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Serotonin Noradrenaline Reuptake Inhibitors (SNRIs)

Ipek Komsuoglu Celikyurt,
Oguz Mutlu and Guner Ulak

*Kocaeli University, Medical Faculty, Pharmacology Department,
Psychopharmacology Laboratory, Umuttepe, Kocaeli,
Turkiye*

1. Introduction

Antidepressants that block the reuptake of serotonin (5-HT) and noradrenaline (NA) are called 5-HT and NA reuptake inhibitors (SNRIs). SNRIs are agents that show “dual action” on 5-HT and NA. These drugs bind the 5-HT transporters (SERT) and NA transporters (NAT) similar to tricyclic antidepressants (TCAs). However, SNRIs differ from TCAs in that SNRIs do not exert much affinity for other receptors. Although SNRIs are called “dual action” 5-HT - NA agents they increase dopamine levels in the prefrontal cortex via NAT inhibition. In this way, they have a third action on neurotransmitters in the prefrontal cortex.

The main use of SNRIs is in the treatment of major depression. Other applications include treatment of pain disorders (including neuropathies and fibromyalgia), generalized anxiety, vasomotor symptoms of menopause and stress urinary incontinence (Susman N, 2003). The class of SNRIs now comprises five medications: venlafaxine (Effexor XR, Efexor XR), its metabolite desvenlafaxine (Pristique), milnacipran (Ixel, Toledomin), duloxetine (Cymbalta, Xeristar) and mirtazapine (Remeron).

1. Venlafaxine XR (Effexor)
25, 37.5, 50, 75, 100 mg tablets; 37.5, 75, 150 mg extended release capsules
2. Desvenlafaxine (Pristique)
50, 100 mg capsules
3. Milnacipran (Ixel, Toledomin)
100 mg/day (given as 50 mg 2 times daily,
with a starting period of 4 days on 25 mg/day).
4. Duloxetine (Cymbalta)
20, 30, 50 mg capsules
5. Mirtazapine (Remeron)
15 mg to 45 mg/day

Table 1. Serotonin norepinephrine reuptake inhibitors (SNRIs)

2. Pharmacology

2.1 Pharmacodynamics

SNRIs bind to 5-HT and NA transporters to selectively inhibit the reuptake of these neurotransmitters from the synaptic clefts. They have a “dual mode of action”. SNRIs block the reuptake of both 5-HT and NA with differing selectivity. Whereas milnacipran blocks 5-HT and NA reuptake with equal affinity, duloxetine has a 10-fold greater selectivity for 5-HT, and venlafaxine has a 30-fold greater selectivity for 5-HT (Stahl et al., 2005).

Venlafaxine was the first SNRI to be introduced. Venlafaxine inhibits neuronal uptake of 5-HT (most potent, present at low doses), NA (moderate potency, present at high doses) and dopamine (DA) in order of decreasing potency. Venlafaxine has no affinity for α - or β -adrenoceptors, benzodiazepine or opiate receptors. It has a much greater affinity for the 5-HT transporter than for the norepinephrine (NE) transporter. At low doses, it inhibits the 5-HT transporter almost exclusively, acting like a selective serotonin reuptake inhibitor (SSRI), with significant NE reuptake inhibition only occurring at higher doses (Saletu et al., 1992).

Desvenlafaxine is a synthetic form of the isolated major active metabolite of venlafaxine. The neurotransmitters affected by the drug are 5-HT and NE. It is approximately 10 times more potent at inhibiting 5-HT uptake than NE uptake. It has low affinity for other brain neurotransmitter targets, including muscarinic, cholinergic, histamine (H1) and α -adrenergic receptors (Whyte & Dawson, 2003; Septien-Velez et al., 2007).

Previous studies demonstrated that duloxetine potently inhibits neuronal 5-HT and NE re-uptake. It has been demonstrated that this inhibition is balanced throughout the dosing range compared to venlafaxine, which demonstrates low inhibition of NA at low doses and rises as the dose escalates. Duloxetine is also considered a less potent inhibitor of dopamine re-uptake. Duloxetine has no significant affinity for adrenergic, cholinergic, histaminergic, opioid, glutamate, or GABA receptors. It binds selectively with high affinity to both NA and 5-HT transporters and lacks affinity for monoamine receptors within the central nervous system. Additionally, duloxetine is a more potent 5-HT reuptake inhibitor compared to fluoxetine (SSRI) (Westanmo & Gayken, 2005; Bymaster et al., 2001).

Milnacipran is the most balanced SNRI, and some studies have even found it to be slightly more effective for the NE transporter compared with the 5-HT transporter. Milnacipran inhibits the re-uptake of 5-HT and NA in an approximate 1:3 ratio; in practical use, this means a relatively balanced action upon both neurotransmitters. Milnacipran shows antidepressive activity due to suppression of 5-HT re-uptake and NA in postsynaptic receptors. Milnacipran exerts no significant actions on H1, α 1, DA1, DA2, and mACh receptors or on benzodiazepine and opioid binding sites. The biochemical profile of milnacipran and its lack of interaction with other neurotransmitters indicate that the drug may be maximally effective in the treatment of depression while being free of the side-effects associated with other antidepressants. Simultaneous inhibition of both 5-HT and NA works synergistically to treat both fibromyalgia and depression (Vaishnavi & Nemeroff, 2004).

Mirtazapine is a tetracyclic compound with antidepressant activity. It has a unique mechanism of action that is different from classical tricyclic antidepressants, the SSRIs and monoamine oxidase inhibitors. Therefore, it could be described as a noradrenergic and

specific serotonergic antidepressant. Mirtazapine's pharmacological profile is characterized by a potent presynaptic alpha-2-adrenergic antagonist activity, 5-HT₁ agonist activity, and potent 5-HT₂ and 5-HT₃ antagonist activities as well as by a potent H₁ antagonistic activity. The blockade of presynaptic alpha-2-adrenergic receptors is considered as a possible mechanism for the antidepressant activity of mirtazapine. It is also a strong H₁ receptor antagonist, therefore, it causes sedative side effects (Dekeyne & Millan, 2008; Millan et al., 2000).

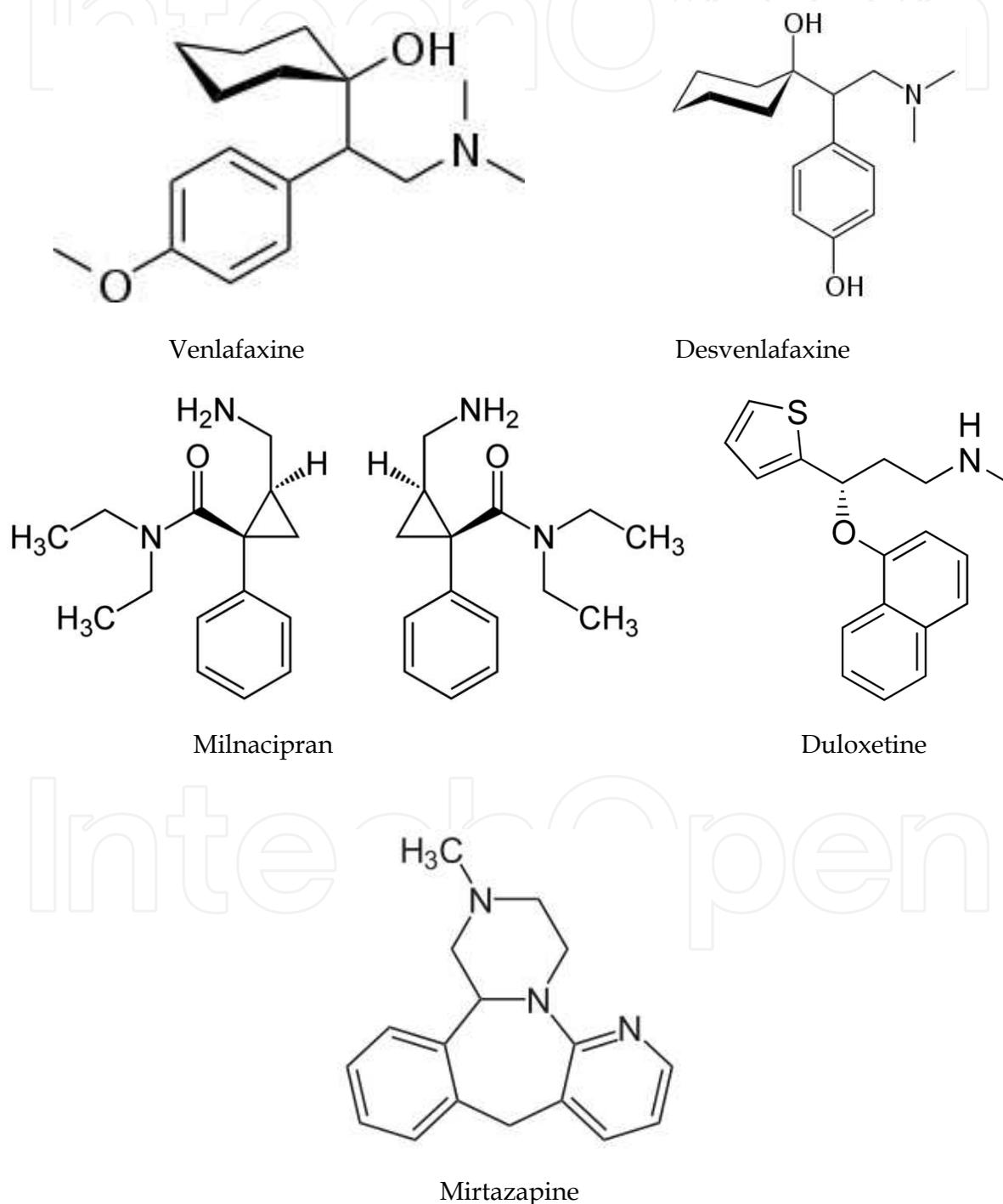
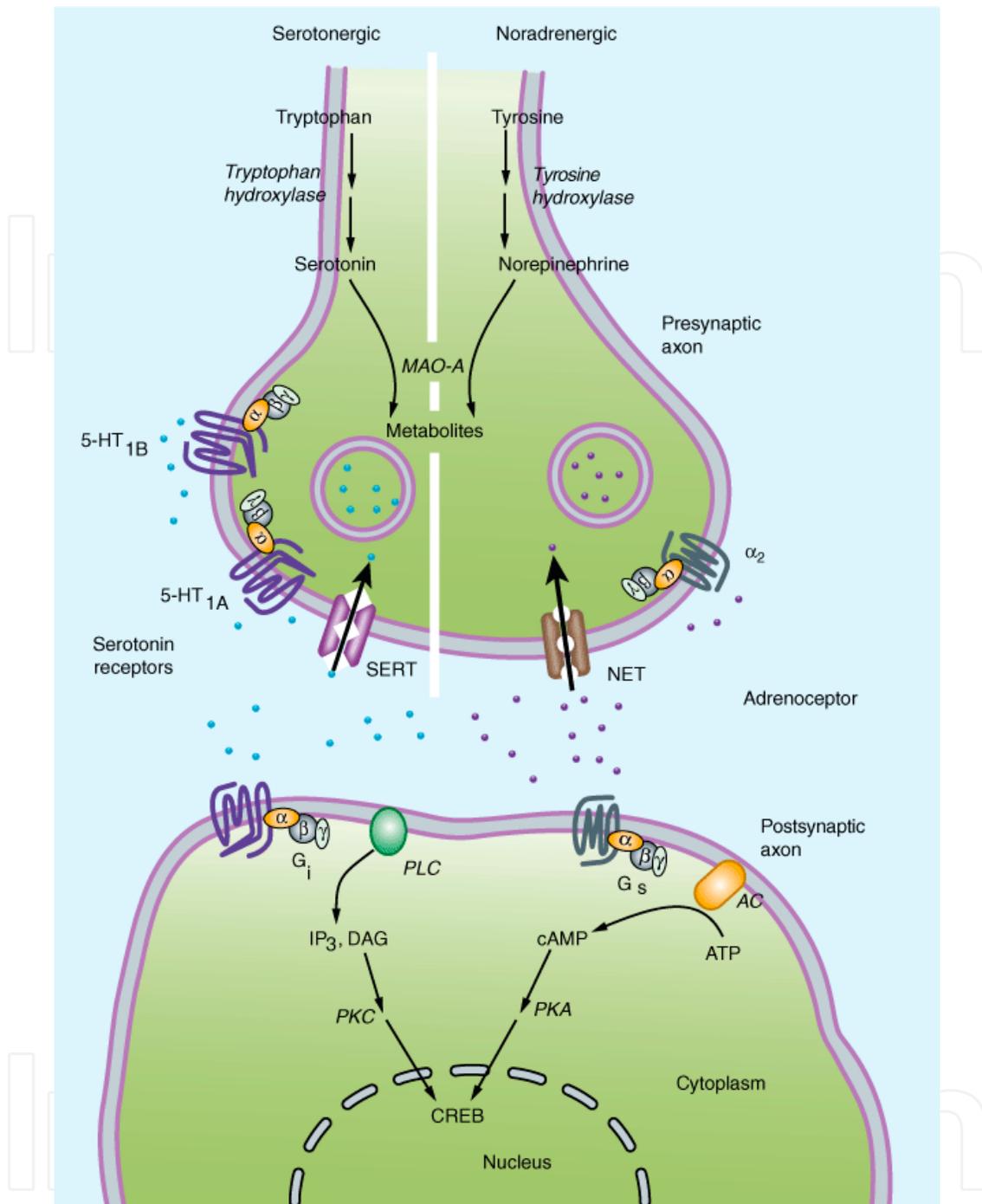


Fig. 1. Structure of SNRI-class antidepressants



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th Edition: <http://www.accessmedicine.com>
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Fig. 2. The aminohypothesis of major depression. Depression appears to be associated with changes in serotonin and norepinephrine signaling in brain (or both) with significant downstream effects. Most antidepressants cause changes in amine signaling. AC, adenylyl cyclase; 5-HT, serotonin; CREB, cAMP response element binding (protein); DAG, diacylglycerol; IP₃, inositol trisphosphate; MAO (monoamine oxidase), NET (norepinephrine transporter), PKC: protein kinase C; PLC, phospholipase C; SERT, serotonin transporter (From: Katzung, B.G.; Masters, S.B.; Trevor, A.J. 11th edition. Basic and clinical pharmacology. International edition).

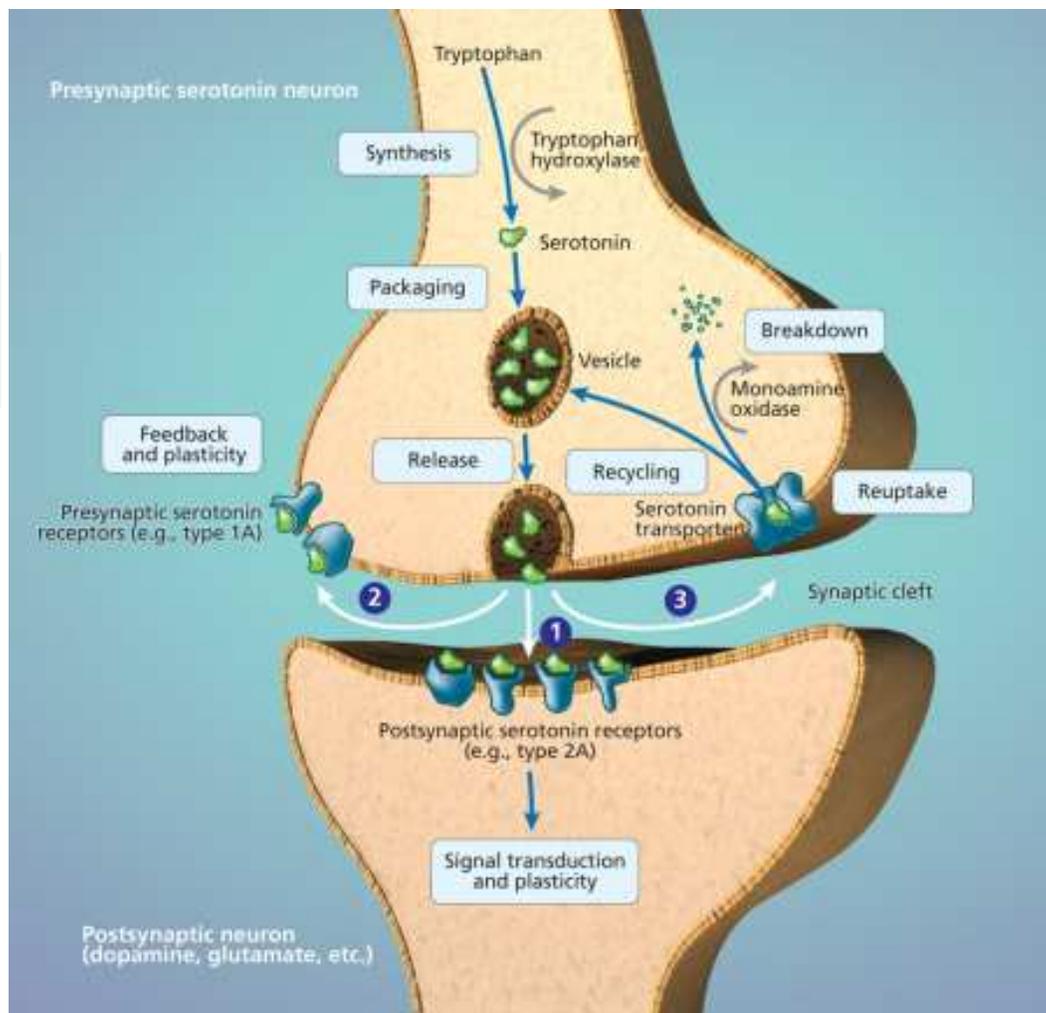


Fig. 3. The serotonin synapse. Serotonin is synthesized from tryptophan by the enzyme tryptophan hydroxylase. Serotonin is then packaged into vesicles for release into the synaptic cleft, which occurs when there is sufficient stimulation of the neuron. Serotonin released from the serotonin neuron into the synaptic cleft has multiple actions. (1) Serotonin binds to its receptors on other neurons. Activation of postsynaptic receptors results in transduction of the signal that initially stimulated the serotonin neuron. (2) Serotonin also binds to presynaptic serotonin receptors on the neuron from which it was released, which provides feedback and regulates plasticity of the neuron. (3) Serotonin is taken up back into the presynaptic serotonin neuron by the serotonin transporter. Serotonin is then recycled for future release or broken down by monoamine oxidase and excreted in urine (From: aan het Rot, M., Mathew, S.J.; Charney, D.S. (2009). Neurobiological mechanisms in major depressive disorder. *CMAJ*. 3;180(3):305-13).

2.2 Pharmacokinetics

Venlafaxine is a bicyclic phenylethylamine derivative. The mean half-life of venlafaxine is approximately 4 h and is relatively short. Venlafaxine is well-absorbed from the gastrointestinal tract and is a substrate for CYP450. It is extensively metabolized in the liver via the CYP2D6 isoenzyme to desvenlafaxine (O-desmethylvenlafaxine), which is just as potent a 5-HT-NA reuptake inhibitor as the parent compound. This means that the

differences in the metabolism between extensive and poor metabolizers are not clinically important in terms of efficacy. Therapeutic effects are usually achieved within 3 to 4 weeks. The primary route of excretion of venlafaxine and its metabolites is via the kidneys (Wellington and Perry, 2001). Desvenlafaxine has linear pharmacokinetics, low protein binding, a half-life of approximately 10 h and is metabolized primarily via glucuronidation and to a minor extent, through CYP3A4. The desvenlafaxine succinate has a good oral bioavailability. Clearance rates are reduced in the elderly, those with severe renal dysfunction and those with moderate to severe hepatic dysfunction, each of which may require dosage adjustments. Desvenlafaxine is excreted in the urine, is minimally metabolized via the CYP450 pathway and is a weak inhibitor of CYP2D6 (De Martinis et al., 2007; Liebowitz & Yeung, 2007; Septien- Velez et al., 2007).

Duloxetine shows linear kinetics. The therapeutic dose range is 60-120 mg/day. Duloxetine has an elimination half-life of approximately 12.5 hours (range of 8 to 17 hours), and its pharmacokinetics are dose proportional over the therapeutic range. Steady-state is usually achieved after 3 days. Elimination of duloxetine is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP1A2 (Papakostas GI et al., 2007).

Properties of SNRIs	Venlafaxine	Desvenlafaxine	Duloxetine	Milnacipran	Mirtazapine
Therapeutic dose range	75-375 mg/day	50 mg/day	60-120 mg/day	25-200 mg/day	15-45 mg/day
Biotransformation	CYP2D6	CYP3A4	CYP2D6, CYP1A2	CYP2D6, CYP2C9	CYP2D6, CYP3A4, CYP1A2
Half -life	4 h	9-10 h	12.5 h	12 h	20-40 h
Elimination route	renal	renal	renal, urine (72%), faeces (19%)	renal	Renal urine (75%), faeces (15 %)
NE/5HT affinity ratio	15:7	13:8	9:3	2:1	-
5HT/NE selectivity	30	3 x higher (NE binding)	10	1	300
Efficacy	SNRI action is dose dependent	Beter efficacy at low doses	May require higher than the approved doses	Beter efficacy at higher doses	Dose dependent
Hepatic side effects	Elevated liver enzymes	-	Complicated by alcohol consumption	Elevated liver enzymes	Hepatic insufficiency
Cardiac side effects	+	QTc interval prolongation	-	-	-
Sexual dysfunction	Loss of libido, anorgasmia	Delayed ejaculation	Loss of libido, anorgasmia	Decrease in sexual desire and ability	Not cause significant sexual dysfunction

Table 1. Quote from: Dell'Osso B, Buoli M, Baldwin DS, Altamura AC. Serotonin norepinephrine reuptake inhibitors (SNRIs) in anxiety disorders: a comprehensive review of their clinical efficacy. *Hum Psychopharmacol.* 2010 Jan;25(1):17-29.

Milnacipran shows linear pharmacokinetics over a dose range of 25-200 mg/day. Milnacipran is rapidly and extensively absorbed and has a high bioavailability. Peak plasma concentrations are reached 2 hours after oral dosing. The elimination half-life is relatively short (12 hours) and

is increased by significant renal disease. Milnacipran is conjugated to an inactive glucuronide and excreted in the urine as an unchanged drug and conjugate. Enzymes of the CYP class do not play a role in the metabolism of this antidepressant drug so the risk of interactions with drugs metabolized by CYP enzymes is minimal (Puozzo & Panconi, 2002).

Mirtazapine has an elimination half-life of 20-40 hours. Like most other antidepressants with a therapeutic-latency mirtazapine may require as long as 2-4 weeks for the therapeutic benefits of the drug to become evident. It is metabolized in the liver by the enzymes CYP2D6, CYP3A4 and CYP1A2. It does not have an active metabolite (Timmer & Ad Sitsen, 2000).

3. Medical uses

3.1 Efficacy and tolerability

Depression is characterized by the presence of depressed mood and anhedonia (decreased pleasure or interest). It is also accompanied by a plethora of other signs and symptoms such as changes in appetite and sleeping, fatigue and loss of energy, psychomotor agitation or retardation, feelings of worthlessness or inappropriate guilt and diminished ability to think or concentrate (Bauer & Bschor, 2007). In general, antidepressants that are used today are effective in treating depression regardless of whether they primarily affect serotonergic or noradrenergic neurotransmission or both. It has been suggested that there may be differences in efficacy of antidepressants among certain patients. Evidence has demonstrated significantly greater remission rates with the SNRI venlafaxine compared with SSRIs (Bauer et al., 2009).

Evidence demonstrates that 5-HT and NA are involved in both the pathogenesis and recovery from depression. Preliminary results showed that dual acting antidepressants may have an advantage over single acting agents in terms of treating patients to remission. Dual acting agents may also be preferable for the treatment of chronic painful conditions and somatic symptoms (Sussman, 2003).

Venlafaxine is used primarily for the treatment of depression, general anxiety disorder, social phobia, panic disorder, and vasomotor symptoms. Venlafaxine inhibits the reuptake of both 5-HT and NA, thus combining two therapeutic mechanisms in one agent. The anticholinergic and cardiotoxic side effects are not as common compared with tricyclic antidepressants. Venlafaxine's serotonergic actions are present at low doses, while its noradrenergic actions are progressively enhanced as the dose increases. Venlafaxine treatment stimulated expression of brain derived neurotrophic factor protein in the frontal cortex and inhibited long-term potentiation in the hippocampus (Cooke et al., 2009).

Desvenlafaxine is a recently introduced antagonist of the human NE and 5HT transporters (hNET and hSERT) that is currently in clinical development for use in the treatment of major depressive disorder and vasomotor symptoms associated with menopause. Desvenlafaxine succinate is the succinate salt of the isolated major active metabolite of venlafaxine. Desvenlafaxine is being tested for the treatment of fibromyalgia with promising results (Wood, 2007).

Duloxetine is a newly developed tiophenpropanamin derivative. It is a SNRI indicated for the treatment of depression and for anxiety disorders but also approved for stress urinary incontinence, diabetic neuropathy and fibromyalgia. Duloxetine is approved for the treatment of major depressive disorder and diabetic peripheral neuropathic pain (Ormseth & Scholz, 2011).

Milnacipran has a balanced activity on NA and 5-HT reuptake inhibition. Its efficacy in mild, moderate, and severe depression and suitable overall tolerability are combined with a low risk of causing pharmacokinetic drug-drug interactions, sexual dysfunction, changes in body weight in normal-weight patients, and toxicity due to overdose. This particular profile qualifies milnacipran as a first-line antidepressant for many depressed patients. Patients who have been withdrawn from SSRIs or other antidepressants due to lack of efficacy or intolerance may find milnacipran to be an effective therapeutic option. Also, milnacipran is an effective treatment option for patients with fibromyalgia. Current studies do not yet provide convincing evidence supporting the efficacy of mirtazapine, reboxetine, milnacipran and duloxetine for the treatment of panic disorder patients (Kasper et al., 2010; Serretti et al., 2010).

Mirtazapine is a piperidine analogue of mianserine. Mirtazapine is a newer antidepressant that exhibits both noradrenergic and serotonergic activity. It is a tetracyclic antidepressant used primarily in the treatment of major depressive disorder. It is unlike other agents used for depression both in its mechanism of action as well as its side effects. It is at least as effective as the older antidepressants for treating mild to severe depression. Mirtazapine is relatively safe in overdose. Many clinicians consider mirtazapine a second-line or even third-line antidepressant to be used when older antidepressants are not tolerated or are ineffective. Physicians who are concerned about the risks of elevated lipid levels and agranulocytosis may choose to reserve mirtazapine as a third-line choice. It is particularly useful in patients who experience sexual side effects from other antidepressants. Mirtazapine is also a good choice in depressed patients with significant anxiety or insomnia. (Hartmann, 1999). It has been found to be useful in the treatment of generalized anxiety disorder, social anxiety disorder, obsessive-compulsive disorder, panic disorder and post-traumatic stress disorder (Benjamin & Doraiswamy, 2011).

4. Studies with SNRIs in animal models

Newer dual-acting antidepressants appear to possess analgesic effects similar to that of the TCAs but have a more favorable safety and tolerability profile. These drugs also may have an advantage over SSRIs in treating the painful physical symptoms of depression and in achieving remission of all symptoms of depression. Some animal models have been used to characterize the pathological conditions and the effects of drugs on these conditions. Researchers have compared the performance of SNRIs using novel animal models to evaluate the effects on depression, obsessive compulsive disorder, pain and learning and memory functions.

4.1 Research via SNRIs and depression in animal models

Antidepressants inhibiting the reuptake of both 5-HT and NA may exhibit efficacy superior to that of SSRIs.

Ulak et al. (2008) showed that the neuronal NOS inhibitor, 1-(2-trifluoromethylphenyl)-imidazole, augments the effects of antidepressants acting via the serotonergic system in a forced swimming test (FST) in rats.

The effects of subchronic treatment (24 days) with antidepressants displaying differential effects on NA and 5-HT reuptake on behavior, neurochemistry, and hypothalamic-pituitary-adrenal (HPA) axis activity following FST exposure in the rat were studied. Desipramine significantly decreased immobility in the FST, while paroxetine and venlafaxine were without effect. Nonetheless, treatment with all three antidepressants significantly attenuated stress-related increases in amygdaloid and cortical serotonin turnover. Desipramine attenuated the stress-associated elevation in serum corticosterone. Connor and colleagues (2000) concluded that although FST-induced increases in serotonin turnover in the frontal cortex and amygdala were attenuated following treatment with all three antidepressants, FST-induced behavioral changes and increased HPA axis activity were normalized only following desipramine treatment.

The rat forced swimming test distinguishes between selective 5-HT and selective NA reuptake inhibitors, which increase swimming and climbing behaviors, respectively. Since adaptive neurochemical processes occur in the treatment of depression, the influence of long-term antidepressant treatment on these interactions was examined. Fluoxetine, desipramine, milnacipran and mirtazapine were administered subacutely and chronically. A subacute fluoxetine-desipramine combination was administered in rats that were pre-treated with chronic-desipramine. NA system-mediated interactions were further examined by combining clonidine with fluoxetine. Results of this study showed that long-term treatment with either fluoxetine or desipramine did not modify the behavioral response produced by subacute administration. In contrast, whereas subacute-milnacipran increased climbing solely, chronic-milnacipran produced greater anti-immobility effects and increased both climbing and swimming behaviors. Similarly, the fluoxetine-desipramine combination produced climbing solely but increased both climbing and swimming behaviors in animals pre-treated with chronic desipramine. Chronic, but not subacute, mirtazapine increased swimming behavior. Clonidine dose-dependently antagonized fluoxetine-induced anti-immobility effects and swimming behavior. It was concluded that chronic enhancement of NA transmission alters NA system-mediated inhibition of 5-HT-induced behavior in the FST, which may involve alpha (2)-receptors (Rénéric & Bouvard, 2002).

Mochizuki D, et al. (2002) aimed to characterize, both neurochemically and behaviorally, the SNRI milnacipran in the prefrontal cortex in comparison with tricyclic antidepressants and selective serotonin reuptake inhibitors. It was concluded that milnacipran acts as an SNRI *in vitro* and *in vivo* and may be useful for the treatment of anxiety as well as depression (Mochizuki et al., 2002).

Researchers aimed to investigate whether estrogen level changes in ovariectomized rats may lead to depression and memory disorders and whether the effects of such changes may be reversible following administration of venlafaxine using the Porsolt forced swimming test and Morris water maze test. It was reported that the regulatory role of estrogen and venlafaxine in antidepressant activity and memory function could be related to the interactions between noradrenergic and serotonergic systems (Nowakowska & Kus, 2005).

In another study, the relationship between the antidepressant effect of venlafaxine and its ability to protect animals against stress-induced oxidative lipid peroxidation and DNA damage was investigated. It was reported that long-term venlafaxine treatment using effective antidepressant doses can protect against stress-induced oxidative cellular and DNA damage. It was concluded that this action may occur by antagonizing oxidative stress and enhancing antioxidant defense mechanisms (Abdel-Wahab & Salama, 2011).

In animal models detecting antidepressant activity, distinct NO synthase inhibitors displayed antidepressant-like action. Previous studies found that pretreatment with L-arginine counteracted the antidepressant-like effect of imipramine and venlafaxine but not the effects of bupropion or fluoxetine. Increasing the dose of L-Arg to 1000 mg/kg attenuated the antidepressant-like effects of bupropion but did not modify the action of fluoxetine. L-Arginine was devoid of any locomotor effects on the animals. In that study, the idea that some antidepressants are able to inhibit nitric oxide synthesis in the brain, an effect that could be mechanistically related to the ability of L-arginine to counteract the antidepressant-like effects, was supported (Krass et al., 2011).

Milnacipran was active in various animal models of depression, such as the forced swimming test in the mouse, learned helplessness in the rat and the olfactory bulbectomized rat model. Milnacipran represents an interesting new therapeutic option for depression being that it is as well tolerated as SSRIs but offers clinical efficacy similar to TCAs (Boyer & Briley, 1998).

Effects of co-treatment with mirtazapine and low doses of risperidone on immobility time in the forced swimming test in mice were evaluated. It was found that MIR (2.5, 5 and 10 mg/kg) and FLU (5 and 10 mg/kg) or risperidone in low doses (0.05 and 0.1 mg/kg) given alone did not change the immobility time of mice in the forced swimming test. Joint administration of MIR (5 and 10 mg/kg) or FLU (10 mg/kg) and risperidone (0.1 mg/kg) produced antidepressant-like activity in the forced swimming test (Rogó z et al., 2010).

The effect of venlafaxine, a dual reuptake inhibitor of 5-HT and NA, was evaluated in a murine model of chronic fatigue. It was concluded that daily treatment with venlafaxine for 15 days produced a significant reduction in the immobility period and reversed various behavioral, biochemical and neurotransmitter alterations induced by chronic fatigue. Therefore, venlafaxine could be of therapeutic potential in the treatment of chronic fatigue (Dhir & Kulkarni, 2008).

4.2 Research via SNRIs and anxiety and obsessive compulsive disorder in animal models

The effects of milnacipran, a 5-HT and NA reuptake inhibitor (SNRI), on the obsessive compulsive disorder (OCD) model and marble burying behavior were investigated in mice. At doses above 10 mg/kg milnacipran inhibited marble burying behavior significantly in mice similar to fluvoxamine. Milnacipran doses inhibiting marble burying behavior did not affect locomotor activity. These results suggest that the inhibition of marble burying behavior may indicate that milnacipran may be useful for OCD therapy (Sugimoto et al., 2007).

Milnacipran has not yet been systematically studied preclinically or clinically for the treatment of anxiety disorders. In the four-plate test (FPT) which is known to predict anxiolytic-like activity in mice, milnacipran demonstrated strong anti-punishment effects following acute administration. It was concluded that the activation of 5-HT_{2A} receptors is critically involved in the anxiolytic activity of milnacipran (Bourin et al., 2005).

Methods for detection of anxiolytic-like behavioral effects of serotonin uptake inhibitors are limited. Venlafaxine dose-dependently suppressed nestlet shredding and marble burying at doses that were generally without effect on rotorod performance. The amine-based antidepressant agents, imipramine and desipramine, as well as the selective NA transport inhibitor, nisoxetine, produced similar qualitative effects on these behaviors (Li & Morrow, 2006).

The effect of chronic treatment with venlafaxine on beta₁ and 5-HT₂ receptor populations was examined in the frontal cortex of olfactory bulbectomised (OB) and sham operated (SO) animals. The effect of these drugs on the behaviour of the animals on the elevated plus maze and the open field was also assessed. Removal of the bulbs resulted in a characteristic increase in locomotor activity in the OB animals in the open field which was reversed by chronic venlafaxine treatment. Venlafaxine produced a slight reduction in the number of open arm entries made by the OB animals although this failed to reach significance. A decrease in the affinity of beta₁-adrenoceptors was found following olfactory bulbectomy and this was normalised by treatment with venlafaxine. Olfactory bulbectomy did not produce any changes in 5-HT₂ receptor populations but venlafaxine administration significantly reduced the density of these receptors in both SO and OB animals. It was concluded that the usefulness of the OB as an animal model, for the detection of antidepressants from a wide variety of classes. (McGrath & Norman, 1998). The effect of acute treatment with seven antidepressants covering the classes selective serotonin reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, noradrenaline reuptake inhibitors and tricyclic antidepressants were compared with the benzodiazepine, chlordiazepoxide, on the mouse zero maze, an unconditioned model of anxiety. Duloxetine was anxiolytic after chronic but not acute treatment, reflecting clinical experience with antidepressants in general (Troelsen, 2005).

Mirtazapine is an antidepressant with a unique mechanism of action and has been categorized as a noradrenergic and specific serotonergic antidepressant. Although numerous clinical trials suggested the usefulness of mirtazapine for not only major depressive disorders but also a variety of anxiety disorders, efficacy studies in animal anxiety models have been rarely reported. A potential anxiolytic-like profile of mirtazapine in rat conditioned fear stress model was investigated. It was reported that the anxiolytic-like action of mirtazapine involves activation of 5-HT_{1A} receptor and alpha₁ adrenoceptor to different extents, and are compatible with one aspect of mirtazapine's pharmacological profile (Kakui et al., 2009).

4.3 Research via SNRIs and learning-memory in animal models :

Extensive evidence indicates that noradrenaline and serotonin modulate memory formation. In the literature there are a few works evaluating the effects of SNRIs on cognitive parameters such as learning, memory and habituation to novel environments.

Duloxetine, a potent inhibitor of 5-HT and noradrenaline reuptake with weak effects on dopamine reuptake, is used in the treatment of major depression. It has been recognized that some antidepressants can affect memory in humans, but there are no studies that report duloxetine effects on memory using the inhibitory avoidance method. A recent report investigated the effect of duloxetine on short- and long-term memory (STM and LTM) in the inhibitory avoidance task in mice. Duloxetine did not produce any effect on memory after acute and subacute administration, suggesting that this antidepressant does not affect either memory acquisition or consolidation (Pereira et al., 2009).

The effects of milnacipran in animal models of anxiety and memory were evaluated via Vania K.M. Moojen and colleagues, 2006; it was concluded that milnacipran can be useful in the treatment of anxiety disorders. The pharmacological characteristics of milnacipran, in modulation of the synaptic plasticity were investigated. It was found that Milnacipran, suppresses long-term potentiation in the rat hippocampal CA1 field via 5-HT_{1A} receptors and α 1-adrenoceptors (Tachibana et al., 2004). It was reported that chronic treatment with milnacipran reverses the impairment of synaptic plasticity induced by conditioned fear stress. And it is concluded that anxiolytic mechanism(s) of chronic treatment with milnacipran may be explained by reversal effects on the psychological stress-induced impairment of synaptic plasticity (Matsumoto et al., 2004).

Effect of venlafaxine on cognitive function and hippocampal brain-derived neurotrophic factor expression in rats with post-stroke depression were evaluated and it was reported that venlafaxine can improve post-stroke depression-induced learning and memory dysfunction, possibly through the enhancement of the BDNF level in the CA3 area of hippocampus. (Dai & Li, 2011).

Ulak et al. (2006) reported that chronic administration of fluoxetine or venlafaxine induces memory deterioration in an inhibitory avoidance task in rats. In this study, the comparison of training latencies versus test latencies showed inhibition of passive avoidance learning in fluoxetine- or venlafaxine-treated rats (e.g., no significant difference between training and test latencies) in a step-through test. There was no significant difference between fluoxetine- and venlafaxine-induced reduction of latency in rats in this test.

4.4 Research via SNRIs and pain in animal models

5-HT and NA are implicated in modulating descending inhibitory pain pathways in the central nervous system. Duloxetine is a selective and potent dual 5-HT and NA reuptake inhibitor (SNRI). Iyengar et al. (2004) reported that inhibition of both 5-HT and NA uptake may account for attenuation of persistent pain mechanisms. Thus, duloxetine may be useful in the treatment of human persistent and neuropathic pain states.

Data from numerous animal and clinical studies suggest that dual acting antidepressants are more active in alleviating pain than specific NA reuptake inhibitors, which themselves are more potent than the SSRI (Fishbain, 2000 & Fishbain, 2000).

Milnacipran, duloxetine and pregabalin (an α 2- δ 1 Ca²⁺ channel blocker) are efficacious against fibromyalgia, a condition characterized by diffuse chronic pain and associated with stress. These compounds were compared in the study of Bardin et al. (2010) using rat models of acute/inflammatory pain and stress-induced ultrasonic vocalization. In the

formalin test, milnacipran dose-dependently attenuated paw elevation and licking. Duloxetine was slightly more potent. Pregabalin also reduced paw licking/late phase. Milnacipran dose-dependently reduced USV; duloxetine was less potent. Milnacipran, duloxetine and pregabalin possess analgesic activity in the formalin test on paw licking/late phase (corresponding to inflammatory pain with a central sensitization component). In the stress-induced USV model, milnacipran was the most potent and efficacious compound. To summarize, the reduction of formalin-induced paw licking/late phase might constitute a useful indicator of the potential activity against inflammatory/centrally sensitized pain, as might be expressed in fibromyalgia (Bardin et al., 2010).

Milnacipran has shown efficacy against several chronic pain conditions including fibromyalgia. A previous report evaluated its anti-allodynic effects following acute or sub-chronic treatment in a rat model of neuropathic pain (chronic constriction injury (CCI) of the sciatic nerve). It is reported that milnacipran is as efficacious as the reference compound amitriptyline in a pre-clinical model of injury-induced neuropathy and demonstrates, for the first time, that it is active acutely and sub-chronically against cold allodynia. It is also suggested that milnacipran has the potential to alleviate allodynia associated with nerve compression-induced neuropathic pain in the clinic (for example, following discal hernia, avulsion or cancer-induced tissue damage) (Berrocso et al., 2011).

5. Side effects

Sexual dysfunction is often a side effect of drugs that inhibit 5-HT reuptake in general. Specifically, common side effects with venlafaxine include difficulty becoming aroused, lack of interest in sex, and anorgasmia. Genital anesthesia, loss of or decreased response to sexual stimuli, and ejaculatory anhedonia are also possible. Other side effects include nausea, somnolence, dry mouth, dizziness, insomnia, constipation and yawn. With desvenlafaxine nausea was consistently the most common complaint and the most common reason for discontinuation. Less common mild side effects, but more serious, adverse effects reported includes hypertension, QTc interval prolongation, exacerbation of ischemic cardiac disease, elevated lipids and elevated liver enzymes (Sproule BA and Hazra M, 2008). Nausea, somnolence, insomnia, and dizziness were the main side effects reported by approximately 10% to 20% of patients using duloxetine. In a trial for mild major depressive disorder (MDD), the most commonly reported treatment-emergent adverse events among duloxetine-treated patients were nausea (34.7%), dry mouth (22.7%), headache (20.0%) and dizziness (18.7%), and except for headache, these were reported significantly more often than the placebo group. Duloxetine and SSRIs have been shown to cause sexual side effects in some patients, including both males and females. (Bitter & Filipovits, 2011).

Common side effects of mirtazapine included dizziness, blurred vision, sedation, somnolence, malaise/lassitude, increased appetite and subsequent weight gain, dry mouth, constipation, vivid, bizarre, lucid dreams or nightmares, joint pain (arthralgia), muscle pain (myalgia) and back pain. Less common side effects included agitation/restlessness, irritability, aggression, apathy and/or anhedonia (i.e., inability to experience pleasurable emotions), loss of interest in previously enjoyed activities, excessive mellowness or calmness, difficulty swallowing, shallow breathing, decreased body temperature, miosis, nocturnal emissions, spontaneous orgasm, loss of balance, and restless legs syndrome. Mirtazapine has a lower risk of many of the side effects encountered with other

antidepressants, such as decreased appetite, insomnia, nausea and vomiting, diarrhea, urinary retention, increased body temperature, increased perspiration/sweating, mydriasis, and sexual dysfunction (consisting of loss of libido and anorgasmia). Sedation is the most common side effect of mirtazapine. Although agranulocytosis is the most serious side effect, it is rare (approximately one in 1,000) and usually reversible when the medication is stopped. In general, some antidepressants may have the capacity to exacerbate some patients' depression or anxiety or cause suicidal ideation, particularly early in the treatment. It has been proven that mirtazapine has a faster onset of antidepressant action compared to SSRIs (Hartmann, 1999).

With milnacipran the most frequently occurring adverse reactions were nausea, headache, constipation, dizziness, insomnia, hot flush, hyperhidrosis, vomiting, palpitations, heart rate increase, dry mouth, and hypertension. Milnacipran can have a significant impact on sexual function, including both a decrease in sexual desire and ability. Milnacipran can cause pain and swelling of the testicles in men as well as blood in the urine and stools. The incidence of cardiovascular and anticholinergic side effects was significantly lower compared with TCAs in a controlled study with over 3,300 patients. Elevation of liver enzymes without signs of symptomatic liver disease has been infrequent. Mood swing to mania has also been observed and dictates termination of treatment. In psychotic patients, emergence of delirium has been noticed. Milnacipran has a low incidence of sedation but improves sleep (both duration and quality) in depressed patients. In agitated patients or those with suicidal thoughts, additive sedative/anxiolytic treatment is usually indicated (Nakagowa et al., 2009; Montgomery et al., 1996).

6. Conclusion

In this chapter of antidepressants including the SNRIs, pharmacology, medical uses, tolerability, experimental studies and side effects of SNRIs are overviewed. They include venlafaxine, desvenlafaxine, duloxetine, milnacipran and mirtazapine. Pharmacology of SNRIs is characterized by the inhibition of both serotonin and noradrenaline at the presynaptic membrane and by weak affinity with receptors at the postsynaptic membrane, which expects well efficacy on major depressive disorder with less adverse effects in clinical use. SNRIs are well tolerated in general. SNRIs can be considered to be the first-line antidepressant drugs.

7. References

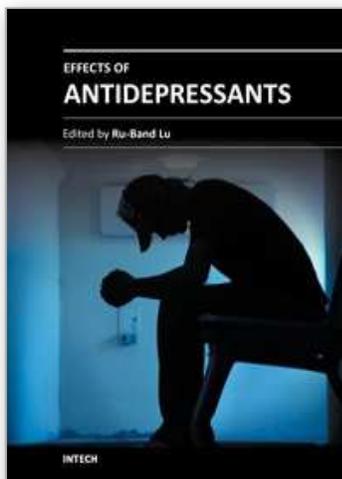
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Over the last fifty years, many studies of psychiatric medication have been carried out on the basis of psychopharmacology. At the beginning, researchers and clinicians found the unexpected effectiveness of some medications with therapeutic effects in anti-mood without knowing the reason. Next, researchers and clinicians started to explore the mechanism of neurotransmitters and started to gain an understanding of how mental illness can be. Antidepressants are one of the most investigated medications. Having greater knowledge of psychopharmacology could help us to gain more understanding of treatments. In total ten chapters on various aspects of antidepressants were integrated into this book to help beginners interested in this field to understand depression.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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