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Comparison of pharmacological profiles of serotonin norepinephrine reuptake inhibitors

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ABSTRACT

Serotonin norepinephrine reuptake inhibitors (SNRIs) work by inhibiting the reuptake of the neurotransmitters serotonin and norepinephrine. This results in an increase in the extracellular concentrations of serotonin and norepinephrine and therefore an increase in neurotransmission. The three SNRIs milnacipran, duloxetine, and venlafaxine have different affinity and selectivity profiles. Milnacipran and duloxetine inhibit the reuptake of serotonin and norepinephrine at all doses. In contrast, venlafaxine selectively inhibits the reuptake of serotonin at low doses, but this serotonin transporter specificity disappears as the dose increases (i.e., it acts as an SNRI). In addition, the SNRIs, as well as the SSRIs, have few significant side effects because they interact only infrequently with other neurotransmitter receptors. Milnacipran and duloxetine seem to have fewer side effects and essentially show no cardiovascular toxicity. However, venlafaxine appears the least well-tolerated because of a high incidence of serotonergic adverse events (nausea, sexual dysfunction, withdrawal problems) and dose-dependent hypertension. SNRIs have increased efficacy and good tolerability and are used for the treatment of anxiety disorders and chronic pain. Our results suggest that SNRIs may have more advantages than other kinds of antidepressants and that the differences in the pharmacological profiles of each should be understood when using them.

Keywords: Antidepressants; depression; SNRI; milnacipran; duloxetine; venlafaxine

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INTRODUCTION

Pharmacotherapy of depression was achieved primarily through studies of drugs such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) in the 1950s. TCAs increase the synaptic concentrations of serotonin (5-HT) and norepinephrine (NA) by blocking the reuptake of both transmitters. MAOIs prevent the breakdown of monoamine neurotransmitters and increase their availability by inhibiting the activity of monoamine oxidase. Studies of these drugs revealed that antidepressants act by increasing the synaptic concentrations of neurotransmitters such as 5-HT and NA, which gave rise to the hypothesis that abnormal monoaminergic transmission was relevant for the onset of depression.

Though TCAs have an important role in the treatment of depression, their interactions with a variety of neurotransmitter receptors (i.e., serotonergic, adrenergic, histaminergic, and cholinergic receptors) result in poor tolerability and toxicity in

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overdose. The use of TCAs is now mostly limited to patients who do not respond to other antidepressants.

Selective serotonin reuptake inhibitors (SSRIs) enhance serotonergic neurotransmission by selective inhibition of the 5-HT transporter. They are well-tolerated and result in fewer side effects due to their higher specificity for the relevant neurotransmitter system. However, they have limited efficacy, with response rates of 60% to 70% and remission rates of 30% to 40%, and they are considered comparable to TCAs in terms of efficacy. It is controversial whether SSRIs are as effective as TCAs, especially for the treatment of severely depressed patients [1]. It is generally considered to take 2 to 4 weeks to achieve the antidepressant effects of SSRIs, which is comparable to the situation with TCAs. Although Taylor and colleagues [2] reported the early onset of antidepressant action of SSRIs in their review, which compared SSRIs with placebo, they suggested that it took several weeks to get a statistically significant benefit in terms of remission. For the treatment of depression, the SSRIs are considered the first-line treatment due to their good tolerability.

SNRIs enhance serotonergic and noradrenergic neurotransmission by inhibiting both transporters. Therefore, the effect of SNRIs is thought to be related to that of TCAs. Papakostas and colleagues [3] reported that serotonergic-noradrenergic drugs seem to have a modest efficacy advantage over SSRIs in major depressive disorder. Similar to SSRIs, SNRIs have few interactions at other neurotransmitter receptors, and are therefore expected to be ideal antidepressants. There are currently three SNRIs: milnacipran, duloxetine, and venlafaxine. In this review, we will compare the pharmacological profiles of these three drugs.

PHARMACOLOGICAL PROFILES

SNRIs block the 5-HT and NA transporters, which results in increased levels of 5-HT and NA available for postsynaptic receptor binding. SNRIs also inhibit dopamine (DA) reuptake to some extent, which has little clinical significance [4].

SNRIs have low affinity for other neurotransmitter receptors, such as muscarinic, alpha 1 adrenergic, dopamine D2, histaminergic H1, serotonergic (5-HT1A, 5-HT1B, 5-HT1D, 5-HT2A, 5-HT2C), and opioid receptors. Thus, the administration of SNRIs causes neither cardiovascular nor anticholinergic side effects.

Although milnacipran, duloxetine, and venlafaxine share the same pharmacological mechanism (5-HT and NA transporter inhibition), they differ considerably in terms of affinity and selectivity.

In vitro studies have found that milnacipran has almost equal affinity for 5-HT and NA transporters and may even be slightly more adrenergic than serotonergic (Table 1) [5, 6]. Milnacipran is considered to be the most balanced drug, and the pharmacological profile of milnacipran is similar to that of TCAs.

Similarly, duloxetine acts on both neurotransmitters, and inhibition is balanced throughout the dosing range, although it is more selective for the 5-HT transporter.

On the other hand, venlafaxine has a high affinity for the 5-HT transporter and a low affinity for the NA transporter at low doses. Therefore, it acts as an SSRI at low doses. The dual-action mechanism of venlafaxine is dose-dependent, and inhibition of norepinephrine increases as the dose increased.

Whereas milnacipran blocks 5-HT and NA reuptake with equal affinity, duloxetine has a 10-fold selectivity for 5-HT and venlafaxine a 30-fold selectivity for 5-HT [7].

Table 1.
In vitro inhibition of binding to human monoamine transporter

Inhibitor	Ki (nmol/L)		
	Serotonin	Norepinephrine	Dopamine
Milnacipran	8.44 ± 1.57*	22 ± 2.58*	>100,000*
	123 ± 11†	200 ± 2†	>10,000†
Duloxetine	0.07 ± 0.01*	1.17 ± 0.11*	230 ± 17*
	0.8 ± 0.04†	7.5 ± 0.3†	240 ± 23†
Venlafaxine	7.80 ± 0.28*	1920 ± 158*	6050 ± 676*
	82 ± 3†	2483 ± 43†	7647 ± 793†

* Data by Vaishnavi et al. (2004). [3]
† Data by Koch et al. (2003). [4]

MICRODIALYSIS STUDIES

The extracellular levels of the monoamines in brain regions can be measured using the microdialysis technique in conscious, freely moving animals [8]. This method can measure changes in a variety of neurotransmitters following the systemic administration of drugs. For example, the extracellular level of NA in various brain regions increases after administration of selective norepinephrine reuptake inhibitors such as reboxetine and atomoxetine, but that of 5-HT does not. In contrast, the extracellular level of 5-HT increases after administration of an SSRI.

Mochizuki and colleagues [9] found dose-dependent increases in both the 5-HT and NA concentrations in the medial prefrontal cortex of rats after oral administration of milnacipran 10 and 30 mg/kg. In another study, however, the intraperitoneal injection (IP) of milnacipran 5 mg/kg produced a minimal increase in the levels of 5-HT and NA in the prefrontal cortex of rats, and 40 mg/kg IP resulted in only a small increase in NA levels and an even smaller increase in 5-HT levels [6].

The oral administration of duloxetine 3.125-12.5 mg/kg produced dose-dependent increases in the levels of both 5-HT and NA in the rat frontal cortex [10]. Similar increases were obtained for 5-HT and NA after the subcutaneous administration of duloxetine 5 mg/kg [11]. In another study, IP administration of duloxetine produced increases in the levels of 5-HT and NA in the hypothalamus [12]. Duloxetine 5 mg/kg IP administration resulted in equal increases in the levels of 5-HT and NA, and 15 mg/kg IP resulted in a greater increase in the level of NA than that of 5-HT [6].

The IP administration of venlafaxine 5-40 mg/kg produced a dose-dependent increase in the levels of both 5-HT and NA in the prefrontal cortex of freely moving rats [6]. Similar increases were obtained in the levels of 5-HT and NA in the rat frontal cortex [13, 14] and hippocampus [15]. Moret and colleagues [16] found that the administration of venlafaxine >40 mg/kg IP resulted in a dose-dependent increase in 5-HT; 160 mg/kg IP only enhanced the NA level in the hypothalamus of guinea pigs. The IP administration of venlafaxine 8 mg/kg increased the level of 5-HT more than that of NA in the frontal cortex of freely moving mice.

HUMAN STUDIES

Several studies have been conducted in man. The tyramine pressor response was reduced after high doses (375 mg/day) of venlafaxine, but not after low doses (75 mg/day) [17]. Similarly, duloxetine did not reduce the response at doses between 20 and 120 mg/day, but had other effects, such as increased blood pressure, suggesting that it has some effect on NA reuptake at higher doses [18]. To the best of our knowledge, there have been no similar studies for milnacipran.

HYPOTHESIS ON ANTIDEPRESSANT ACTION

As mentioned above, all effective antidepressants produce an antidepressant effect by blocking one or more of the presynaptic transporters and boosting the synaptic action of monoamines such as 5-HT and NA. This pharmacological action is consistent with the monoamine hypothesis of depression, which postulates that the synaptic concentration of monoamines is decreased and antidepressants have to stimulate monoaminergic transmission in order to be effective. The inhibition of monoamine transporters is an acute pharmacological effect and can raise monoamine levels quite rapidly. However, 2 to 4 weeks will be needed for therapeutic pharmacological efficacy to be realized. If this hypothesis were true, the antidepressant effect would be achieved more rapidly.

Therefore, it is widely accepted that there is a time delay between the acute increases in neurotransmitter levels and they adaptive changes in neurotransmitter receptor sensitivity that they cause.

The administration of an SSRI blocks the presynaptic 5-HT transporter and inhibits the reuptake of 5-HT. The level of 5-HT rises much more at the somatodendritic area located in the dorsal raphe rather than in the areas of the brain where the axons terminate. 5HT1A receptors exist in the midbrain raphe, so the increased 5-HT levels in the somatodendritic area stimulate the nearby 5-HT1A.

After more than 2 weeks of administration, the increased 5-HT levels act at the somatodendritic 5HT1A autoreceptors continuously and cause them to downregulate and become desensitized. Once the 5-HT1A somatodendritic autoreceptors are desensitized, the negative feedback mechanism of 5-HT release is inhibited. Subsequently, 5-HT neurons are disinhibited, resulting in an increase in the synaptic concentration of 5-HT.

This may be the most convincing theory of the pharmacodynamics of antidepressants. Adaptive changes in neurotransmitter receptor sensitivity are thought to be consistent with the delayed onset of the antidepressant effects. The combination of an SSRI and a selective 5-HT1A antagonist increased the release of 5-HT in the frontal lobe in the initial stages [19]. Similarly, the combination of an SNRI, milnacipran or duloxetine, and a selective 5-HT1A antagonist increased the release of 5-HT [20].

5-HT1A autoreceptor desensitization was reported to occur earlier with SNRI administration than SSRI administration [21].This may be due to the fact that the NA neuron promotes the firing of the 5-HT neuron by stimulating the alpha adrenergic receptor in the 5-HT nerve cell body.

CONCLUSIONS

There is demand for more effective and faster-acting antidepressants. All SNRIs inhibit the reuptake of 5-HT and NA, increasing the extracellular concentrations of both neurotransmitters. The dual-acting SNRIs may be more effective and faster-acting than SSRIs, selectively inhibiting 5-HT reuptake [3]. The three SNRIs milnacipran, duloxetine, and venlafaxine have different affinity and selectivity profiles. Milnacipran and duloxetine inhibit the reuptake of both 5-HT and NA at all doses. In contrast, venlafaxine selectively inhibits the reuptake of 5-HT at low doses, but inhibits both neurotransmitters at high doses. At low doses, venlafaxine acts as an SSRI.

In addition, SNRIs, as well as SSRIs, have fewer clinically significant side effects because they interact only infrequently with other neurotransmitter receptors. Milnacipran and duloxetine seem to have fewer side effects, and exhibit virtually no cardiovascular toxicity. However, venlafaxine appears the least well-tolerated due to its high incidence of serotonergic adverse events (nausea, sexual dysfunction, withdrawal problems) and dose-dependent hypertension [7].

Furthermore, SNRIs are now considered to be effective for treating various anxiety disorders [7, 22] and chronic pain [23, 24].

SNRIs are thus more effective, and are well-tolerated and are available for treating anxiety disorders and chronic pain. Our results suggest that the SNRIs may have more advantages than other kinds of antidepressants and that the differences in the pharmacological profiles of each should be understood when using them.

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