

Monoamines

The reuptake and breakdown of monoamines are key concepts in the pharmacotherapy of anxiety and depression:

After reuptake into the presynaptic neurone, monoamines are broken down by an enzyme called **monoamine oxidase**. This stops monoamine levels from becoming too high and prevents overstimulation of the neurone. These reuptake and breakdown processes are targets for antidepressant drugs.

Both serotonin and noradrenaline are very important in depression and anxiety, and most antidepressants aim to increase the concentration of one or the other. Dopamine is involved in many psychiatric conditions and there is some evidence that it, too, may play a role in depression.

Serotonin^{1,2}

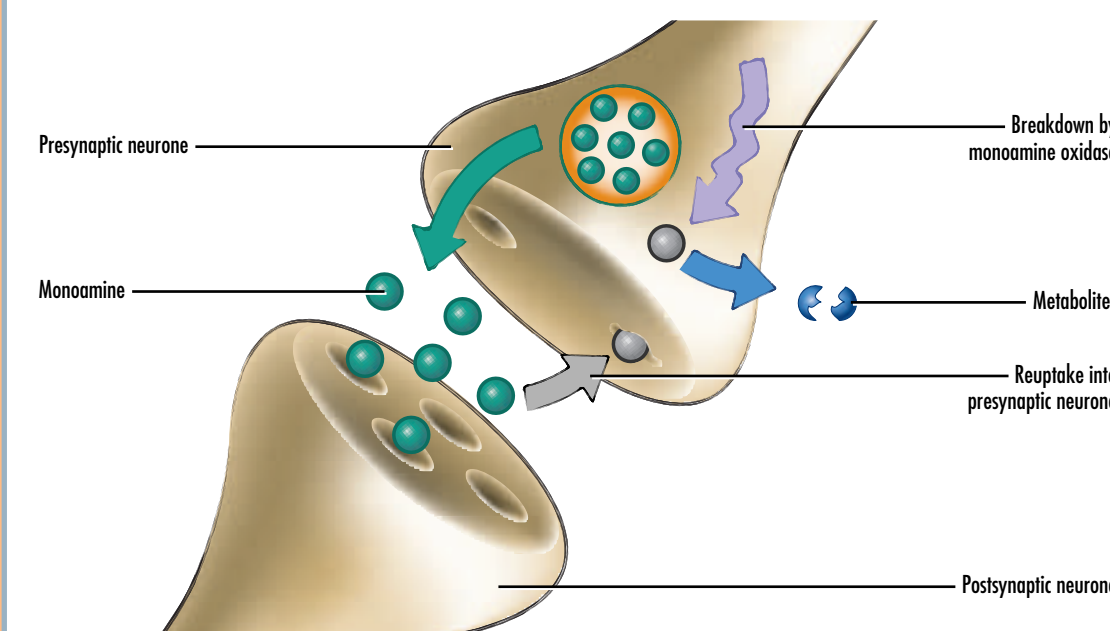
This is also called **5-hydroxytryptamine** or **5-HT**. It is an important neurotransmitter in the brainstem (and in platelets and the digestive system) and is involved in the control of mood, sensory perception, and sleep patterns. It binds to serotonin receptors and undergoes reuptake into the presynaptic neurone. Nerves which use serotonin as a neurotransmitter are called **serotonergic** neurones and are mainly concentrated in the **raphe nuclei** of the brain.

There are at least fourteen sub-types of serotonin receptor, each of which may have a slightly different role in neurotransmission. The main subtypes important in the treatment of depression and anxiety are known as **5HT₂** and **5HT₃** receptors.

Serotonin receptors and its reuptake mechanism are central to the understanding of antidepressant drugs.

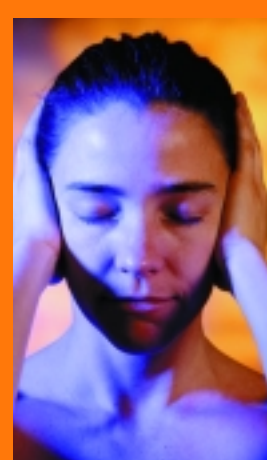
Seroxat is one of a class of antidepressants called selective serotonin re-uptake inhibitors. These drugs effectively increase serotonin levels by preventing its re-uptake and subsequent metabolism.

Figure 1: Monoamine oxidase action



3 THE ROLE OF NEUROTRANSMITTERS IN DEPRESSION

Case studies & activities



Complete the following activities in your learning log:

- 1) Imagine you are visiting a psychiatric nurse who has a patient suffering from depression. During your conversation, the nurse tells you that this patient's wife believes that the illness is 'all in the mind' and that pharmacological treatment will not help since he just needs to pull himself together.

Draw up a list of arguments you would use to convince the patient's wife that her husband is suffering from a genuine illness that can be helped by pharmacotherapy.

aropax
seroxat
paxil



3

The role of neurotransmitters in depression

Objectives

After completing this TOOL worksheet you should be able to:

- list the actions of the main neurotransmitters important in depression and anxiety
- outline the current theories of depression and anxiety
- relate these theories to the treatment of depression and anxiety.



YOUR TASK IS

- to be familiar with the specific neurotransmitters important in depression and anxiety (serotonin, noradrenaline and acetylcholine)
- to understand the biochemical causes of depression and anxiety.

Major neurotransmitters¹

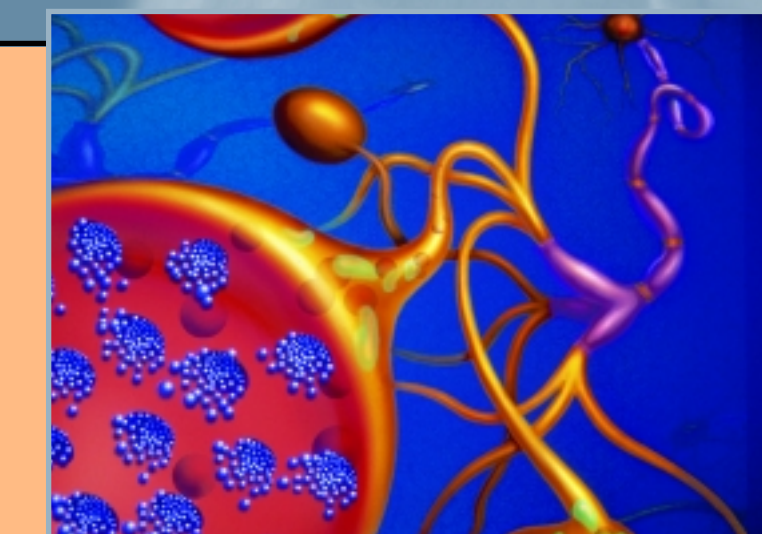
Nerves use a variety of different neurotransmitters. However, each individual nerve can use only one type of transmitter. The most important transmitters in depression and anxiety are members of a group known as monoamines, which are present in many parts of the brain.

The major monoamines are:

- **serotonin**
- **noradrenaline**
- **dopamine**.

Other common neurotransmitters include acetylcholine.¹

As levels of monoamines in the brain rise, so positive mood increases. Conversely, anything that reduces monoamine concentration can lead to feelings of depression.



S. Davidson, Custom Medical Stock Photo/Science Photo Library

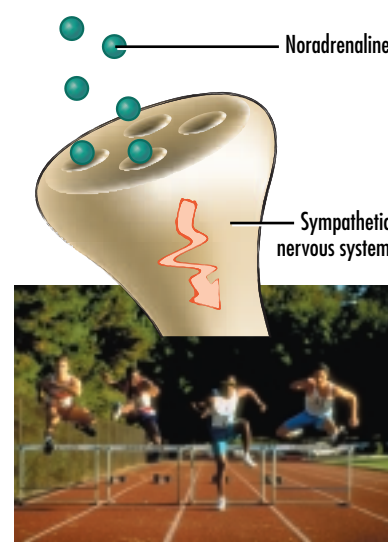
Monoamines (continued)

Noradrenaline¹

This is also found in the brainstem and is involved in mood control, arousal and dreaming. Nerves which transmit messages using noradrenaline are known as **noradrenergic** neurones.

Noradrenaline is distributed widely throughout the body where it is a mediator of the **sympathetic nervous system**, causing sweating, increased heart rate, dilated pupils and dry mouth. These reactions are sometimes known as the 'fight or flight' response since they prepare the body for action. Some antidepressants which act on noradrenaline stimulate this system, causing sympathetic side effects.

Figure 2: Noradrenaline action



Dopamine³

Neurones which release dopamine are known as dopaminergic and are concentrated in an area of the brain known as the **substantia nigra**. Dopamine is involved in movement and coordination and is implicated in many psychiatric conditions (especially schizophrenia). It may also be a factor in depression and anxiety. Abnormalities in dopamine pathways in the brain are the cause of Parkinson's disease.

Interaction between monoamines³

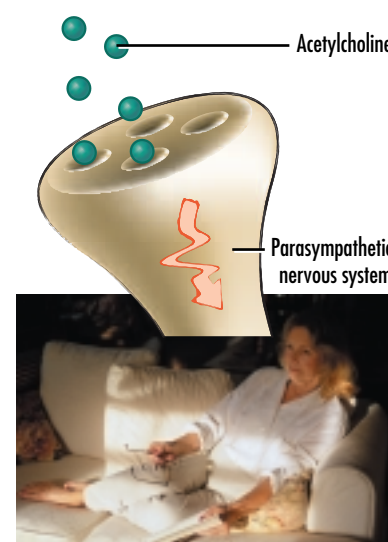
The mechanisms controlling serotonin and noradrenaline are very similar, and both are involved in functions such as mood control and sleep patterns. It is thought that noradrenaline and serotonin may affect each other's transmission. It has also been found that serotonin can inhibit dopamine release in certain areas of the brain.

Other neurotransmitters

Acetylcholine¹

Acetylcholine is not directly affected by antidepressant medications, but since it is responsible for many of their side effects, it is helpful to understand its function. Nerves which transmit messages using acetylcholine are called **cholinergic** neurones. Acetylcholine is involved predominantly in the **parasympathetic nervous system**, which prepares the body for relaxation and digestion. Its effects include decreased heart rate, constriction of the pupils and stimulation of the digestive system. Many antidepressant medications have **anticholinergic** side effects – they block the action of acetylcholine. This means they decrease the effects of the parasympathetic nervous system which causes a relative increase in the sympathetic nervous system. You will come across these side effects later.

Figure 3: Acetylcholine action



Theories of depression and anxiety

Depression and anxiety have been the subject of much research, and several theories currently exist as to their cause. The most established of these is the **monoamine theory**, although scientists generally agree that it does not fully explain the processes involved in affective and anxiety disorders.

A puzzling aspect of the conditions has been the delayed onset of action of antidepressant medication (usually about 1–2 weeks). More recent theories have been developed that try to address this issue

The monoamine theory^{2,3}

The monoamine theory suggests that depression is caused by a reduction in monoamine levels in the brain. This is a widely accepted theory that was first developed in the 1960s through the observation of antidepressant medication effects. The two major antidepressant classes of the time, though both effective, were known to work on different pathways:

- 1) Tricyclic antidepressants inhibit monoamine reuptake from the synaptic cleft after nerve transmission. They affect noradrenaline to a larger degree than serotonin.
- 2) Monoamine oxidase inhibitors (MAOIs) prevent the breakdown of monoamines into their metabolites by inhibiting the enzyme that catalyses the reaction. They affect serotonin and noradrenaline equally.

Figure 4: Action of tricyclics

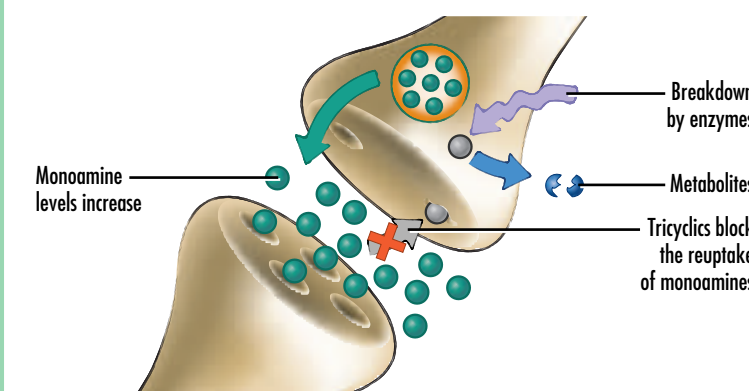
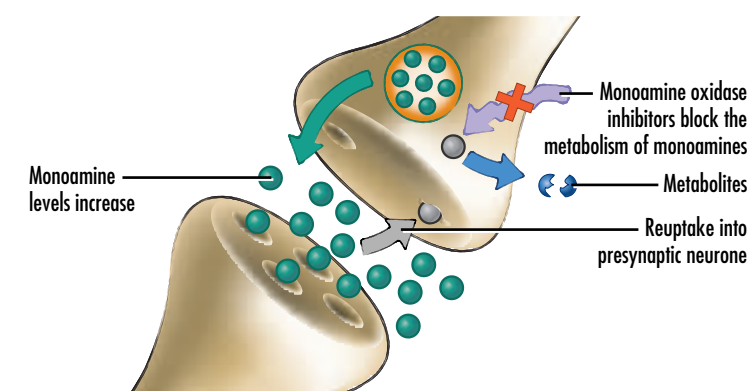


Figure 5: Action of MAOIs



However, both pathways ultimately lead to an increase in monoamine levels in the brain. This, along with findings of reduced dopamine turnover in depression, is taken as evidence that reduced monoamine levels are the cause of depression.

The receptor theory³⁻⁵

The receptor theory suggests that depression is caused by changes in the monoamine receptors in the brain. There are three abnormalities that may be involved:

1. **Upregulation of postsynaptic receptors.** If a neurone has more postsynaptic receptors than usual, it will need a higher concentration of monoamines in the synaptic cleft to trigger a response in the postsynaptic neurone.
2. **Decrease in postsynaptic receptor sensitivity.** A decrease in the sensitivity of the postsynaptic receptors will also require higher levels of monoamines in the synaptic cleft to produce a response in the postsynaptic neurone.
3. **Increase in presynaptic receptor sensitivity.** If presynaptic receptors are over-sensitive to monoamines, presynaptic neurotransmitter release will be switched off prematurely. This prevents the propagation of the nerve impulse.

Figure 6: Receptor upregulation

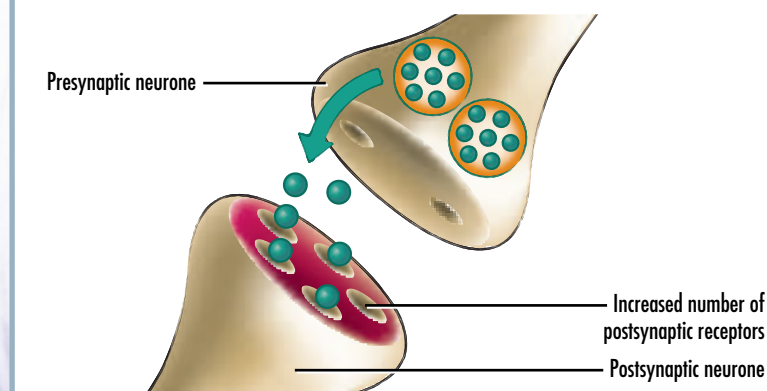


Figure 7: Decreased receptor sensitivity

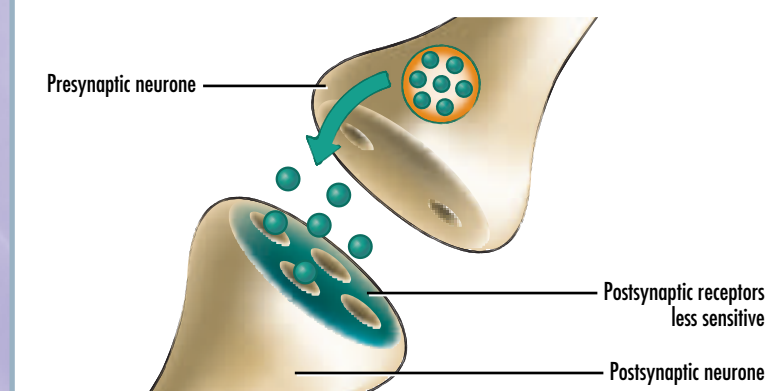
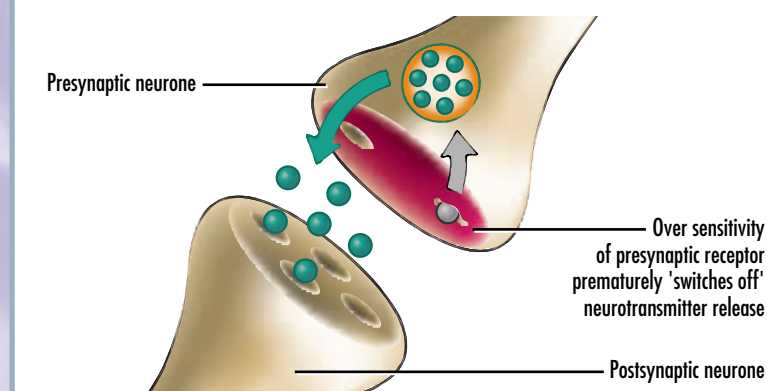


Figure 8: Increase in receptor sensitivity



Combining the theories^{2,3}

All these theories are probably involved in depression and anxiety. Antidepressants are known to cause changes in both receptor sensitivity and monoamine levels in the brain, and both these mechanisms could account for their efficacy. While monoamine levels increase very quickly with antidepressant treatment, synthesis of new receptor proteins takes much longer and could account for the delayed onset of action of most antidepressant treatments (usually 2–3 weeks).

