Serotonin–Norepinephrine Reuptake Inhibitors

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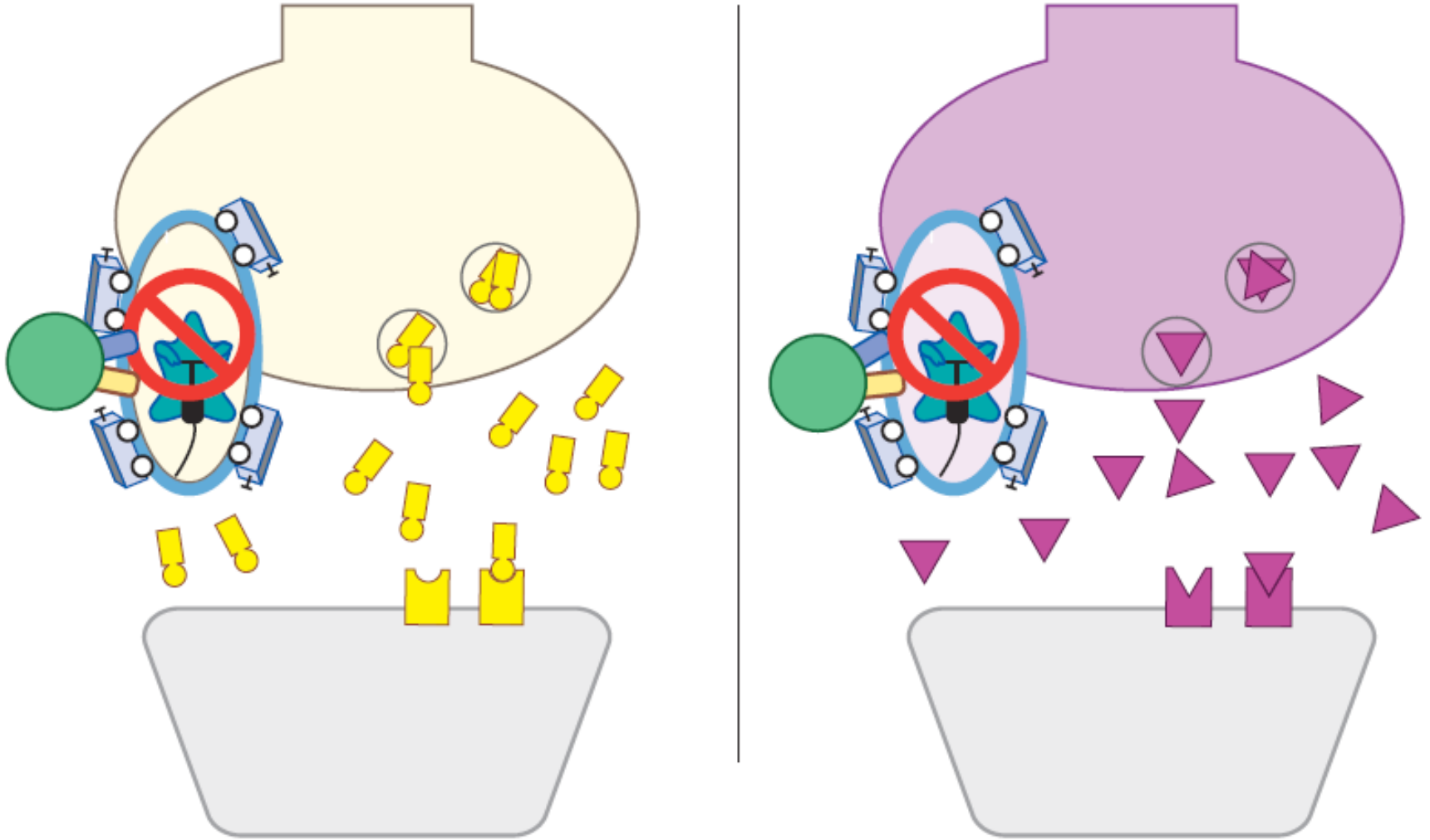
blockade of neuronal serotonin (5-HT) and norepinephrine (NE) uptake transporters.



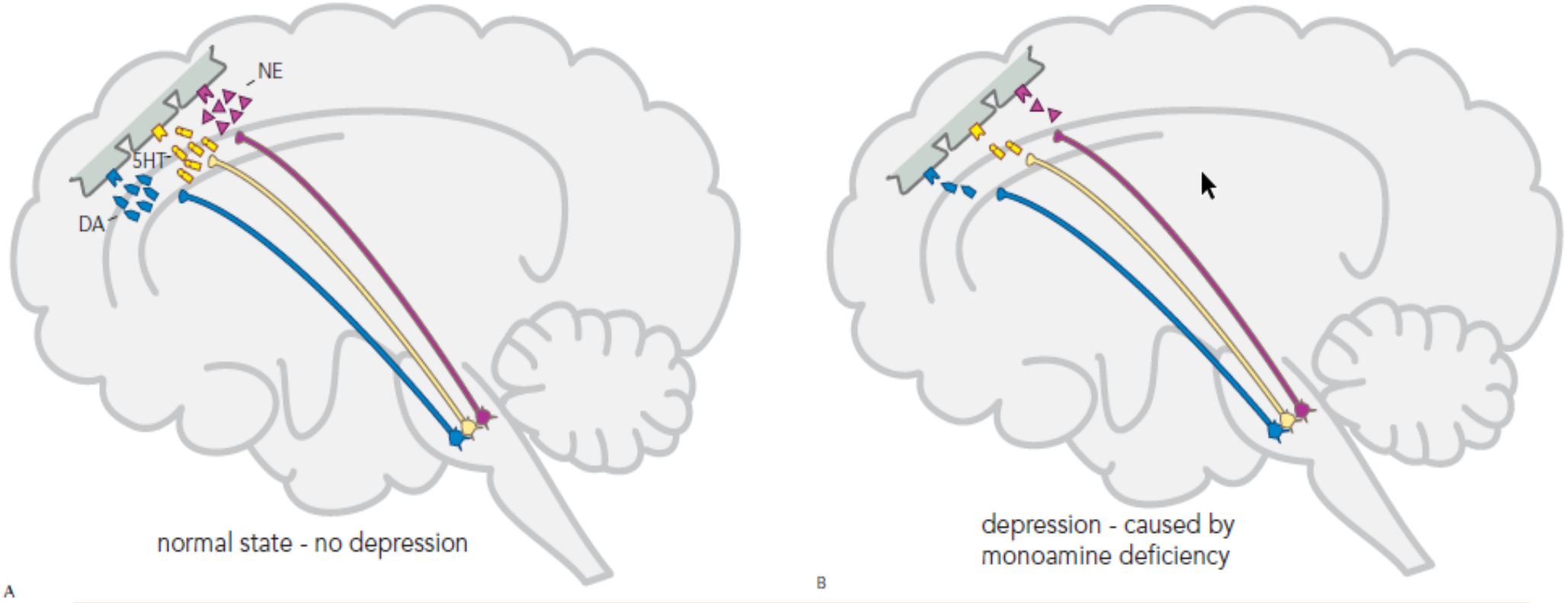
- The SNRIs are also sometimes referred to as dual reuptake inhibitors, a broader functional class of antidepressant medications that includes tricyclic antidepressants (TCAs) such as clomipramine and, arguably, imipramine and amitriptyline.
- What distinguishes the SNRIs from TCAs is selectivity, which in this context refers to a relative lack of affinity for other receptors, especially muscarinic, histaminergic, and the families of α- and β-adrenergic receptors.
- This distinction is an important one because the SNRIs have a more favorable tolerability profile than the older TCA dual reuptake inhibitors.

Dopamine reuptake inhibitor

Although SNRIs are commonly called “dual action” serotonin–norepinephrine agents, they actually have a third action on dopamine (DA) in the prefrontal cortex, but not elsewhere in the brain.

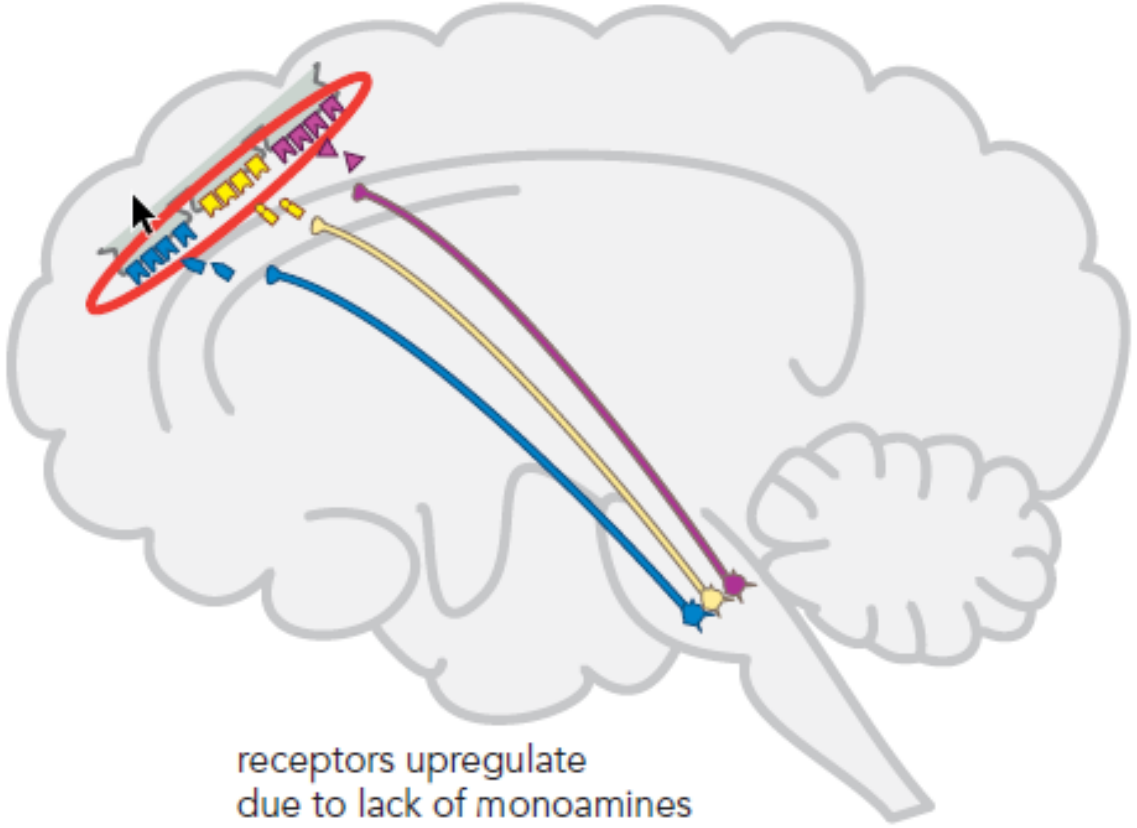
This third mechanism of boosting DA in an important area of the brain associated with several symptoms of depression should add another theoretical advantage to the pharmacology of SNRIs and to their efficacy in the treatment of major depression.

The Monoamine Hypothesis of Depression



The “normal” amount of monoamine neurotransmitters became depleted by an unknown disease process, stress, or drugs, leading to the symptoms of depression

The Monoamine Receptor Hypothesis and Neurotrophic Factors



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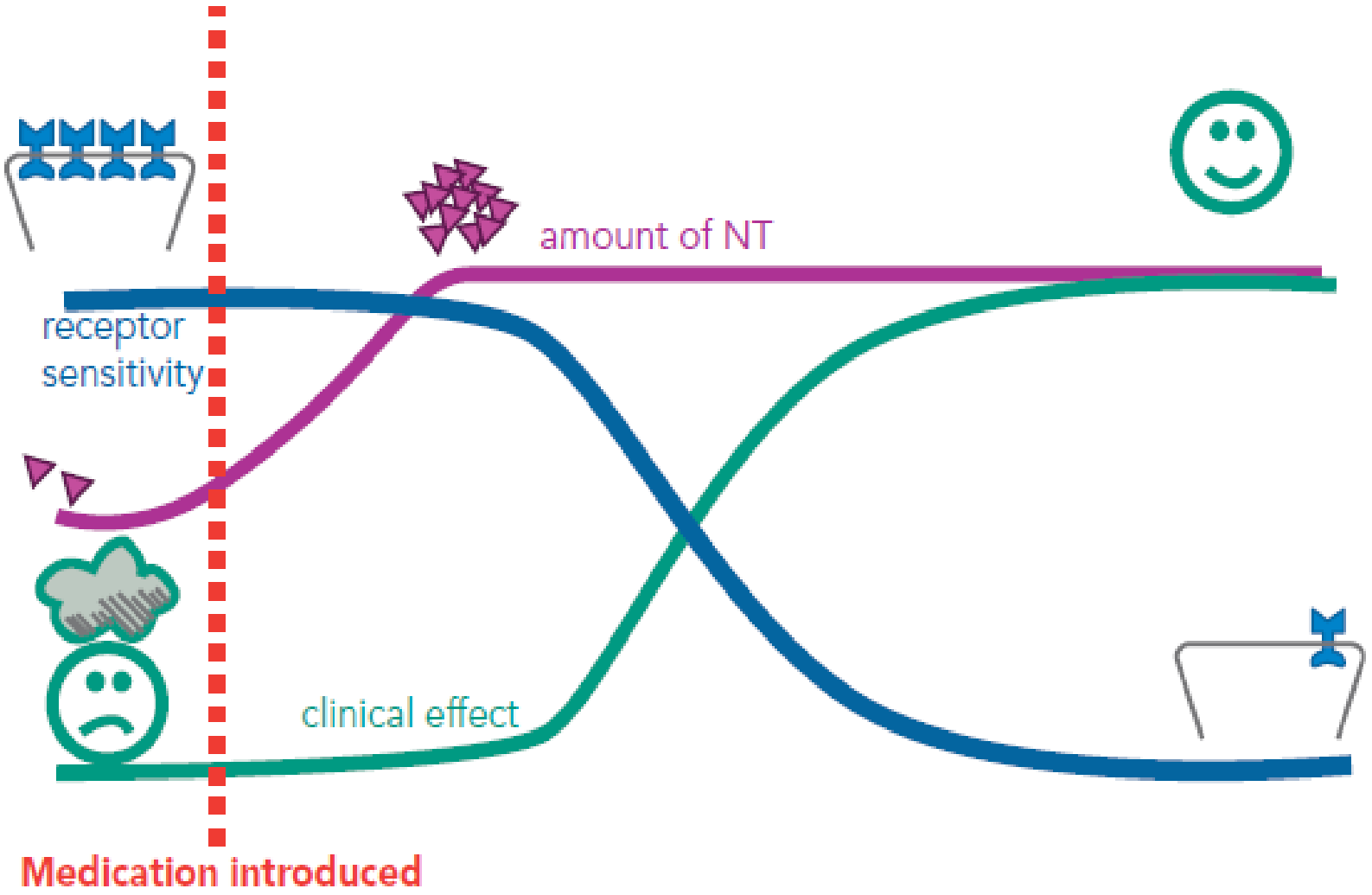
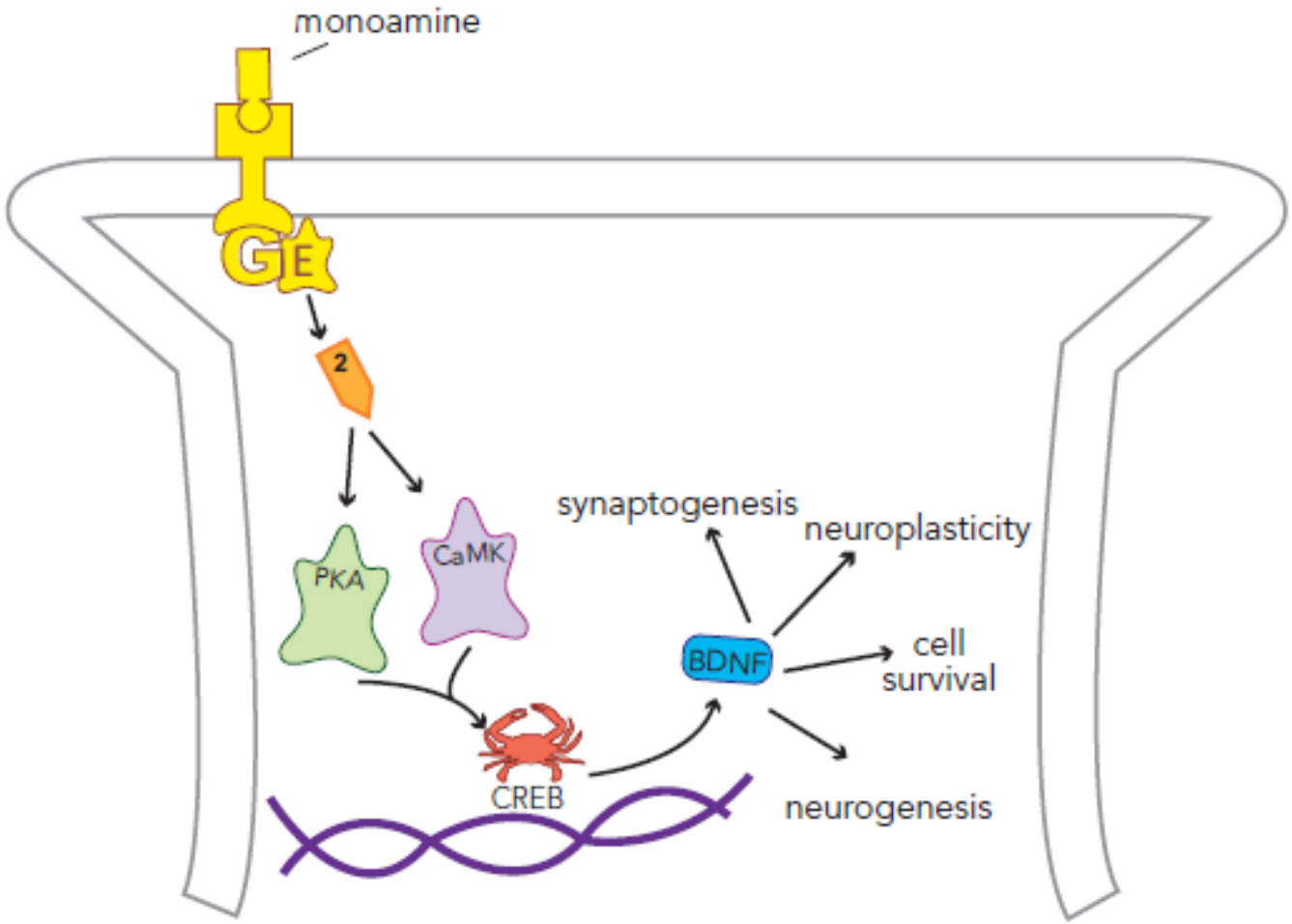


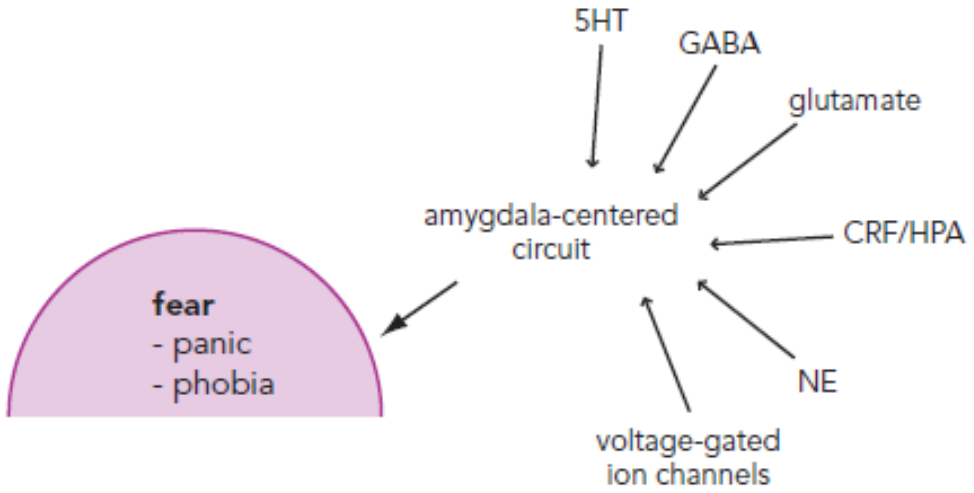
-Delayed downregulation of neurotransmitter receptors following immediate elevation of monoamines after administration of drugs for depression correlates in time with the onset of clinical antidepressant effects

-Downregulation of neurotransmitter receptors also correlates in time with the onset of tolerance to some of the side effects of drugs used to treat depression.

Monoamine Signaling Increases BDNF Release, Which Modifies Monoamine Innervation



Associate Symptoms with Brain Regions, Circuits, and Neurotransmitters That Regulate Them



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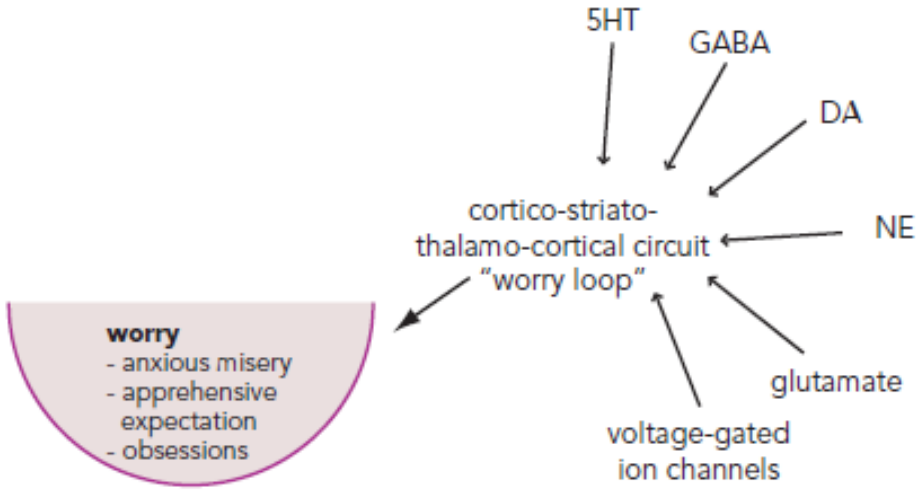
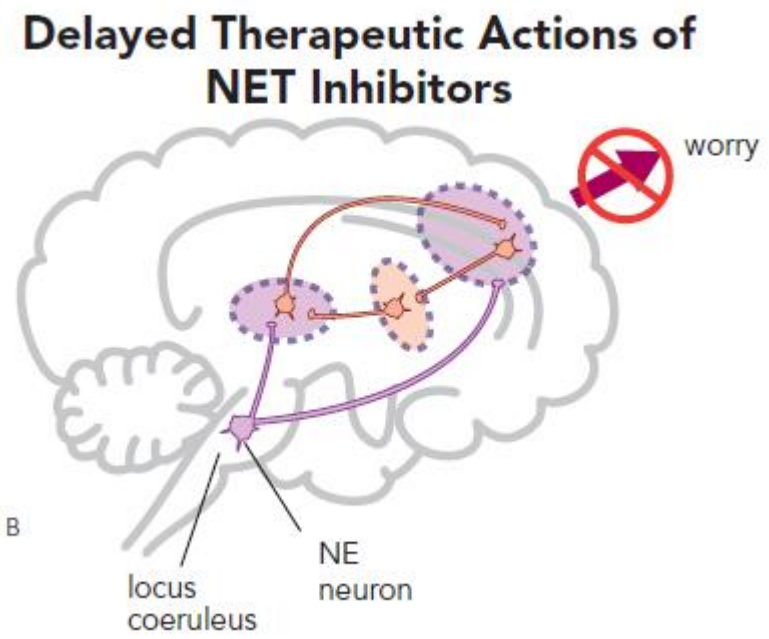


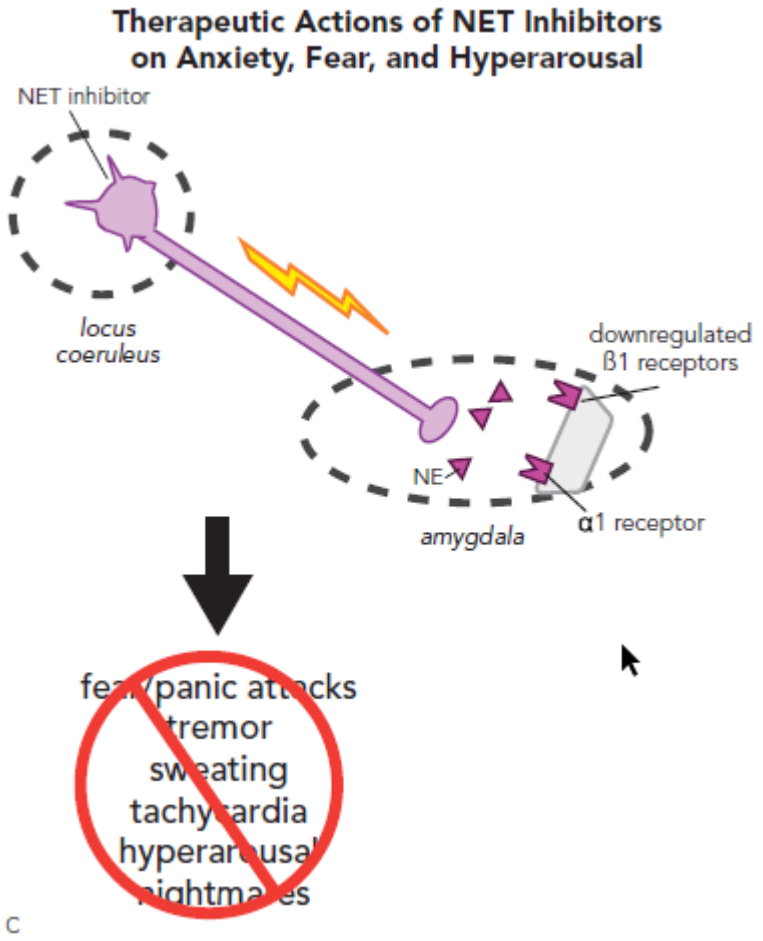
NET inhibition and Anxiety

The clinical effects of NET inhibitors can be confusing because:

symptoms of anxiety can actually be made transiently worse immediately following initiation of an SNRI or selective NET inhibitor, when noradrenergic activity is initially increased but the postsynaptic receptors have not yet adapted.

However, these same NET inhibitory actions, if sustained over time, will downregulate and desensitize postsynaptic norepinephrine receptors such as β1 receptors, and hypothetically lead to the delayed reduction in symptoms of fear and worry long term


Delayed Therapeutic Actions of NET Inhibitors
worry
B
locus coeruleus
NE neuron


Therapeutic Actions of NET Inhibitors on Anxiety, Fear, and Hyperarousal
NET inhibitor
locus coeruleus
downregulated ß1 receptors
NE
α1 receptor
amygdala
panic attacks
tremor
sweating
tachycardia
hyperarousal
nightmares
C

SNRIs

- Venlafaxine
- desvenlafaxine succinate
- duloxetine
- milnacipran
- levomilnacipran

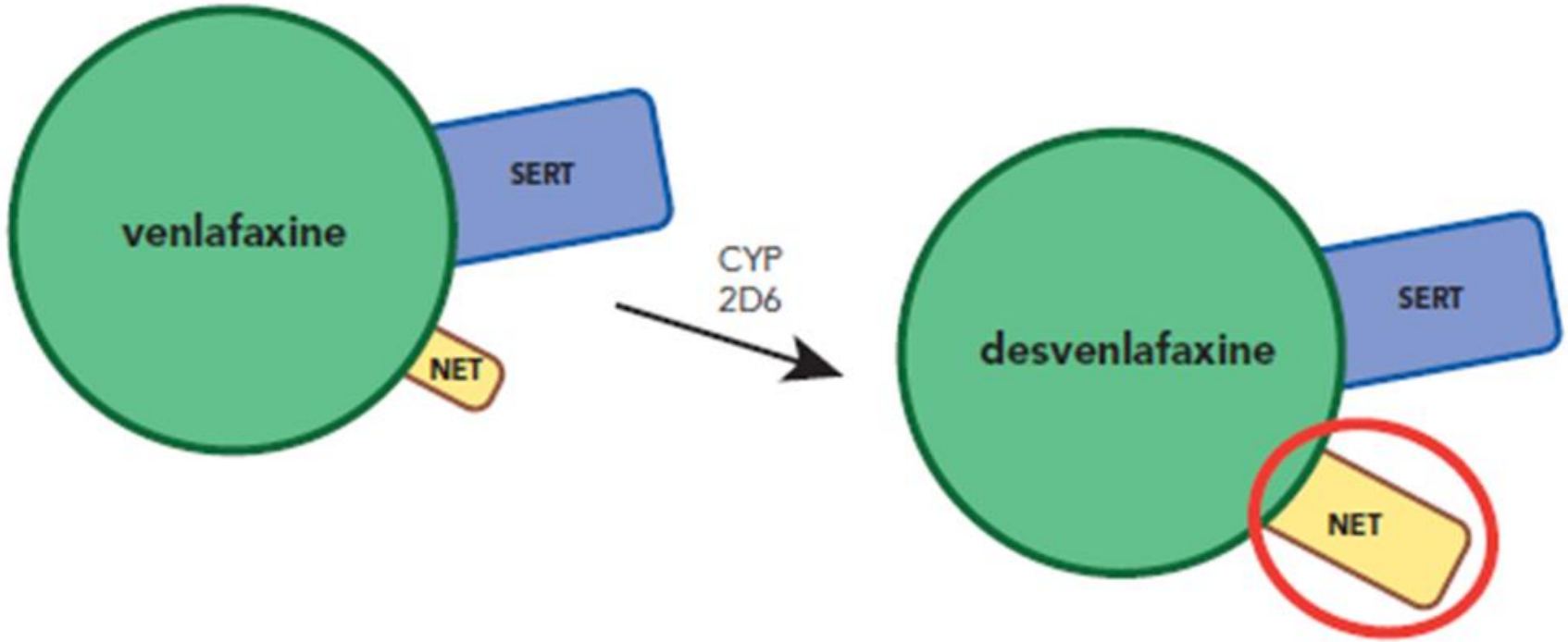
Venlafaxine

Venlafaxine and ODV inhibit neuronal uptake of 5-HT and NE.

the relative affinities of venlafaxine for inhibition of 5-HT and NE uptake underpin an ascending dose–response relationship.

Specifically, venlafaxine is essentially an SSRI at the lowest therapeutic dose (i.e., 75 mg/day) and that noradrenergic effects increase progressively as the dose is advanced.

Orally administered venlafaxine and DVS are well absorbed from the GI tract and undergo extensive first-pass metabolism in the liver.
During venlafaxine therapy, ODV accumulates in higher concentrations (typically about twofold higher) than the parent drug. It thus can be said that ODV accounts for a majority of the therapeutic activity of venlafaxine.



Peak plasma concentrations are achieved within 2 to 3 hours after ingestion of the IR formulation of venlafaxine. During therapy with the XR formulation, peak plasma concentrations are achieved within 5.5 hours for venlafaxine and 9 hours for ODV.

Venlafaxine and ODV have linear kinetics over a dose range of 75 to 450 mg/day.

Venlafaxine and ODV are primarily eliminated by the kidneys.

The elimination half-lives of venlafaxine and its metabolite are short (i.e., 4 and 10 hours, respectively).

Neither venlafaxine nor ODV is highly bound to plasma albumin (i.e., 25 to 30 percent protein binding at therapeutic concentrations).

Venlafaxine is approved by the FDA for treatment of four therapeutic disorders:

- major depressive disorder
- generalized anxiety disorder
- social anxiety disorder
- panic disorder

Depression

- The recommended starting dose of both formulations of venlafaxine, 75 mg/day, is the minimum effective dose for treatment of depression.
- It should be administered with meals
- on a two- or three-times a-day basis for the IR.

Depression

In clinical trials a modal daily dose of 150 mg/day is typically observed, regardless of the formulation used.

When therapy at modest doses is ineffective, further increases up to 375 mg/day can be considered, as tolerated.

However, the maximum recommended daily dose of the XR formulation is only 225 mg because of a lack of data on once-daily ingestion of higher dosages.

Consistent with this general approach to therapy, higher mean doses are observed in studies of treatment-resistant depression.

Generalized Anxiety Disorder

Venlafaxine XR received FDA approval for treatment of generalized anxiety disorder in 1999.

Efficacy and tolerability data for this indication are documented in published randomized, controlled trials.

Social Anxiety Disorder

The FDA approved venlafaxine for treatment of social anxiety disorder in early 2003.

The trials demonstrated efficacy and tolerability of venlafaxine at doses of 75 to 225 mg/day

both therapeutic effects and tolerability appear to be comparable to those of paroxetine.

Other Psychiatric Disorders-venlafaxine

With respect to panic disorder, efficacy has been established in two RCTs, one including a 40 mg/day regimen of the SSRI paroxetine. In the latter study, 225 mg/day of venlafaxine outperformed 75 mg/day and the paroxetine treatment.

Despite the obvious parallels with clomipramine, the anti-obsessional effects of venlafaxine have not been as extensively studied.

Two large RCTs have shown the efficacy of venlafaxine XR in PTSD, but it is an off-label use.

Premenstrual dysphoric disorder may be thought of as a gender-specific form of brief recurrent depression, and it is known to be responsive to SSRIs.

A randomized, double-blind, placebo-controlled study evaluated flexible doses of venlafaxine therapy (range from 50 to 200 mg/day) across four menstrual cycles among 157 women with premenstrual dysphoric disorder.

There was significantly greater improvement in the venlafaxine group compared to the placebo group across measures of emotion, function, physical symptoms, and pain.

Tolerability

Venlafaxine has a safety and tolerability profile that approaches that of the more widely prescribed SSRI class.

For example, in the pooled data set of Michael Thase and colleagues, 9 percent of venlafaxine-treated patients withdrew because of adverse events, as compared to 7 percent of SSRI- treated patients.

Nausea is the most frequently reported treatment-emergent adverse effect associated with venlafaxine therapy.

The mechanism mediating this side effect is thought to be stimulation of central 5-HT type 3 (5-HT3) receptors. With an incidence of as great as 35 percent in short-term placebo-controlled trials, nausea is approximately one-third more likely than seen with SSRIs.

Initiating therapy at lower dosages may also attenuate nausea.

When extremely problematic, treatment Induced nausea can be controlled by prescribing a selective 5-HT3 antagonist or mirtazapine (Remeron).

Sexual dysfunction

As with other 5-HT reuptake inhibitors, venlafaxine therapy is associated with sexual side effects, predominantly decreased libido, and a delay to orgasm or ejaculation.

The incidence of these side effects is underreported in clinical trials and may exceed 30 to 40 percent when there is direct, detailed assessment of sexual function.

Although the exact mechanisms of the sexual side effects are not known

Other common (reported by >10 percent of subjects in published studies) side effects include

headache, insomnia, somnolence, dry mouth, dizziness, constipation, asthenia, sweating, and nervousness.

Although several side effects are suggestive of anticholinergic effects, the drug has no affinity for muscarinic or nicotinic receptors. Thus, noradrenergic agonism is likely to be the culprit.

Hypertension

Higher-dose venlafaxine therapy is associated with an increased risk of sustained elevations of BP.

Experience with the instant-release (IR) formulation in studies of depressed patients indicated that sustained hypertension was dose-related, increasing from 3 to 7 percent at doses of 100 to 300 mg/day and 13 percent at doses greater than 300 mg/day.

In this dataset, venlafaxine therapy did not adversely affect BP control of patients taking anti-hypertensives and lowered the mean values of patients with elevated BP readings before therapy.

In controlled studies of the extended-release formulation, venlafaxine therapy resulted in only approximately 1 percent greater risk of high BP when compared with the placebo.

discontinuation syndrome

Venlafaxine and DVS are commonly associated with discontinuation syndrome.

This syndrome is characterized by the appearance of a constellation of adverse effects during a rapid taper or abrupt cessation,

including dizziness, dry mouth, insomnia, nausea, nervousness, sweating,

anorexia, diarrhea, somnolence, and sensory disturbances.

It is recommended that, whenever possible, a slow taper schedule should be used when longer term treatment must be stopped.

On occasion, substituting a few doses of the sustained-release formulation of fluoxetine may help to bridge this transition.

overdose

There were no overdose fatalities in premarketing trials of venlafaxine, although electrocardiographic changes (e.g., prolongation of QT interval, bundle branch block, QRS interval prolongation), tachycardia, bradycardia, hypotension, hypertension, coma, serotonin syndrome, and seizures were reported.

Fatal overdoses have been documented subsequently, typically involving venlafaxine ingestion in combination with other drugs, alcohol, or both.

Drug Interactions

Venlafaxine is metabolized in the liver primarily by the CYP2D6 iso-enzyme.

Because the parent drug and principal metabolite are essentially equipotent, medications that inhibit this iso-enzyme usually do not adversely affect therapy.

Venlafaxine is itself a relatively weak inhibitor of CYP2D6, although it can increase levels of substrates, such as desipramine or risperidone (Risperdal).

In vitro and in vivo studies have shown venlafaxine to cause little or no inhibition of CYP1A2, CYP2C9, CYP2C19, and CYP3A4.

Venlafaxine is contraindicated in patients taking MAOIs because of the risk of a pharmaco-dynamic interaction

An MAOI should not be started for at least 7 days after stopping venlafaxine.

Few data are available regarding the combination of venlafaxine with atypical neuroleptics, benzodiazepines, lithium (Eskalith), and anticonvulsants; therefore, clinical judgment should be exercised when combining medications.

Laboratory Interferences

Data are not currently available on laboratory interferences with venlafaxine.

There have been some reports of patients taking venlafaxine who have false-positive results on liquid chromatography testing for tramadol.

Dosage and Administration

In depressed persons, venlafaxine demonstrates a dose–response curve. The initial therapeutic dosage is 75 mg a day, given once a day. However, most persons are started at a dosage of 37.5 mg for 4 to 7 days to minimize adverse effects, particularly nausea.

If a rapid titration is preferred, the dosage can be raised to 150 mg/day after day 4. As a rule, the dosage can be raised in increments of 75 mg a day every 4 or more days.

Although the recommended upper dosage of the extended-release preparation (venlafaxine XR) is 225 mg/day, it is approved by the FDA for use at dosages up to 375 mg a day.

The dosage of venlafaxine should be halved in persons with significantly diminished hepatic or renal function.

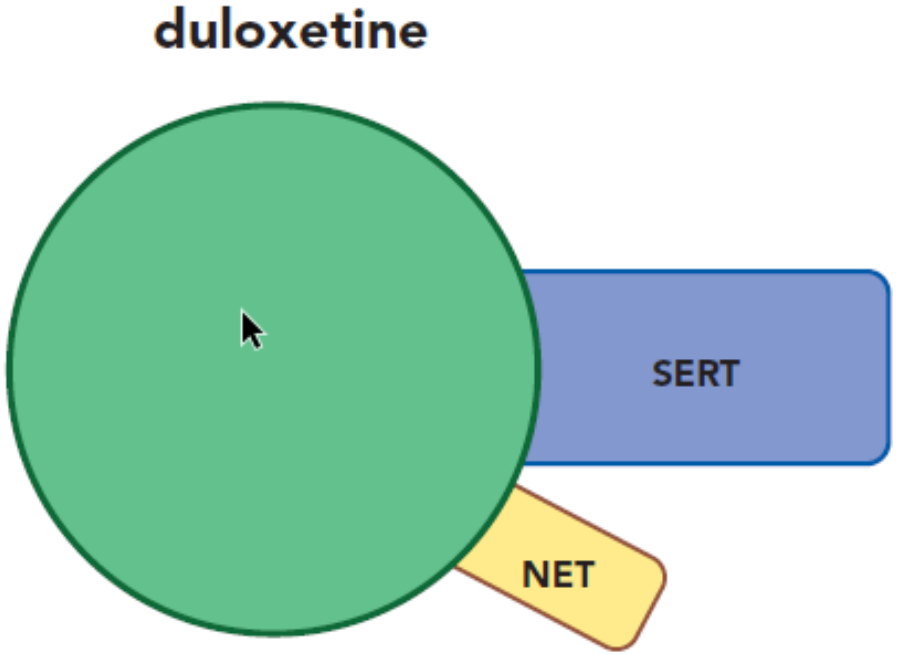
If discontinued, venlafaxine use should be gradually tapered over 2 to 4 weeks to avoid withdrawal symptoms.

There are minor differences in the doses used for major depression, GAD, and social anxiety disorder.

In the treatment of these disorders, for example, a dose–response effect has not been found.

Also, lower mean dosages are typically used, with most patients taking 75 to 150 mg/day.

DULOXETINE



duloxetine is a potent 5- HT and NE uptake inhibitor and lacks affinity for muscarinic, histaminic, and αand β-adrenergic receptors.

duloxetine was found to be a substantially more potent NE reuptake inhibitor than venlafaxine. If these studies predict effects in the brain, duloxetine should be expected to produce dual reuptake inhibition at lower absolute doses than observed with venlafaxine.

Duloxetine was approved by the FDA for treatment of major depressive disorder in 2004;

other indications include:

- generalized anxiety disorder,

- fibromyalgia,

- neuropathic pain associated with diabetic peripheral neuropathy, and

- chronic musculoskeletal pain.

Orally administered duloxetine is well absorbed, and

peak plasma levels are achieved approximately 3 hours after ingestion.

Duloxetine has no active metabolites and exhibits linear pharmacokinetics within a dose range of 20 to 120 mg.

Steady-state concentrations are achieved within 3 days of oral dosing, and the drug has an elimination half-life of approximately 12 hours

In the plasma, approximately 90 percent of the drug is protein bound.

After hepatic oxidation, metabolites of duloxetine are primarily eliminated by the kidneys. Duloxetine is metabolized by CYP 1A2 and is a moderately potent inhibitor of the CYP 2D6 iso-enzyme

No evidence of a dose–response relationship was observed between 60 mg/day and 120 mg/day; somewhat weaker antidepressant effects were observed at 40 mg/day.

These clinical results are fully consistent with the observations that 40 mg of duloxetine reached the 80 percent occupancy level of the 5-HT transporter in the brain, achieved with the minimal effective doses of SSRIs and venlafaxine, but that 60 mg once daily was necessary to maintain it.

Six of the initial registration studies of duloxetine (40 to 120 mg/day) included an SSRI as an active comparator.

A meta-analysis confirmed that both duloxetine and the comparators were effective and, among the subset of patients with moderate-to-severe depressive symptoms, there was a significant advantage favoring the SNRI in remission rates

STRESS URINARY INCONTINENCE-duloxetine

Duloxetine is currently awaiting approval as a treatment for stress urinary incontinence, the inability to voluntarily control bladder voiding, which is the most frequent type of incontinence in women.

The action of duloxetine in the treatment of stress urinary incontinence is associated with its effects in the sacral spinal cord, which in turn increases the activity of the striated urethral sphincter.

NEUROPATHIC PAIN

Duloxetine is the first drug to be approved by the FDA as a treatment for neuropathic pain associated with diabetes.

Its pain effects have not been compared with other agents, such as venlafaxine and the TCAs.

Side effect-duloxetine

The discontinuation rate due to adverse events in the studies summarized by Charles Nemeroff and colleagues was 15 percent in duloxetine-treated patients and 5 percent in placebo-treated patients.

The most commonly reported side effects during duloxetine therapy were nausea (22 percent), dry mouth (16 percent), fatigue (11 percent), dizziness (11 percent), and somnolence (8 percent).

Duloxetine therapy resulted in a small increase in resting pulse rate (approximately two beats per minute)

In clinical trials, treatment with duloxetine was associated with mean increases in BP averaging 2 mm Hg systolic and 0.5 mm Hg diastolic versus placebo.

the risk of sustained high blood pressure during duloxetine therapy was approximately 1 percent greater than observed in placebo-treated patients.

the risk of increased blood pressure does not appear to be dose dependent.

Side effect-duloxetine

Like other 5-HT uptake inhibitors, duloxetine therapy has been associated with sexual dysfunction. The true incidence of sexual dysfunction is unknown.

the long-term effects on body weight are also unknown.

Duloxetine has been shown to increase blood sugar and hemoglobin A1C levels during long-term treatment.

Abrupt discontinuation of duloxetine should be avoided because it may produce discontinuation syndrome similar to that of venlafaxine. A gradual dose reduction is recommended.

Drug Interactions

Although the CYP enzyme inhibition profile of the drug looks generally favorable, duloxetine levels are about 30 percent lower in smokers, likely as a result of CYP 1A2 induction

increased fourfold by potent CYP 1A2 inhibitors, like fluvoxamine and some fluoroquinolone antibiotics.

A lethal interaction with MAOIs is expected with duloxetine

Dosage and Administration

The recommended therapeutic and maximum dosage is 60 mg/day.

The 20- and 30-mg doses are useful for either initial therapy or for twice-daily use as strategies to reduce side effects.

In clinical trials, dosages of up to 120 mg/day were studied, but no consistent advantage in efficacy was noted at doses higher than 60 mg/day.

Duloxetine thus does not appear to demonstrate a dosage–response curve.

However, there were difficulties in tolerability with single doses above 60 mg.

Accordingly, when dosages of 80 and 120 mg/day were used, they were administered as 40 or 60 mg twice daily.

It remains to be seen to what extent dosages above 60 mg/day will be necessary and whether this will require divided doses to make the drug tolerable