Αντικαταθλιπτικά Φάρμακα

Αλεξανδρούπολη 18/04/2021
Θεοφάνης Βορβολάκος
Ψυχιάτρος
Επ. Καθηγητής Δ.Π.Θ.

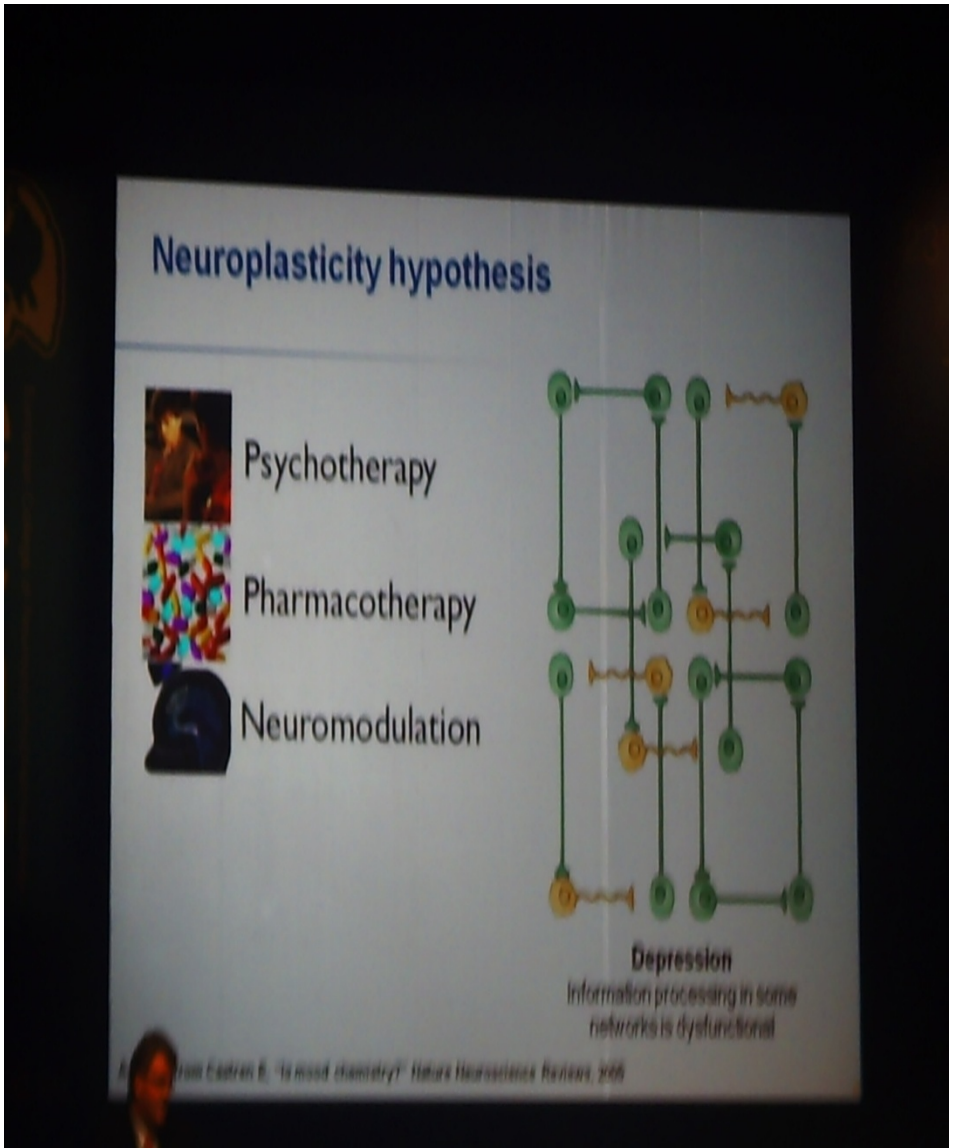
Κατάθλιψη Παλιά Θεωρία

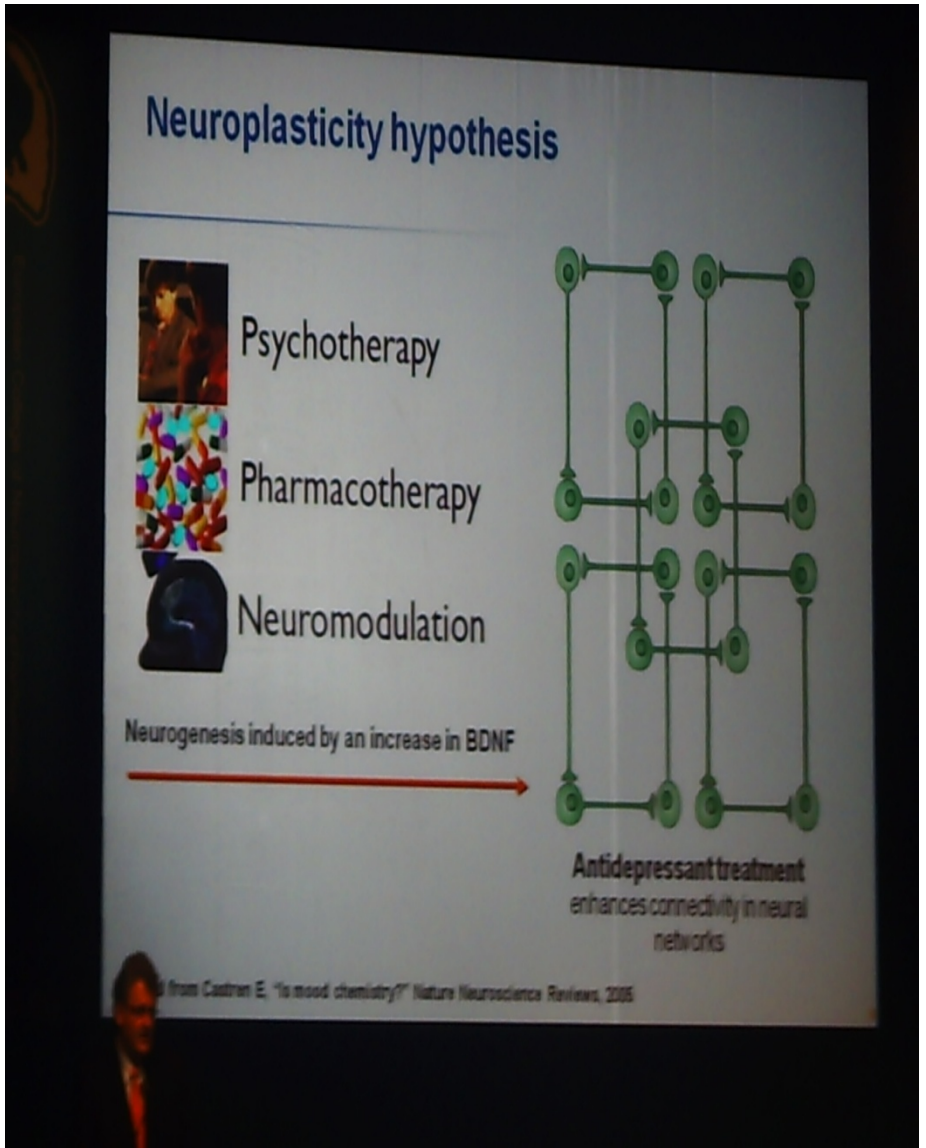
- Διαταραχή της σκέψης
- Οξεία διαταραχή
- Δυσλειτουργική νευροδιαβίβαση

Κατάθλιψη Νέα Θεωρία

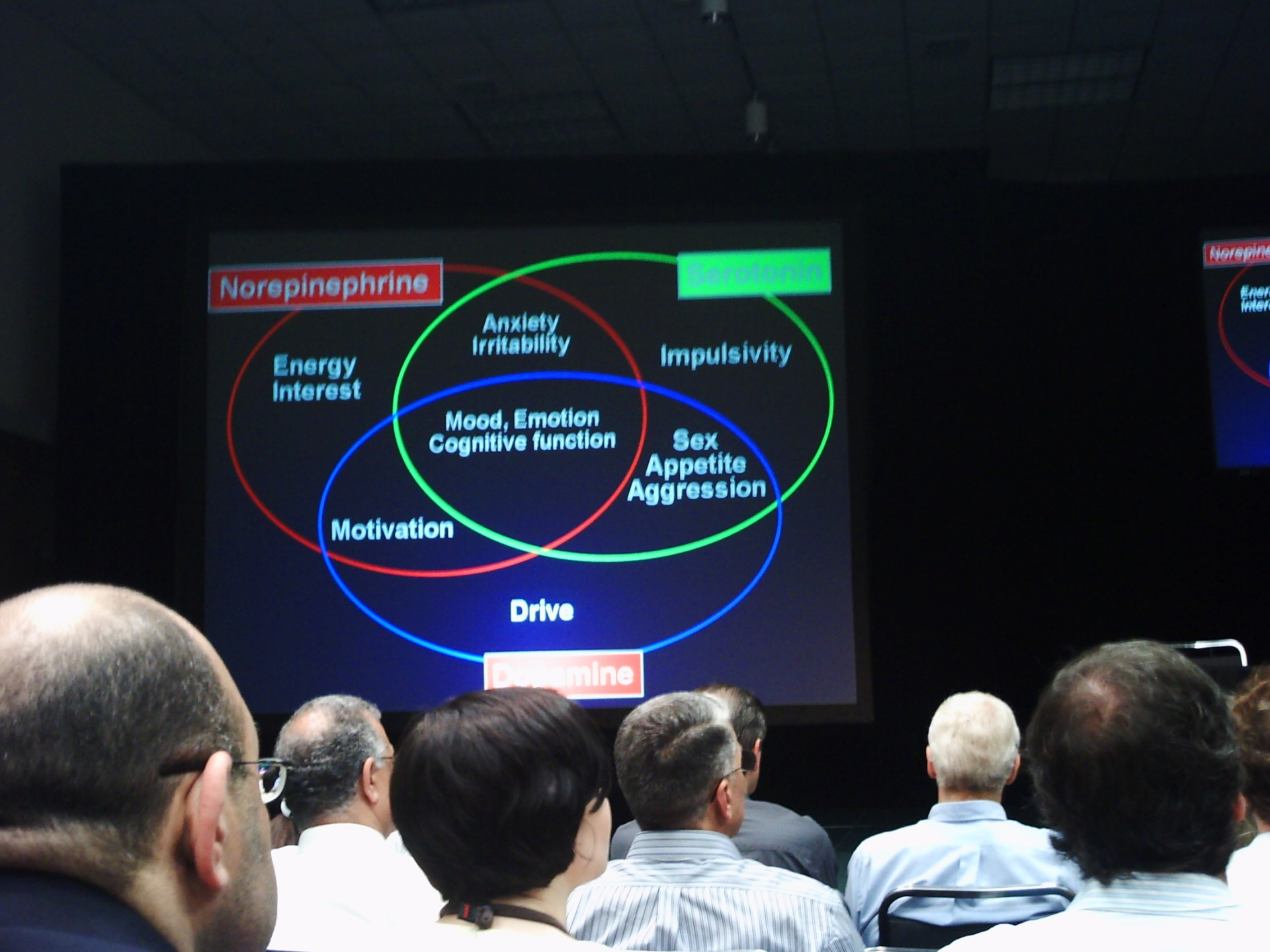
- Διαταραχή της σκέψης
- Οξεία διαταραχή
- Δυσλειτουργική νευροδιαβίβαση
- Διαταραχή της σκέψης του εγκέφαλου και του σώματος
- Χρόνια νευροεκφιλιστική διαταραχή
- Δυσλειτουργική νευροδιαβίβαση σε δυσλειτουργικά δίκτυα

Αποκατάσταση της νευροεκφύλισης





ΤΡΕΙΣ ΝΕΥΡΟΔΙΑΒΙΒΑΣΤΕΣ ΕΝΕΧΟΝΤΑΙ ΣΤΗ ΣΥΜΠΤΟΜΑΤΟΛΟΓΙΑ ΤΗΣ ΚΑΤΑΘΛΙΨΗΣ


Norepinephrine
Serotonin
Anxiety
Irritability
Energy
Interest
Impulsivity
Mood, Emotion
Cognitive function
Sex
Appetite
Aggression
Motivation
Drive

ΑΝΤΙΚΑΤΑΘΛΙΠΤΙΚΑ

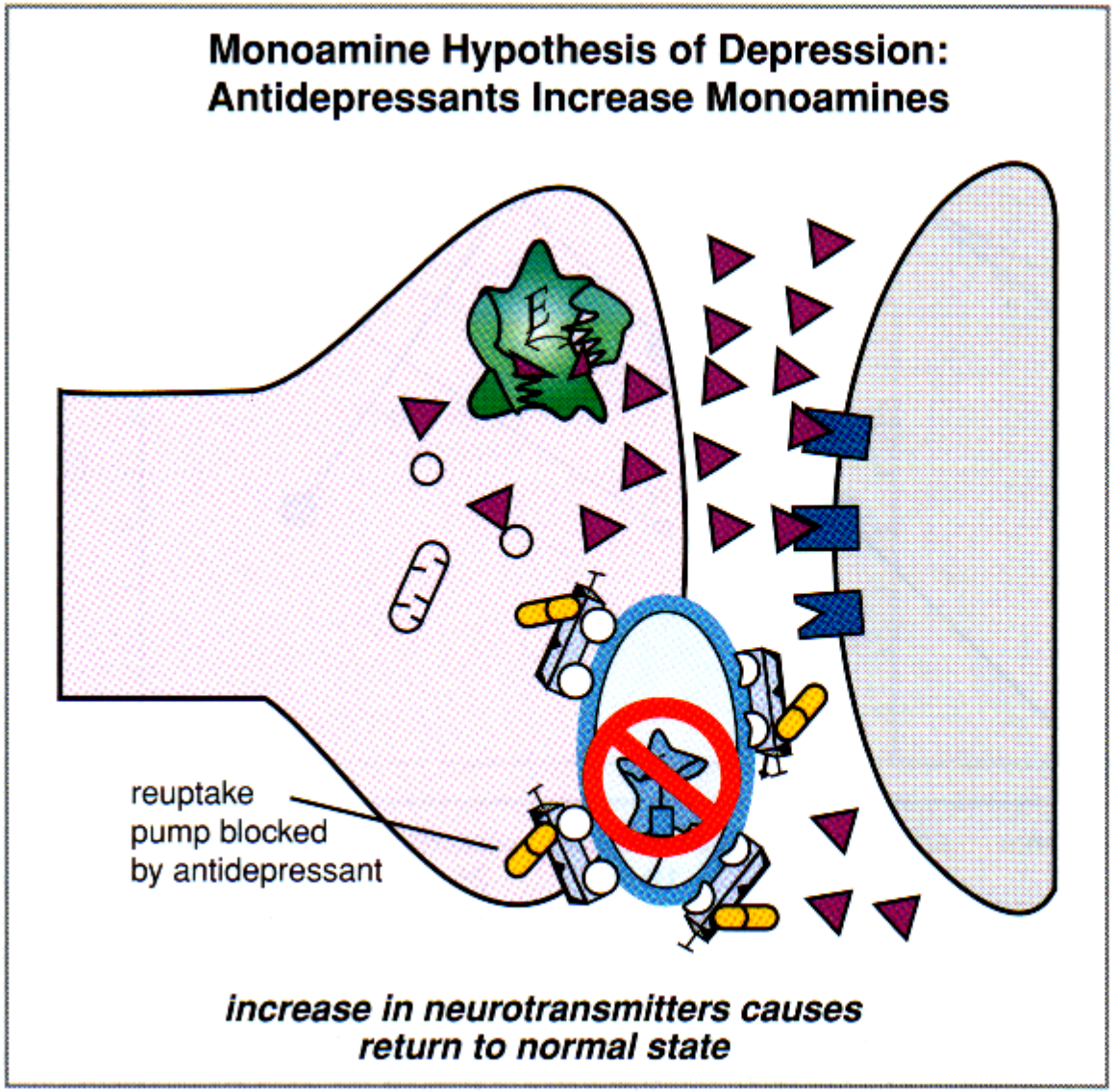


FIGURE 12-12
Antidepressants increase monoamines. According to the monoamine hypothesis of depression, a deficiency in serotonin, norepinephrine, and/or dopamine leads to depression. Thus an increase in these neurotransmitters should cause a return to a normal state. In general, all antidepressants boost the synaptic action of one or more of the monoamines, in most cases by blocking presynaptic transporters. In this figure, an antidepressant is blocking the norepinephrine transporter (NET), thus increasing synaptic availability of norepinephrine and theoretically reducing symptoms of depression.

ΑΝΤΙΚΑΤΑΘΛΙΠΤΙΚΑ

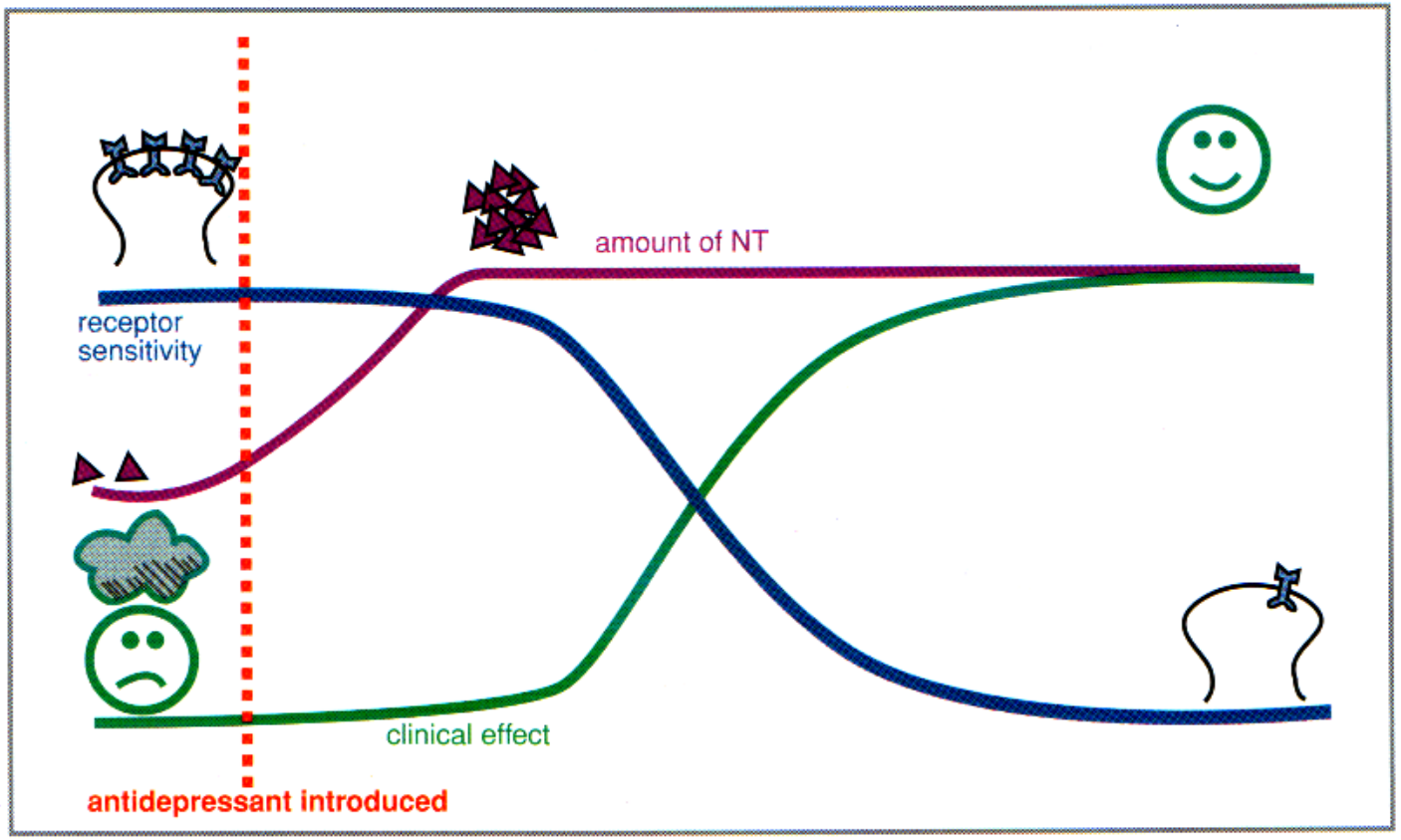


FIGURE 12-13 Time course of antidepressant effects. This figure depicts the different time courses for three effects of antidepressant drugs – namely, clinical changes, neurotransmitter (NT) changes, and receptor sensitivity changes. Specifically, the amount of NT changes relatively rapidly after an antidepressant is introduced. However, the clinical effect is delayed, as is the desensitization, or downregulation, of neurotransmitter receptors. This temporal correlation of clinical effects with changes in receptor sensitivity has given rise to the hypothesis that changes in neurotransmitter receptor sensitivity may actually mediate the clinical effects of antidepressant drugs. These clinical effects include not only antidepressant and anxiolytic actions but also the development of tolerance to the acute side effects of antidepressant drugs.

ΑΝΤΙΚΑΤΑΘΛΙΠΤΙΚΑ

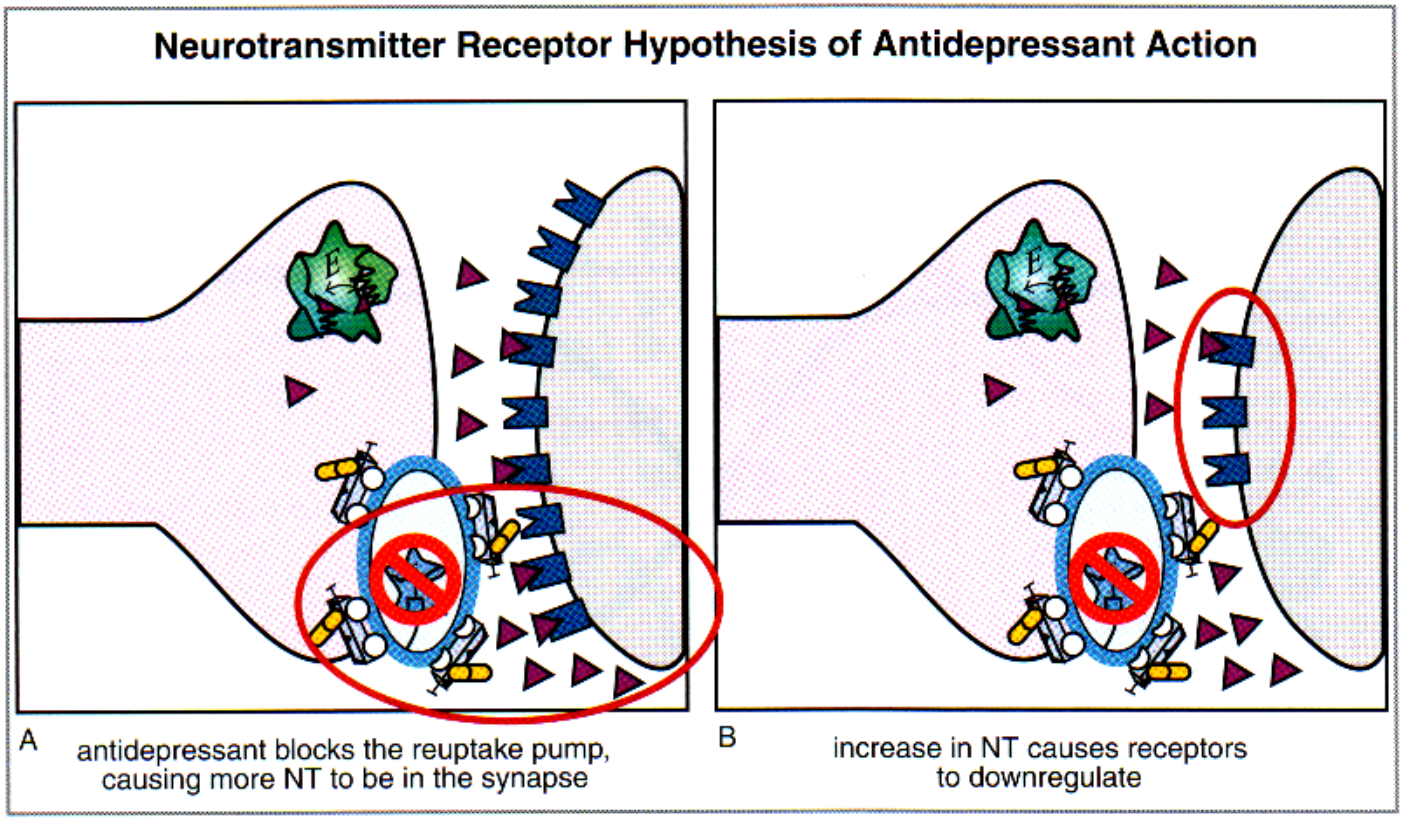


FIGURE 12-14A and B Neurotransmitter receptor hypothesis of antidepressant action. Although antidepressants cause an immediate increase in monoamines, they do not have immediate therapeutic effects. This may be explained by the monoamine receptor hypothesis of depression, which states that depression is caused by upregulation of monoamine receptors; thus antidepressant efficacy would be related to downregulation of those receptors, as shown here. (**A**) When an antidepressant blocks a monoamine reuptake pump, this causes more neurotransmitter (NT) (in this case, norepinephrine) to accumulate in the synapse. (**B**) The increased availability of NT ultimately causes receptors to downregulate. The time course of receptor adaptation is consistent both with the delayed clinical effects of antidepressants and with development of tolerance to antidepressant side effects.

ΑΝΤΙΚΑΤΑΘΛΙΠΤΙΚΑ

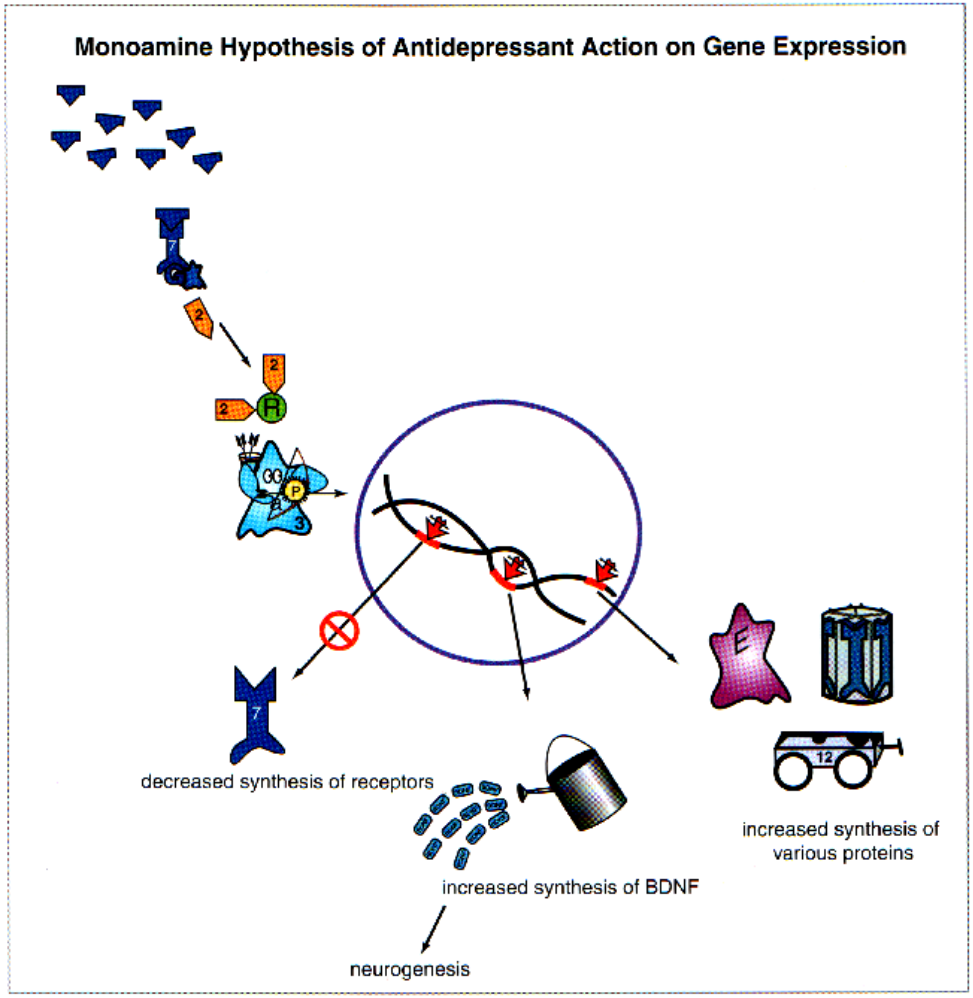


FIGURE 12-15 Monoamine hypothesis of antidepressant action on gene expression. Adaptations in receptor number or sensitivity are likely due to alterations in gene expression, as shown here. The neurotransmitter at the top is presumably increased by an antidepressant. The cascading consequence of this is ultimately to change the expression of critical genes in order to effect an antidepressant response. This includes downregulating some genes so that there is decreased synthesis of receptors as well as upregulating other genes so that there is increased synthesis of critical proteins, such as brain-derived neurotrophic factor (BDNF).

ΑΝΤΙΚΑΤΑΘΛΙΠΤΙΚΑ

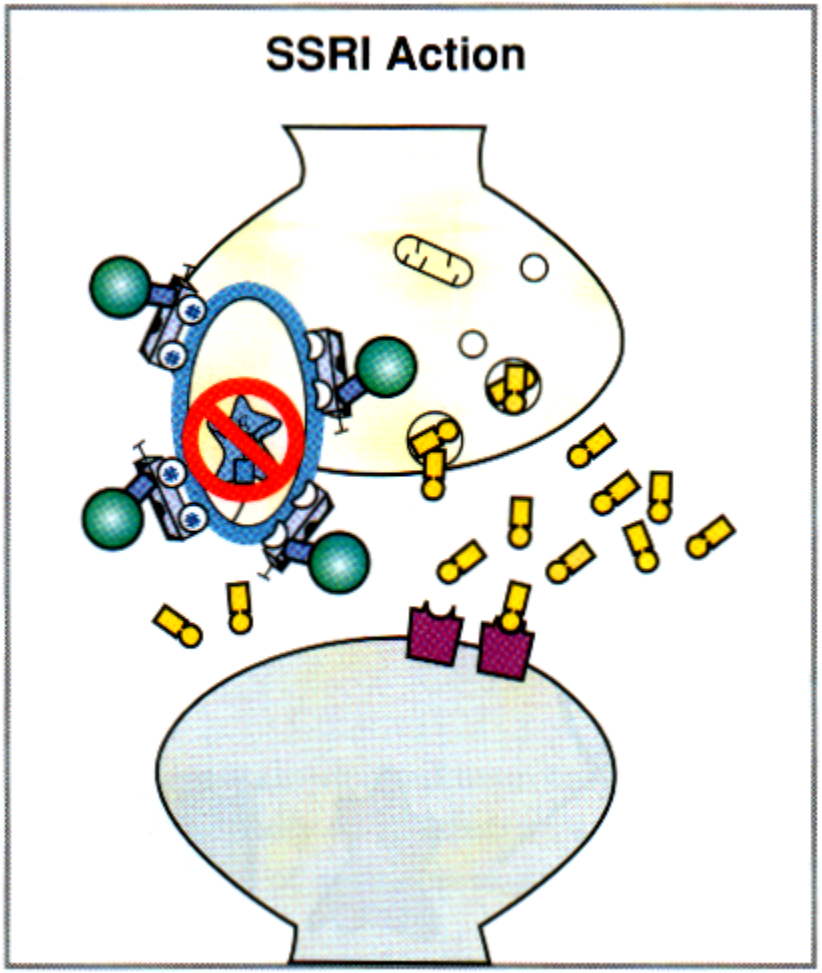


FIGURE 12-17 SSRI action. In this figure, the serotonin reuptake inhibitor (SRI) portion of the SSRI molecule is shown inserted into the serotonin reuptake pump (the serotonin transporter, or SERT), blocking it and causing an antidepressant effect.

ΑΝΤΙΚΑΤΑΘΛΙΠΤΙΚΑ

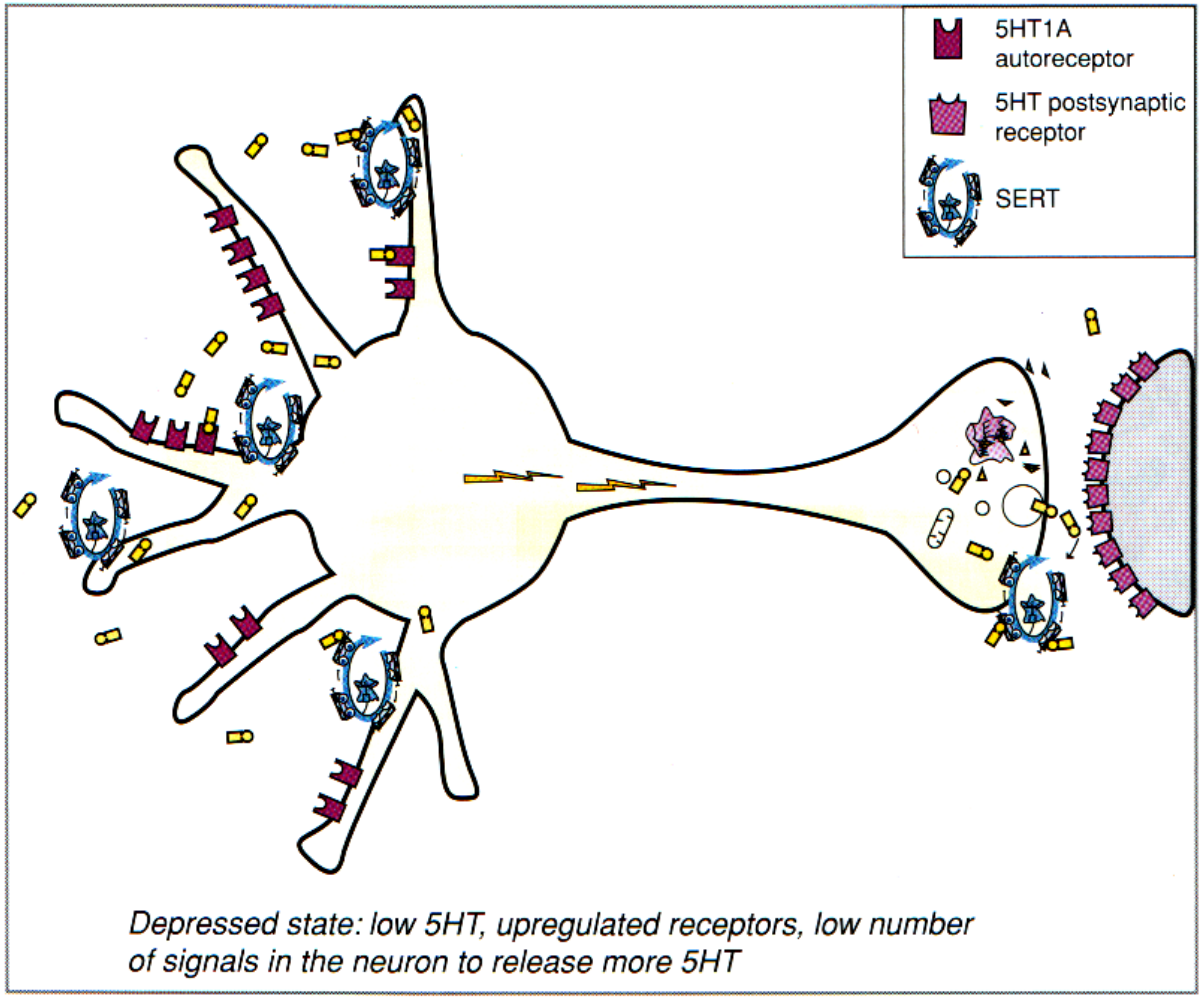


FIGURE 12-18 Mechanism of action of serotonin selective reuptake inhibitors (SSRIs), part 1. Depicted here is a serotonin (5HT) neuron in a depressed patient. In depression, the 5HT neuron is conceptualized as having a relative deficiency of the neurotransmitter 5HT. Also, the number of 5HT receptors is upregulated, including presynaptic 5HT1A autoreceptors as well as postsynaptic 5HT receptors.

ΑΝΤΙΚΑΤΑΘΛΙΠΤΙΚΑ

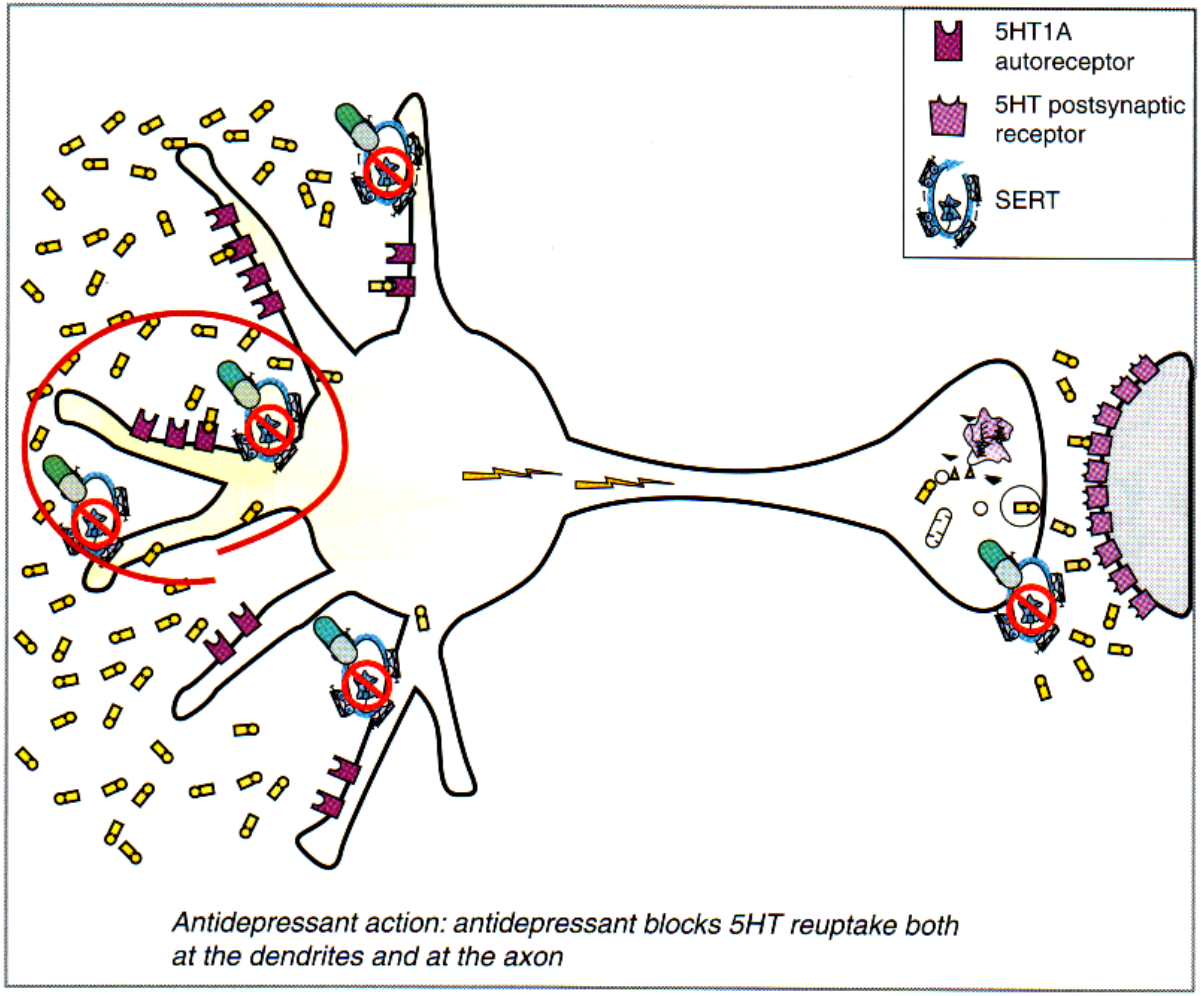


FIGURE 12-19 Mechanism of action of serotonin selective reuptake inhibitors (SSRIs), part 2. When an SSRI is administered, it immediately blocks the serotonin reuptake pump [see icon of an SSRI drug capsule blocking the reuptake pump, or serotonin transporter (SERT)]. However, this causes serotonin to increase initially only in the somatodendritic area of the serotonin neuron (left) and not very much in the axon terminals (right).

ΑΝΤΙΚΑΤΑΘΛΙΠΤΙΚΑ

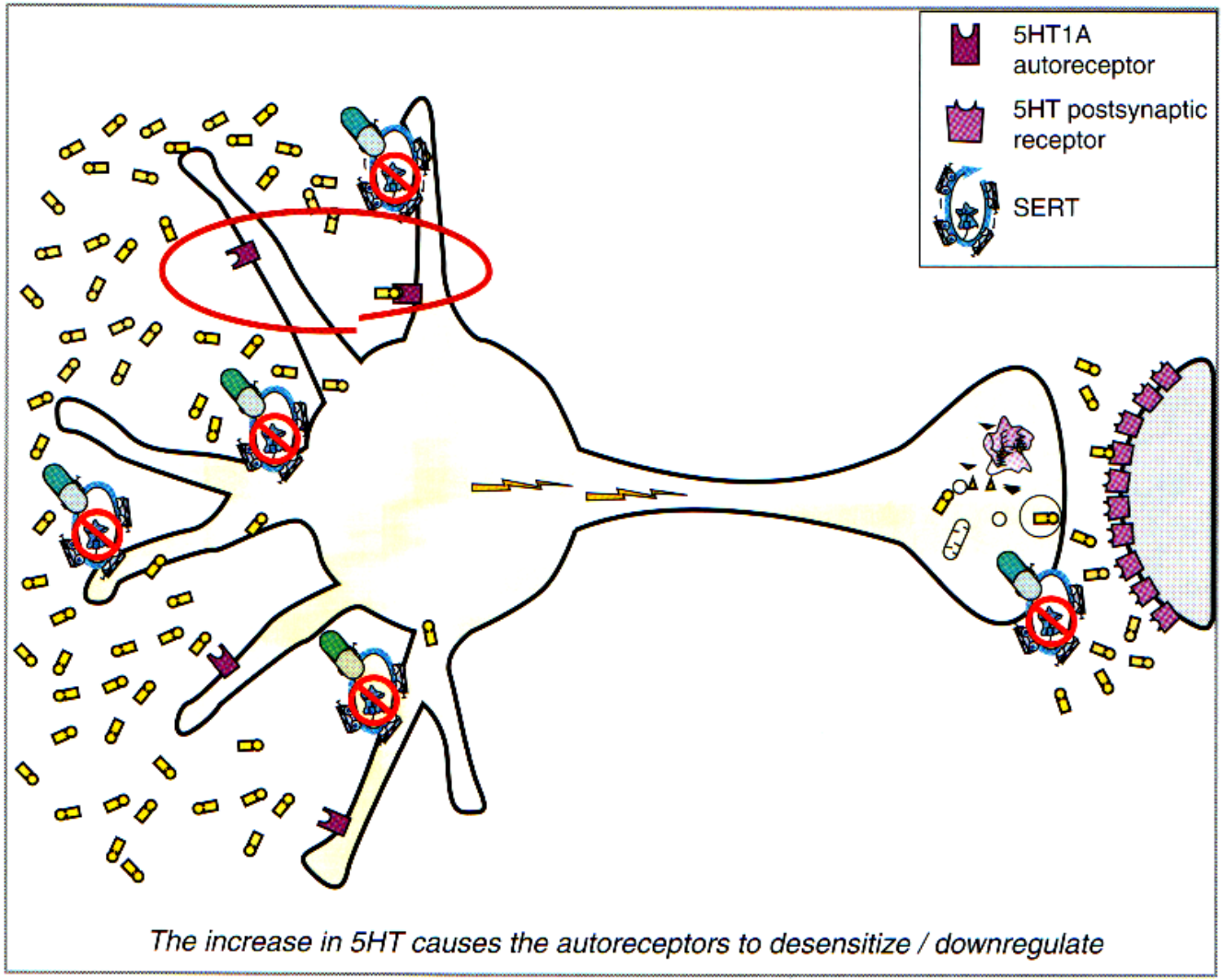


FIGURE 12-20 Mechanism of action of serotonin selective reuptake inhibitors (SSRIs), part 3. The consequence of serotonin increasing in the somatodendritic area of the serotonin (5HT) neuron, as depicted in Figure 12-19, is that the somatodendritic 5HT1A autoreceptors desensitize or downregulate (red circle).

ΑΝΤΙΚΑΤΑΘΛΙΠΤΙΚΑ

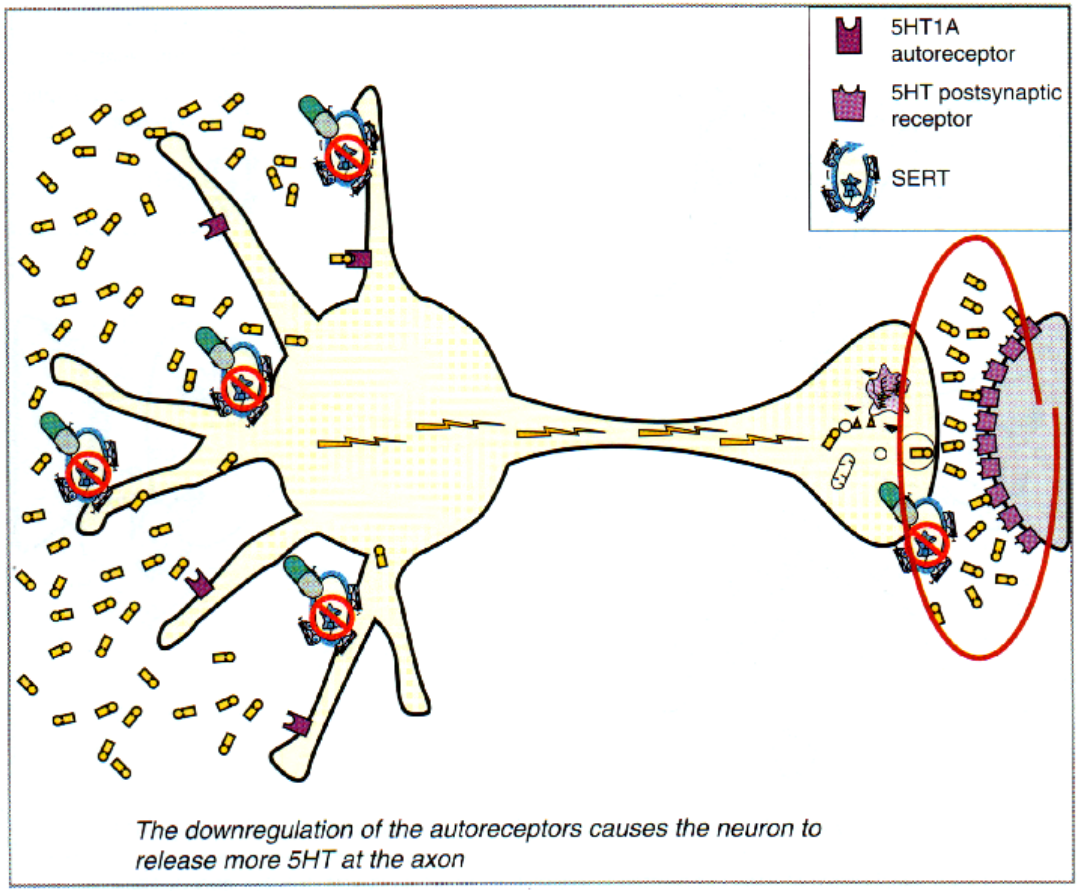


FIGURE 12-21 Mechanism of action of serotonin selective reuptake inhibitors (SSRIs), part 4. Once the somatodendritic receptors downregulate, as depicted in Figure 12-21, there is no longer inhibition of impulse flow in the serotonin (5HT) neuron. Thus, neuronal impulse flow is turned on. The consequence of this is release of 5HT in the axon terminal (red circle). However, this increase is delayed as compared with the increase of 5HT in the somatodendritic areas of the 5HT neuron, depicted in Figure 12-20. This delay is the result of the time it takes for somatodendritic 5HT to downregulate the 5HT1A autoreceptors and turn on neuronal impulse flow in the 5HT neuron. This delay may explain why antidepressants do not relieve depression immediately. It is also the reason why the mechanism of action of antidepressants may be linked to increasing neuronal impulse flow in 5HT neurons, with 5HT levels increasing at axon terminals before an SSRI can exert its antidepressant effects.

ΑΝΤΙΚΑΤΑΘΛΙΠΤΙΚΑ

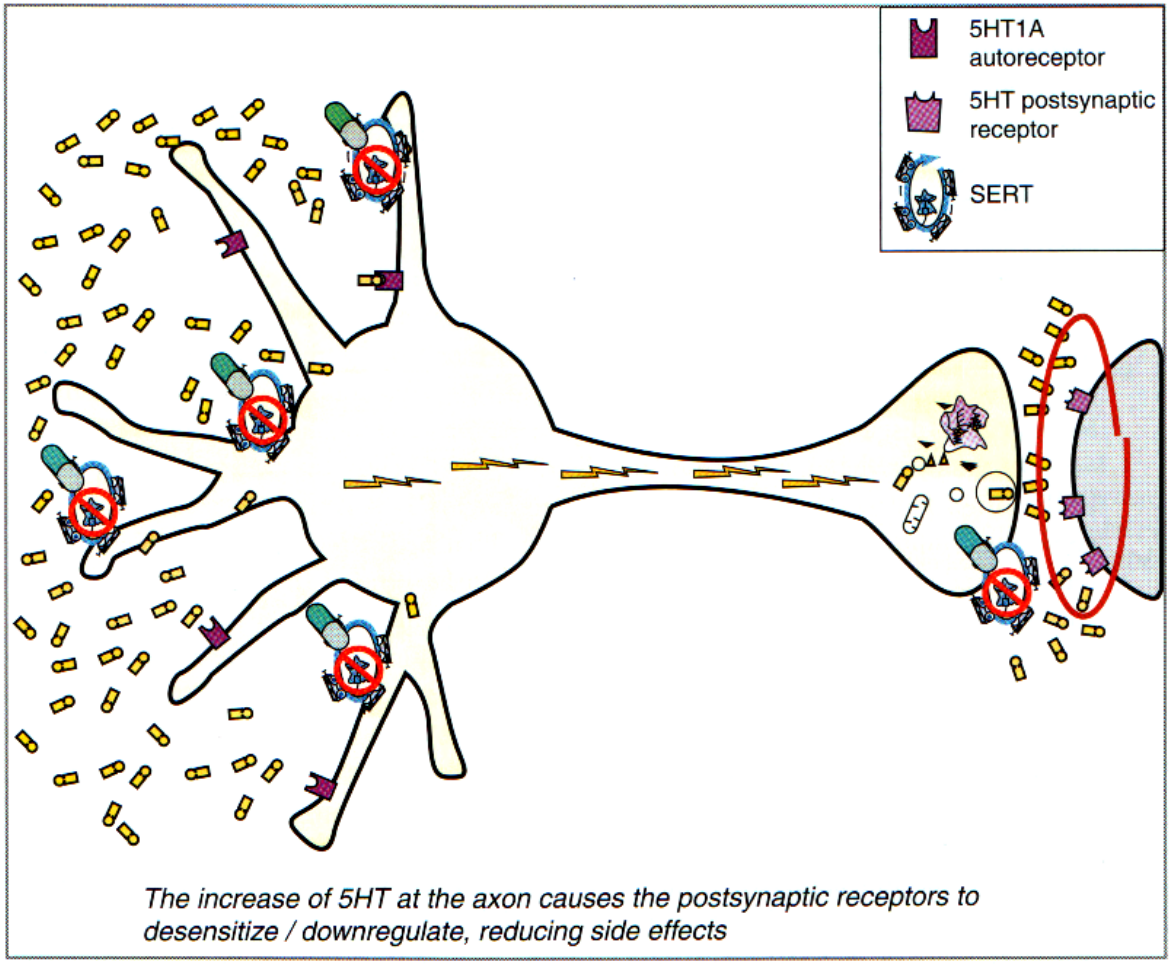


FIGURE 12-22 Mechanism of action of serotonin selective reuptake inhibitors (SSRIs), part 5. Finally, once the SSRIs have blocked the reuptake pump [or serotonin transporter (SERT) in Figure 12-19], increased somatodendritic serotonin (5HT) (Figure 12-19), desensitized somatodendritic 5HT1A autoreceptors (Figure 12-20), turned on neuronal impulse flow (Figure 12-21), and increased release of 5HT from axon terminals (Figure 12-21), the final step (shown here) may be the desensitization of postsynaptic 5HT receptors. This desensitization may mediate the reduction of side effects of SSRIs as tolerance develops.

Εκλεκτικοί αναστολείς επαναπρόσληψης σεροτονίνης (SSRI)

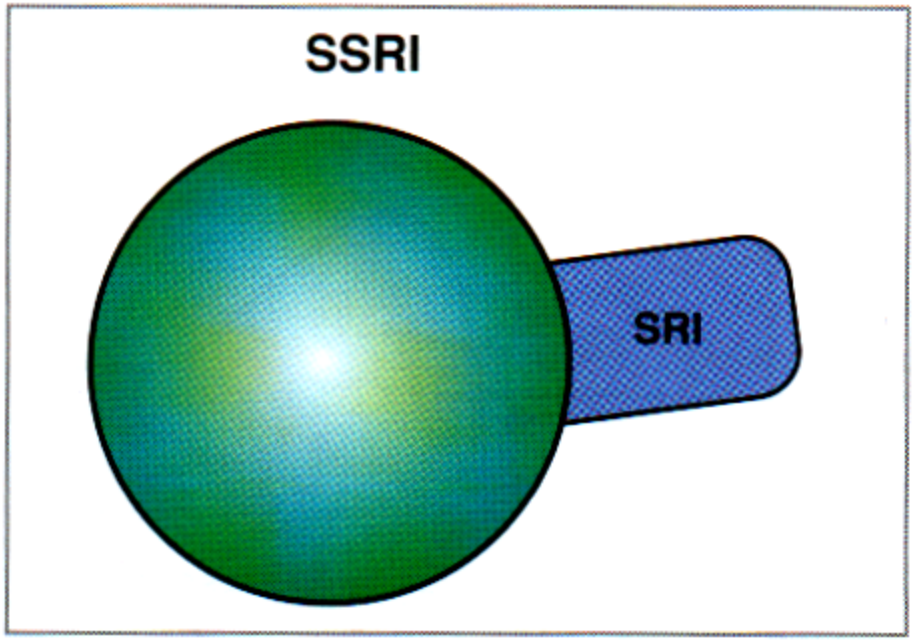


FIGURE 12-16 Serotonin selective reuptake inhibitors. Shown here is an icon depicting the core feature of serotonin selective reuptake inhibitors (SSRIs), namely serotonin reuptake inhibition. Although the six agents in this class have unique pharmacological profiles, they all share the common property of serotonin transporter (SERT) inhibition.

ΑΝΤΙΚΑΤΑΘΛΙΠΤΙΚΑ

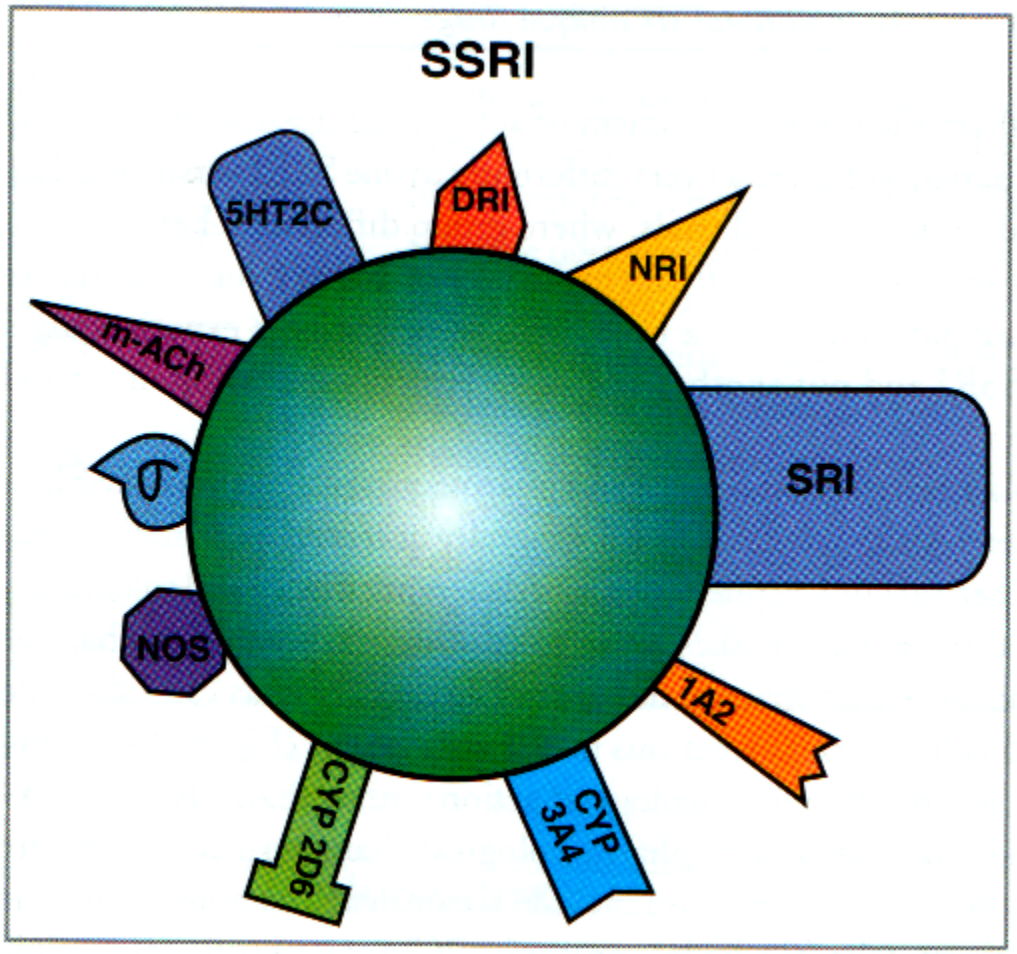


FIGURE 12-23 Secondary pharmacological properties of SSRIs. This icon depicts the various secondary pharmacological properties that may be associated with one or more of the six different serotonin selective reuptake inhibitors (SSRIs). These include not only serotonin reuptake inhibition (SRI) but also lesser degrees of actions at other neurotransmitters and enzymes, including norepinephrine reuptake inhibition (NRI), dopamine reuptake inhibition (DRI), serotonin 2C antagonist actions (5HT2C), muscarinic/cholinergic antagonist actions (M1), sigma 1 receptor actions (σ), inhibition of nitric oxide synthetase (NOS), and inhibition of CYP450 2D6, 3A4, and 1A2.

Φλουοξετίνη Ladose

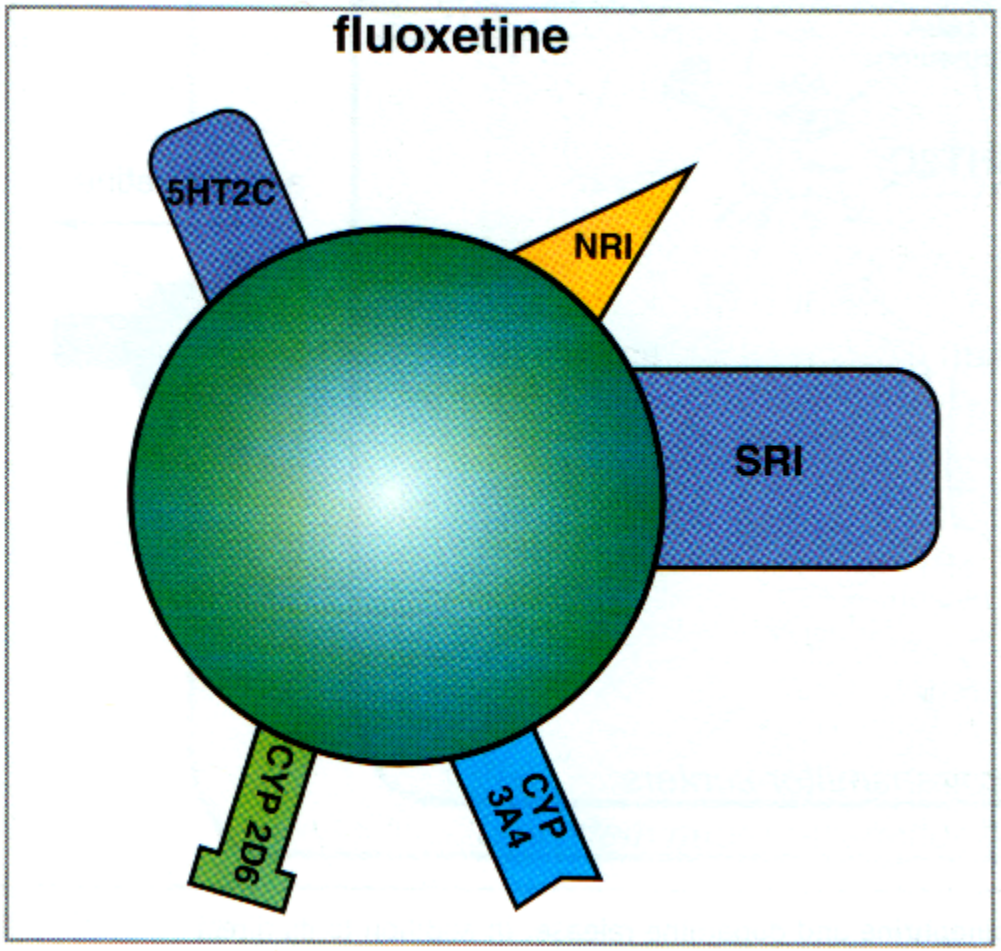


FIGURE 12-24 Icon of fluoxetine. In addition to serotonin reuptake inhibition, fluoxetine has norepinephrine reuptake inhibition (NRI), CYP450 2D6 and 3A4 inhibition, and serotonin 2C antagonist actions (5HT2C). Fluoxetine's activating effects may be due to its actions at serotonin 2C receptors. Norepinephrine reuptake inhibition may be clinically relevant only at very high doses.

Σεταλίνη Zoloft

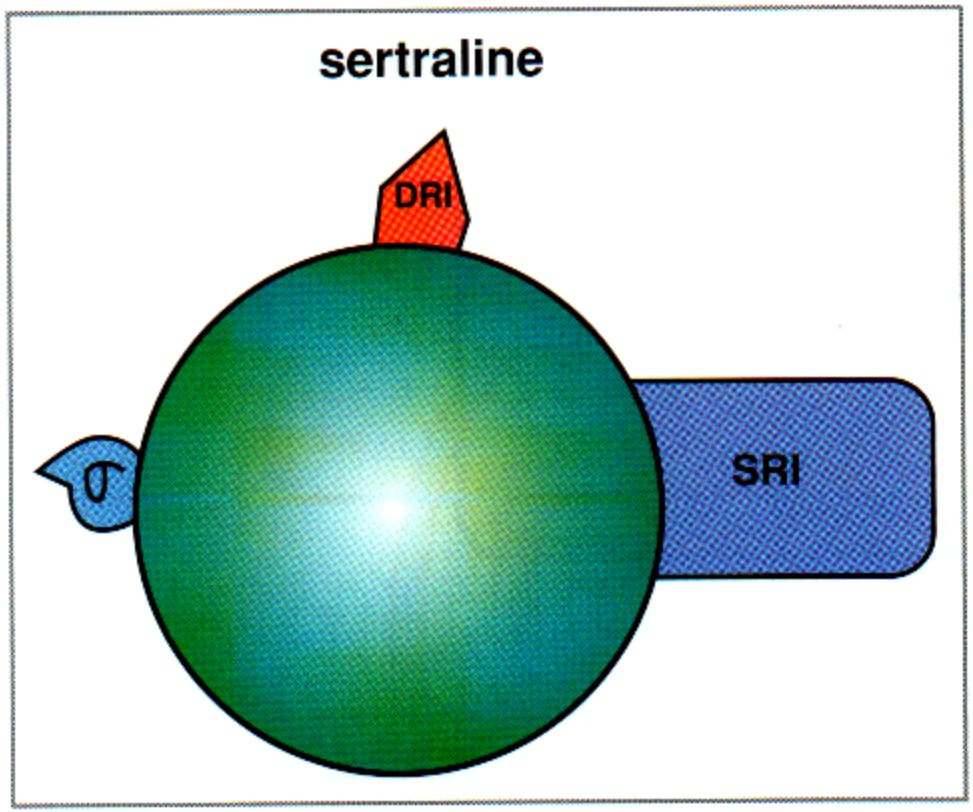


FIGURE 12-26 Icon of sertraline. Sertraline has dopamine reuptake inhibition (DRI) and sigma 1 receptor binding in addition to serotonin reuptake inhibition (SRI). The clinical relevance of sertraline's DRI is unknown, although it may improve energy, motivation, and concentration. Its sigma properties may contribute to anxiolytic actions and may also be helpful in patients with psychotic depression.

Παροξετίνη Seroxat

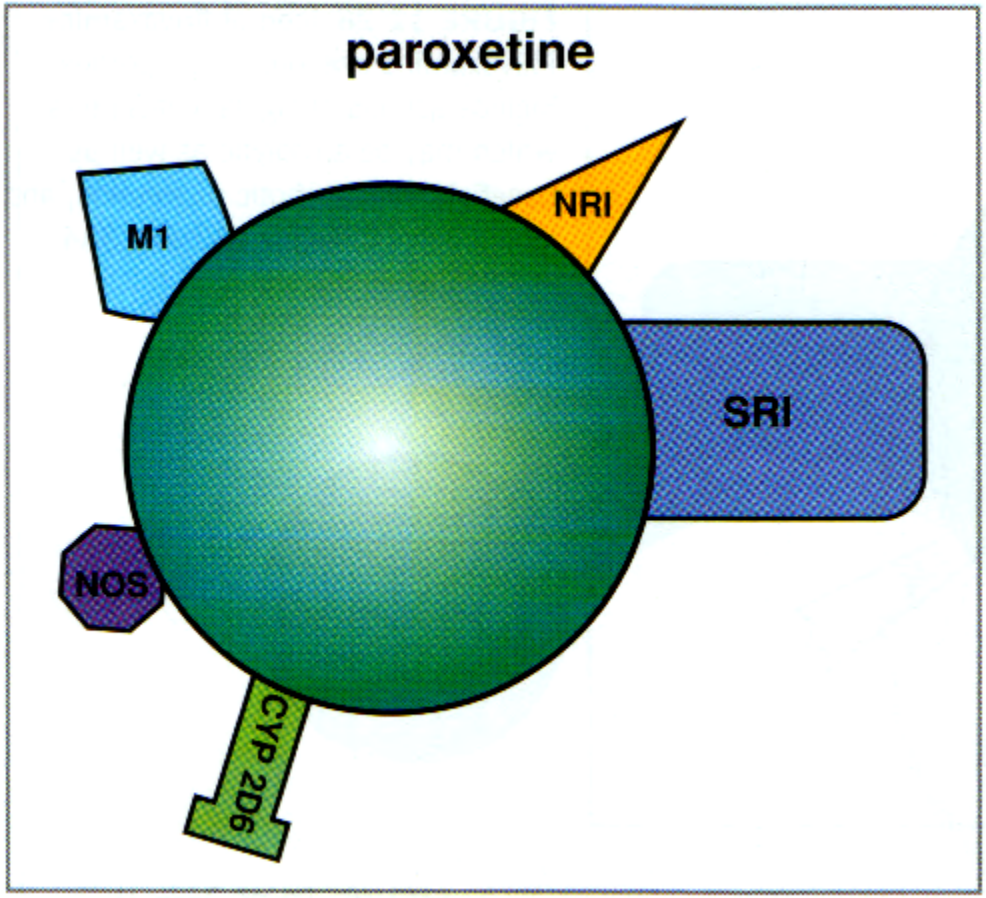


FIGURE 12-27 Icon of paroxetine. In addition to serotonin reuptake inhibition (SRI), paroxetine has mild anticholinergic actions (M1), which can be calming or possibly sedating, weak norepinephrine reuptake inhibition (NRI), which may contribute to further antidepressant actions, and inhibition of the enzyme nitric oxide synthetase (NOS), which may contribute to sexual dysfunction. Paroxetine is also a potent inhibitor of CYP450 2D6.

Φλουβοξαμίνη Dumyrox

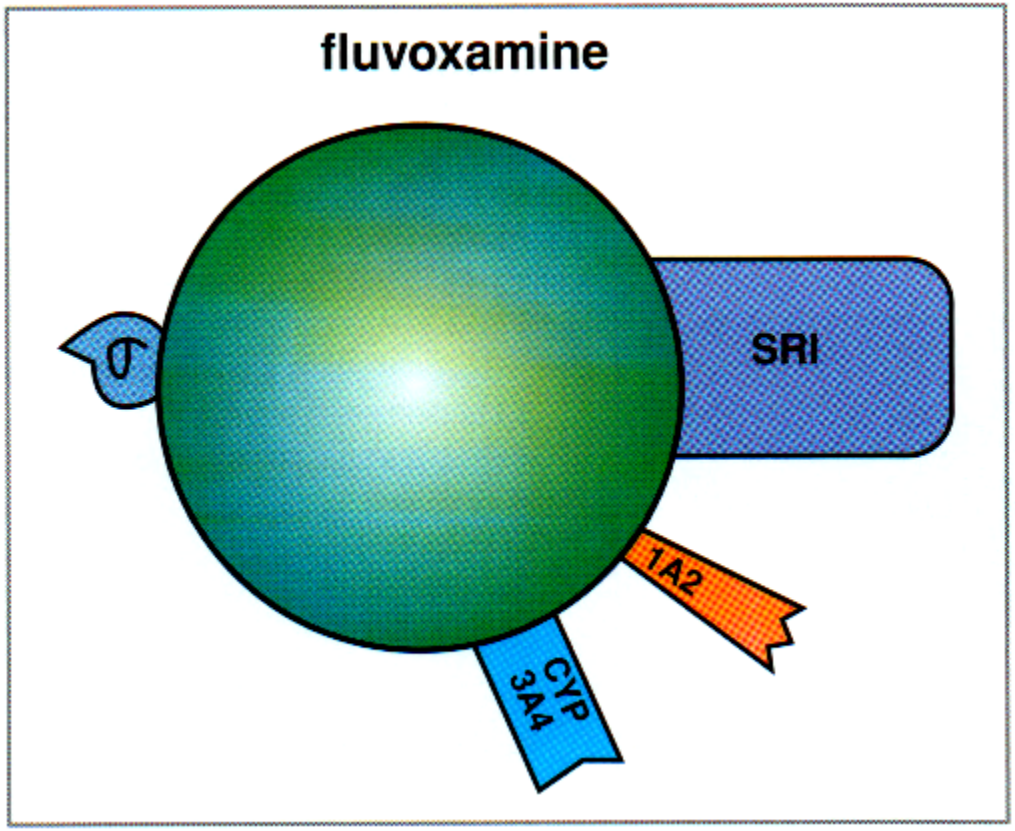


FIGURE 12-28 Icon of fluvoxamine. Fluvoxamine's secondary properties include actions at sigma 1 receptors, which may be anxiolytic as well as beneficial for psychotic depression, and inhibition of CYP450 1A2 and 3A4.

Σιταλοπράμη Seropram

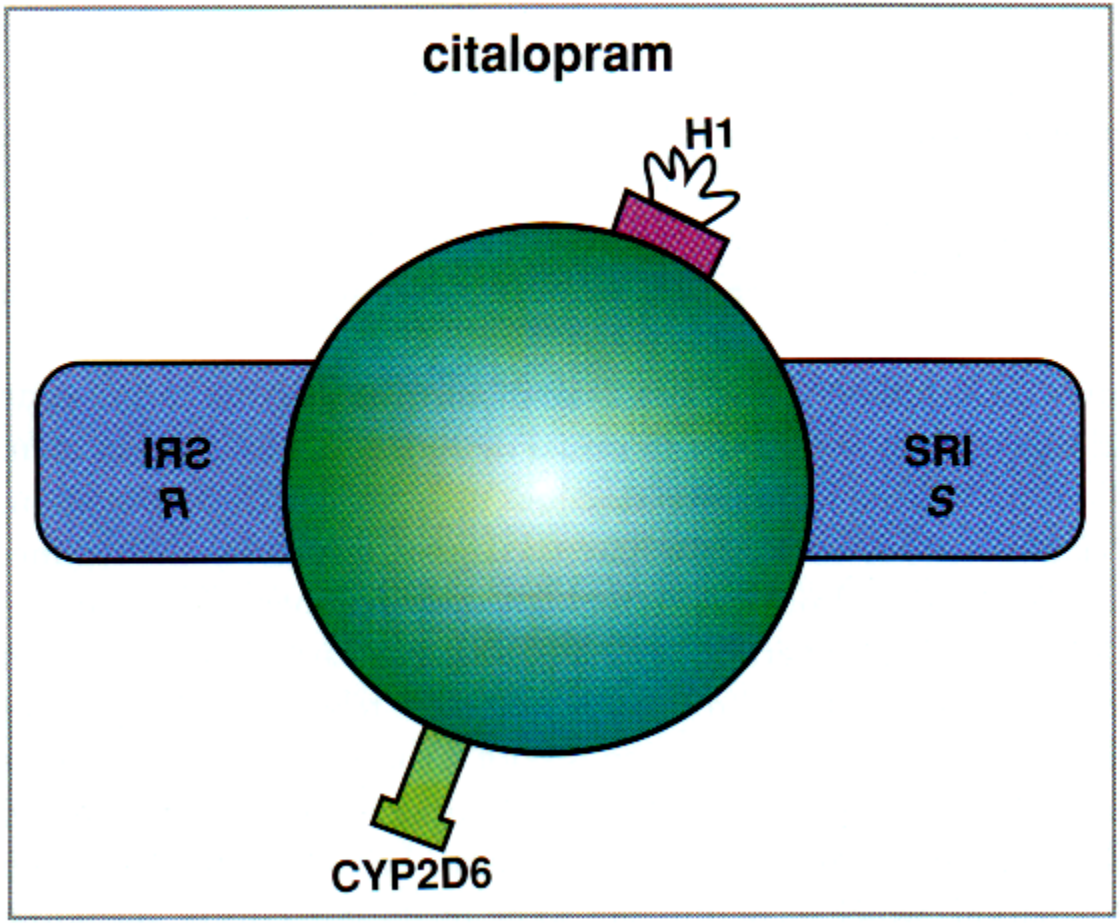


FIGURE 12-29 Icon of citalopram. Citalopram consists of two enantiomers, R and S. The R enantiomer has weak antihistamine properties and is a weak inhibitor of CYP450 2D6.

Εσιταλοπραμη Cipralex

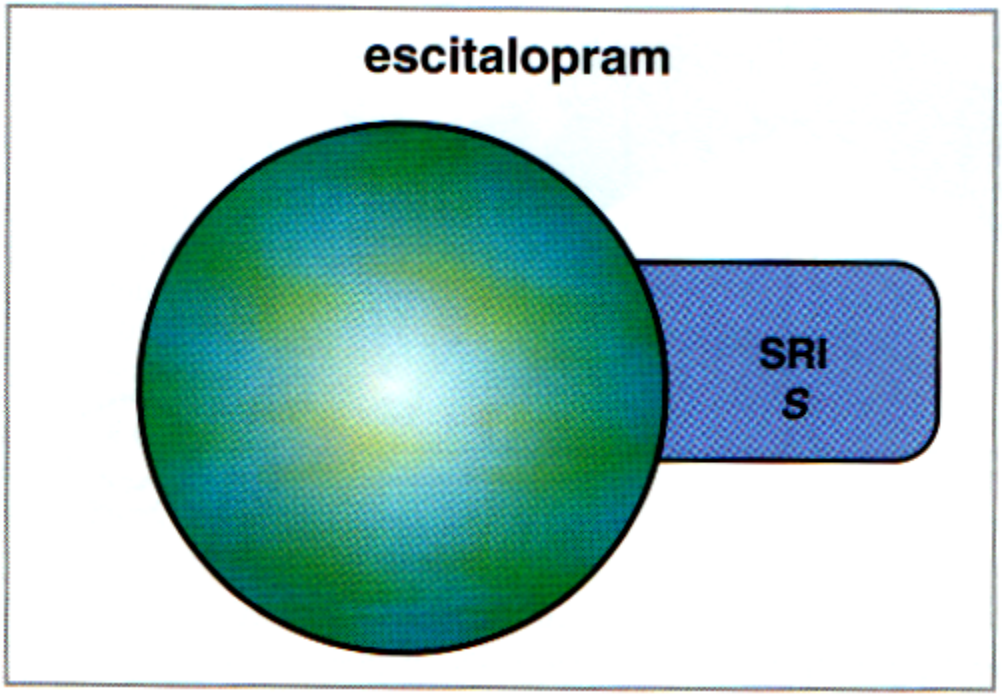
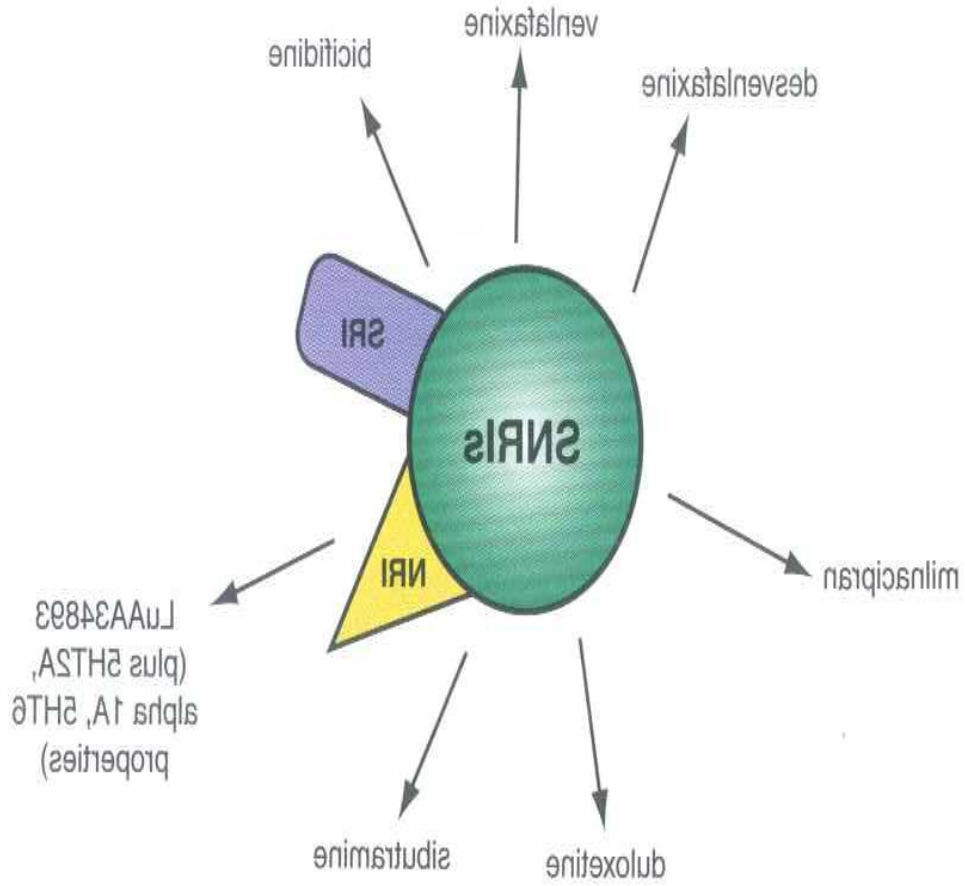
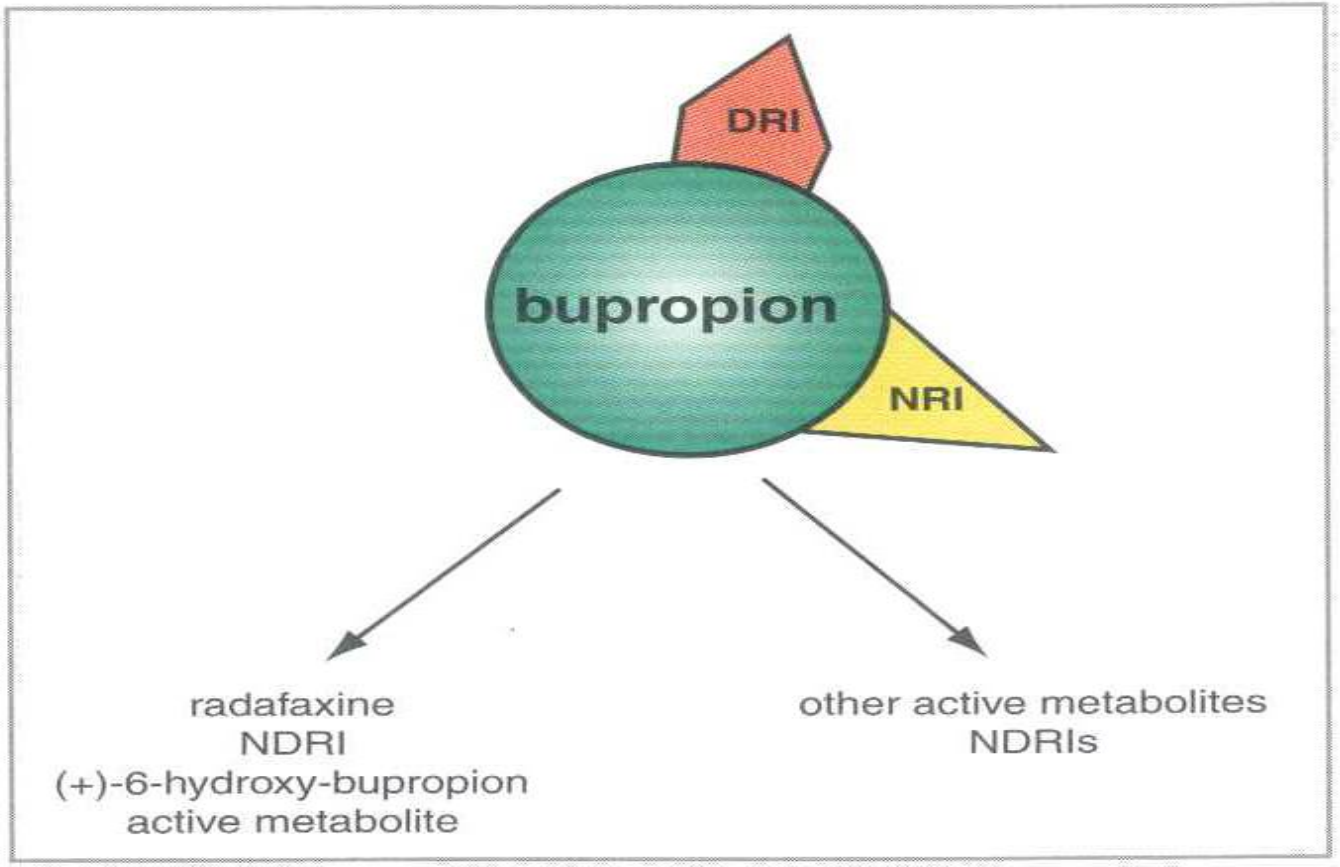


FIGURE 12-32 Icon of escitalopram. The S enantiomer of citalopram has been developed and marketed as the antidepressant escitalopram. This agent is the most selective of the serotonin selective reuptake inhibitors (SSRIs).

Εκλεκτικοί αναστολείς επαναπρόσληψης σεροτονινής νοραδρεναλίνης (SNRI)



Εκλεκτικοί αναστολείς επαναπρόσληψης νοραδρεναλίνης-ντοπαμίνης



Παρενέργειες

- Καταστολή
- Κεφαλαλγία
- Ζάλη
- Ναυτία
- Άγχος κρίσεις πανικού
- Σεξουαλικές διαταραχές
- ΟΙ ΠΕΡΙΣΣΟΤΕΡΕΣ ΠΑΡΕΝΕΡΓΕΙΕΣ ΔΙΑΡΚΟΥΝ ΓΙΑ 4-5 ΗΜΕΡΕΣ

Τρικυκλικά αντικαταθλιπτικά (σεροτονινεργική και νοραδρενεργική δράση)

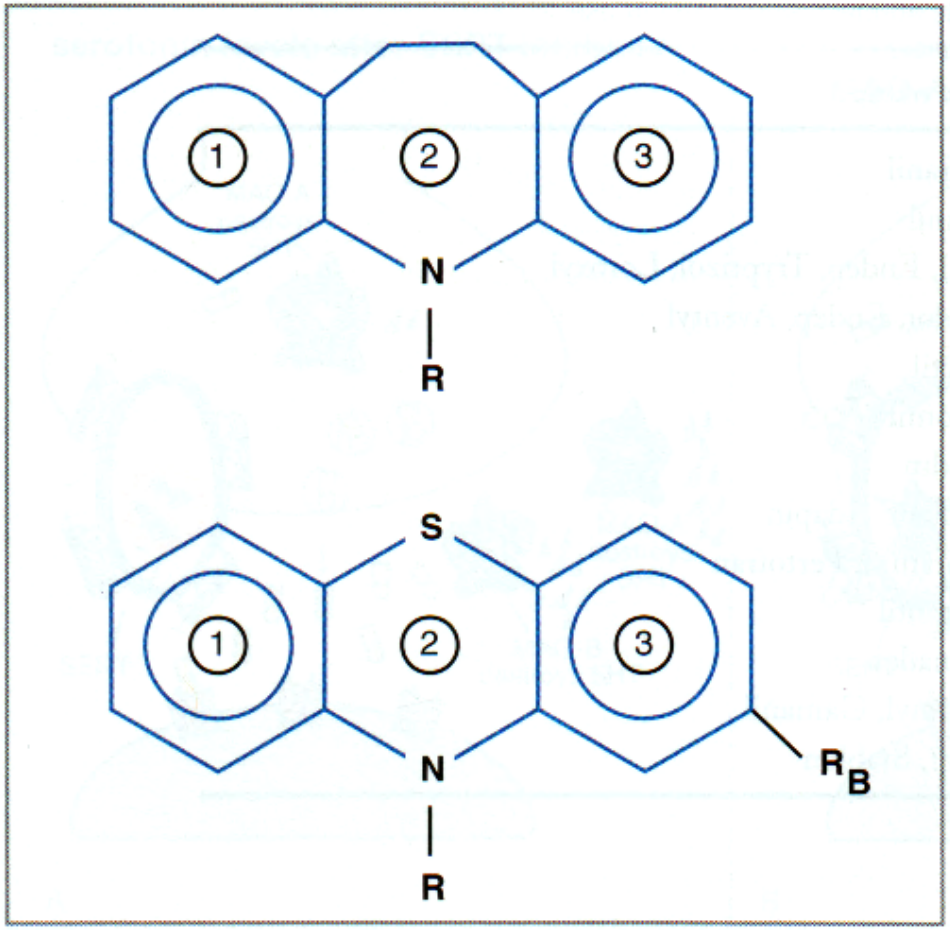


FIGURE 12-80 Tricyclic structure. At top is the chemical structure of a tricyclic antidepressant (TCA). The three rings show how this group of drugs got its name. At bottom is the general chemical formula for the phenothiazine antipsychotic drugs. These drugs also have three rings, and the first antidepressants – the TCAs – were modeled after such drugs.

ΑΝΤΙΚΑΤΑΘΛΙΠΤΙΚΑ

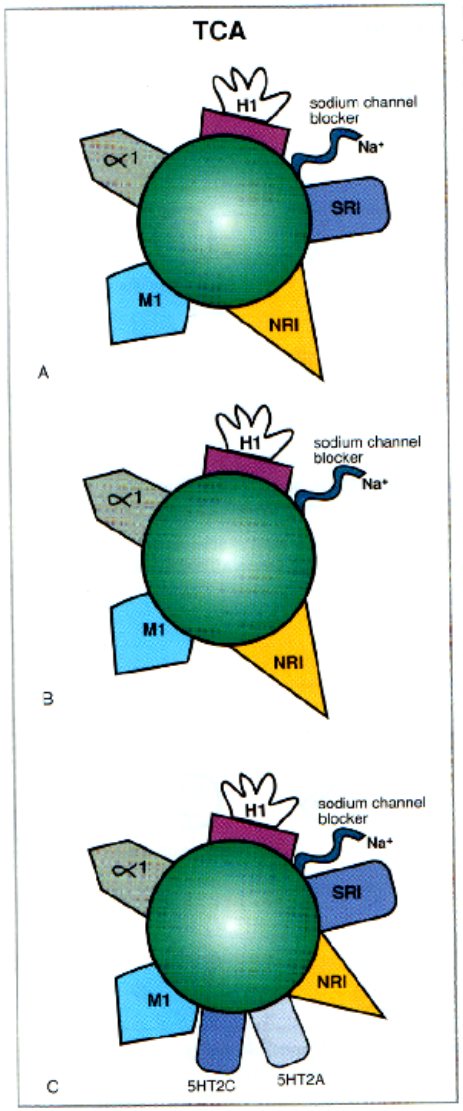


FIGURE 12-81 Icons of tricyclic antidepressants. All tricyclic antidepressants block reuptake of norepinephrine and are antagonists at histamine 1, alpha 1 adrenergic, and muscarinic cholinergic receptors; they also block voltage-sensitive sodium channels (**A, B, and C**). Some tricyclic antidepressants are also potent inhibitors of the serotonin reuptake pump (**A**), and some may additionally be antagonists at serotonin 2A and 2C receptors (**C**).

Αύξηση Βάρους- Υπνηλία

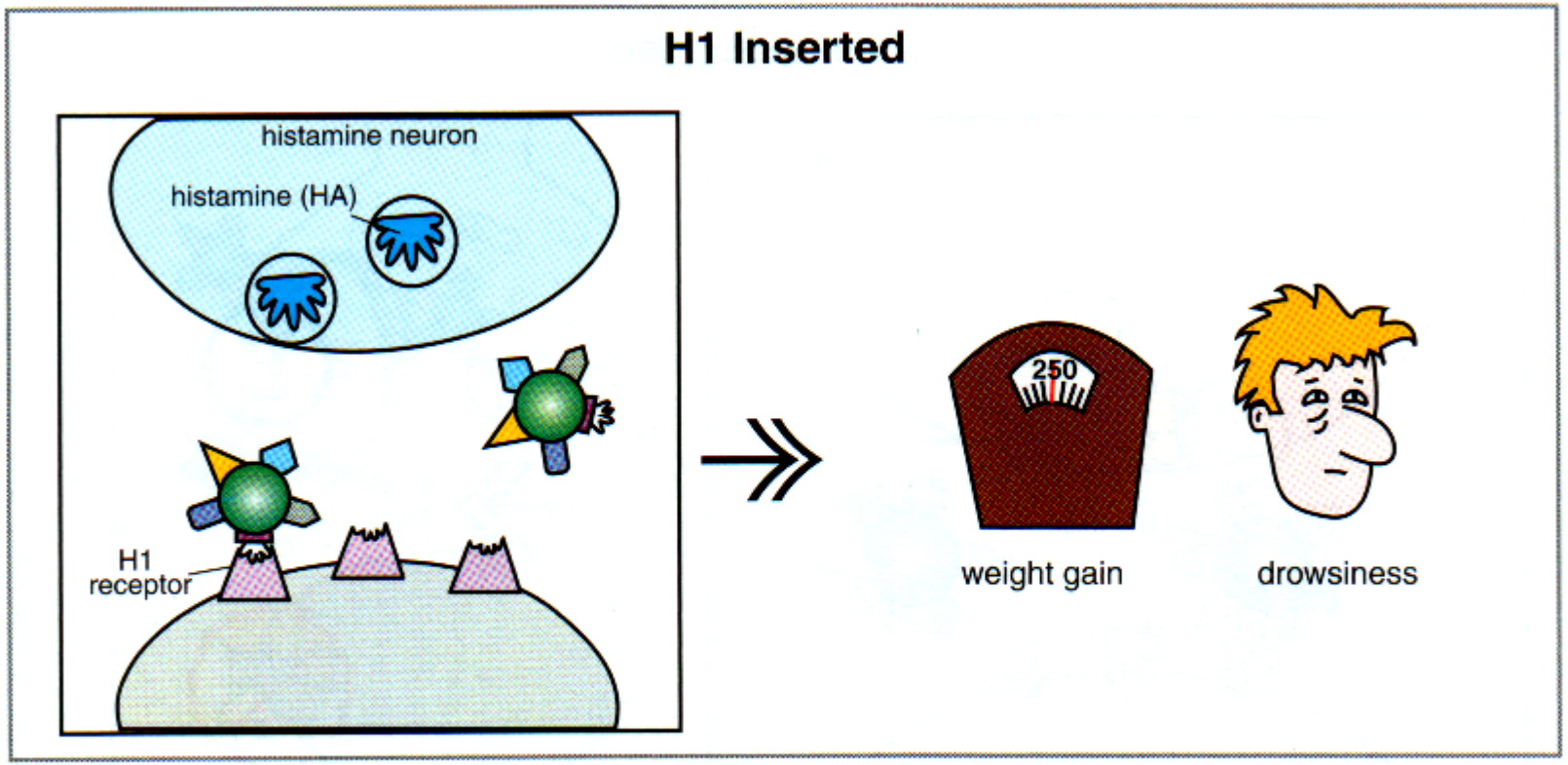


FIGURE 12-86 Side effects of tricyclic antidepressants (TCAs), part 1. In this figure, the icon of the TCA is shown with its antihistamine (H1) portion inserted into histamine receptors, causing the side effects of weight gain and drowsiness.

Δυσκοιλίοτητα- Θολή όραση

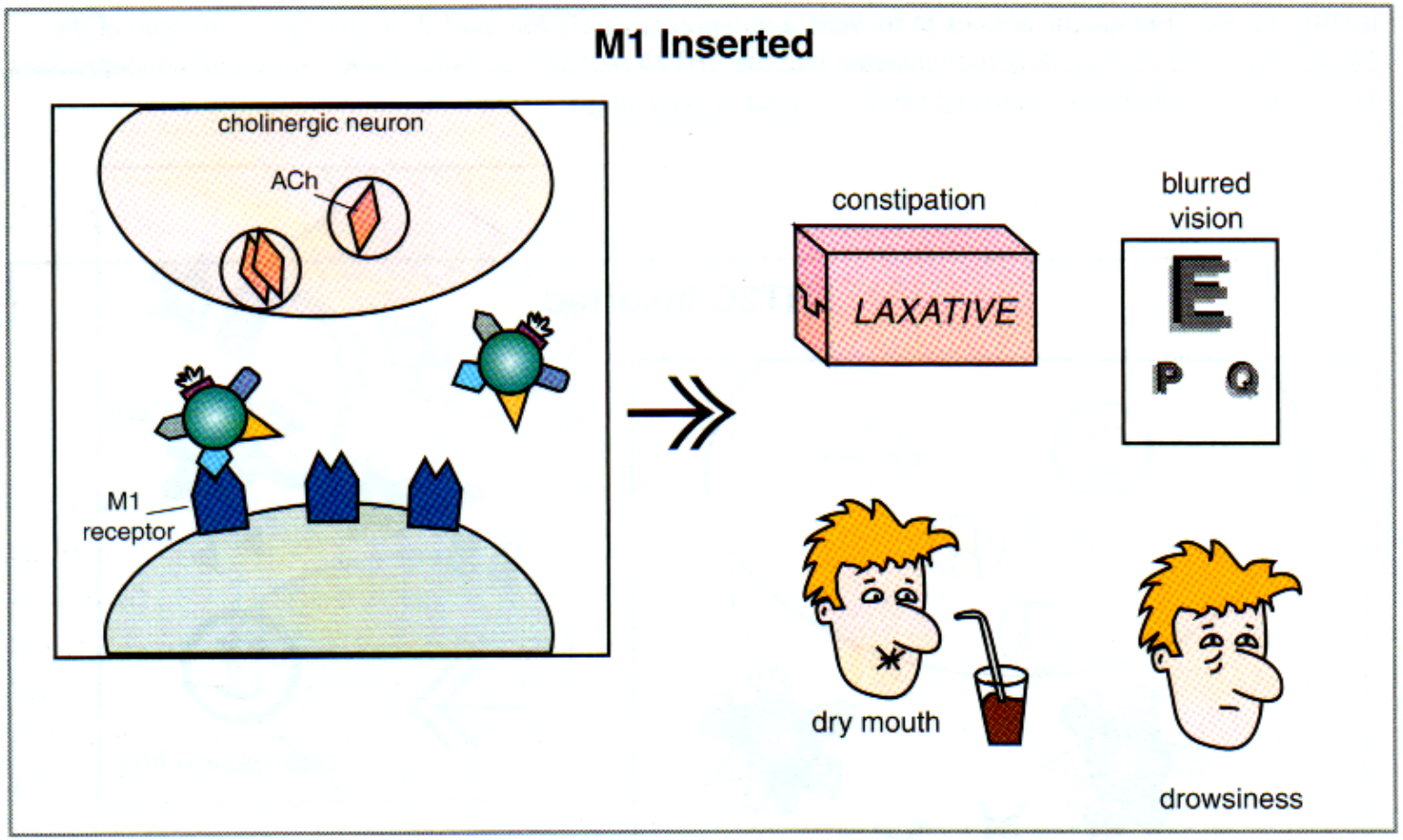


FIGURE 12-87 Side effects of tricyclic antidepressants (TCAs), part 2. In this figure, the icon of the TCA is shown with its anticholinergic/antimuscarinic (M1) portion inserted into acetylcholine receptors, causing the side effects of constipation, blurred vision, dry mouth, and drowsiness.

Καταβολή-Καταστολή

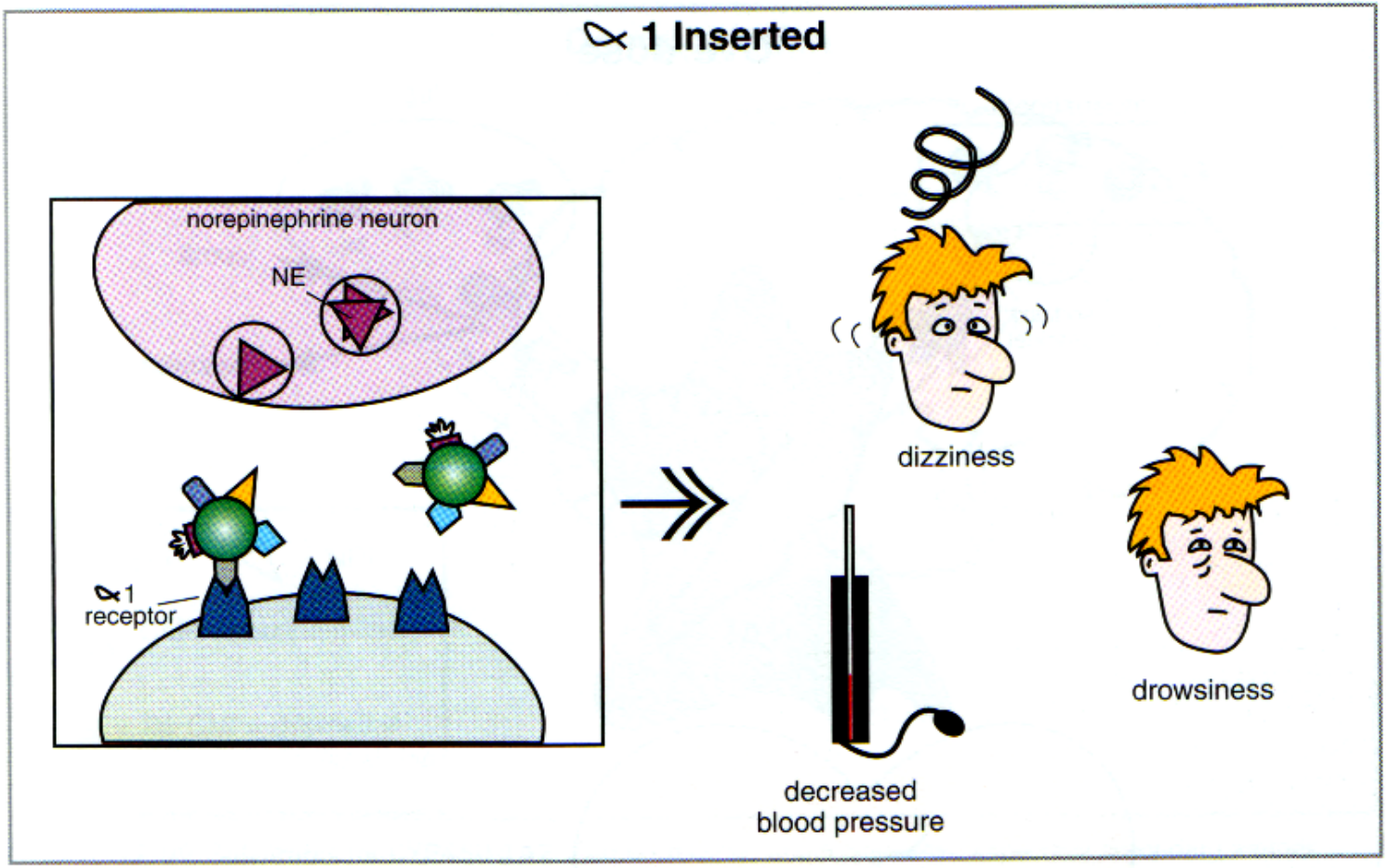


FIGURE 12-88 Side effects of tricyclic antidepressants (TCAs), part 3. In this figure, the icon of the TCA is shown with its alpha-adrenergic antagonist (alpha) portion inserted into alpha 1 adrenergic receptors, causing the side effects of dizziness, drowsiness, and decreased blood pressure.

Αγομελατίνη

- Νέος παράγοντας
- Δρα στους μελατονενεργικούς υποδοχείς στην νοραδρεναλίνη και την ντοπαμίνη
- Βοηθά στον ύπνο
- Βοηθά στο αίσθημα του καλώς έχειν
- Βοηθά στα υπολειματικά συμπτώματα
- Πιθανά λιγότερες παρενέργειες

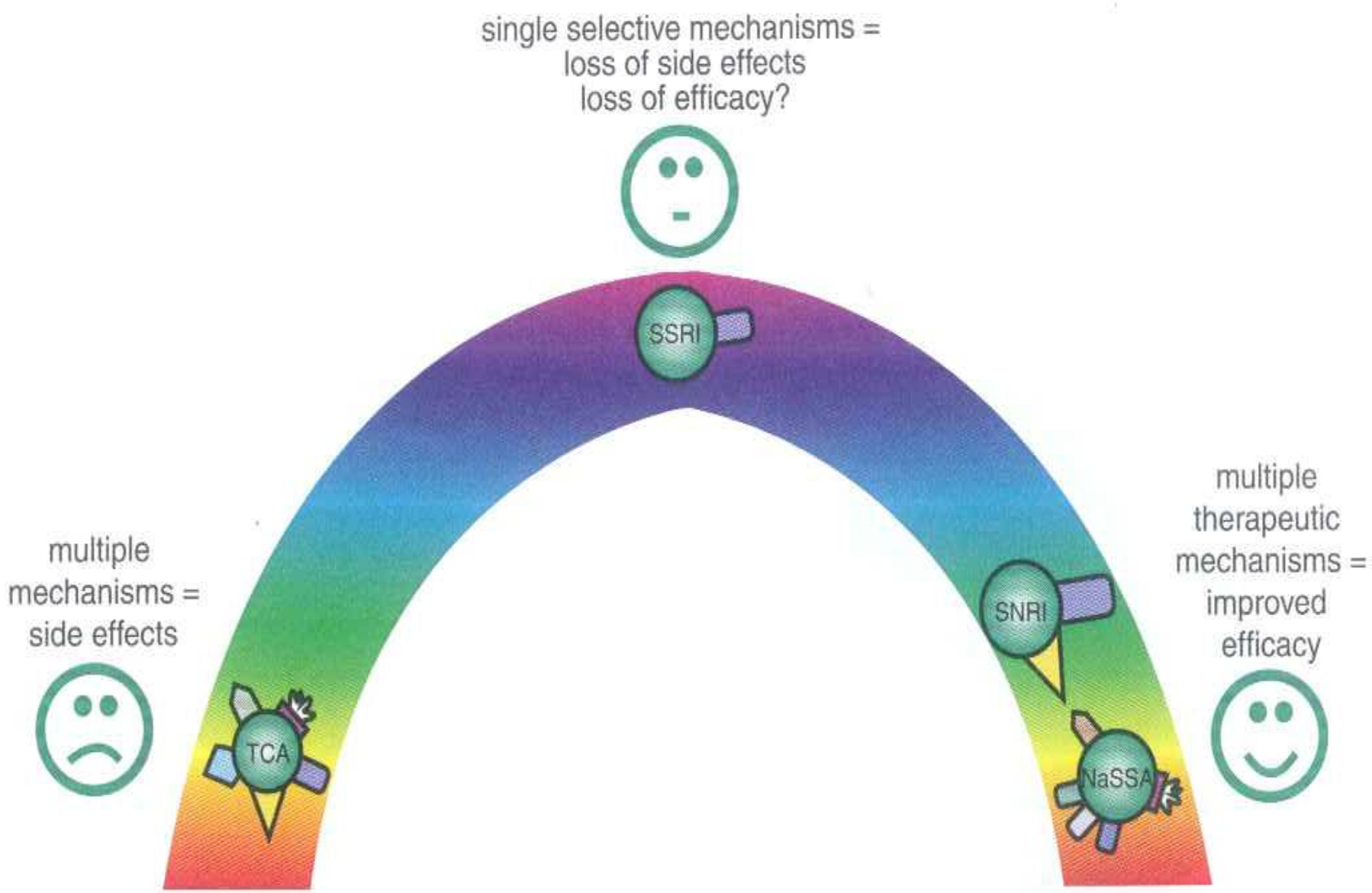
Παλαιότερα αντικαταθλιπτικά-Αναστολείς Μονοάμινο Οξειδάσης (ΜΑΟ)

- Φάρμακα με ντοπαμινεργική δράση
- Δεύτερης γραμμής φάρμακα για την κατάθλιψη
- Πρώτης γραμμής για την άτυπη κατάθλιψη
- Παρενέργειες
- Διαιτητικές οδηγίες
- ΠΡΟΣΟΧΗ ΣΤΙΣ ΑΛΛΗΛΕΠΙΔΡΑΣΕΙΣ ΚΑΙ ΤΗ ΣΥΓΧΟΡΗΓΗΣΗ

Επιλογή θεραπείας

- Προηγούμενη ανταπόκριση
  - 80% πιθανότητα η νέα αγωγή να είναι επίσης αποτελεσματική
- Επαρκής ανταπόκριση
  - Πρώιμη ανταπόκριση
  - Ανταπόκριση χωρίς υπολειμματικά συμπτώματα
- Γενετικός πολυμορφισμός
  - Ένα ποσοστό (περίπου 5% των ασθενών λόγω πολυμορφισμού του υποδοχέα σεροτονίνης ανταποκρίνονται καλλίτερα στους αναστολείς σεροτόνινης νοραδρεναλίνης και όχι στους αναστολείς μόνο σεροτονίνης)

Are Two Antidepressant Mechanisms Better Than One?



Να θυμάστε!!!

- Η κατάθλιψη είναι μια **ΙΑΣΙΜΗ** νόσος η θεραπεία της όποιας **αποτρέπει τη νευροεκφύλιση** του εγκεφάλου και οδηγεί σε σημαντικά **καλλίτερη ποιότητα ζωής**.

Σας ευχαριστώ πολύ