stimulatory effects on mesolimbic dopamine neurons (34). Taken together, these results suggest that the ability of reuptake inhibitors to increase extracellular levels of 5-HT may be limited by autoinhibition mediated at the 5-HT_{1A} autoreceptor. It is likely that the robust increases evident in NE and dopamine concentrations with concurrent duloxetine and LY206130 co-administration result from enhanced serotonergic actions on both central NE-containing neurons and mesocortical dopaminergic neurons. Thus, increased serotonergic tone, due to 5-HT_{1A} autoreceptor blockade, may ultimately potentiate NE and dopamine release (22).

Additional evidence also supports the notion of noradrenergic, serotonergic, and dopaminergic neuronal system interdependence. The subcutaneous administration of atipamezole, a selective α_2 -adrenoceptor antagonist, increases extracellular levels of NE and dopamine without affecting 5-HT levels in the frontal cortex of freely moving rats. When administered concurrently with duloxetine, atipamezole potentiates duloxetine-induced increases of NE, 5-HT, and dopamine, implying that α_2 -adrenoceptors tonically inhibit norepinephrine and dopamine and phasically inhibit 5-HT release in the frontal cortex (26). Taken together, the data reported by Engleman et al. and Gobert et al. are consistent with the notion of monoamine interdependence (22,26). This suggests that α_2 -adrenoceptor blockade or 5-HT_{1A} receptor blockade with simultaneous inhibition of NE or 5-HT reuptake may provide even greater antidepressant efficacy than either NET or SERT inhibitors used alone.

Adaptive Changes Following Chronic Administration

While modulation of noradrenergic and serotonergic neurotransmission provides beneficial effects in treating depression, the molecular and cellular mechanisms underlying these benefits are unclear. For example, following acute administration of antidepressants, NE and 5-HT levels are profoundly elevated. However, the therapeutic efficacy of antidepressants is not evident for several weeks, suggesting that elevations in monoamine levels

alone are not responsible for the antidepressant effect. Instead, this implies that elevated concentrations of monoamines induce long-term compensatory changes in monoaminergic neurotransmission (7).

Rueter et al. examined physiologic changes within noradrenergic and serotonergic systems following chronic duloxetine administration (51). In contrast to short-term administration of duloxetine that decreased cell firing rates, by chronic administration to rats for 21 days duloxetine caused firing rates of serotonergic neurons in the dorsal raphe nucleus to return to baseline values. Additionally, the recovery of cell firing is accompanied by desensitization of somatodendritic 5-HT_{1A} autoreceptors in the dorsal raphe nucleus. WAY 100635, a selective 5-HT_{1A} receptor antagonist, significantly increased the spontaneous firing rate of hippocampal neurons following 21-day-long duloxetine administration. It failed, however, to affect the spontaneous firing rate of CA3 pyramidal neurons in vehicle-treated rats (51). Taken together, WAY 100635 increased overall serotonergic tone in animals treated chronically with duloxetine, causing enhanced stimulation of post-synaptically located hippocampal 5-HT_{1A} receptors. These results are consistent with the notion of desensitization of 5-HT_{1A} autoreceptors over long-term and/or repeated administration of antidepressants.

While the application of clonidine normally attenuates 5-HT-inhibition of hippocampal cell firing, long-term treatment with duloxetine diminishes the effects of this negative feedback suggestive of a desensitization of α_2 -adrenoceptors. In agreement with changes induced by chronic administration of other NET inhibitors (7,40), attenuated α_2 -adrenoceptor function presumably serves to free 5-HT terminals of the increased inhibitory influence observed following blockade of NE reuptake (51).

As found previously with selective serotonin reuptake inhibitors, chronic treatment with duloxetine significantly increases recovery times following microiontophoretically applied 5-HT or NE in rat hippocampus (51,52). These physiological results demonstrate that the activation of NET and SERT mechanisms may not be functionally altered following long-term duloxetine administration. Furthermore, IT₅₀ values for 5-HT, defined as the current required to decrease cell firing rate by 50%, are not significantly altered following long-term administration of duloxetine. These results suggest that chronic treatment with duloxetine does not alter the sensitivity of postsynaptic 5-HT_{1A} receptors. However, a trend toward an increase in IT₅₀ values is observed following microiontophoretically applied NE suggesting a decreased sensitivity of postsynaptic α_2 -adrenoceptors with duloxetine treatment (51). However, no such trend was observed in a subsequent set of experiments (52) leading to questions regarding the functional significance of chronic duloxetine administration.

The combined results of Rueter et al. (51,52) provide evidence for adaptive changes in monoaminergic neurotransmission following long-term duloxetine administration. Specifically, these studies demonstrate that following long-term administration, duloxetine inhibits the reuptake of both NE and 5-HT without significantly altering the sensitivity of post-synaptic 5-HT_{1A} receptors or α_2 -adrenoceptors in the rat hippocampus. In addition, Rueter et al. (52) demonstrated that in the rat dorsal raphe nucleus, electrical stimulation increases release of 5-HT in the hippocampus. This enhancement may be due to desensitization of somatodendritic 5-HT_{1A} receptors (51,52) since 5-HT_{1A} somatodendritic autoreceptors negatively control the firing of dorsal raphe neurons and 5-HT release in this brain region. Furthermore, chronic duloxetine administration may also result in desensitization of α_2 -adrenergic autoreceptors on noradrenergic terminals in the hippocampus. Consistent

with this hypothesis, an overflow of NE release in the hippocampus is observed following stimulation, perhaps due to the α_2 -adrenoceptor (autoreceptor) negative control of the release of NE (52). Taken altogether, alterations in monoamine neurotransmission following chronic duloxetine treatment are similar to the physiologic effects observed after chronic treatment with other antidepressants (8,10,13,40).

Consistent with the current leading hypothesis of antidepressant efficacy, Rueter et al. (51,52) demonstrated that duloxetine may desensitize 5-HT_{1A} autoreceptors and modulate α_2 -adrenoceptors. However, it is also conceivable that duloxetine administration modulates serotonergic or noradrenergic receptors other than those that were specifically investigated by these authors (51,52). Furthermore, adaptive alterations that occur within the central nervous system as a result of treatment with duloxetine or other antidepressants, may be a reflection of indirect cross-talk with other neurotransmitter systems. Thus, the precise mechanisms underlying adaptive changes within the central nervous system following chronic duloxetine administration are not fully understood and whether these alterations (or other adaptive changes, as yet undefined) are responsible for the agent's putative therapeutic benefits remains to be elucidated.

DULOXETINE IN MODELS OF AGING

Although a delay in clinical improvement of four to six weeks is not uncommon following initiation of antidepressant treatment, in elderly patients, six to twelve weeks may be necessary before therapeutic benefits are observed (59). This delay may be due to adaptive changes in monoaminergic systems that occur across the lifespan. Duloxetine has been utilized to investigate alterations in monoaminergic neurotransmission that occur with aging using rodents at various ages which represent different stages of the reproductive lifespan.

In one model of aging, young (3–5 month) and old (17–20 month) rats were chronically administered either duloxetine or fluoxetine prior to extracellular recordings of spontaneously firing CA1 and CA3 pyramidal neurons. Following 5-HT application, RT₅₀ values were significantly increased in both young and old fluoxetine-treatment groups, but not in chronically treated duloxetine groups. These different patterns of recovery may be due to the differences in reuptake profile of fluoxetine vs. duloxetine (62). In a similar model of aging, microiontophoretically applied 5-HT in the hippocampus increased sensitivity to microiontophoretically administered duloxetine with increasing age (64). In the oldest group of rats examined, 24 to 27 months of age (which are comparable to senescent stages of life), initial co-application of 5-HT and duloxetine significantly increased RT₅₀ values. This result indicates an enhancement of the inhibitory response produced by application of 5-HT alone. However, with continued co-application of 5-HT and duloxetine the prolonged recovery phase is lost. One possible explanation for these results may be that, with advancing age, the number of 5-HT transporter sites declines such that there is no longer effective 5-HT reuptake or inactivation of serotonergic neurotransmission.

Indeed, others have reported age related changes in the responsiveness of hippocampal neurons to both NE and 5-HT. For example, in the aging rodent hippocampus there is a reduction in the number of pyramidal cells that spontaneously discharge in response to

microinjection of NE and 5-HT. There is also a progressive increase in ED_{50} for 5-HT in rodents aged 18–20 months and older (5). Additionally, our laboratory has previously demonstrated that independent of age-related changes in sensitivity to microiontophoretic application of 5-HT to hippocampal pyramidal neurons, the selective neurotoxin, 5,7-dihydroxytryptamine, induces significant increases in RT_{50} values in old vs. young rodents. These results suggest that serotonergic neurotransmission is altered even more with aging if a neurotoxic insult is also present (17). Taken together, these results support the notion that age related changes definitely occur within both noradrenergic and serotonergic systems as a result of aging and suggest that different treatment regimens may be especially advantageous in treating elderly patients with symptoms of depression.

BEHAVIORAL EFFECTS OF DULOXETINE

In addition to physiologic and molecular evidence, duloxetine produces behaviors characteristic of other antidepressants in well-characterized animal models of depression. For example, when administered either alone (37,50) or in combination with a 5-HT_{1A} receptor antagonist (39), duloxetine significantly attenuates immobility in rodent forced swim tests. Immobility during forced swimming is also prevented by other antidepressant treatments including monoamine oxidase inhibitors, tricyclic antidepressants, and electroconvulsive shock. The immobility induced by duloxetine is greater than that produced by either amitriptyline or maprotiline suggesting enhanced efficacy of this new pharmacologic agent (37). Furthermore, similar to amitriptyline and maprotiline, in EEG studies duloxetine decreases REM sleep. However, unlike tricyclic antidepressants, duloxetine increases awake periods and decreases slow wave deep sleep (37). These discrepancies may be due to the dual reuptake inhibition profile of duloxetine and its lack of affinity for other receptors within the central nervous system.

SAFETY AND EFFICACY OF DULOXETINE IN THE TREATMENT OF DEPRESSION

In clinical studies, pharmacokinetic evaluation of duloxetine has established its plasma half-life as approximately 12.5 h. However, neither the therapeutic levels required within the central nervous system for efficacy nor the drug's half-life within the brain has yet been determined (48). Duloxetine follows a one-compartment model with first order absorption and first order elimination rates. This indicates linear pharmacokinetics with respect to both dose and duration of treatment (56). Duloxetine undergoes extensive biotransformation to form an active metabolite. The primary amine of duloxetine inhibits NE and 5-HT reuptake with approximately one-fifth the potency of the parent compound (21). As such, this metabolite may extend the duration of duloxetine's therapeutic effects. It should also be noted that the neurochemical profile of duloxetine in human subjects closely matches the preclinical findings, including inhibition of binding to the human 5-HT and NE transporters with K_i values of 0.8 and 7.5 nM, respectively (2). In a study of

healthy human volunteers receiving duloxetine (20 or 60 mg/day) or placebo, duloxetine has a profile of a selective 5-HT reuptake inhibitor; its effect on whole blood 5-HT content, confirms the serotonergic profile of this agent (64).

The efficacy of duloxetine as an antidepressant was evaluated following a 6-week open-label uncontrolled multicenter study of 79 patients (3). Clinical efficacy, determined by a 50% reduction in the Hamilton Depression Rating Score, was obtained in 78% of patients. Moreover, remission, defined as a Hamilton Depression Scale score less than 6, occurred in 60% of patients. Adverse events, reported by more than 5% of patients, were relatively minor in severity and included insomnia, nausea, headache, diarrhea, somnolence, dry mouth, tremor, constipation, dizziness, flu, and agitation. Treatment with duloxetine is associated with a small increase in blood pressure presumably due to blockade of NE reuptake. Abrupt discontinuation of duloxetine is associated with transient sleep disturbances, a mild withdrawal effect. However, overall, duloxetine is well tolerated, with an adverse effect profile similar to that of other established antidepressants.

A recent placebo-controlled double blind study compared 120 mg duloxetine (60 mg b.i.d.), fluoxetine (20 mg q.d.), and placebo, in 173 patients diagnosed with moderate depression (23). Despite methodological flaws, early evidence from this study suggests that, in comparison with placebo, duloxetine is both effective and safe in the treatment of major depressive disorders.

Duloxetine treatment resulted in a significantly greater mean improvement than placebo on Hamilton Depression Rating Scores and most secondary outcomes, including anxiety and retardation. Furthermore, a subset analysis indicates that duloxetine may provide more robust antidepressant effects in patients with greater symptom severity. Only insomnia and weakness are reported to occur with significantly greater frequency among those receiving duloxetine compared to placebo. Although vital sign changes such as increased heart rate and elevated diastolic blood pressure occurred more frequently among patients receiving duloxetine, the increases were not of clinical significance. Despite elevations in liver function tests in the duloxetine treatment group, transaminase levels were <3 times the upper limit of normal and resolved with continued treatment or discontinuation. Overall, results from this study indicate that duloxetine possesses a favorable cardiovascular profile and suggest that further evaluation of duloxetine in the treatment of depression is warranted.

OTHER USES FOR DULOXETINE

In addition to duloxetine's use as a centrally active compound, the agent is also under investigation for potential use in the periphery. Since the parasympathetic, sympathetic, and somatic systems, which control urinary tract function, are innervated by 5-HT and NE neuronal systems, duloxetine has been investigated for effects on urinary tract function. Duloxetine dose-dependently suppressed bladder activity by increasing neural activity to the external urethral sphincter and increased bladder capacity under conditions of bladder irritation in anesthetized female felines (63). These effects are antagonized by methiothepin, a nonselective 5-HT receptor antagonist. Since bladder contractions evoked by direct electrical stimulation of efferent fibers in the pelvic nerve are not affected by duloxetine, it is presumed that duloxetine mediates its effects on the bladder via central mechanisms.

Thus, preliminary evidence also supports a possible role for duloxetine in the treatment of urinary stress incontinence and mixed incontinence.

CONCLUSIONS

Questions remain regarding the mechanisms of duloxetine action and precise clinical utility. For example, will dual inhibition of NE and 5-HT reuptake yield a more rapid response in treating depression than current antidepressants? Will the dual inhibition of duloxetine prove to have increased efficacy for patients suffering from treatment-resistant depression? While the answers to these questions remain to be answered, it is clear that duloxetine possesses neurochemical, physiological, and behavioral properties consistent with other efficacious antidepressants. As such, duloxetine may well be a new prototypic compound for the treatment of depression due to its role as a dual monoamine modulator.

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