Essential Psychopharmacology
Neuroscientific Basis and Practical Applications
Second Edition
ESSENTIAL
PSYCHOPHARMACOLOGY

Neuroscientific Basis and Practical Applications
Second Edition

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With illustrations
by Nancy
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CME Post Tests and Evaluations
Sex-Specific and Sexual Function-Related Psychopharmacology

I. Neurotransmitters and the psychopharmacology of the human sexual response
II. Erectile dysfunction
III. Estrogen as a neurotrophic factor in the brain
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VI. Summary

Psychopharmacology can affect the sexes quite differently. This is just beginning to be recognized and investigated in a systematic manner. This chapter will explore some of the concepts behind treating men and women differently with psychopharmacological agents. One topic that affects both sexes is sexual activity, and this has become of great interest to psychopharmacologists since psychotropic medications are now widely recognized to affect sexual functioning, often negatively. Also, treatments for sexual dysfunction based on altering chemical neurotransmission are becoming available, and therefore the relevant psychopharmacological principles underlying these treatments are reviewed here.

The profound behavioral and neurobiological properties of reproductive hormones, particularly estrogen, are now recognized and are increasingly being exploited for their therapeutic potential in psychopharmacology. These properties will be reviewed in this chapter. Also reviewed here will be the movement to integrate the role of reproductive hormones into psychopharmacology by taking account of a woman's stage in her life cycle (i.e., child, child-bearing potential, pregnant, postpartum, lactating/nursing, perimenopausal, postmenopausal) and whether she is taking estrogens when choosing a psychotropic drug for her.
Libido

The first stage, libido, is linked to desire for sex, or sex drive, and is hypothetically a dopaminergic phenomenon mediated by the mesolimbic dopaminergic "reward center" (Fig. 14—1). This pathway has already been discussed in Chapter 13 and is well known for being the site of action of drugs of abuse as well as the site of...
Sexual arousal in peripheral genitalia is accompanied by **erections** in men and **lubrication and swelling** in women. Both nitric oxide and acetylcholine mediate these actions.

"natural highs" (see Figs. 13—1 and 13—2). This site may not only mediate orgasm but also libidinous desire prior to the sex act.

Prolactin is hypothesized to have a negative influence on sexual desire, which is interesting because there is a generally reciprocal relationship between dopamine and prolactin (as discussed in Chapter 11; see Fig. 11—30). However, the relationship between prolactin and sexual dysfunction is not well documented and relatively poorly understood.

**Arousal**

The second psychopharmacological stage of the sexual response is arousal (Fig. 14—2)—arousal of peripheral genitalia, that is. In men, that means an erection; in women, it means lubrication and swelling. This type of arousal prepares the genitalia for penetration and sexual intercourse. The message of arousal starts in the brain, is relayed down the spinal cord, then into peripheral autonomic nerve fibers that are both sympathetic and parasympathetic, next into vascular tissues, and finally to the genitalia. Along the way, at least two key neurotransmitters are involved, acetylcholine in the autonomic parasympathetic innervation of the genitalia and nitric oxide, which acts on the smooth muscle of the genitalia. Acetylcholine and nitric oxide both promote erections in men and lubrication and swelling in women. Cholinergic psychopharmacology has been extensively discussed in Chapter 12 (see Figs. 12—8 to 12—10). However, nitric oxide is a relatively recently characterized neurotransmitter system in brain and peripheral tissues, and more detailed discussion of this system will help explain its actions in mediating sexual arousal in the human sexual response.

**Nitric Oxide Psychopharmacology**

Nitric oxide, a gas, is an improbable compound for a neurotransmitter. It is not an amine, amino acid, or peptide; it is not stored in synaptic vesicles or released by
exocytosis; and it does not interact with specific receptor subtypes in neuronal membranes, but it is "NO laughing matter." Specifically, it is not nitrous oxide (N₂O) or "laughing gas," one of the earliest known anesthetics. Nitric oxide (NO) is a far different gas, although the two of them are often confused. It is NO that is the neurotransmitter, not N₂O. Incredible as it may seem, NO is a poisonous and unstable gas, a component of car fumes, which helps to deplete the ozone layer, yet is also a chemical messenger both in the brain and in blood vessels, including those that control erections in the penis.

Yes, there is NO synthesis by neurons and the penis. Certain neurons and tissues possess the enzyme nitric oxide synthetase (NOS), which forms NO from the amino acid l-arginine (Fig. 14—3). Nitric oxide then diffuses to adjacent neurons or smooth muscle and provokes the formation of the second messenger cyclic guanosine monophosphate (cGMP) by activating the enzyme guanylyl cyclase (GC) (Fig. 14—4). Nitric oxide is not made in advance nor is it stored, but it seems to be made on demand and released by simple diffusion. Glutamate and calcium can trigger the formation of NO by activating NOS.

No, there are no NO membrane receptors, in striking contrast to classical neurotransmitters, which have numerous types and subtypes of membrane receptors on neurons. Rather, the target of NO is iron in the active site of GC (Fig. 14—4). Once NO binds to the iron, GC is activated and cGMP is formed. The action of cGMP is terminated by a family of enzymes known as phosphodiesterases (PDEs), of which there are several forms, depending on the tissue (Fig. 14—5).

Yes, there is NO neurotransmitter function. The first known messenger functions for NO were described in blood vessels. By relaxing smooth muscles in blood vessels of the penis, NO can regulate penile erections, allowing blood to flow into the penis. Nitric oxide also can modulate vascular smooth muscle in cardiac blood vessels and mediate the ability of nitroglycerin to treat cardiac angina. Nitric oxide is also a key regulator of blood pressure, platelet aggregation, and peristalsis. Its central nervous system (CNS) neurotransmitter function remains elusive, but it may be a retrograde neurotransmitter. That is, since presynaptic neurotransmitters activate postsynaptic receptors, it seems logical that communication in this direction should be accompanied by some form of back talk from the postsynaptic site to the presynaptic neuron. The idea is that NO is prompted to be formed in postsynaptic synapses by some presynaptic neurotransmitters and then diffuses back to the presynaptic neuron, carrying information in reverse. Nitric oxide may also be involved in memory formation, neuronal plasticity, and neurotoxicity.

**Orgasm**

The third stage of the human sexual response is orgasm (Fig. 14—6), accompanied by ejaculation in men. Descending spinal serotonergic fibers exert inhibitory actions on orgasm via 5HT2A receptors (see Fig. 5—57). Descending spinal noradrenergic fibers (Fig. 5—28) and noradrenergic sympathetic innervation of genitalia facilitate ejaculation and orgasm.

In summary, there are three major psychopharmacological stages of the human sexual response (Fig. 14—7). Multiple neurotransmitters mediate these stages, but only some of them are understood. Libido (stage 1) has dopaminergic dimensions to its pharmacology. The mechanism of arousal (stage 2), which is characterized by
FIGURE 14—3. Nitric oxide (NO) is formed by the enzyme nitric oxide synthetase (NOS), which converts the amino acid l-arginine into nitric oxide and l-citrulline.

FIGURE 14—4. Once formed, nitric oxide activates the enzyme guanylyl cyclase (GC) by binding to iron (heme) in the active site of this enzyme. When activated, GC makes a messenger, cyclic guanylate monophosphate (cGMP), which relaxes smooth muscle and performs other physiological functions. In the penis, relaxation of vascular smooth muscle opens blood flow and causes an erection.
FIGURE 14—5. The action of cGMP is terminated by the enzyme phosphodiesterase. In the penis, the type of phosphodiesterase is type V (PDE V).

FIGURE 14—7. The neurotransmitters involved in the three stages of the psychopharmacology of the human sexual response are summarized here. In stage 1, libido, dopamine exerts a positive influence and prolactin a negative effect. In stage 2, arousal correlates with erections in men and lubrication and swelling in women. Both nitric oxide and acetylcholine facilitate sexual arousal. In stage 3, orgasm, which is associated with ejaculation in men, is inhibited by serotonin and facilitated by norepinephrine.

erection in men and lubrication and swelling in women, involves both cholinergic and nitric oxide pharmacology. Finally, orgasm (stage 3), with ejaculation in men, involves both inhibitory serotonergic input and excitatory noradrenergic input. Although sexual functioning is certainly complex and there are many overlapping functions of these neurotransmitters as well as exceptions to the rules, there are general principles of neurotransmission for each of the various stages of the human sexual response, some of which are reviewed in Figure 14—7.

Erectile Dysfunction

Impotence, the inability to maintain an erection sufficient for intercourse, is more properly called erectile dysfunction. Up to 20 million men in the United States have this problem to some degree. Another way of stating the problem is that for normal men living in the community who are between 40 and 70 years old, only about half do not have some degree of erectile dysfunction (Fig. 14—8). The problem worsens with age (Fig. 14—9), since 39% of 40-year-olds have some degree of impotence (5% are completely impotent), but by age 70 two-thirds have some degree of impotence (and complete impotence triples to 15%). The multiple causes of erectile
dysfunction include vascular insufficiency, various neurological causes, endocrine pathology (especially diabetes mellitus, but also reproductive hormone and thyroid problems), drugs, local pathology in the penis, and psychological and psychiatric problems.

Until recently, psychopharmacologists were not very useful members of the treatment team for patients with erectile dysfunction, other than to stop the medications they had been prescribing. Effective treatment of "organic" causes of erectile dysfunction until recently was often elusive and usually involved a urological approach, such as prostheses and implants. The old-fashioned surgical strategy bypasses diseased peripheral nerves and inadequate vascular blood supply to the penis to create erections mechanically and on demand, but this approach has serious limitations in terms of patient and partner acceptability. In men who have a "functional" etiology to their erectile dysfunction, the treatment strategy has traditionally taken a psychodynamic and behavioral approach, with attention to partners and functional disorders, psychoeducation, lifestyle changes, and where appropriate, starting (or stopping) psychotropic drugs to treat associated disorders. The typical case of erectile dysfunction, however, has neither a single "organic" cause nor a single "functional" cause but is usually caused by some combination of problems, including use of alcohol, smoking, diabetes, hypertension, antihypertensive drugs, psychotropic drugs, partner problems, performance anxiety, problems with self-esteem, and psychiatric disorders, especially depression.

The topic of erectile dysfunction has become increasingly important in psychopharmacology, not only because there are several psychotropic drugs that cause it but also because of the strikingly high incidence of impotence in several common psychiatric disorders. For example, some studies show that more than 90% of men with severe depression have moderate to severe erectile dysfunction (Fig. 14—10). Another reason for the importance of this topic in psychopharmacology is that effective and simple new psychopharmacological treatment based upon nitric oxide physiology and pharmacology is now available for men with erectile dysfunction.
FIGURE 14—9. The incidence of erectile dysfunction increased with age in this study of normal men between the ages of 40 and 70, from 39% at age 40 to 67% at age 70.

**Psychopharmacology of Erectile Dysfunction**

Normally, the desire to have sexual relations is a powerful message sent from the brain down the spinal cord and through peripheral nerves to smooth muscle cells in the penis, triggering them to produce sufficient nitric oxide to form all the cyclic GMP necessary to create an erection (Fig. 14—11). The cyclic GMP lasts long enough for sexual intercourse to occur, but then phosphodiesterase (type V in the penis) eventually breaks down the cGMP (Fig. 14—5), and the erection is lost (called detumescence).

However, if a man smokes, eats to the point of obesity, and has elevated blood glucose and elevated blood pressure, his peripheral nervous system "wires" do not respond adequately to the "let's have intercourse" signal from the brain—in other words, neurological innervation of the penis is rendered faulty, usually by diabetes (Fig. 14—12). Furthermore, there may not be much pressure in the "plumbing"—there may be atherosclerosis of the arterial supply of the penis from hypertension and hypercholesterolemia—when cGMP says "relax the smooth muscle and let the
blood flow into the penis.” In these cases, the desire for intercourse is there, but the signal cannot get through, so insufficient cGMP is formed, and therefore no erection occurs (Fig. 14—12). Similarly, even if a depressed patient experiences sexual desire, there is a general shutdown of neurotransmitter systems centrally and peripherally, resulting in inability to become aroused (Fig. 14—12).

Fortunately, there is a way to compensate for inadequate formation of cGMP. That compensation is a slowing of the rate of destruction of that cGMP that is formed, which is accomplished by inhibiting the enzyme that normally breaks down cGMP in the penis, namely phosphodiesterase type V, with an enzyme inhibitor called sildenafil (Viagra) (Fig. 14—13). Sildenafil will stop cGMP destruction for a few hours and allow the levels of cGMP to build up so that an erection can occur even though the wires and plumbing are still faulty (Fig. 14—13). Interestingly, sildenafil only works if the patient is mentally interested in the sex act and attempts to become aroused, so that at least weak signals are sent to the penis (i.e., it does not work during sleep).

Smooth muscle relaxation is thus the key element in attaining an erection. Administration of prostaglandins can also relax penile smooth muscle and elicit erections in a manner that mimics typical physiological mechanisms. Thus, intrapenile
FIGURE 14 — 11. Under **normal conditions**, when young healthy men are sexually aroused, nitric oxide causes cGMP to accumulate, and cGMP causes smooth muscle relaxation, resulting in a physiological [erection](#), indicated here by an inflated balloon. The erection is sustained long enough for sexual intercourse, and then phosphodiesterase V (PDE V) metabolizes cGMP, reversing the erection, indicated here by a pin ready to prick the balloon.

FIGURE 14 — 12. When a man has diabetes or hypertension, or if he smokes, uses alcohol, takes prescription drugs, or is depressed, there is a good chance that not enough of a signal of sexual desire will be able to get through his peripheral nerves and arteries to produce sufficient amounts of cGMP to cause an erection. This leads to **impotence**.

Injection of the prostaglandin alprostadil produces erections not only in men with organic causes of impotence but also in those with functional causes and even in the common situation of multifactorial causes. Limitations of this somewhat masochistic approach include unacceptability of self-injection, lack of spontaneity, and the possibility of "too much of a good thing," namely a prolonged and painful erection.
FIGURE 14-13. **Sildenaﬁl**, a phosphodiesterase V (PDE V) inhibitor, is able to compensate for faulty signals through the peripheral nerves and arteries that produce insuﬃcient amounts of cGMP to produce or sustain erections. Sildenaﬁl does this by allowing cGMP to build up, since PDE V can no longer destroy cGMP for a few hours. This is indicated by a patch on the balloon in the ﬁgure. The result is that normally inadequate nerves and arteries signaling cGMP formation are now suﬃcient to inﬂate the balloon, and therefore an erection can occur and sexual intercourse is now possible, until the sildenaﬁl wears off a few hours later.

FIGURE 14—14. Some **antidepressants** such as serotonin selective reuptake inhibitors (SSRIs) may inhibit nitric oxide synthetase (NOS) and thereby reduce NO and cause erectile dysfunction.

called priapism. Prostaglandin administration will cause an erection whether the man is mentally aroused or not.

Other drugs can affect sexual arousal, including some serotonin selective reuptake inhibitors (SSRIs), which may inhibit NOS directly and can thus cause erectile dysfunction (Fig. 14—14), and some dopaminergic agents, which boost NOS and might some day help erectile dysfunction (Fig. 14—15). Anticholinergic agents can interfere directly with arousal and cause erectile dysfunction. Thus, agents such as
FIGURE 14—15. Some agents that boost dopamine (perhaps like apomorphine) are promising experimental drugs for enhancing NOS and may be useful to reverse erectile dysfunction.

antipsychotics and tricyclic antidepressants and others with similar properties can cause erectile dysfunction (Fig. 14—16).

Psychopharmacology of Sexual Dysfunction

In summary, numerous agents used in psychopharmacology can facilitate or interfere with each of the three stages of the human sexual response (Fig. 14-16). Understanding the basic mechanisms of neurotransmission for each of these stages (Fig. 14—7), as well as the psychopharmacological mechanisms of action of the various psychotropic drugs that impact these neurotransmitter systems, will facilitate the management of psychotropic drugs in patients with sexual dysfunction.

Estrogen as a Neurotrophic Factor in the Brain

It is well known that ovarian estrogens, especially 17-beta-estradiol, regulate reproductive function and have profound effects on reproductive tissues in women, such as those of the breast and uterus. The long-term positive effects of estrogens outside of the reproductive tissues have also been emphasized, such as estrogen's effects in preserving bone mineralization and in reducing serum cholesterol. Recently there has been growing appreciation for the diversity of effects that estrogen can have on the brain as well, especially in regions of the brain outside of those areas known to be involved in the control of reproductive function and sexual differentiation. These neuronal effects are mediated by the same types of receptors for estrogen that exist in other tissues and have trophic actions on the brain, just as they have on other tissues. Trophic factors have been discussed in Chapter 1 (see Fig. 1 — 19 and Tables 1 — 3 and 1—4). In the brain, estrogen's trophic actions trigger the expression of genes that lead to the formation of synapses.

Estradiol modulates gene expression by binding to estrogen receptors (Fig. 14—17). Estrogen receptors differ from tissue to tissue and may differ from brain region to brain region. In addition to various forms of estrogen receptors, there are receptors for progesterone and androgens, as well as for other steroids such as glucocorticoids.
Psychopharmacological agents can affect all three stages of the human sexual response, both positively and negatively, as summarized here. In stage 1, libido can be enhanced by the norepinephrine and dopamine reuptake inhibitor (NDRI) bupropion, as well as by the dopamine-releasing stimulants amphetamine and methylphenidate. Libido can also be reduced by the dopamine receptor—blocking antipsychotics, some of which also increase prolactin. Stage 2, sexual arousal, can be enhanced by sildenafil, which boosts cGMP action, by prostaglandins, and perhaps by some dopaminergic agents. Sexual arousal can be reduced by some serotonin selective reuptake inhibitors (SSRIs), as well as by agents with anticholinergic properties. Finally, in stage 3, orgasm can be inhibited by SSRIs as well as by beta blockers, which block noradrenergic function.

and mineralocorticoids. Unlike neurotransmitter receptors located on neuronal membranes, receptors for estradiol are located in the neuronal nucleus, so estradiol must penetrate the neuronal membrane and the nuclear membrane to find its receptors, which are therefore located near the genes it wishes to influence. These genes are called estrogen response elements (Fig. 14—17).

The expression of these estrogen response elements within the DNA of the neuron progresses generally in the same manner as the expression of other neuronal genes, which has been discussed in Chapter 2 (see Figs. 2 — 31 to 2—42). The activation of estrogen response elements by estradiol requires "dimerization" (i.e., coupling of two copies of the estrogen receptor) when estrogen binds to the receptor to form an active transcription factor capable of "turning on" the estrogen response element (Fig. 14—18). Formation of transcription factors has also been discussed in Chapter 2 (see Figs. 2 — 33 and 2 — 35 to 2 — 38). Once the estrogen receptors are activated by estradiol into transcription factors, they activate gene expression by the estrogen
Estrogen modulates gene expression by binding to estrogen receptors. Estrogen receptors differ from tissue to tissue and may differ from brain region to brain region. Unlike neurotransmitter receptors located on neuronal membranes, receptors for estradiol are located in the neuronal cell nucleus, so estradiol must penetrate the neuronal membrane and the nuclear membrane to find its receptors, which are therefore located near the genes that are to be influenced. These genes are called estrogen response elements.

Gene products that are expressed include direct trophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which can facilitate synaptogenesis and prevent apoptosis and neurodegeneration.

Gene products also include neurotransmitter-synthesizing enzymes for the key monoamine neurotransmitter systems that regulate mood and memory (Figs. 14—20 to 14—22). Thus, the presence of estradiol can be critical to the adequate functioning of the monoamines serotonin (Fig. 14—20) and norepinephrine (Fig. 14—21) in women. Adult men do not respond to estrogen in this manner. The presence of estradiol in aging women but not in aging men can also be critical to the adequate functioning of acetylcholine in the nucleus basalis of Meynert (Fig. 14—22). The role of these key cholinergic neurons in the regulation of memory (see Fig. 12—11) and in the causation of Alzheimer's disease when they degenerate (see Fig. 12—13) have been discussed in Chapter 12. This may explain the emerging role of estrogen in managing memory and Alzheimer's disease in aging women, as discussed below.

Dramatic evidence of estrogen's trophic properties can be observed in hypothalamic and hippocampal neurons in adult female experimental animals within days.
FIGURE 14—18. The expression of estrogen response elements with the DNA of the neuron must be initiated by estrogen and its receptor. Activation of these genes by estradiol requires "dimerization" (i.e., coupling of two copies of the estrogen receptor) when estrogen binds to the receptor to form an active transcription factor capable of "turning on" the estrogen response element.

and across a single menstrual (estrus) cycle (Figs. 14 — 23 and 14 — 24). During the early phase of the cycle, estradiol levels rise, and this trophic influence induces dendritic spine formation, specifically in the ventromedial hypothalamus and on pyramidal neurons in the hippocampus of female rats. Progesterone administration rapidly potentiates this, so spine formation is at its greatest when both estrogen and progesterone peak, just after the first half of the cycle (Fig. 14—23). However, once estrogen levels fall significantly and progesterone levels continue to rise, the presence of progesterone without estrogen triggers down regulation of these spines and removal of the synapses by the end of the estrus cycle (Fig. 14—23). One hypothesis to explain the mechanism of this cyclical formation and removal of synapses is that estrogen may exert its trophic influence through low levels of glutamate activation (Fig. 14 — 24), leading to spine formation and synaptogenesis: this effect is followed by too much glutamate activation in the absence of estrogen, when progesterone alone leads to excitotoxicity and destruction of these same spines and synapses (Fig. 14 — 24). The hypothesis of how glutamate might mediate excitotoxic synaptic or neuronal toxicity was introduced in Chapter 4 (see Figs. 4—14 to 4—23) and discussed extensively in Chapter 10 (see Figs. 10 — 26 to 10-33).

Other evidence for the trophic influences of estrogen comes from what happens when the estrogen's effects are blocked with estrogen receptor antagonists. Tamox-
FIGURE 14—19. Once the estrogen receptors are activated by estradiol into transcription factors, they activate gene expression by the estrogen response elements in the neuron's DNA. Gene products that are expressed include direct trophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which can facilitate synaptogenesis and prevent apoptosis and neurodegeneration.

Ifen is an estrogen receptor antagonist used for the treatment of breast cancer, especially for breast tumors that themselves express estrogen receptors. Blocking estrogen receptors in breast cancer cells with tamoxifen triggers apoptosis (programmed cell death), presumably due to blocking the trophic effect of estrogen in these tumor cells. Interestingly, tamoxifen is an estrogen receptor antagonist in breast and uterus but is actually a partial agonist in preserving bone mineralization and reducing cholesterol. It is also an estrogen receptor antagonist in brain, since it can induce depression that can be difficult to treat with antidepressants. Thus, individual estrogens such as estradiol and tamoxifen all have tissue-selective estrogen agonist, partial agonist, and antagonist activities. This also extends to the new class of estrogens known as selective estrogen receptor modulators (SERMs), of which raloxifene is the newest available member. Such observations may also explain why some women respond differently to one estrogen preparation than to another, and from a behavioral perspective, why they may have different mood and cognitive responses to one estrogen preparation versus another. Unfortunately, very little work has been done to distinguish the pharmacologic effects of the different available estrogen preparations on estrogen receptor binding in the brain, and the only way...
Gene products activated by estradiol interacting with estrogen response elements in the serotoninergic neurons of the midbrain raphe include not only trophic factors, which nourish the growth and synapses of these neurons with nerve growth factor (NGF) and brain-derived neuro-trophic factor (BDNF), but also the enzymes and receptors that facilitate serotonergic neurotransmission. These receptors may also allow the neuron to have normal mood functions and to be more responsive to antidepressant medications in case of a depressive episode.

Estrogen and Mood Across the Female Life Cycle

Estrogen levels shift rather dramatically across the female life cycle, all in relationship to various types of reproductive events (Fig. 14—25). Thus, levels begin to rise and then cycle during puberty (see also Fig. 14—23). This cycling persists during the childbearing years, except during pregnancy, when a woman's estrogen levels...
FIGURE 14-21. **Gene products** activated by estradiol interacting with **estrogen response elements** in the noradrenergic neurons of the brainstem locus coeruleus include not only **trophic factors** that nourish the growth and synapses of these neurons with nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), but also the **enzymes and receptors** that facilitate **noradrenergic neuro-transmission**. These receptors may also allow the neuron to have normal mood function and to be more responsive to antidepressant medications in case of a depressive episode.

skyrocket (Fig. 14 — 25). Estrogen levels then plummet precipitously immediately postpartum, and regular menstrual cycles begin again once the mother stops nursing (Fig. 14-25).

Although the median age of menopause, which is the time of complete cessation of menstruation, is 51, women do not begin menopause overnight. The transition period from regular menstrual cycles to complete cessation of menstruation, called perimenopause, can begin 5 to 7 years before menopause and is characterized on on-again off-again cycles and anovulatory cycles, prior to complete cessation of menstrual cycles (Fig. 14—25). Hormone levels can be chaotic and unpredictable during these years. This can be experienced both as a physiological and a psychological stressor. Menopause is the final stage of transition of estrogen in the female life cycle and can be associated with estrogen replacement therapy, which can restore estrogen to its physiological levels during the childbearing years.

There are potential links between these shifts in estrogen levels across the female life cycle and the observation that depression is much more common in women than in men during certain stages of the life cycle. In men, the incidence of depression
FIGURE 14—22. Gene products activated by estradiol interacting with estrogen response elements in the cholinergic neurons of the nucleus basalis of Meynert in the basal forebrain include not only trophic factors that nourish the growth and synapses of these neurons with nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), but also the enzymes and receptors that facilitate cholinergic neurotransmission. These receptors may also allow the neuron to function optimally in memory formation, particularly verbal memory in aging women, and to be more responsive to cholinesterase inhibitors in the case of Alzheimer's disease.

rises in puberty and then is essentially constant throughout life, despite a slowly declining testosterone level from age 25 onward (Fig. 14—26). By contrast, in women the incidence of depression mirrors their changes in estrogen across the life cycle (Fig. 14—27). As estrogen levels rise during puberty, the incidence of depression skyrocketed, falling again after menopause (Fig. 14—27). Thus, women have the same frequency of depression as men before puberty and after menopause. However, during their childbearing years when estrogen is high and cycling, the incidence of depression in women is two to three times as high as in men (Fig. 14 — 27).

Several other issues are of particular importance to women in terms of assessing their vulnerability to the onset and recurrence of mood disorders across their lifetimes. These are linked to shifts in reproductive hormone status, as outlined in Figure 14—28. First episodes of depression often begin in puberty or early adulthood, when estrogen is first rising; unfortunately these episodes are frequently unrecognized and untreated. Throughout the childbearing years of normal menstrual cycles,
FIGURE 14 — 23. Dramatic evidence of estrogen's trophic properties can be observed in hypothalamic and hippocampal neurons in adult female experimental animals within days and across a single menstrual (estrus) cycle. During the early phase of the cycle, estradiol levels rise, and this trophic influence induces dendritic spine formation and synaptogenesis. Progesterone administration rapidly potentiates this, so spine formation is at its greatest when both estrogen and progesterone peak just after the first half of the cycle. However, once estrogen levels fall significantly and progesterone continues to rise, the presence of progesterone without estrogen triggers down regulation of these spines and removal of the synapses by the end of the estrus cycle.
FIGURE 14—24. One hypothesis to explain the mechanism of cyclical formation and removal of synapses every menstrual (estrus) cycle in females is that estrogen may exert its trophic influence through low levels of glutamate activation, leading to spine formation and synaptogenesis. This, however, is followed by too much glutamate activation in the absence of estrogen, when progesterone alone leads to excitotoxicity and destruction of these same spines and synapses.

Most women experience some irritability during the late luteal phase just prior to menstrual flow; however, if this is actually incapacitating, it may be a form of premenstrual syndrome (PMS), worthy of treatment with antidepressants or estrogen, sometimes just during the late luteal phase. In other patients, this end-of-the-cycle worsening is unmasking a mood disorder that is actually present during the whole cycle but is sufficiently worse at the end of the cycle that it becomes obvious in a phenomenon called menstrual magnification. This may be a harbinger of further worsening or may also represent a state of incomplete recovery from a previous episode of depression. Nevertheless, both PMS and menstrual magnification are important, not only for the symptoms they cause in the short run but for the risk they represent for a full recurrence in the future, signaling the potential need for both symptomatic and preventive treatment.

Figure 14—28 also indicates the two riskiest periods in a woman’s life cycle for the onset of a first episode of depression or for the recurrence of a major depressive
FIGURE 14-25. **Estrogen levels shift dramatically across the female life cycle**, all in relation to various types of reproductive events. Levels begin to rise and then cycle in puberty. Cycling persists during the childbearing years except in pregnancy, when a woman’s estrogen levels skyrocket. Estrogen levels plummet precipitously immediately postpartum, and regular menstrual cycles begin again once nursing stops. Although the median age of menopause, when all menstruation stops, is 51, women do not stop menstruation overnight. The transition period from regular menstrual periods to complete cessation of menstruation is called perimenopause and can begin 5 to 7 years prior to menopause. The final transition phase is menopause, when estrogen replacement therapy (ERT) can restore estrogen levels to those of the childbearing years.

FIGURE 14 — 26. **In men**, the incidence of depression rises in puberty and then is essentially constant throughout life, despite a slowly declining testosterone level from age 25 on.
In women, the incidence of depression mirrors their changes in estrogen across the life cycle. As estrogen levels rise during puberty, the incidence of depression also rises, and it falls again during menopause, when estrogen levels fall. Thus, women have the same frequency of depression as men before puberty and after menopause. However, during their childbearing years when estrogen is high and cycling, the incidence of depression in women is two to three times as high as in men.

Both are associated with major shifts in estrogen. The first is the postpartum period, when skyrocketing levels of estrogen plummet immediately after delivery of the child. The second occurs during perimenopause, when chaotic hormonal status characterizes the transition from regular menstrual cycles to menopause with no menstrual cycles.

There is an increasing risk that a woman will have a recurrence of a major depressive episode after any shift in her estrogen status across her lifetime, a phenomenon some experts have called "kindling." For example, a woman's risk of having a postpartum depression increases severalfold if she had a depressive episode after a previous pregnancy. A woman who has a depressive episode triggered by any endocrine shift is quite vulnerable to a recurrence of depression after another reproductive "event" later in her life cycle, such as those shown in Figure 14—28, which include puberty, miscarriage, postpartum, perimenopause, taking oral contraceptives, and taking hormone replacement therapy, especially progestins. The increasing chances of a recurrent episode of depression in women whose episodes are linked to reproductive events and shifts in estrogen status may be related to the phenomenon of recurrence in other psychiatric disorders, such as bipolar disorder and schizophrenia. Thus, it is possible that certain mental illnesses, including recurrent depression, are potentially damaging to the brain owing to excitotoxic brain damage (see Chapters 4 and 10). Perhaps life cycle shifts in estrogen status trigger excitotoxicity, just as they seem to do every menstrual cycle (see Figs. 14—23 and 14—24), but huge life cycle shifts in estrogen may trigger depressive episodes in some women that not
FIGURE 14—28. Several issues of importance in assessing women’s vulnerability to the onset and recurrence of depression are illustrated here. These include first onset in puberty and young adulthood; premenstrual syndrome (PMS) and menstrual magnification as harbingers of future episodes or incomplete recovery states from prior episodes of depression; and two periods of especially high vulnerability for first episodes of depression or for recurrence if a woman has already experienced an episode, namely, the postpartum period and the perimenopausal period.

only cause suffering during the episode of depression itself, but also damage the brain, so that recovery is associated with an increased risk of subsequent episodes with diminishing the responsiveness to medication with each subsequent episode. This has also been hypothesized to explain the clinical course of schizophrenia as well, as discussed in Chapter 10 (Fig. 10—20). Whatever the cause of the high recurrence rate of depression in women across their life cycles and the associations with shifts in estrogen status, the importance of recognition and treatment of current episodes of depression in women, as well as use of medications to prevent future episodes, is extremely important since recurrence is so predictable, treatable, and potentially preventable.

Selecting treatments for the symptoms of mood disorders and their prevention must also take into account shifts in estrogen status and reproductive events across the life cycle of a woman. The potential impact of estrogen itself as a treatment, as well as antidepressants, must also be considered. Guidelines on how to use antidepressants and/or estrogen during these various phases of a woman’s life cycle are only now being developed, and the issues to be considered are outlined in Figure 14-29.

First, a high index of suspicion for first episodes of depression should accompany the assessment of adolescent girls (Fig. 14 — 29), since this illness is frequently missed, and despite the lack of formal approval of antidepressants for use in anyone under the age of 18, the newer antidepressants are frequently used for this purpose, and their safety has been well established in children and adolescents for related conditions such as obsessive-compulsive disorder (see Chapter 5). Also, the use of oral
FIGURE 14—29. This figure illustrates some of the issues involved in integrating endocrine shifts and events related to a woman's life cycle with treatment of a mood disorder with antidepressants and/or estrogen. These include use of antidepressants prior to age 18 if necessary; understanding how to select oral contraceptives to minimize depression; calculating risks versus benefits of antidepressant maintenance during pregnancy and during breast-feeding; and deciding whether to include estrogens as adjunctive treatments for women with mood disorders. There are also various options and flexible and creative regimens for administering hormones with antidepressants to perimenopausal and postmenopausal women with mood disorders to optimize their treatments.

contraceptives can affect adolescents as well as all females of childbearing potential and must be taken into consideration (Fig. 14—29), because these agents may sometimes cause depression or worsen preexisting depression. Triggering of depression by oral contraceptives can be especially problematic in those with a previous episode of depression and with contraceptives containing progestins only. Switching to oral contraceptives containing low-dose progestins combined with estrogens can sometimes prevent mood problems in these patients.

Another key treatment issue to be managed in a disorder with such a high risk of recurrence is whether to treat with maintenance antidepressants during pregnancy (Fig. 14—29). This decision involves calculating a risk/benefit ratio for the individual patient in terms of risk to the mother of recurrence of her depression during pregnancy due to stopping antidepressant treatment versus risk to the developing fetus due to the mother taking antidepressant treatment. Since the greatest risk to the fetus is at the beginning of pregnancy (i.e., during the first 12-week trimester, when the brain and other critical tissues are being formed) and the greatest risk to the mother is postpartum, the tradeoff is often to wait until later in pregnancy, until the mother begins to have a recurrent episode, or after delivery.

However, this brings up another problem. What about taking antidepressants during lactation and nursing (Fig. 14—29), in terms of risk of exposure of the baby to anti-
depressants in the mother's breast milk? Again, a risk/benefit ratio must be calculated for each situation, with account taken of the risk of recurrence to the mother if she does not take antidepressants (given her own personal and family history of mood disorder), and the risk to the bonding between baby and mother if she does not breast-feed or to the baby if exposed to trace amounts of antidepressants in breast milk. Although the risk to the infant of exposure to small amounts of antidepressants is only now being clarified, it is quite clear that the risks to the mother with a prior postpartum depression who neglects to take antidepressants after a subsequent pregnancy has a 67% risk of recurrence if she does not take antidepressants and only one-tenth of that risk of recurrence if she does take antidepressants postpartum.

Another issue is whether to use estrogens for the treatment of mood disorder symptoms (Fig. 14—29). Estrogens can improve mood and a sense of well-being in normal women during perimenopause, especially if they are experiencing vasomotor symptoms such as "hot flashes." However, it is quite controversial whether estrogen has any antidepressant role for women with major depressive disorder. Antidepressants are still first-line treatments for major depressive disorder across the female life cycle, but when they fail, novel approaches that integrate the use of estrogen are now being investigated, including the use of estrogen by itself or in combination with antidepressants, particularly during specific life cycle—related mood disorders (Fig. 14 — 29). For example, some patients with PMS seem to benefit from antidepressants and others from late luteal phase supplementation with low doses of estrogens, particularly if delivered transdermally via a skin patch. Some patients with profound collapse into a postpartum depression will respond rapidly to antidepressants, others to electroconvulsive therapy, and still others to reinstitution of estrogen with a "softer landing" to physiological postpartum levels. There are no objective means to determine who will benefit from which approach, but those who receive estrogen tend to be those who fail other better accepted first-line treatment approaches.

Particularly in women with perimenopausal depressions and especially when these are recurrent and resistant to antidepressants, treatment with estrogen replacement therapies can be effective. This was discussed in Chapter 7 as one of the combination strategies to add to antidepressants when various treatment strategies fail and illustrated conceptually in Figure 7 — 34. There are no accepted guidelines for when to try this approach, but these are hopefully evolving. Treating postmenopausal depression may also benefit from a boost from estrogen replacement, as indicated in Figures 14 — 20 and 14-21, as a result of the beneficial effects that estrogen may have on critical monoaminergic systems involved in mood, such as norepinephrine and serotonin. In the absence of estrogen, these systems may not function adequately, resulting both in a mood disorder and in failure to respond to antidepressants. Restoring estrogen to monoaminergic neurons allows their estrogen receptors to "reawaken" estrogen response elements in these neurons and may either extinguish problems with mood or allow the patient to become responsive to antidepressants.

Another issue for postmenopausal women has to do with the roles of both progesterone and estrogen in managing their mood disorder. Since progesterone can act as an estrogen antagonist in some tissues, such as those in the uterus and in some brain areas (see Fig. 14—24), it should not be surprising that progesterone can counteract the positive effects that estrogen has on mood in some women. In these cases, administration of progesterone as a component of hormone replacement ther-
FIGURE 14-30. Psychopharmacology is beginning to identify new therapies that are sex-specific and related to sexual functioning. These include treatments for the human sexual response, especially for erectile dysfunction in men, as well as a better appreciation of the role of hormones in managing mood and cognitive disorders in women.

Therapy may precipitate depression, or cause a magnification reminiscent of menstrual magnification during normal menstruation (when endogenous progesterone was presumably causing the same thing). For postmenopausal women, progesterone is necessary to prevent uterine cancer when estrogen replacement is being given. Thus, in a woman who has had a hysterectomy, progesterone treatment can be avoided. In a woman with her uterus, it may be less disruptive to her mood to give estrogen and progestin daily rather than to give the progestin just at the end of the cycle.

These various hormone strategies to consider in the management of mood and cognition in the treatment of women across their life cycles are summarized in Figure 14—30, along with some therapies for erectile dysfunction in men. Components of this emerging pharmacy for managing issues specific to each sex and issues of sexual function in psychopharmacology include sildenafil and prostaglandins for erectile dysfunction and numerous reproductive hormones, including oral and transdermal
skin patches for estrogens, progestins, and testosterone. Even the pattern of taking these hormones, such as daily, end of the menstrual cycle only, cyclically, counter-cyclically, etc. (i.e., rhythms and regimens) can make a big difference in a woman's response to them. It is also important to avoid some hormones (e.g., progestins) in some patients.

**Cognition, Alzheimer's Disease, and the Role of Estrogen in Sex Differences**

Although there are no sex differences in full-scale IQ scores on standardized tests of general intelligence, some cognitive differences exist between men and women. The best established of these are that on average, men excel in spatial and quantitative abilities, whereas women excel in verbal abilities and in perceptual speed and accuracy. However, the magnitude of these differences is modest. Whatever differences exist may be due to prenatal influences of reproductive hormones on brain organization during fetal brain development. Interestingly, after menopause, there is a loss of verbal memory skills in women, which is restored with estrogen replacement therapy. This suggests that estrogen is necessary to maintain optimal verbal memory functioning in women (Fig. 14 — 22), that loss of estrogen may lead to lack of expression of critical genes necessary to maintain this function in cholinergic memory pathways, and that this process can be reversed and restored with reinstitution of estrogen signals to turn gene expression back on. These effects of estrogen on memory in normal postmenopausal women, like those differences between cognitive functions of men and women, are on the whole modest in magnitude.

Alzheimer's disease is also more common in women than in men. Memory disturbances in Alzheimer's disease are linked to disruption in cholinergic neurotransmission (see Chapter 12, Fig. 12 — 13). About one and one-half to three times as many women have Alzheimer's disease as men. Although women live longer than men on average and so are at greater risk for Alzheimer's disease (because more of them are alive at ages when this illness is most common), this does not account for their increased rates of Alzheimer's disease or for their longer survival as compared with men after the onset of Alzheimer symptoms. After statistical adjustments for these facts, there appears to be a sex-specific risk for Alzheimer's disease, which preliminary studies suggest may be reduced in those women who take estrogen replacement therapy. It is hypothesized that loss of estrogen after menopause may be responsible for this sex-specific increased risk of Alzheimer's disease, perhaps particularly because of loss of the normal trophic actions that estrogen has upon cholinergic neurons that mediate memory (Fig. 14—22), but also due to the general loss of estrogen's trophic influence throughout the brain (Figs. 14—17, 14—18, and 14—19). Thus, estrogen replacement therapy hypothetically allows critical estrogen response elements in cholinergic neurons (Fig. 14—22) and throughout the brain to turn back on and protect against the onset of Alzheimer's disease. In Chapter 12, we discussed how several studies are in progress to determine whether estrogen can protect against the development of Alzheimer's disease in randomized controlled trials. It has also been observed that once Alzheimer's disease is diagnosed, estrogen may boost the effectiveness of cholinesterase inhibitors (cholinesterase inhibitors for Alzheimer's disease were discussed in Chapter 12).
Summary

In this chapter, issues in psychopharmacology related to sex and sexuality were discussed. This included an overview of the neurotransmitter mechanisms involved in the three psychopharmacological stages of the human sexual response, namely libido, arousal, and orgasm. Neurotransmitters that mediate each of these three stages were discussed, as well as drugs that facilitate and inhibit these stages. A specific introduction to the nitric oxide neurotransmitter system was outlined.

The clinical features and pathophysiology of and treatment approaches to erectile dysfunction in men was reviewed, including the new phosphodiesterase inhibitor sildenafil (Viagra). The role of estrogen across the female life cycle, including estrogen's profound behavioral and neurobiological properties, was also reviewed. The role of reproductive hormones, particularly estrogen, was outlined with a view to integrating it into psychopharmacology by taking account of a woman's stage in her life cycle (i.e., childhood, childbearing potential, pregnancy, and the postpartum, lactating/nursing, perimenopausal, and postmenopausal states) and whether she is taking estrogens when choosing a psychotropic drug for her in the treatment of either a mood disorder or a cognitive disorder.
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Brainstorm Features 1997-2000


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Essential Psychopharmacology (2nd Edition)
Stephen M. Stahl

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Instructions

This CME activity incorporates instructional design to enhance your retention of the didactic information and pharmacological concepts which are being presented. You are advised to go through this program unit by unit, in order, from beginning to end. You will first study the figures and read the figure legends for a single unit of instructional materials, and then go back and read the text that corresponds to that unit, reviewing the figures again as you go. After completing the text, you will then go back over the figures alone for another time. This will allow interaction with the materials, and also provide repeated exposure to the data and concepts presented both visually and in written explanations. Hopefully, this will be fun and interesting, and you will retain new information far more efficiently than you would after just reading the text or listening to a lecture on this topic.

Follow these directions to optimize your learning and retention of "Essential Psychopharmacology".

1. Go through each chapter unit one by one, from beginning to end and in order.
2. View each figure and read each figure legend.
3. Next, read the text while reviewing each figure as you go.
4. Complete the written post-test, using the answer sheet located at the end of the textbook.
5. Review the figures once again, checking any answers of which you are uncertain.
6. Photocopy and fill out the evaluation for the unit you just completed.
7. Fill out the CME registration form.
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OVERALL CONTINUING MEDICAL EDUCATION OBJECTIVES 14

INDIVIDUAL EDUCATIONAL UNITS IN TOTAL

*Up to 54 Hours of Category I Credits in Total*

Upon completing this educational program, the participant should be able to:

1. Understand the scientific basis of chemical neurotransmission.
2. Know how abnormalities in neurotransmission underlie major psychiatric disorders, including depression, anxiety disorders, psychosis, and cognitive disorders, including dementia, and drug and alcohol abuse.
3. Know that psychotropic drugs act by specific modifications of chemical neurotransmission.
4. Understand the major psychiatric disorders treated with psychotropic agents, including depression, anxiety disorders, psychosis, cognitive disorders including dementia and drug and alcohol abuse.
5. Be able to understand the unique psychopharmacological mechanisms of action of the major antidepressants, anxiolytics, antipsychotics, cognitive enhancing agents, and drugs of abuse.
6. Be knowledgeable of the mechanism of therapeutic action versus the side effects of the major members of each class of psychotropic agents.

Please see each individual unit for the specific objectives of each individual unit.

UNIT 1: PRINCIPLES OF CHEMICAL NEUROTRANSMISSION

*Up to 3 Hours of Category I CME Credit*

**Objectives**

1. To learn all three dimensions of neurotransmission: namely the spacial dimension, the dimension of time and the dimension of function.
2. To understand the spacial dimension as a chemically addressed vs. an anatomically
dressed nervous system.

3. To understand the time dimension by knowing the difference between fast onset
vs. slow onset chemical neurotransmission.

4. Understand the functional dimension of neurotransmission, gaining familiarity
with excitation secretion coupling, receptor occupancy, and second messenger
systems.

5. To gain an overview of molecular neurobiology as a basis for subsequent concepts
developed later in this text, including how chemical neurotransmission results in
the activation of neuronal genes.

6. To gain an overview of neuronal plasticity, as a basis for understanding the aging
process, the development of the brain, and the action of growth factors.

Self Assessment and Post Test

1. Please indicate which of the following is true for synaptic neurotransmission.
   a. An electrical impulse jumps from one nerve to another
   b. A chemical impulse jumps from one nerve to another
   c. An electrical impulse in one nerve is converted to a chemical impulse at the
      synaptic connection between two nerves which is then reconverted into an
      electrical impulse in the second nerve
   d. An electrical impulse in one nerve is converted to a chemical impulse at the
      synaptic connection between two nerves which is then converted into a chem-
      ical cascade reaching the post-synaptic genome
   e. c and d

2. The anatomically addressed nervous system is analogous to a complex wiring
diagram. True or False.

3. The chemically addressed nervous system acts via a sophisticated chemical soup.
   True or False.

4. Some neurotransmitters act faster than others. True or False.

5. Glutamate is the universal excitatory neurotransmitter. True or False.

6. GABA is the universal excitatory neurotransmitter. True or False.

7. GABA and glutamate act by fast signals and not by slow signals. True or False.

8. Other neurotransmitters such as serotonin and norepinephrine act as slow neu-
   rotransmitters. True or False.

9. The headquarters or command center for the neuron is the DNA in its cell
   nucleus located in the cell body. True or False.

10. Receptor occupancy by neurotransmitters is specific to a single neurotransmitter
    and acts like a key fitting into a receptor lock. True or False.

11. Each neuron only contains one neurotransmitter. True or False.
12. Enzymes and receptors are both proteins synthesized in the cell body by the neuron's cell nucleus. True or False.

13. Alterations in the structure of an enzyme or a receptor can lead to a disease. True or False.

14. Once the brain is wired at the beginning of life, it stays that way forever and does not have the capability of changing once an individual reaches adulthood. True or False.

15. Although it has classically been held that neurons do not replicate after birth, recent evidence suggests that there may be replication of neurons in the mammalian brain, possibly even in humans. True or False.

16. The degree of branching of the dendritic tree of a neuron may imply how much functioning that neuron can perform. True or False.

17. Growth factors can promote synaptic connections. True or False.

18. The brain has a mechanism for revising synapses and even eliminating them throughout the lifetime of a neuron. True or False.

19. A second messenger is electrical, not chemical. True or False.

20. Some therapeutic drugs like Valium, Elavil and morphine as well as some drugs of abuse such as heroin and marijuana can act very similarly to naturally occurring neurotransmitters in the brain. True or False.

### Evaluation

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<tr>
<th>Statement</th>
<th>Strongly Agree</th>
<th>Somewhat in Agreement</th>
<th>Neutral</th>
<th>Somewhat Disagree</th>
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<td>Overall this unit met my expectations to learn about principles of chemical neurotransmission.</td>
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<td>My general knowledge about chemical neurotransmission was enhanced.</td>
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UNIT 2: RECEPTORS AND ENZYMES AS THE TARGETS OF DRUG ACTION

Up to 3 Hours of Category I CME Credit

Objectives

1. To understand how receptors and enzymes are the targets of drug action.
2. To learn about the organization of receptor molecules, including the three parts of each receptor.
3. To gain familiarity with ion channels, transport carriers and active transport pumps.
4. To gain familiarity with second messenger systems.
5. To understand how drugs may modify chemical neurotransmission by interacting with receptors.
6. To understand how drugs may modify chemical neurotransmission by interacting with enzymes.
Self Assessment and Post Test

1. Psychopharmacological agents act by:
   a. Inhibiting enzymes
   b. Antagonizing receptors
   c. Stimulating receptors
   d. All of the above

2. Which is not a property of the receptor super family of G protein linked receptors?
   a. Seven transmembrane regions
   b. Presence of a G protein
   c. Presence of an enzyme
   d. Presence of a second messenger
   e. Presence of an ion channel

3. A receptor is a chain of:
   a. Amino acids
   b. Fatty acids
   c. Sugars
   d. Fats

4. One of the most common organizations of a receptor in the central nervous system is for it to weave in and out of the cell membrane seven times thus creating seven transmembrane regions. True or False.

5. Transmembrane regions of receptors can be quite similar from one family of receptors to the next. True or False.

6. A neurotransmitter released from a neuron travels to a post synaptic neuron and:
   a. Interacts with a receptor in the membrane of the second neuron
   b. Gets inside the cell where it acts as a second messenger
   c. Travels straight to the nucleus of the second neuron
   d. None of the above

7. Receptors are theoretical sites of malfunctioning which could lead to nervous or mental disorders. True or False.

8. Neurotransmitters can serve as a gatekeepers to open or close a channel for an ion in a neuronal membrane. True or False.

9. Transport carriers act as a shuttle bus to allow molecules to get from the outside of the cell to the inside of the cell. True or False.

10. An active transport pump is a type of transport carrier which is linked to an energy utilizing system. True or False.

11. Neurotransmitter reuptake from the synapse is an example of molecular transport using an active transport pump. True or False.

12. In the neurotransmission process, the first event is the firing of the presynaptic neuron which releases neurotransmitter. True or False.
13. Once a neurotransmitter interacts with the receptor, it:
   a. Diffuses off the receptor
   b. Can be destroyed by enzyme
   c. Can be transported back into the presynaptic neuron
   d. All of the above

**Evaluation**

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<th>Strongly Agree</th>
<th>Somewhat in Agreement</th>
<th>Neutral</th>
<th>Somewhat Disagree</th>
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<td>Overall the unit met my expectations.</td>
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<td>My general knowledge about receptors and enzymes was enhanced.</td>
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<td>The time spent reviewing the pharmacology receptors was just right.</td>
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UNIT 3: SPECIAL PROPERTIES OF RECEPTORS

Up to 2 Hours of Category I CME Credit

Objectives

1. To understand how receptors can have multiple subtypes.
2. To know the difference between an agonist and an antagonist.
3. To know the difference between an inverse agonist and an antagonist.
4. To understand both positive allosteric modulation and negative allosteric modulation.

Self Assessment and Post Test

1. Allosteric modulation is:
   a. Two drugs competing for the same enzyme or receptor at the same site
   b. One drug helping or inhibiting another drug at the same receptor but at a different site on that receptor
   c. Unrelated to the presumed mechanism of action of any psychotropic drugs
   d. Presumed to be the cause of depression

2. There is only one type of receptor for each neurotransmitter. For example, there is only one serotonin receptor type. True or False.

3. Which is not a property of the super family of ligand gated ion channels?
   a. Neurotransmitter as gatekeeper ligand
   b. A G protein
   c. Allosteric modulating sites
   d. A column of receptors surrounding a central ion site

4. An agonist is the opposite of an antagonist. True or False.

5. An inverse agonist is the opposite of an agonist. True or False.

6. A partial agonist is in between a full agonist and an antagonist. True or False.

7. An antagonist can reverse both an agonist and an inverse agonist. True or False.

8. A partial agonist can be a net agonist when neurotransmitter is deficient but a net antagonist when a neurotransmitter is in excess. True or False.

9. Allosteric modulators help a neurotransmitter or hinder a neurotransmitter performing that neurotransmitter function. True or False.

10. There are two major super families of receptors including:
    a. Ligand gated ion channel
    b. Seven transmembrane G protein linked second messenger systems
    c. Allosteric modulators
    d. Both a and b
Evaluation

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What is your overall opinion of the usefulness of this training unit to your clinical practice?

UNIT 4: CHEMICAL NEUROTRANSMISSION AS THE MEDIATOR OF DISEASE ACTIONS

Up to 2 Hours of Category I CME Credit

Objectives

1. To understand receptors and enzymes as targets of disease action in the central nervous system.
2. To understand the differences among three disciplines: neuroscience, biological psychiatry and psychopharmacology.

3. To understand various ways in which diseases modify synaptic neurotransmission, including molecular neurobiology and psychiatric disorders.

4. To understand how neuronal plasticity can impact psychiatric disorder.

5. To understand general principles of excitotoxicity.

6. To understand other mechanisms of disease action, including no neurotransmission, too much neurotransmission and ineffective wiring.

**Self Assessment and Post Test**

1. Complex genetics suggests that psychiatric disorders are:
   a. Due to a single gene mutation
   b. Due to two gene mutations which cause all persons with such genetic abnormalities to manifest an illness
   c. The cause of psychiatric disorder is predominantly environmental
   d. Multiple lesions in the victim's DNA must be present in the right sequence and during the correct critical periods possibly with the need to have specific environmental inputs simultaneously in order to manifest the psychiatric illness

2. Neurobiology is the study of brain and neuronal functioning usually emphasizing normal brain functioning in experimental animals rather than man. True or False.

3. Biological psychiatry is the discipline evaluating abnormalities in brain biology associated with the causes or consequences of mental disorders. True or False.

4. Psychopharmacology is the discipline of discovering new drugs and understanding the actions of drugs upon the central nervous system. True or False.

5. Which of the following is not a key factor in the development of a psychiatric disorder:
   a. Genetic vulnerability to the expression of a disease
   b. Life event stressors
   c. The individual's personality, coping skills and social support
   d. Environmental influences
   e. All of the above are critical

6. For a neuron to develop properly, it must have adequate plasticity. True or False.

7. The neuron has a mechanism to destroy its synapses called excitotoxicity. True or False.

8. If excitotoxicity gets out of control, it could potentially destroy a dendrite or an entire neuron. True or False.

9. Drugs may at times be able to replace neurotransmitters which are absent from a synapse due to the death of a neuron. True or False.
10. Glutamate is the neurotransmitter which mediates excitatory neurotransmission as well as excitotoxicity. True or False.

11. Potassium is the ion which works with glutamate to mediate both excitation and excitotoxicity. True or False.

**Evaluation**

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UNIT 5: DEPRESSION AND BIPOLAR DISORDERS

Up to 6 Hours of Category 1 CME Credit

Objectives

1. To review the diagnostic criteria for depression and bipolar disorders.
2. To review the definitions of response, remission and recovery.
3. To learn the epidemiology and natural history as well as longitudinal course of depression.
4. To understand the biological basis of depression, including the monoamine hypothesis, the neurotransmitter receptor hypothesis and the hypothesis of reduced activation of brain neurotrophic factors.
5. To understand the functioning of noradrenergic, dopaminergic and serotonergic neurons.

Self Assessment and Post Test

1. The standard(s) usually targeted by studies seeking approval of most new antidepressants is (are):
   a. Response rates
   b. Remission rates
   c. Recovery rates
   d. Both a and b
   e. All of the above

2. Risk of relapse from depression is related to:
   a. The number of previous episodes
   b. Incomplete recovery
   c. Severity of index episode of depression
   d. Duration of index episode of depression
   e. All of the above

3. What is the best estimate for the risk of relapse into another episode of depression if an antidepressant is stopped within the first 6 to 12 months following a treatment response:
   a. Less than 5%
   b. At least 10%
   c. At least 33%
   d. At least 50%

4. What is the best estimate for the risk of relapse into another episode of depression while taking an antidepressant for the first six months following a treatment response:
   a. Less than 5%
   b. At least 10%
   c. At least 33%
   d. At least 50%
5. The chances of a depressed patient responding to any known antidepressant is one out of three.
   a. True
   b. False

6. The chances of a depressed patient responding to a placebo is one out of three.
   a. True
   b. False

7. Presynaptic alpha 2 receptors:
   a. Control norepinephrine release
   b. Control serotonin release
   c. Both
   d. Neither

8. Which serotonin receptor(s) is (are) most involved with regulating the release of serotonin?
   a. 5HT1A
   b. 5HT1D
   c. 5TH2A
   d. Both a and b
   e. All the above

9. The locus coeruleus is the principal location of the cell bodies of serotonergic neurons.
   a. True
   b. False

10. The locus coeruleus in the brainstem is the principal location of the cell bodies of nonadrenergic neurons.
    a. True
    b. False

11. The monoamine hypothesis of depression suggests that depression is predominantly caused by deficiency of serotonin.
    a. True
    b. False

12. The monoamine receptor hypothesis of depression suggests that depression is caused predominantly by an absence of key monoamine receptors in the brain.
    a. True
    b. False

13. The monoamine receptor hypothesis of gene activation suggests that depression is caused by:
    a. A problem in monoamines activating critical neuronal genes
    b. An inherited genetic deficiency in a specific gene for monoamines
    c. Stress-induced reduction in the expression of genes for neurotrophic factors such as BDNF
    d. a and c
    e. All of the above
14. The neurokinin neurotransmitters include:
   a. Substance P
   b. Neurokinins A and B
   c. Tachykinins 1 and 2
   d. a and b

15. Neurokinin receptor antagonists:
   a. Are effective in reducing pain
   b. Are potential antidepressants
   c. Are effective in reducing neurogenic inflammation

**Evaluation**

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UNIT 6: CLASSICAL ANTIDEPRESSANTS, SEROTONIN SELECTIVE REUPTAKE INHIBITORS AND NOREPINEPHRINE REUPTAKE INHIBITORS

Up to 4 Hours of Category I CME Credit

Objectives

1. To review the monoamine receptor hypothesis of depression.

2. To review the two classical categories of antidepressants, namely MAO inhibitors and tricyclic antidepressants.

3. To review the mechanism of action of the five serotonin selective reuptake inhibitors.

4. To review adrenergic modulators such as dopamine and norepinephrine uptake inhibitors.

5. To review selective inhibitors of norepinephrine reuptake.

6. To understand how drug actions can explain not only therapeutic effects but also side effects for antidepressants.

7. To review pharmacokinetic interactions of antidepressants with other drugs.

Self Assessment and Post Test

1. All antidepressants act by inhibiting the reuptake pump for serotonin, norepinephrine, or both.
   a. True
   b. False

2. When tricyclic antidepressants are given concomitantly with SSRIs such as fluoxetine or paroxetine:
   a. Plasma levels of the tricyclic antidepressants may rise
   b. Plasma levels of the tricyclic antidepressants may fall
   c. Plasma levels of fluoxetine or paroxetine may rise
   d. a and c

3. MAO inhibitors should not be administered concomitantly with:
   a. SSRIs (serotonin selective reuptake inhibitors)
   b. Meperidine
   c. Tyramine-containing foods
   d. All of the above

4. The mechanism of therapeutic action of SSRIs is:
   a. Stimulation of the serotonin transport pump
   b. Increasing the sensitivity of 5HT2A receptors
   c. Desensitizing somatodendritic 5HT1A autoreceptors
   d. None of the above
5. Side effects of the SSRIs such as anxiety, insomnia and sexual dysfunction may be mediated by stimulation of which serotonin receptor subtype?
   a. 5HT1A
   b. 5HT1D
   c. 5HT2A
   d. 5HT3

6. At high doses, which secondary property may apply to sertraline:
   a. 5HT2C agonist actions
   b. Blockade of dopamine transporters
   c. Blockade of muscarinic cholinergic receptors
   d. Blockade of cytochrome P450 1A2
   e. None of the above

7. At high doses, which secondary property may apply to fluoxetine:
   a. 5HT2C agonist actions
   b. Blockade of dopamine transporters
   c. Blockade of muscarinic cholinergic receptors
   d. Blockade of cytochrome P450 1A2
   e. None of the above

8. At high doses, which secondary property may apply to paroxetine:
   a. 5HT2C agonist actions
   b. Blockade of dopamine transporters
   c. Blockade of muscarinic cholinergic receptors
   d. Blockade of cytochrome P450 1A2
   e. None of the above

9. At high doses, which secondary property may apply to citalopram:
   a. 5HT2C agonist actions
   b. Blockade of dopamine transporters
   c. Blockade of muscarinic cholinergic receptors
   d. Blockade of cytochrome P450 1A2
   e. None of the above

10. The therapeutic action of bupropion is mediated in part via direct interactions with serotonergic neurotransmission.
    a. True
    b. False

11. The therapeutic action of reboxetine is mediated in part via direct interactions with serotonergic neurotransmission.
    a. True
    b. False

12. Increasing norepinephrine may cause:
    a. Antidepressant effects
    b. Improvement in attention
    c. Increase in motivation/reduction of apathy
    d. All of the above
### Evaluation

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### UNIT 7: NEWER ANTIDEPRESSANTS AND MOOD STABILIZERS

*Up to 4 Hours of Category I CME Credit*

### Objectives

1. To review the mechanism of action of dual reuptake inhibitors such as venlafaxine as well as other dual action antidepressants such as mirtazapine, and serotonin 2A antagonists such as nefazodone.
2. To review the mechanism of action of lithium and five anticonvulsants used as mood stabilizers (valproic acid, carbamazepine, lamotrigine, gabapentin and topiramate).

3. To discuss the use of antidepressants in combination with other drugs and antidepressants for the treatment of patients nonresponsive to monotherapies for depression and bipolar disorders.

**Self Assessment and Post Test**

1. Which of the following are serotonin 2A antagonists:
   a. Fluoxetine
   b. Nefazodone
   c. Paroxetine
   d. Mirtazapine
   e. b and d

2. Blocking a monoamine reuptake pump with an antidepressant can oppose the actions of drugs which block presynaptic alpha 2 receptors.
   a. True
   b. False

3. Dual neurotransmitter action at both serotonin and norepinephrine is possible only by combining two different psychopharmacological agents simultaneously.
   a. True
   b. False

4. Which of the following does not have selectivity for the noradrenaline transporter over the serotonin transporter:
   a. Desipramine
   b. Maprotiline
   c. Reboxetine
   d. Venlafaxine

5. Venlafaxine is a dual reuptake inhibitor of both serotonin and norepinephrine with equal potency for both transporters.
   a. True
   b. False

6. Lithium:
   a. Inhibits inositol monophosphatase
   b. Interacts with second messenger systems
   c. Blocks monoamine reuptake
   d. a and b
   e. All of the above

7. Which mood stabilizers are thought to act in part by interacting with ion channels:
   a. Carbamazepine
   b. Valproic acid
   c. Lithium
d. a and b  
e. All of the above

8. Antidepressants can worsen depression in patients with bipolar disorders by inducing mania or rapid cycling.  
   a. True  
   b. False

9. Successful combinations of drugs for treating depressed patients resistant to monotherapies exploit pharmacologic synergies, where the total therapeutic effect may be greater than the sum of the parts.  
   a. True  
   b. False

10. The most accurate statement about psychotherapy for depression is that psychotherapy:  
   a. Can be used instead of antidepressants for patients with marked to severe depression  
   b. Has been proven to be useful for depression in all its different types, including psychodynamic, group, cognitive, behavioral and psychoanalytical psychotherapies  
   c. Has been demonstrated to be synergistic with antidepressants for standard cognitive behavioral psychotherapy  
   d. All of the above

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UNIT 8: ANXIOLYTICS AND SEDATIVE HYPNOTICS

Up to 4 Hours of Category 1 CME Credit

Objectives

1. To review a clinical description of generalized anxiety.
2. To gain an overview of the biological basis of anxiety emphasizing gamma aminobutyric acid (GABA) and benzodiazepines.
3. To gain an overview of the biological basis of anxiety with an emphasis on norepinephrine and the locus coeruleus.
4. To gain an overview of the biological basis of anxiety emphasizing the role of serotonin.
5. To discuss how the treatment of anxiety disorders is transitioning from anxiolytics such as benzodiazepines to various antidepressants.
6. To discuss and understand the mechanism of action of benzodiazepines in the treatment of anxiety.
7. To understand the role of serotonin 1A partial agonists in the treatment of anxiety.
8. To gain perspective on long term possibilities for future treatments of anxiety.
9. To review a clinical description of insomnia and sleep disorders.
10. To review the drug treatments for insomnia, including newer nonbenzodiazepine hypnotics as well as benzodiazepine and other hypnotics.
Self Assessment and Post Test

1. Which of the following is an effective treatment for generalized anxiety disorder.
   a. Benzodiazepines
   b. Buspirone
   c. Venlafaxine
   d. a and b
   e. All the above

2. Generalized anxiety disorder is more likely to remit spontaneously or with treatment than is major depressive disorder.
   a. True
   b. False

3. If a full agonist benzodiazepine reduces anxiety, it would follow that an inverse agonist benzodiazepine would actually produce anxiety.
   a. True
   b. False

4. All of the following are true for benzodiazepines except:
   a. They are allosteric modulators of the GABA A receptor subtype
   b. They are cotransmitters with GABA itself for the GABA A receptor subtype
   c. They facilitate the influx of chloride to a cell
   d. They facilitate the inhibition of neural firing

5. The locus coerulus:
   a. Is the principle site of axon terminals for the noradrenergic system
   b. Can regulate serotonergic cell firing by its innervation of the raphe
   c. Theoretically malfunctions in obsessive compulsive disorder
   d. Regulates release of norepinephrine from its neurons through presynaptic alpha 1 receptors.

6. Buspirone's mechanism of action is:
   a. Like the benzodiazepines only on serotonin neurons
   b. Partial agonist actions on serotonin 2A receptors
   c. Partial agonist actions on serotonin 1A receptors
   d. Partial agonist actions on serotonin 1A and serotonin 2A receptors

7. Excessive activity of noradrenergic neurons can accompany some of the signs and symptoms of anxiety.
   a. True
   b. False

8. Generalized anxiety disorder (GAD) is distinct from major depressive disorder with anxiety in that it is unusual for a patient to have GAD at one point in time and major depressive disorder with anxiety at another time.
   a. True
   b. False
9. GAD is distinct from major depressive disorder with anxiety in that the drugs which are well documented to treat major depressive disorder with anxiety are not necessarily also well documented to treat GAD.
   a. True
   b. False

10. There is no major difference in outcome or risk factors for major depressive disorder with anxiety versus major depressive disorder without anxiety.
   a. True
   b. False

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UNIT 9: DRUG TREATMENTS FOR OBSESSIVE COMPULSIVE DISORDER, PANIC DISORDER AND PHOBIC DISORDERS

Up to 4 Hours of Category I CME Credit

Objectives

1. To review a clinical description of obsessive compulsive disorder.
2. To review the biological basis of obsessive compulsive disorder based upon serotonin and dopamine.
3. To review drug treatments of obsessive compulsive disorder, emphasizing serotonin reuptake inhibitors.
4. To review the clinical description of panic attacks and panic disorders.
5. To review the biological basis of panic attacks and panic disorder.
6. To review the drug treatments of panic disorder, including benzodiazepines, serotonin selective reuptake inhibitors, cognitive behavioral therapy and other treatments.
7. To review the clinical description and pharmacological treatments for phobic disorders, including social phobia.
8. To review the clinical description and pharmacological treatments for post traumatic stress disorder.

Self Assessment and Post Test

1. The therapeutic efficacy and onset of action of an SSRI in obsessive compulsive disorder is very similar to that of an SSRI in major depressive disorder.
   a. True
   b. False

2. Only those SSRIs with FDA approved indications for different anxiety disorder subtypes actually are efficacious in such anxiety disorder subtypes.
   a. True
   b. False

3. It is best to start with a higher dose of an SSRI for the treatment of panic compared to the dose of an SSRI for the treatment of depression.
   a. True
   b. False

4. It is best to start with a higher dose of an SSRI for the treatment of bulimia compared to the dose of an SSRI for the treatment of depression.
   a. True
   b. False
5. The tricyclic antidepressant desipramine is effective in panic disorder and obsessive compulsive disorder.
   a. True
   b. False

6. A leading theory of panic disorders called the false suffocation alarm theory, postulates that false alarm is triggered by the brain during a panic attack.
   a. True
   b. False

7. SSRIs are the only antidepressants which have efficacy in the treatment of panic disorder.
   a. True
   b. False

8. Behavioral therapies and cognitive therapies are commonly less effective for the treatment of panic disorder and obsessive compulsive disorder than are the SSRIs.
   a. True
   b. False

9. If an SSRI is effective in an anxiety disorder, this implies that serotonin levels are deficient in that anxiety disorder.
   a. True
   b. False

10. If an SSRI is effective in an anxiety disorder, this implies that enhanced serotonergic neurotransmission is therapeutic for that anxiety disorder.
   a. True
   b. False

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UNIT 10: PSYCHOSIS AND SCHIZOPHRENIA

Up to 4 Hours of Category I CME Credit

Objectives

1. To review the clinical descriptions of psychosis.

2. To understand the difference between paranoid, disorganized and depressive psychosis.

3. To discuss the five dimensions of symptoms in schizophrenia, including positive, negative, cognitive, aggressive/hostile and anxious/depressed symptoms.

4. To review the biological basis of the positive psychotic symptoms.

5. To understand the different functions of the various dopamine pathways in the brain, including the mesolimbic dopamine pathway, the nigrostriatal dopamine pathway, the mesocortical dopamine pathway and the tuberoinfundibular dopamine pathway.
6. To review neurodevelopmental and neurodegenerative hypotheses of schizophrenia.

**Self Assessment and Post Test**

1. A psychotic disorder is defined as one with delusions, hallucinations, and a thought disorder. True or False.

2. Schizophrenia and drug induced psychotic disorders require the presence of psychosis as a defining feature of the diagnosis. True or False.

3. Mania, depression, and cognitive disorders like Alzheimer's disease may or may not be associated with psychotic features. True or False.

4. Paranoid psychosis is characterized by severe retardation, apathy and anxious self-punishment and blame. True or False.

5. It is rare for a schizophrenic patient to commit suicide. True or False.

6. Schizophrenia is more common than depression. True or False.

7. The following are characteristic of the negative symptoms of schizophrenia except:
   a. Affective flattening
   b. Alogia
   c. Anhedonia
   d. Acalculia

8. The leading hypothesis for explaining the positive symptoms of psychosis is the overactivity of dopamine in the nigrostriatal dopamine pathway. True or False.

9. Movement disorders are mediated by abnormalities in the mesolimbic dopamine pathway. True or False.

10. The tuberoinfundibular dopamine pathway mediates the secretion of prolactin. True or False.

11. Prolonged blockade of dopamine receptors in the nigrostriatal pathway may lead to an increased sensitization of post-synaptic dopamine 2 receptors and a disorder called:
   a. Parkinsonism
   b. New symptoms of schizophrenia
   c. Tardive dyskinesia
   d. Galactorrhea

12. The severity of which dimension of symptoms in schizophrenia is best correlated with long term outcome:
   a. Positive symptoms
   b. Cognitive symptoms
   c. Affective symptoms
   d. a and b
13. Cognitive deficits in schizophrenia
   a. Include problems with sustaining and focusing attention, and prioritizing and modulating behaviors based upon social cues
   b. Include problems with verbal fluency and serial learning
   c. Resemble the short term memory deficits seen in Alzheimer’s disease
   d. a and b
   e. All the above

14. A neurodevelopmental etiology for schizophrenia is suggested by all the following except:
   a. Increased incidence in those with obstetric complications in utero
   b. Premorbid and prodromal negative and cognitive symptoms in childhood and adolescence prior to onset of psychotic symptoms
   c. Increased incidence in first degree relatives
   d. Adult onset of psychotic symptoms with a downhill course during adulthood

15. A neurodegenerative etiology for schizophrenia is suggested by:
   a. Functional and structural abnormalities of brains in schizophrenic patients
   b. A downhill course after onset of psychosis
   c. Less responsiveness to antipsychotic medications the longer treatment is delayed and the more episodes of illness experienced
   d. a and c
   e. All the above

Evaluation

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**UNIT 11: ANTIPSYCHOTIC AGENTS**

*Up to 6 Hours of Category 1 CME Credit*

**Objectives**

1. To review the pharmacology of conventional antipsychotic treatments: the neuroleptics.
2. To contrast the older conventional antipsychotics with the newer atypical antipsychotics.
3. To review the importance of serotonin 2A antagonism to the atypical clinical properties of atypical antipsychotics.
4. To review the regulatory role of serotonin in each of the four major dopamine pathways.
5. To explain why atypical antipsychotics have fewer extrapyramidal side effects, less tardive dyskinesia, less prolactin elevation and better improvement of negative and cognitive symptoms of schizophrenia compared to conventional antipsychotics.
6. To review the unique pharmacological properties of several atypical antipsychotics, including olanzapine, risperidone, quetiapine, clozapine, ziprasidone and others.
7. To discuss the pharmacokinetics and drug interactions of atypical antipsychotics.
8. To discuss new drug discovery efforts in schizophrenia, including serotonin dopamine antagonists and other novel agents such as those based upon molecular and neurodevelopmental approaches to drug discovery.
**Self Assessment and Post Test**

1. The first treatments for schizophrenia were based upon the knowledge that dopamine was hyperactive in the brain. True or False

2. Conventional antipsychotic drugs are also called neuroleptics. True or False.

3. Atypical antipsychotic drugs
   a. Can theoretically block mesolimbic dopamine 2 receptors preferentially, compared to nigrostriatal dopamine 2 receptors
   b. Have selective dopamine 2 antagonist properties whereas conventional antipsychotics have serotonin 2A antagonist properties as well as dopamine 2 antagonist properties.
   c. Have less EPS side effects but also less efficacy for positive symptoms than conventional antipsychotics
   d. None of the above

4. Clozapine is the atypical antipsychotic best documented to improve psychotic symptoms which are resistant to treatment with conventional antipsychotics. True or False.

5. Which of the following serotonin dopamine antagonists (SDAs) is not considered to be a first line atypical antipsychotic drug?
   a. Risperidone
   b. Quetiapine
   c. Loxapine
   d. Olanzapine

6. The pharmacological property which all atypical antipsychotics share is serotonin dopamine antagonism. True or False.

7. The new atypical antipsychotics including risperidone, olanzapine and quetiapine act by:
   a. Blocking dopamine-2 receptors
   b. Blocking serotonin-2 receptors
   c. Both of the above
   d. None of the above

8. The ratio between the blockade of serotonin receptors and dopamine receptors differs for various classes of antipsychotic drugs. True or False.

9. The interaction between dopamine and serotonin in the nigrostriatal dopamine pathway may explain why serotonin dopamine antagonists have propensity for reducing extrapyramidal reactions. True or False.

10. Which pharmacologic properties in addition to serotonin 2A/dopamine 2 antagonism characterize one or more atypical antipsychotics?
    a. Dopamine 1, 3, and 4 antagonism
    b. Serotonin 1D, 3, 6 and 7 antagonism
    c. Serotonin and norepinephrine reuptake blockade
    d. Alpha 1, alpha 2, muscarinic and histaminic receptor blockade
    e. All of the above
11. Which atypical antipsychotics are substrates for CYP450 1A2?
   a. Clozapine
   b. Olanzapine
   c. Risperidone
   d. a and b
   e. All the above

12. Which atypical antipsychotics are substrates for CYP450 2D6?
   a. Risperidone
   b. Clozapine
   c. Olanzapine
   d. All of the above

13. Smoking could lower clozapine and olanzapine plasma levels. True or False.

14. Molecular approaches to the treatment of schizophrenia attempt to identify an abnormal gene product in order to compensate for this abnormality. True or False.

15. Treatment of schizophrenia in the future may involve the combinations of various mechanisms of action simultaneously. True or False.

**Evaluation**

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UNIT 12: COGNITIVE ENHANCERS

Up to 4 Hours of Category I CME Credit

Objectives

1. To review the clinical description of cognitive disorders, including both disorders of attention and disorders of memory.
2. To review the psychopharmacology of attention, including the roles of norepinephrine and dopamine.
3. To review the use of stimulants in disorders of attention, including attention deficit disorder in children and adults.
4. To discuss the role of acetylcholine pharmacology and cholinergic pathways in mediating memory functions.
5. To discuss how memory disorders, including Alzheimer's disease, impact cholinergic neurotransmission.
6. To discuss the new cholinesterase inhibitors and treatments for enhancing memory or slowing the pace of memory loss in Alzheimer's disease.
7. To compare and contrast the cholinesterase inhibitors tacrine, donepezil, metrifonate, rivastigmine, and others.
8. To review the neuropathology of Alzheimer's disease, and its relationship to the amyloid cascade hypothesis and the glutamate excitotoxic hypothesis of Alzheimer's disease.
9. To discuss future cognitive enhancers, including enhancement of attention and memory.

Self Assessment and Post Test

1. Disorders of attention may be mediated via disruption of dopaminergic and/or noradrenergic neurotransmission in the cerebral cortex. True or False
2. The following are enhancers of attention in attention deficit disorder:
   a. Stimulants such as methylphenidate and d-amphetamine
   b. Alpha 2 agonists such as guanfacine and clonidine
   c. Stimulating antidepressants such as bupropion
   d. a and b
   e. All of the above

3. What is true about the pharmacology of d-amphetamine versus the pharmacology of d,l-amphetamine?
   a. d-Amphetamine acts at both norepinephrine and dopamine synapses whereas d,l-amphetamine acts predominantly at dopamine synapses
   b. d-Amphetamine acts predominantly at dopamine synapses whereas d,l-amphetamine acts at both dopamine and norepinephrine synapses
   c. d-Amphetamine acts predominantly at norepinephrine synapses
   d. d,l-Amphetamine acts predominantly at dopamine synapses

4. In attention deficit hyperactivity disorder
   a. Inattention and hyperactivity are both mediated by the nigrostriatal dopamine pathway
   b. Inattention and hyperactivity are both mediated by the mesocortical dopamine pathway
   c. Inattention is mediated by the mesocortical dopamine pathway but hyperactivity is mediated by the nigrostriatal dopamine pathway
   d. Inattention is mediated by the nigrostriatal dopamine pathway but hyperactivity is mediated by the nigrostriatal dopamine pathway.

5. Acetylcholine can be destroyed by:
   a. Acetylcholinesterase
   b. Butyrylcholinesterase
   c. Both
   d. Neither

6. The area of the brain where acetylcholine controls memory includes:
   a. Cholinergic pathways throughout the brain
   b. Cholinergic pathways in brainstem and striatum
   c. Cholinergic pathways arising from the nucleus basalis of Meynert
   d. a and c

7. Alzheimer's disease is a clinical diagnosis and not a pathological diagnosis. True or False.

8. Neuropathology of Alzheimer's disease includes:
   a. Neuritic plaques
   b. Amyloid deposition
   c. Neurofibrillary tangles
   d. All of the above

9. The amyloid cascade hypothesis of Alzheimer's disease states that:
   a. The DNA codes for an abnormal amyloid precursor protein
   b. The amyloid precursor protein initiates a lethal chemical cascade in neurons resulting in the formation of plaques and tangles
c. Plaques and tangles are linked to the formation of dementia symptoms in patients who develop these abnormalities in their neurons
d. All of the above

10. Apo-E is:
a. A binding protein which binds to beta amyloid and normally removes it
b. The amyloid itself
c. Only exists in an abnormal form
d. Is unrelated to theories of Alzheimer's disease

11. The pharmacological benefits of cholinesterase inhibitors include:
a. Functional improvement of central cholinergic neurotransmission at cholinergic synapses in the neocortex
b. Stimulation of both muscarinic and nicotinic cholinergic receptors
c. Possible protection against neuronal degeneration mediated through nicotinic receptor activation
d. Possible modification of amyloid precursor protein processing, mediated through muscarinic receptor activation
e. All of the above

12. Which of the following cholinesterase inhibitors is selective for acetylcholinesterase over butyrylcholinesterase:
a. Donepezil
b. Tacrine
c. Rivastigmine
d. Metrifonate
e. a and c

13. There are two major subtypes of acetyl choline receptors called:
a. Muscarinic and nicotinic
b. M1 and M2
c. Cholinergic and adrenergic

14. Current drugs approved for the treatment of Alzheimer's disease in the United States have the common mechanism of action being:
a. Blockade of cholinergic receptors
b. Direct stimulation of cholinergic receptors
c. Blockade of cholinesterase, destruction of acetyl choline
d. Enhancing release of acetyl choline

15. Treatments of Alzheimer's disease in the future will likely involve multiple pharmacology approaches with mixing and matching different mechanisms of therapeutic action. True or False.
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UNIT 13: PSYCHOPHARMACOLOGY OF REWARD AND DRUGS OF ABUSE

Up to 4 Hours of Category I CME Credit

Objectives

1. To define various terms used in the study of drug abuse, including use, abuse, dependence, intoxication, withdrawal.
2. To review the psychopharmacology of reward, with special reference to the mesolimbic dopamine pathway use and abuse of benzodiazepines.
3. To review the pharmacology of marijuana and the endocannabinoids (i.e., the brain's own marijuana).
4. To review the pharmacology of stimulants, including cocaine and amphetamine and their actions on dopaminergic systems.
5. To review the hallucinogens and designer drugs and their actions on serotonin neurons.
6. To review the pharmacology of phencyclidine and its actions on glutamate neurons.
7. To review the pharmacology of nicotine.
8. To review the pharmacology of alcohol, and agents to reduce alcohol consumption including acamprosate and naltrexone.
9. To review the pharmacology of the opiates.
10. To review the psychopharmacology of obesity.

Self Assessment and Post Test

1. DSM-IV has an accepted definition for addiction based upon a very severe form of drug abuse. True or False.
2. Benzodiazepines are rarely abused and are not known to create dependence or to produce withdrawal when discontinued. True or False.
3. There are three types of opiate receptors called alpha, beta and gamma. True or False.
4. Stimulants are thought to act predominantly upon the dopamine system. True or False.
5. Hallucinogens are thought to have important actions as partial agonists at serotonin-2A receptors. True or False.
6. Marijuana acts on:
   a. Norepinephrine receptors
   b. Serotonin receptors
c. Glutamate receptors
d. Endogenous cannabinoid receptors

7. Nicotine from smoking acts upon:
   a. Muscarinic cholinergic receptors
   b. Nicotinic cholinergic receptors
   c. Both a and b
   d. None of the above

8. A leading hypothesis for a final common pathway of drug abuse is the meso-limbic dopamine pathway and the psychopharmacology of pleasure. True or False.

9. Transdermal nicotine administration can assist in the withdrawal of:
   a. Alcohol
   b. Smoking cessation
   c. Benzodiazepine cessation

10. Pharmacology of alcohol is understood to be:
    a. Action as an enhancer of GABA neurotransmission
    b. Action as an inhibitor of glutamate neurotransmission
    c. Possible modulator of opioid systems
    d. Possible modulator of endogenous cannabinoid systems
    e. All of the above

11. Treatment of alcohol abuse and dependence can be facilitated by:
    a. Acamprosate which can reduce the withdrawal distress and craving when alcohol is withdrawn
    b. Naltrexone which blocks the euphoria of alcohol when alcohol is drunk
    c. 12 Step programs
    d. a and b
    e. All of the above

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**UNIT 14: SEX-SPECIFIC AND SEXUAL FUNCTION-RELATED PSYCHOPHARMACOLOGY**

*Up to 4 'Hours of Category I CME Credit*

**Objectives**

1. To explore the psychopharmacology of the human sexual response, including libido, arousal and orgasm.
2. To discuss the pathophysiology of erectile dysfunction (impotence) in men.
3. To review nitric oxide as a neurotransmitter system.
4. To review estrogen's function as a neurotrophic factor in the brain.
5. To clarify the role of estrogen and how it is linked to mood and mood disorders across the female life cycle.
6. To discuss the potential role of estrogen in cognitive function and cognitive disorders such as Alzheimer's disease.
Self Assessment and Post Test

1. Which psychopharmacological mechanism(s) are most closely linked to libido (sexual desire):
   a. Dopamine
   b. Prolactin
   c. Nitric oxide
   d. Phosphodiesterase
   e. a and b

2. Which psychopharmacological mechanism(s) are most closely linked to sexual arousal (i.e., erections in men and lubrication and swelling in women)
   a. Nitric oxide
   b. Acetylcholine
   c. Phosphodiesterase
   d. All of the above

3. Which neurotransmitter can inhibit orgasm (and ejaculation in men)?
   a. Nitric oxide
   b. Serotonin
   c. Acetylcholine
   d. Norepinephrine

4. What percentage of men with severe depression experience erectile dysfunction?
   a. 15%
   b. 33%
   c. 60%
   d. 90%

5. What is false about nitric oxide?
   a. It is an anesthetic
   b. It is present in car exhaust fumes
   c. It is synthesized from arginine
   d. Its target of neurotransmission is iron in the enzyme guanylate cyclase

6. Sildenafil (Viagra) is
   a. An inhibitor of nitric oxide synthetase (NOS)
   b. An inhibitor of guanylate cyclase
   c. An inhibitor of phosphodiesterase V
   d. An inhibitor of adenylate cyclase

7. Estrogen receptors
   a. Can form transcription factors when they bind to estrogen that activate genes called estrogen response elements
   b. Are active in brain only during neurodevelopment and sexual differentiation
   c. Have neurotrophic actions on monoamine neurons through the lifetime of both men and women
   d. a and c
   e. All of the above
8. Which of the following is true about depression and reproductive hormones?
   a. Depression is linked to testosterone levels in men across their life cycles
   b. Depression is linked to estrogen levels, especially rapid shifts in estrogen levels, in women across their life cycles
   c. Depression is linked to reproductive events in women
   d. b and c
   e. All the above

9. Which are the greatest periods of vulnerability for depression across the female life cycle?
   a. Prepubescence
   b. Postpartum
   c. Postmenopausal
   d. Perimenopausal
   e. b and c

10. Which of the following is not true about estrogen?
    a. It is an antidepressant with comparable efficacy to SSRIs in the treatment of major depressive disorder
    b. Can improve mood in perimenopausal women with prominent vasomotor symptoms such as hot flushes and insomnia
    c. Can enhance the actions of antidepressants in some women
    d. Can reduce the chances of developing Alzheimer's disease
    e. All are true

**Evaluation**

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<tr>
<td>The time spent reviewing the actions of psychotropic drugs upon libido, arousal and orgasm was just right.</td>
<td></td>
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</tr>
<tr>
<td>The time spent reviewing nitric oxide pharmacology and neurotransmission were just right.</td>
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</tr>
<tr>
<td>The time spent reviewing estrogen as a neurotrophic factor, and its links to mood and cognition across the female life cycle was just right.</td>
<td>Strongly Agree</td>
<td>Somewhat in Agreement</td>
<td>Neutral</td>
<td>Somewhat Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>What topics would you like to see deleted or condensed from this unit?</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>What topics would you like to see added or expanded in this unit?</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>What is your overall opinion of this unit?</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>What is your overall opinion of the usefulness of this unit to your practice?</td>
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</tbody>
</table>
**ANSWER SHEET**

**UNIT 1: PRINCIPLES OF CHEMICAL NEUROTRANSMISSION**

|   | a | b | c | d | e | n | f | g | h | i | j | k | l | m | n | o | p | q | r | s | t | u | v | w | x | y | z |
| 1. | a | b | c | d | e | 11. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 2. | True | False |   |   |   | 12. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 3. | True | False |   |   |   | 13. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 4. | True | False |   |   |   | 14. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 5. | True | False |   |   |   | 15. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 6. | True | False |   |   |   | 16. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 7. | True | False |   |   |   | 17. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 8. | True | False |   |   |   | 18. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 9. | True | False |   |   |   | 19. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 10. | True | False |   |   |   | 20. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

**UNIT 2: RECEPTORS AND ENZYMES AS TARGETS OF DRUG ACTION**

|   | a | b | c | d | n | f | g | h | i | j | k | l | m | n | o | p | q | r | s | t | u | v | w | x | y | z |
| 1. | a | b | c | d |   | 8. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 2. | a | b | c | d | e | 9. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 3. | a | b | c | d |   | 10. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 4. | True | False |   |   |   | 11. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 5. | True | False |   |   |   | 12. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 6. | a | b | c | d |   | 13. a | b | c | d |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 7. | True | False |   |   |   | 14. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

**UNIT 3: SPECIAL PROPERTIES OF RECEPTORS**

|   | a | b | c | d |   | 6. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 1. | a | b | c | d |   | 7. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 2. | True | False |   |   |   | 8. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 3. | a | b | c | d |   | 9. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 4. | True | False |   |   |   | 10. a | b | c | d |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 5. | True | False |   |   |   | 11. True | False |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
UNIT 4: CHEMICAL NEUROTRANSMISSION AS THE MEDIATOR OF DISEASE ACTIONS

1. a b c d
2. True False
3. True False
4. True False
5. a b c d e
6. True False
7. True False
8. True False
9. True False
10. True False
11. True False

UNIT 5: DEPRESSION AND BIPOLAR DISORDERS

1. a b c d e
2. a b c d e
3. a b c d
4. a b c d
5. True False
6. True False
7. a b c d
8. a b c d e
9. True False
10. True False
11. True False
12. True False
13. a b c d e
14. a b c d
15. a b c

UNIT 6: CLASSICAL ANTIDEPRESSANTS, SEROTONIN SELECTIVE REUPTAKE INHIBITORS AND NORADRENERGIC REUPTAKE INHIBITORS

1. True False
2. a b c d
3. a b c d
4. a b c d
5. a b c d
6. a b c d e
7. a b c d e
8. a b c d e
9. a b c d e
10. True False
11. True False
12. a b c d

UNIT 7: NEWER ANTIDEPRESSANTS AND MOOD STABILIZERS

1. a b c d e
2. True False
3. True False
4. a b c d
5. True False
6. a b c d e
7. a b c d e
8. True False
9. True False
10. a b c d
UNIT 8: ANXIOLYTICS AND SEDATIVE HYPNOTICS

1. a b c d e 6. a b c d
2. True False 7. True False
3. True False 8. True False
4. a b c d 9. True False
5. a b c d 10. True False

UNIT 9: DRUG TREATMENTS FOR OBSESSIVE COMPULSIVE DISORDER, PANIC DISORDERS AND PHOBIC DISORDERS

1. True False 6. True False
2. True False 7. True False
3. True False 8. True False
4. True False 9. True False
5. True False 10. True False

UNIT 10: PSYCHOSIS AND SCHIZOPHRENIA

1. True False 9. True False
2. True False 10. True False
3. True False 11. a b c d
4. True False 12. a b c d
5. True False 13. a b c d e
6. True False 14. a b c d
7. a b c d 15. a b c d e
8. True False

UNIT 11: ANTIPSYCHOTIC AGENTS

1. True False 9. True False
2. True False 10. a b c d e
3. a b c d 11. a b c d e
4. True False 12. a b c d
5. a b c d 13. True False
6. True False 14. True False
7. a b c d 15. True False
8. True False
UNIT 12: COGNITIVE ENHANCERS

1. True False
2. a b c d e
3. a b c d
4. a b c d
5. a b c d
6. a b c d
7. True False
8. a b c d
9. a b c d
10. a b c d
11. a b c d e
12. a b c d e
13. a b c
14. a b c d
15. True False

UNIT 13: PSYCHOPHARMACOLOGY OF REWARD AND DRUGS OF ABUSE

1. True False
2. True False
3. True False
4. True False
5. True False
6. a b c d
7. a b c d
8. True False
9. a b c
ten. a b c d e
11. a b c d e

UNIT 14: SEX-SPECIFIC AND SEXUAL-FUNCTION RELATED PSYCHOPHARMACOLOGY

1. a b c d e
2. a b c d
3. a b c d
4. a b c d
5. a b c d
6. a b c d
7. a b c d e
8. a b c d e
9. a b c d e
10. a b c d e
Essential Psychopharmacology has established itself as the preeminent source of education and information in its field. This much expanded second edition relies on advances in neurobiology and recent clinical developments to explain with renewed clarity the concepts underlying drug treatment of psychiatric disorders. New neurotransmitter systems, theories on schizophrenia, clinical advances in antipsychotic and antidepressant therapy, coverage of attention deficit disorder, sleep disorders and drug abuse, and a new chapter on gender and sexual psychopharmacology are all features of this edition.

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Stephen M. Stahl is Adjunct Professor of Psychiatry at the University of California at San Diego. He has conducted numerous research projects awarded by the National Institute of Mental Health, the Veterans Administration, and the pharmaceutical industry. Author of more than 200 articles and chapters, Dr. Stahl is an internationally recognized clinician, researcher, and teacher in psychiatry with subspecialty expertise in psychopharmacology.