Brown Medical School

Biomed 370
The Brain and Human Behavior

The Brain and Human Behavior

Biomed 370

A first year, second semester course sponsored by the Department of Psychiatry and Human Behavior

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Overall Course Objectives

1. Students will better understand the neural organization of key functional brain systems that regulate behavior such as fear, mood, psychosis, feeding, executive function and memory.

2. Students will learn about the diagnosis and treatment of the major syndromes in psychiatry.

3. Students will appreciate the importance of anatomy, neurochemistry and brain imaging for understanding brain and behavior relationships.

Overview And Format

The brain mediates all complex behaviors. Advances in brain imaging and basic neuroscience have greatly increased our understanding of the brain systems involved in behavior. Advances in pharmacology have greatly improved the treatment of mental illness. This course will highlight the functional organization of key brain systems involved in behavior and review the diagnosis and treatment of major psychiatric disorders. The importance of anatomy, brain imaging and neurochemistry for understanding behavior will be emphasized. Becoming more familiar with the neurobiology of neural systems underlying behavior will provide a foundation for understanding the clinical syndromes that you will learn about in Neurosciences 262 and will better prepare you for diagnosing and treating neurological and psychiatric disorders in your future practice of medicine. This course will contribute to lifelong learning by providing a basis for incorporating new advances in the rapidly evolving area of brain and behavior research.

Biomed 370 has been reorganized as the initial step toward achieving the Medical School's goal of developing an integrated pre-clinical neuroscience curriculum. The new Biomed 370, Brain and Behavior, has integrated the core material from Biomed 278, Introduction to Clinical Psychiatry, and the old Biomed 370, The Human Brain and Behavior plus added introductory lectures on neuroanatomy and psychopharmacology lectures. The intention of the new curriculum is to provide students with a more organized multidisciplinary framework for understanding, diagnosing and treating neuropsychiatric disorders. The first part of the course will present an overview of functional neuroanatomy, psychophamacology and neuroimaging. Clinical disorders will be discussed in the second part of the course.

Direction Of The Course

Dr. Salloway and Dr. Boland are the course leaders for Brain and Behavior. Their telephone numbers and email addresses are located on the first page of the syllabus. Brown is fortunate to have many faculty with expertise in brain/behavior relationships to teach in this course. The lectures will be given by faculty with strong teaching skills from the Department of Psychiatry and Human Behavior, and the Departments of Clinical Neurosciences, Psychology and Neuroscience.

The faculty appreciates your constructive suggestions for improving this class. Please feel free to contact the course directors or lecturers with your suggestions.

Relationship To MD 2000 Objectives And Other Medical Student Courses

This course helps prepare students for Part I and II of the Boards and provides education toward competencies III (using basic science to guide therapy), IV (diagnosis, management and prevention) and V (lifelong learning) outlined in the Educational Blueprint for the Medical School and addresses a number of the content areas under Knowledge Base II (single organ system), and IX (behavioral encounters) in the MD 2000 curriculum plan.

Small Groups

In addition to lectures, the class will have an opportunity to visit an area clinical site and observe patients directly in a small group setting. This small groups experience is an opportunity to both see psychiatric disorders in a clinical setting, and to practice psychiatric interviewing skills.

Syllabus, Computer, And Internet Resources

The syllabus contains material relevant to of each lecture. Lecture slides, sample questions, relevant background reading, links to related sites, review packets and other information will be posted on the course website.

The course website is part of Brown's WebCT and can be accessed at the WebCT home page:

https://webct.brown.edu/

Simply log in with your Brown ID and password, and you should see a link for Biomed 370. Click on that to access the Brown web page.

There is no specific textbook assigned for this course.   Reading relevant to each lecture are available online.

The outlines and background reading complement the lectures and will help you integrate material presented in the course.   Students are strongly encouraged to use a self guided introductory neuroimaging

tutorial software program developed by members of the faculty for learning about brain imaging, which is installed in the Biomed Computer Learning Cluster. Additionally, the neuroanatomy tutorial installed on the same computers will be very useful, particularly in understanding the anatomy of the limbic system.

Grading

Grading is based on 2 tests and a paper.

Tests. There will be one midterm worth 40% and a final examination worth 60%. A multiple choice format will be used with material drawn from the lectures and syllabus. The lectures will highlight the material most relevant to the course, and therefore most represented on the test. The examinations will be similar in format and complexity to the USMLE examinations, and as is typical of that format, many questions will utilize clinical vignettes.

Honors Paper. 2 pages maximum. In the paper you are to describe, clinically, a patient you have seen this year. This can be a patient you have seen during the small group hospital experience (which takes place on 4/4/06) or a patient during any other clinical encounter, such as during your On Doctoring course. Preferably, this will be a patient you either interviewed yourself, or saw interviewed in a small group setting. Patients seen on film, or interviewed in a large group setting (ex. brought in by one of the lecturers during the course) are not eligible. You should describe the patient in a formal way and discuss more the diagnosis/syndrome with which the patient presents. References are encouraged. The purpose of the paper is to show that you can integrate your didactic and clinical experiences.

Grading. Grading will be Honors/Satisfactory/No Credit. To achieve honors, students should score in the top 15-20% on the examinations, and complete an honors paper that is judged to be at least satisfactory. An honors paper must be completed to be eligible for honors in this course (but is not a guarantee of honors, of course).

We hope that all students will pass this course. However, students with very low scores will not receive credit.

Section 1. Basic Principles.

Chapter 1. Limbic System Anatomy

The brain is organized into three tiers (Figure 1): a **lower tier** made up by the brainstem and cerebellum, a **middle tier** containing the thalamus, basal ganglia and many components of the limbic system, and an **upper tier** comprised by the cortex. The **brainstem** regulates arousal, autonomic function and internal states. The cell bodies for the key neurotransmitters that regulate behavior are found in the upper brainstem. The **central core** modulates emotion and memory and helps control speed of movement and rate of thinking. The **upper tier** carries out higher level sensory processing and motor control, complex thought, and memory storage. This lecture will focus on the **middle tier** with special emphasis on the **limbic system** and the **prefrontal-subcortical circuits** that regulate behavior (Figure 3).
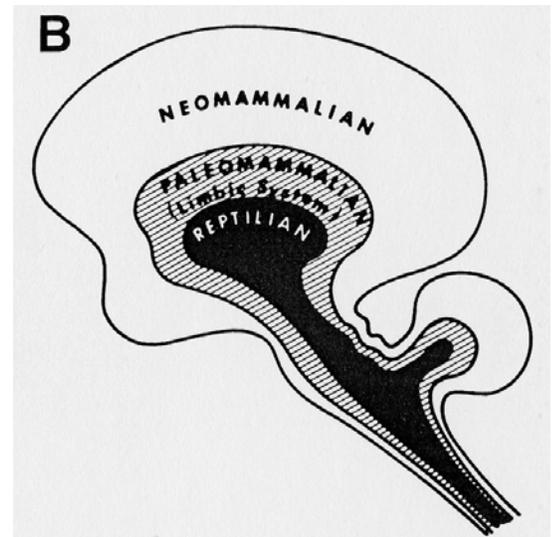

Figure 1-1

What is the limbic system?
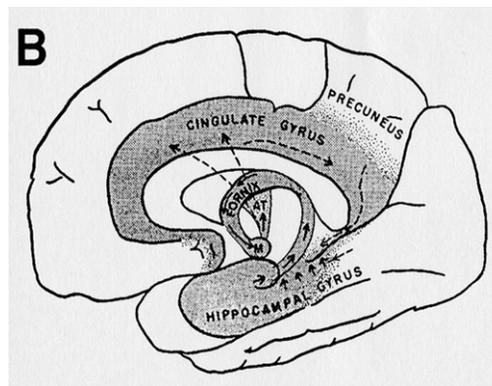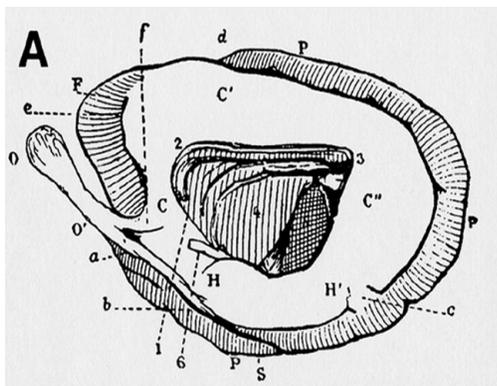
Figure 1-2A: *Le grand lobe limbique* common to all mammals as identified by Broca in 1878.
Figure 1-2B: The medial circuit of Papez, as depicted by MacLean, was proposed in 1937 to support emotional processing.

The term limbic, meaning "belt or border", was introduced by Paul Broca in 1878 because the cingulate and parahippocampal gyri appeared to form a border or edge around the diencephalon (Figure 2A). Papez later proposed that the **hypothalamus, anterior nucleus of the thalamus, cingulate gyrus, hippocampus and their connections formed a system that mediated emotional expression** (Figure 2B). Today the limbic system has expanded to include the **amygdala and entorhinal cortex in the medial temporal lobe**, **the septal nucleus at the base of the frontal lobe**, **the anterior cingulate gyrus and orbitofrontal cortex**. The limbic system plays a key role in **memory**, **cognition**, **mood and anxiety**, **social behavior**, and **regulation of drives and impulses**.

The Cognitive Belt (Papez's Circuit)
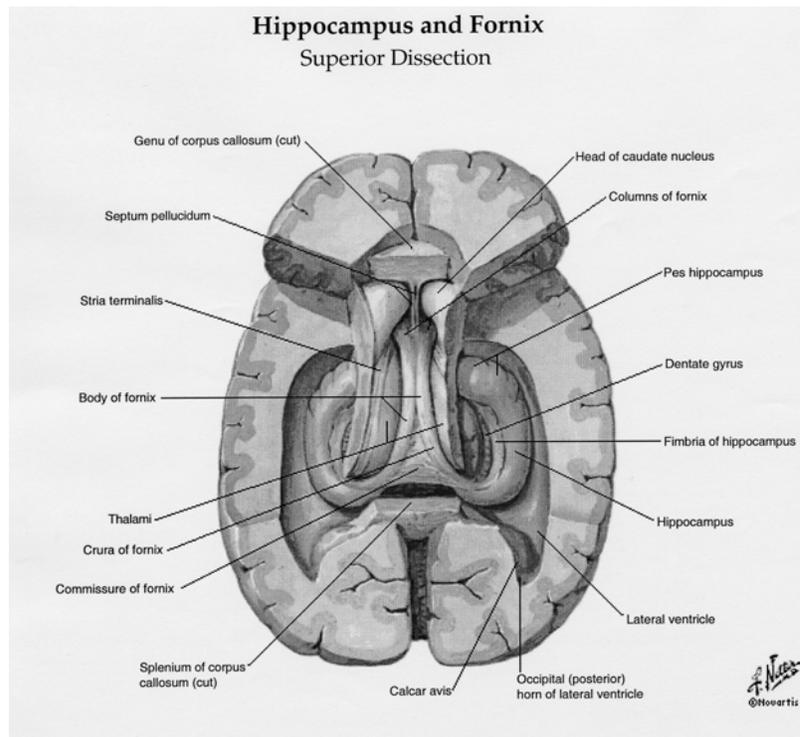
Figure 1-3

The cognitive belt (or Papez's Circuit) is a loop of limbic structures that are integral to emotional processing and memory. Deficits in these functions can be created by interfering with any one of the structures composing the cognitive belt. The sequence of the cognitive belt is as follows:

Hippocampus → Fornix → Mammillary Bodies → Anterior Nucleus of the Thalamus → Anterior Cingulate Gyrus → Cingulum Bundle → Hippocampus

The **hippocampus (hc),** meaning "seahorse" because of its shape, is located underneath the parahippocampal gyrus. The blood supply to the posterior two thirds is provided by the **posterior cerebral artery** and the anterior third by the **middle cerebral artery**. It is composed of a three-layer archicortex. The main gateway to the hippocampus is via the **entorhinal cortex** and **subiculum**. The hippocampus is made up of regions called CA1-4
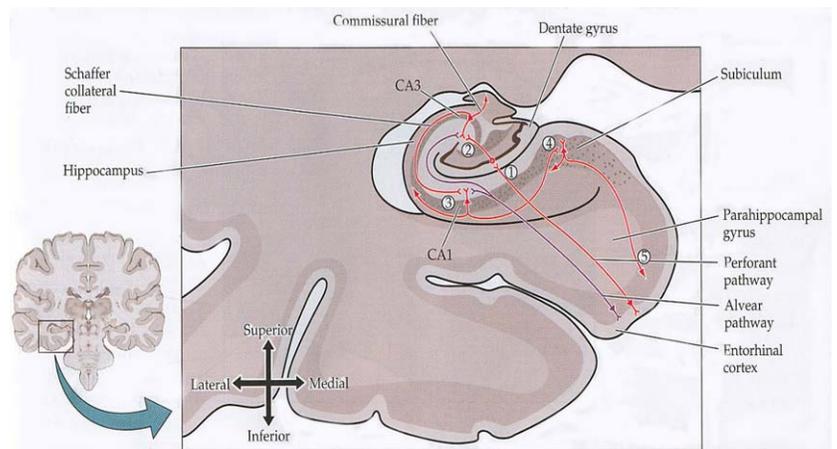
Figure 1-4

which surround the **dentate gyrus** (Figure 4). The main outflow is via a thick white matter bundle called the <u>fornix</u> (Figure 3) which connects the hc to the **septal nuclei** and **mammillary bodies**.

The **hippocampus** is involved in **short-term memory formation**, **spatial memory** and **orientation**, **attention** and **regulation of mood**. The right hippocampus is specialized for spatial memory and the left hippocampus is dominant for verbal memory. Experienced London cabbies were recently found to have a thicker right hippocampus than their more pedestrian peers did. The hc is richly innervated by forebrain cholinergic, brainstem dopamine, noradrenalin and serotonin, plus local glutamatergic and gaba-ergic neurons. Activity in the hippocampus is modulated by adrenal steroids and estrogen. The hc is frequently involved in **partial complex seizures** and is a focal area of infection in **herpes encephalitis** and is **sensitive to anoxic injury**. The entorhinal cortex degenerates

Figure 1-5: An MRI of patient HM who underwent bilateral medial temporal lobe resection to treat intractable epilepsy and developed a classic case of dense anterograde amnesia. The T1 image (left) and T2 image (right) show large areas of encephalomalacia in the anteromedial temporal lobe bilaterally.

early in **Alzheimer's disease (AD)** and the hippocampus is a site of heavy plaque and tangle formation in AD. The <u>septal nuclei</u> are rich in cholinergic neurons and degeneration of the hippocampal-septal pathway underlies the memory disturbance seen in AD. Histological abnormalities have also been reported in the hc and entorhinal cortex in schizophrenia and autism.

The <u>mammillary bodies</u> (Figure 6) are the most posterior nuclei of the hypothalamus. Necrosis of the mammillary bodies may occur due to **thiamine deficiency** in alcoholics. This is associated with amnesia, confusion and confabulation called the **Wernicke-Korsakoff syndrome**.

The mammillothalamic track connects the mammillary bodies to the <u>anterior nucleus of the thalamus</u>. A lesion in the


Figure1-6

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anterior nucleus of the thalamus caused by infarction in one of the small perforating arteries from the posterior cerebral artery can produce significant **amnesia**.

Thalamocortical projections connect the anterior nucleus of the thalamus with the **anterior cingulate gyrus**. The anterior cingulate is involved in **attention, drive motivation, and initiation of speech**. Lesions to the anterior cingulate most commonly cause **apathy**. Bilateral injury to the anterior cingulate can produce a condition of **akinetic mutism** in which the person is alert but has tremendous inertia with little spontaneous movement or speech. This profound inertia is called **abulia**. The anterior cingulate sits at the crossroads between cognitive and emotional components of the limbic system and **activity in this area may predict response to antidepressant treatment**.
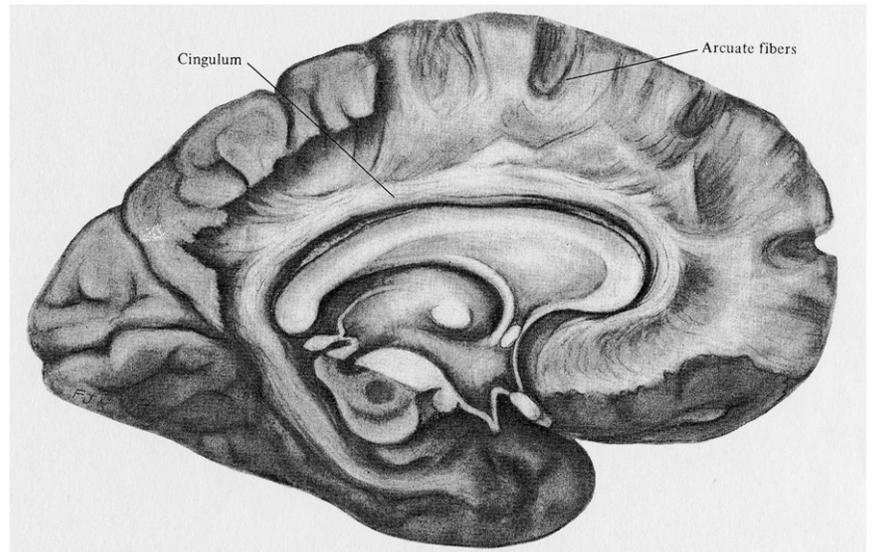
Figure 1-7

The anterior cingulate gyrus communicates back to the hippocampus via the **cingulum bundle** (Figure 1-7). **Cingulotomies** (small cuts in the cingulum bundle) are still occasionally used for the treatment of refractory depression, pain and obsessive compulsive disorder.

Processing Of Emotional Stimuli
Amygdala/Olfactory/Orbitofrontal Division

The **amygdala,** or "almond," lies anterior and medial to the hippocampus. It is comprised of a cluster of nuclei divided into basolateral and corticomedial divisions. The basolateral region of the amygdala receives major input from the **visual system** and other sensory modalities. The amygdala has been referred to as the *valence center* because it attaches **affective color and social meaning to sensory information**. The amygdala also receives **primary olfactory afferents** from the olfactory stria which probably accounts for the major role that olfaction plays in emotion and behavior, especially in lower animals. The amygdala has rich reciprocal connections with the **orbitofrontal cortex**. The amygdala connects to the basal forebrain cholinergic neurons in the septal nucleus via the **stria terminalis** and to hypothalamic and brainstem autonomic areas via the **ventral amygdalofugal pathway** (Figure 8). The amygdala also connects to the nucleus accumbens in the ventral striatum via the extended amygdala.

Figure 1-8

The amygdala plays a key role in the **startle reflex** and can generate *flight or fight responses*. The amygdala also helps regulate **appetite**, **mood**, **aggressive and sexual behavior**, **social behavior, and comprehension of social cues**. *Auras* from partial seizures arising in the amygdala can cause olfactory sensations (funny smells like burning rubber), autonomic sensations (a gnawing in the stomach or heart racing), automatic behaviors such as picking at clothing, or psychic experiences such as déjà vu, dreamy states, depersonalization, hallucinations and a wave of fear. Many of these symptoms may be present during **panic attacks**. The amygdala and overlying parahippocampal gyrus receive rich **noradrenergic innervation** from the locus coeruleus in the pons. These structures have been implicated in panic disorder. Rare cases of individuals with degeneration of the bilateral amygdala cannot recognize fear in others, though they are capable of feeling fear themselves. Surgical bilateral amygdalectomies for refractory epilepsy or aggression have produced the **Kluver Bucy syndrome.** This syndrome causes individuals to be placid. Hyperorality is prominent and they may attempt to eat non-food items. Animals with this syndrome may fail to recognize dominant animals and may initiate sex with animals from other species.

Dorsal view of some of the connections of the amygdala. 1-4, olfactory structures; 5, anterior commissure; 6, olfactory tubercle; 7, limen insulae; 8, diagonal band (of Broca); 9, inferior thalamic peduncle; 10, medial telencephalic fasciculus; 11, ventral amygdalofugal pathway; 12-17, amygdala; 18, lateral hypothalamic area; 19-20, nucleus and stria medullaris; 21, stria terminalis; 22, habenular commissure; 23, habenular nuclei; S, septal nuclei. (Modified with permission from Nieuwenhuys, R., Voogd, J., and Van Huijzen, C. 1988. The Human Nervous System. New York: Springer-Verlag.)

The amygdala also plays an important role in forming **emotional memories**. Emotionally arousing experiences tend to be remembered long and well. Extensive evidence indicates that stress-released adrenal hormones, norepinephrine and cortisol regulate the strength of emotional memory. These hormones act on the amygdala to enhance the storage of recent experiences. Lesions of the amygdala and β blockers block the memory enhancing effects of emotional arousal and infusion of norepinephrine in the amygdala enhances emotional memory. **Post-traumatic stress disorder** may represent a hyperactivation of this system.

Chapter 2. Frontal Lobe Function And Dysfunction

Regions Of The Frontal Lobes
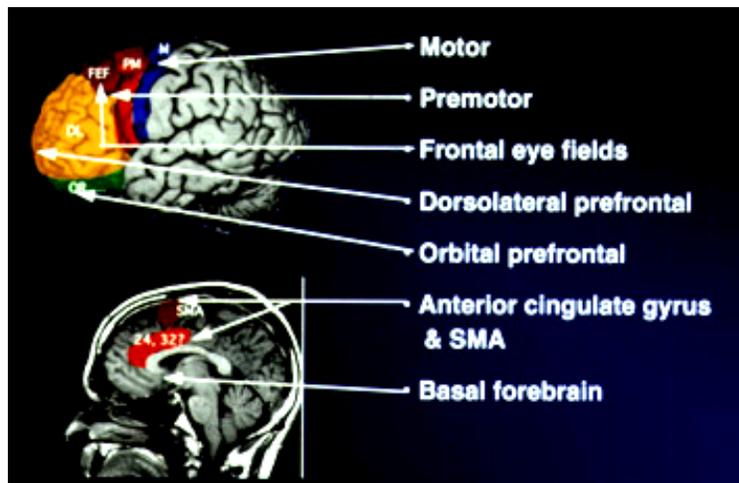
Figure 2-1

Primary Motor Cortex (M1, Brodmann area 4): The primary motor cortex is located on the precentral gyrus just rostral to the central sulcus. It is the source of cortical neurons that will project to the brainstem and spinal cord to activate neurons involved in the control of voluntary movements. It receives input from the neighboring **primary somatosensory area** (S1, on the postcentral gyrus) and **premotor cortex**, as well as from the **ventral lateral nucleus** of the thalamus (a relay nucleus with projections from the cerebellum). These inputs modulate the output of M1 by providing information about the positioning, timing, and coordination of voluntary movements. The output of M1 goes by way of the **internal capsule** to synapse in the brainstem (the projection referred to as the corticobulbar tract) or the spinal cord (the corticospinal tract). Damage to M1 will cause **contralatereral motor deficits**, initially a flaccid hemiplegia/hemiparesis and later a spastic hemiplegia/hemiparesis. Depending on the extent of cortical damage, these deficits may be localized to a specific region of the body or can be more widespread.

Premotor Cortex (BA6): The premotor cortex is located immediately rostral to M1. Its primary function is to assist in integration of sensory and motor information for the performance of an action (praxis). Thus it receives input from **secondary somatosensory area** (immediately caudal to S1 in the parietal cortex) and the **ventral anterior thalamic nucleus** (a relay nucleus with projections from the basal ganglia, which themselves are a group of subcortical nuclei that modulate motor activity). The output of premotor cortex is to **M1** and **contralateral premotor area** (by way of the corpus callosum). Damage to premotor cortex may result in (1) **apraxia**, an acquired inability to carry out skilled actions that could previously be performed (but without paralysis); (2) **deficits in contralateral fine motor control,** such as the performance of complex serial movements; and (3) **difficulty in using sensory feedback** for the control and performance of movements.

Frontal eye fields (BA8): The frontal eye fields are located rostral to premotor cortex. Their primary function is associated with control of voluntary eye movements in the contralateral visual field for processes such as active visual search. Their connections with the rest of the brain are complex and beyond the scope of this discussion. Damage to the frontal eye fields will cause **deficits in voluntary eye movement** to the contralateral visual field (leading to active visual search deficits), but preserved passive eye movement (as in the following of a moving object).

Dorsolateral prefrontal cortex (BAs 45-49): The dorsolateral prefrontal cortex makes up the largest proportion of frontal cortex, located rostral to the frontal eye fields and superior to orbitofrontal cortex. The functions of this region of the brain fall under the heading of "**executive**" processes, which in a general sense involves the ability to utilize sensory input from multiple modalities (i.e. visual, auditory) in the generation of appropriate responses. Its connections with the rest of the brain are extensive, but one circuit of considerable importance involves input from the **thalamus** (primarily ventral anterior and mediodorsal nuclei) and output to the **caudate** nucleus of the basal ganglia (this circuit will be described in greater detail later). The function of the dorsolateral cortex is probably best reflected in the tasks used to assess dysfunction of this region. There are several tests currently in use that aim to characterize qualitative deficits of the dorsolateral cortex.
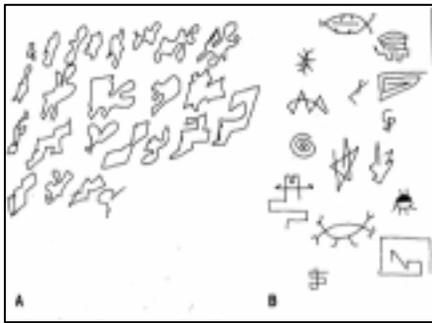
Figure 2-2

- *Figural fluency tasks* (Figure 2-2): Patients are asked to draw as many different shapes as possible within a limited time period. Patients with dorsolateral dysfunction might get "stuck" on one shape and continue to draw either the same figure or something very similar (an error called **perseveration**). Here one can observe that the patient is having difficulty generating **multiple response alternatives**.

- *Luria's Alternating Figures Test:* Patients are asked to copy a sequence of alternating +'s and 0's and then to continue the pattern across the page (figure 2-3Ae). Patients with dorsolateral dysfunction may persist in drawing only +'s or only 0's (perseveration), or they may change the task entirely and begin drawing x's (exhibiting **impersistence** in completion of the appropriate task). Again, one can note difficulty in **generating appropriate responses** to the task at hand. Note that similar tests to assess errors of this sort may be performed using alternating hand movements or the drawing of different patterns of peaks and valleys (Figure 2-3B).
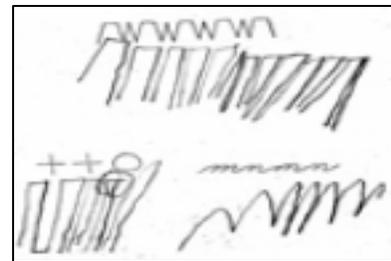
Figure 2-3A

Figure 2-3B

- *Visual Organization Test* (not pictured): Patients are presented with pictures of common objects that have been cut apart and rearranged on the page like a puzzle. A patient with dorsolateral dysfunction will not be
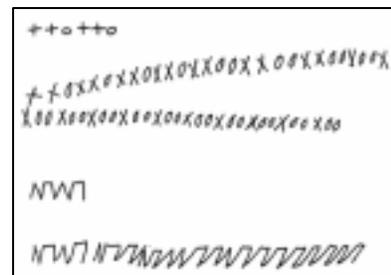
able to "piece" back together the cut-apart object, instead focusing on a single aspect of one of the shapes on the page. Here **difficulties in integration of sensory information** are especially apparent.

- *Copy/Free Recall Tests:* Patients are presented with a figure that is first to be copied (Figure 2-4, top image) and then later to be drawn from recall (Figure 2-4, bottom image). When drawing from recall, patients with dorsolateral dysfunction will remember to draw certain details of the figure without regard for the general shape and organization of the figure as a whole. This deficit reflects **poor organization of learning and recall** in these patients.
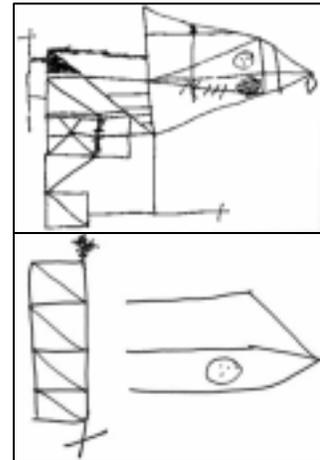

Figure 2-4

Orbitofrontal Cortex (BAs 10-14): The orbitofrontal cortex is located inferior to dorsolateral prefrontal cortex in the most rostral portion of the frontal lobe. It has several functions, including the **modulation of affective and social behavior**, **working memory for feature information**, and **smell discrimination**. The orbitofrontal cortex receives input from **limbic and olfactory systems**, along with **inferotemporal lobe** areas (memory formation), **and ventral visual pathways** (analysis of form and color of visual input). Its output is to autonomic musculature and the basal forebrain cholinergic system (both targets are involved in regulation of behavior). General observation of patients exhibiting **behavioral disinhibition** or **socially inappropriate actions** might suggest orbitofrontal deficits, particularly if on neurological exam the patient also exhibits anosmia (an inability to discriminate smells). Tests of orbitofrontal dysfunction are fewer in number than those used to assess dorsolateral problems:

- Drawing tasks may show **disinhibition and intrusion** in the construction of figures and shapes for a patient with orbitofrontal dysfunction (Figure 2-5).

- The *"go/no-go"* task requires patients to make a response to a "go" signal and withhold a response to a "no-go" signal. The task is often made more difficult by changing the habitual

  meaning of the signals (i.e. the patient is instructed to tap their fist when the examiner says "stop" and not tap when the examiner says, "go"). A patient with orbitofrontal dysfunction will have difficulties **inhibiting their behavior** during these tasks.

Patient begins correctly, demonstrating comprehension of the task instruction.

Pauses at decision point, loses task.

Shape reminds patient of a truck, leading to a stimulus-bound intrusion.
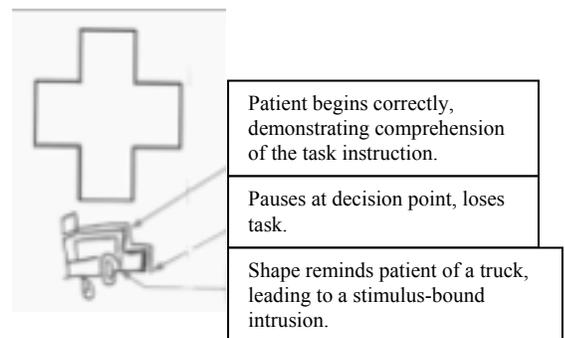
Figure 2-5. Elderly women with a history of schizophrenia and a frontal CVA. Neuropsychological testing revealed deficits in executive functioning and memory abilities, with spatial perception and construction problems secondary to disorganization, intrusions an and perseveration.

Cingulate Cortex/Supplementary motor area (BAs 24, 32): The cingulate cortex is located in the medial portion of the cortex just superior to the corpus callosum. The supplementary motor area is located medial to the premotor cortex just anterior to M1. These regions of the brain have functions that are involved with **drive and motivation** along with **environmental exploration**. Their connections are with **deep limbic structures** of the brain (i.e. basal forebrain structures such as the nucleus accumbens). Dysfunctions in the

cingulate/SMA are associated with several uniquely bizarre characteristics, **including apathy and akinetic mutism** (reflecting a loss of drive and motivation) along with **complex attentional deficits** and **delayed habituation** to external stimuli. The **alien hand syndrome** may also be present, whereby patients report experiencing a loss of conscious control over the movements and actions of their hand, which proceeds to "explore" the surrounding environment by, for instance, unbuttoning clothes.

Frontal: Subcortical Connections

The frontal cortex has connections to subcortical structures such as the thalamus and basal ganglia that function in regulation of behavior. As alluded to earlier, the dorsolateral prefrontal cortex is a part of a circuit with input from the **thalamus** and output to the **striatum** (a basal forebrain nucleus). The striatum then projects to **globus pallidus/substantia nigra** (another basal forebrain structure), which projects to the **thalamus** to complete the circuit. Other parallel but distinct connections exist between the orbitofrontal/cingulate frontal regions and their corresponding subcortical structures. In a very general sense, the frontal:subcortical:frontal circuits may be thought of a "filter" that serves to modulate the output of the frontal cortices to regions of the brain involved in motor control of behavior. **Small subcortical lesions** that affect any one of these circuits can **mimic large cortical lesions**.

Frontal Cortex→Striatum→Globus Pallidus/Substantia Nigra→Thalamus→Frontal Cortex

Disorders Associated With Frontal Lobe Dysfunction

Frontal lobe dysfunction may be found in a host of disorders ranging from cortical degenerative disorders often seen in the elderly, including Alzheimer's Disease and Fronto-Temporal Lobar Dementia, to disorders of a psychiatric nature (schizophrenia, obsessive-compulsive disorder). As noted above, subcortical damage can also result in frontal dysfunction; such damage may be seen in disorders of basal ganglia nuclei such as Huntington's Disease and Parkinson's Disease. Some representative examples of disorders associated with frontal lobe dysfunction are as follows:

Fronto-Temporal Lobar Degeneration: This is a degenerative disorder of the cerebral cortex that preferentially affects the frontal and temporal lobes of the brain (Figure 2-6). The symptoms exhibited by patients with fronto-temporal lobar degeneration are reflected in the brain areas affected.

- **Orbitofrontal** dysfunction may cause **behavioral disinhibition.**
- **Cingulate** deficits may cause **apathy**.
- **Dorsolateral** deficits may cause problems with **executive** functions.
- **Temporal lobe** lesions may adversely affect the amygdala (a structure involved in **emotional processing and social behavior**) or the left
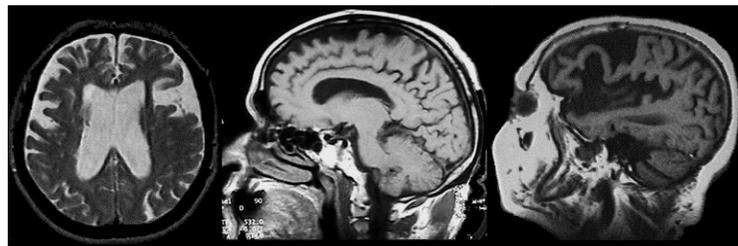

Figure 2-6

temporal lobe (associated with language functions—deficits can result in **aphasia, semantic dementia**).

The deficits associated with frontotemporal dementia (FTD) may be contrasted with those of Alzheimer's disease (AD), another cortical degenerative disorder that preferentially affects the temporal lobes (specifically the hippocampus). While FTD may be associated with early dysfunction in behavior/personality and executive functioning, **Alzheimer's patients** will show **preservation of personality and behavior** while exhibiting **deficits more specific to memory function**. Cortical patterns of atrophy, visualized through brain imaging methods (MRI or CT) will also typically distinguish the frontotemporal degeneration of FTD (Figure 2-6) from the hippocampal atrophy seen in AD{}.

Traumatic brain injury: Blows to the head are especially likely to affect the orbitofrontal poles of the brain, sometimes causing such a patient to exhibit **behavioral disinhibition and inappropriate actions**. Figure 2-7 shows damage to a patient in the orbitofrontal region following trauma.
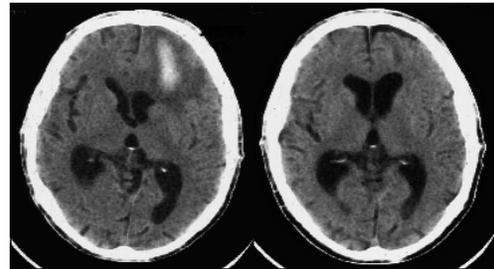
Figure 2-7

Schizophrenia: This is a psychiatric disorder characte touch with reality) and bizarre behavior interspersed with periods of "negative" symptoms, characterized by flattening of affect (showing no emotions), lack of motivation, social withdrawal, and speech deficiencies. These **negative symptoms** are thought to be due to **decreased neural activity** (mediated by dopamine-secreting neurons) in **dorsolateral prefrontal: subcortical circuits**.

Obsessive-Compulsive Disorder: This is a disorder whose patients have recurrent unwanted, intrusive thoughts (obsessions) that cause anxiety; the anxiety is relieved to some extent by performing repetitive actions (compulsions). **Overactivity** in **frontal:subcortical circuits** are thought to be central to the pathogenesis of this disorder, and surgical treatment for refractory (resistant to treatment) OCD involves the interruption of these circuits.

Korsakoff's dementia: Korsakoff's dementia is a disorder caused by a **deficiency of vitamin B1 (thiamine)** and often occurs in chronic alcoholics (since alcohol serves as a substitute for foods with essential nutrients). The disease is characterized by **severe amnesia** and causes degeneration of the medial thalamus, mamillary bodies, and cerebral atrophy in regions such as the frontal lobes (Figure 2-8). Patients with Korsakoff's dementia often exhibit many of the same neuropsychological deficits that are seen in other frontal patients.
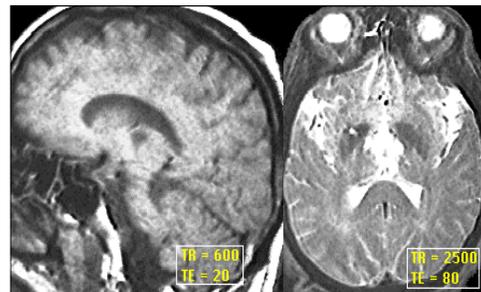
Figure 2-8

Other Indicators Of Frontal Lobe Dysfunction

Working Memory Tests: Working memory tests are often used to evaluate frontal lobe function in patients. Some of the more common working memory tests include:

- *Spatial working memory tasks:* An example would be a **delayed response task**, which might require a patient to take note of the position of a dot that briefly flashes on a screen, withstand a variable delay in which they are asked to perform another task, and then after this delay point to the position where they remember seeing the dot (hence testing the ability to remember the spatial position of the dot). Another test of spatial working memory, which also is able to detect perseverance errors, is **delayed alternation**.
- *Feature working memory tasks:* An example would be a **delayed matching to sample** task, which might require a patient to view a figure presented briefly on a screen, withstand a variable delay in which they would be shown a number of other figures, and then after this delay have to identify the original figure when presented among several choices. **Delayed object alternation** is a variant on this test that, like spatial delayed alternation, assesses the presence of perseverance errors.

Reflexes: Patients with frontal lobe dysfunction may exhibit reflexes (often referred to as "release signs") that are present in infancy but disappear with normal development. These include the **snout**, **suck**, **glabellar**, and **grasp** reflexes.

Dystonias: Patients with frontal lobe lesions may exhibit **gegenhalten**, a behavior in which resistance to movement of a limb increases throughout flexion and extension. This phenomenon should be distinguished from **cogwheeling**, which is another dystonia characterized by ratchet-like movements of joints and is characteristic of Parkinson's disease.

Gait abnormalities: Patients with frontal lobe dysfunction may exhibit characteristic abnormalities in gait, such as difficulty in picking their feet up off the ground when they ambulate (**magnetic gait**).

Chapter 3. Clinical Neurochemistry

Rapid advances in neuropharmacology are revitalizing the treatment of neurological and psychiatric disorders. This lecture will provide an overview of the neurotransmitter systems that are involved in regulation of mood, anxiety, psychosis, motor control, learning, and memory. A good working knowledge of clinical neurochemistry is essential for understanding and treating neurological and psychiatric disorders. It is important to learn the basics now so you can update your clinical management as new information becomes available.

When studying neurotransmitter systems, there are several issues on which to focus. This chapter will outline for each neurotransmitter system the location of primary cell bodies, sites of action, and mechanisms of termination. The most common receptor subtypes as well as drugs that act on those receptors will also be included.

Neurotransmitter Systems

There are several types of neurotransmitters released by a presynaptic cell at a synapse. Some neurotransmitters are in the monoamine family such as dopamine, norepinephrine, epinephrine, and serotonin (5-HT). Of the monoamines, three are classified as catecholamines (Figure 3-1): dopamine, norepinephrine, and epinephrine. These neurotransmitters often bind to post-synaptic receptors that trigger signal pathways including G-proteins and second messengers, and are considered "slow neurotransmitters." Other types of neurotransmitters include GABA, glutamate, and others, which bind to receptors, linked to ion-gated channels, which act very quickly and are considered "fast neurotransmitters."

Dopamine

Dopamine (DA) is a catecholamine neurotransmitter that functions in motor activity, as well as cognition. It has also been implicated as a primary neurotransmitter in *abuse/reward pathways*. Dopamine is able to function in all these capacities by acting on different types of receptors, which will be discussed below.

Main Cell Bodies

There are several tracts of the brain that use dopamine as the primary neurotransmitter.

Figure 3-1

- Long Tracts
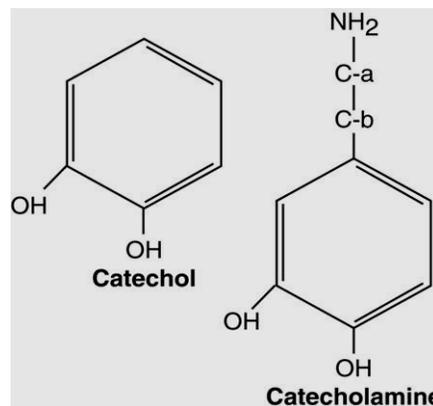
Section 1. Basic Principles

- o **Substantia nigra** → primarily *to caudate nucleus and putamen*; motor function pathway
  - o **Ventral tegmental area** → *Striatum, limbic system, frontal cortex*; forms the **mesolimbic** and **mesocortical pathways** which have been implicated in the pathology behind *thought disorders* such as schizophrenia
- Intermediate Tracts
  - o **Hypothalamic-pituitary axis**; endocrine activity
- Short Tracts
  - o Olfactory
  - o Retina
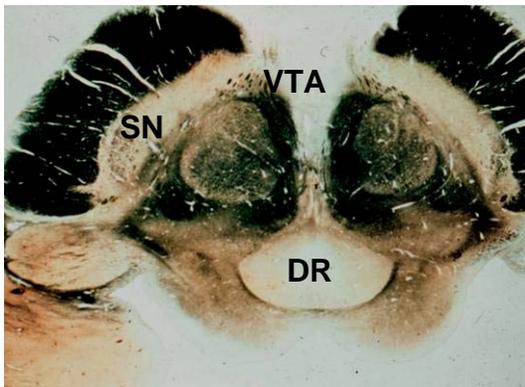
Figure 3-2. Weigert stain of the midbrain.

SN=substantia nigra,
VTA= ventral tegmental area
DR= dorsal raphe,

The main cell bodies for the dopamine pathways most important to behavior lie in the substantia nigra and the ventral tegmental area. By altering the synthesis or termination of dopamine at these sites, drugs can affect motor functioning (such as treatment for Parkinson's disease) or schizophrenia (by blocking dopamine receptors).

Synthesis And Degradation
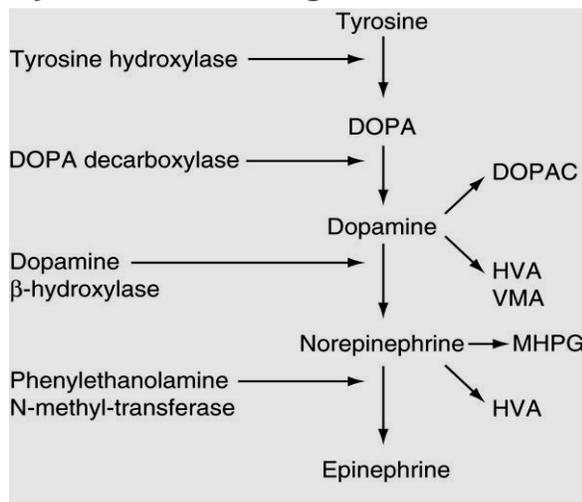
Figure 3-3. Dopamine is synthesized in a pathway that includes all the catecholamines (Figure 3-3).

In catecholamine synthesis, the action of **tyrosine hydroxylase** is the rate-limiting step.

After dopamine has been released into the synapse, its action is terminated by a combination of several mechanisms. The most important mechanism of termination is reuptake by the *presynaptic* cell. There are also enzymes that degrade dopamine in the synapse such as monoamine oxidase (MAO-B) and catechol-O-methyltransferase (COMT).

Receptor Subtypes

The main receptor subtypes for dopamine are designated D1, D2, D3, D4, and D5. These subtypes are all composed of similar structures, with 7 membrane-spanning regions. They all exert their effect through G-proteins and second-messenger pathways that cause protein phosphorylation/ion channel regulation. They differ, however, in whether they increase or decrease adenylate cyclase and the level of cyclic AMP.

> **D1**: most common subtype, increases adenylate cyclase and increases cAMP; found mainly in the striatum but also abundantly in cortical and limbic regions.

> **D2:** located primarily in the striatum; decreases adenylate cyclase

> **D3, D4, D5:** occur primarily in cortical and limbic regions.

Pharmacology

Too much dopamine can cause *euphoria, confusion and psychosis*. Too little dopamine can produce *Parkinsonism*. When using pharmaceuticals to alter dopamine levels to treat psychosis or Parkinsonism, negative side effects in other dopamine systems can occur.
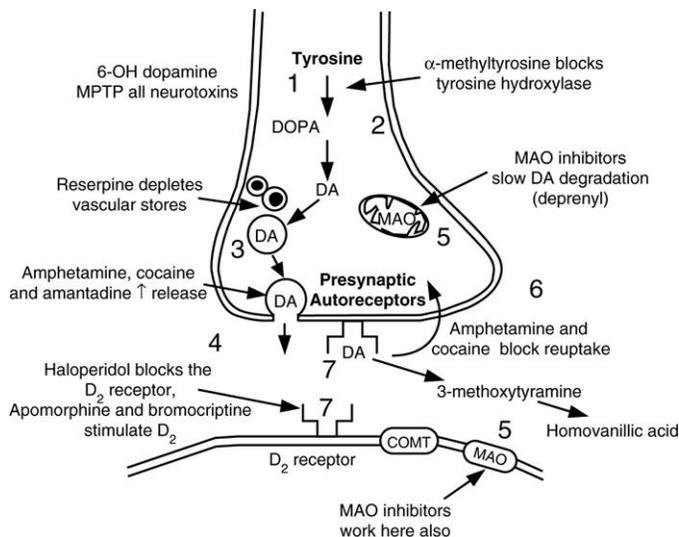
Figure 3-4. Model of synapse depicting synthesis of dopamine from tyrosine, release into synaptic cleft, and the effects of various drugs on levels of dopamine in synapse.

In the case of Parkinsonism, where dopamine cell death leads to motor symptoms, the goal is to increase the level of dopamine to that pathway. Because dopamine cannot

Section 1. Basic Principles

cross the blood-brain barrier, a precursor in the synthesis pathway is given (**L-DOPA**).
It is often combined with **carbidopa**, which inhibits dopa-decarboxylase in the
periphery.

Apomorphine, bromocriptine and **pergolide** are post-synaptic D2 agonists and are
helpful in Parkinson's disease.

Amantadine and **amphetamine** promote presynaptic release of dopamine.

MAO-B inhibitors increase the level of dopamine at a synapse by blocking the enzyme
that degrades dopamine. These include **deprenyl**, and at the usual dose of 5mg/BID are
specific and do not cause the "tyramine effect." At high doses, they become nonspecific
and can cause tyramine reactions.

Cocaine increases the level of dopamine at the synapse *by blocking reuptake of
dopamine*, which is an important transmitter in the neurobiology of abuse/reward
pathways. Part of the euphoria induced by cocaine is probably due *to enhanced
dopaminergic transmission*. Chronic cocaine use leads *to downregulation of the
dopaminergic system* and depressive symptoms.

Neuroleptics *(antipsychotics)* function to decrease the action of dopamine by blocking
dopamine receptors. Neuroleptics are classified as typical or atypical based on their
degree of blockade of the D2 receptor:

> Typical- **Haloperidol** is a potent D2 blocker; it is an effective antipsychotic, but
> can cause Parkinsonism, tardive dyskinesia (TD) and cognitive slowing.

> Atypical- **Clozapine** is a weak D1 and D2 blocker, but also blocks 5HT-2
> receptors. It may exert its antipsychotic effect by blocking D4 receptors, thereby
> sparing the striatum and reducing the frequency of motor side effects. Atypical
> drugs do not normally cause extrapyramidal symptoms or tardive dyskinesia.

Most typical neuroleptics increase *prolactin production* because they inhibit dopamine
in the hypothalamic-pituitary system. However, clozapine does not lead to elevated
production.

Norepinephrine

Norepinephrine (NE) is a catecholamine neurotransmitter that plays an important role in panic disorder, maintenance of attention and transmission of pleasurable stimuli via the brainstem reticular activating system and medial forebrain bundle.

Main Cell Bodies
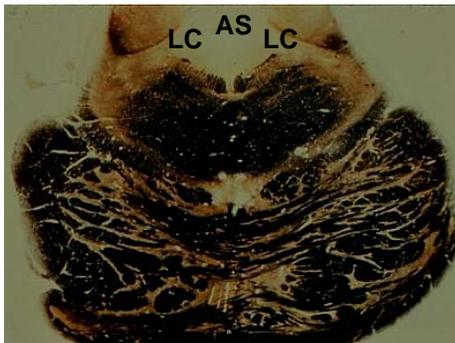
Figure 3-5. Weigert myelin stain of pons.
LC=locus ceruleus,
AS=aqueduct of Sylvius

Cell bodies for neurons using norepinephrine as a transmitter are primarily in pigmented neurons of the locus ceruleus at the upper posterior border of the pons and midbrain (Figure 3-6). They project widely to the limbic system, cortical regions and the cerebellum. The amygdala is richly innervated by noradrenergic neurons in the locus ceruleus. A lower pontine NE system projects downward to the spinal cord and may play a role in mediation of pain.
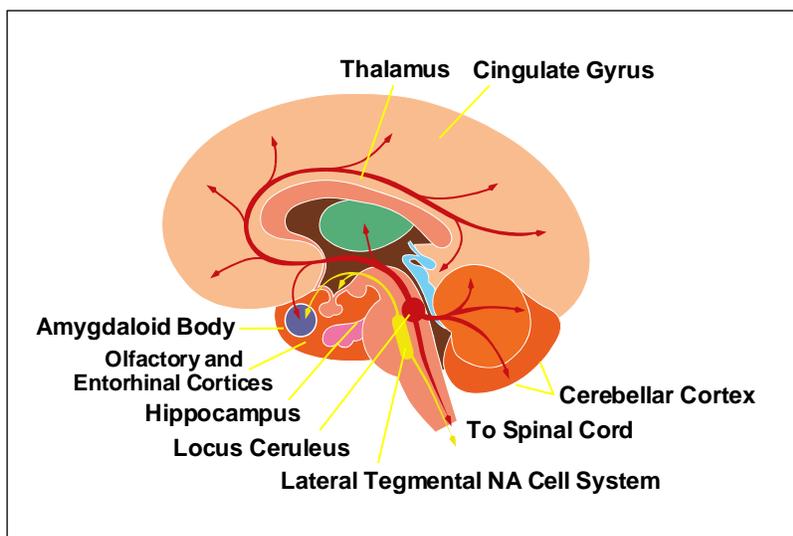
Figure 3-6

Synthesis And Degradation

Dopamine is converted to norepinephrine via **dopamine β-hydroxylase**. **Tyrosine hydroxylase** is the rate-limiting step (*see dopamine synthesis*).

The action of norepinephrine is terminated *primarily by reuptake*, but is also metabolized in the synapse by COMT to form VMA and by MAO to form MHPG.

Receptor Subtypes

Norepinephrine receptors can be post-synaptic (α_1 or β_1) or pre-synaptic (α_2 or β_2). These receptors all work by second-messenger systems (g-proteins).

Norepinephrine is also a main neurotransmitter of the autonomic nervous system. Agonists of α_1 receptors cause vasoconstriction. Agonists of $\beta 1$ receptors can increase heart rate. α_2 receptors are pre-synaptic and are inhibitory- when these receptors are activated less NE is released. Agonists of β_2 receptors activate bronchodilation. Although these receptors have different affinities for norepinephrine, no one type of receptors is activated/blocked exclusively.

Pharmacology

Tricyclic antidepressants such as **nortriptyline** or **desipramine** block NE and serotonin reuptake and can help in panic disorder and depression.

Phenoxybenzamine and **phentolamine** are α_1 blockers and are used in the treatment of hypertension.

Clonidine is an α_2 agonist also used occasionally to treat hypertension, because it causes a decrease in sympathetic tone. It is also useful in opiate withdrawal. **Yohimbine** is an α_2 antagonist and causes an increase in sympathetic tone, which may lead to increased arousal, panic, anxiety, and sexual potency.

Serotonin

Serotonin (**5-hydroxytryptamine**, or **5-HT**) is a monoamine involved in the regulation of mood and sleep. It is also one of the neurotransmitters involved in psychosis, and has been implicated in the regulation of pain and nausea.

Main Cell Bodies

The main cell bodies are in the dorsal raphe nuclei surrounding the cerebral aqueduct in the midbrain (Figure 3-7). They project diffusely to the striatum, limbic system, cortex and cerebellum. Caudal raphe nuclei in the pons and medulla project to the spinal cord and probably play a role in the mediation of pain in the dorsal horn of the spinal cord.
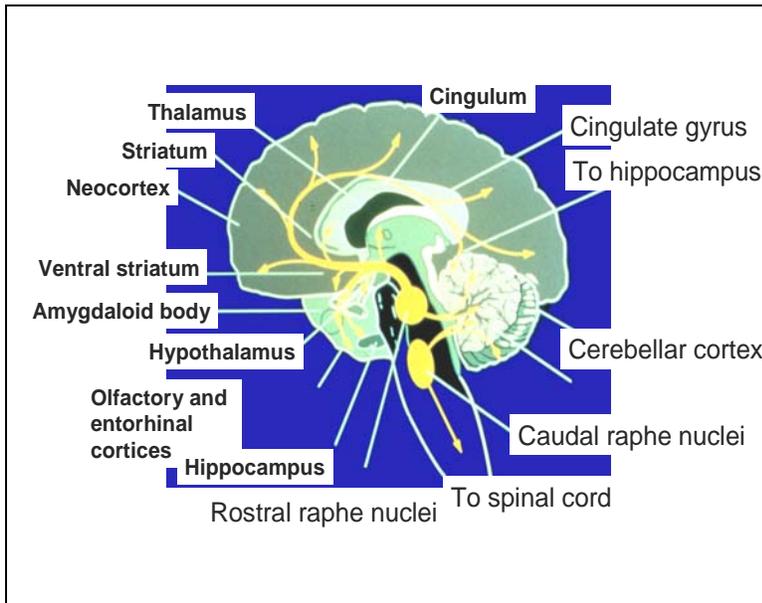
Figure 3-7

Synthesis And Degradation
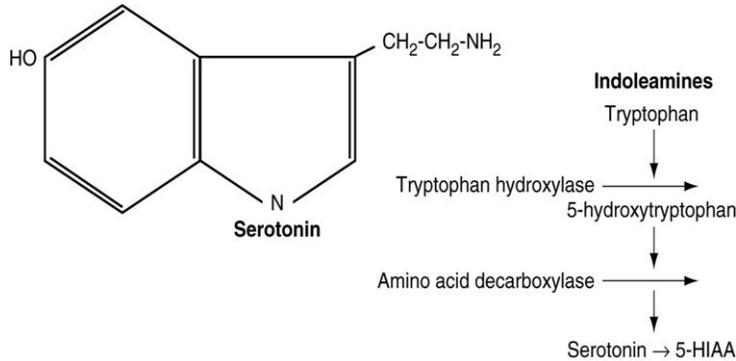
Figure 3-8. Serotonin is synthesized from tryptophan as shown by pathway on left. The availability of tryptophan is the rate-limiting step.

The primary mechanism for termination of serotonin is reuptake. It is also metabolized by MAO into 5-HIAA.

Receptor Subtypes

Determining serotonergic receptor subtypes is a very active area of research. 5-HT receptors 1-7 have been described, with subtypes of each of those. 5-HT_1 works primarily to increase or decrease levels of adenylate cyclase. 5-HT receptors affect phosphatidylinositol systems.

Pharmacology
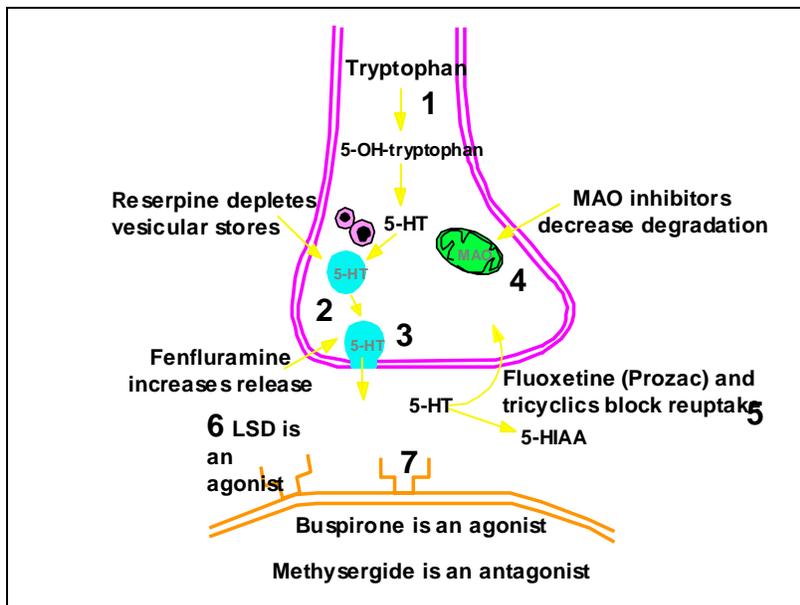
Figure 3-9.
   Reserpine depletes vesicular stores and may exacerbate depression.
   Fenfluramine promotes presynaptic release.
   5HT_{1d} agonist **sumatriptan** (Imitrex) is used to treat migraine.
   MAO-inhibitors slow metabolism.
   Serotonin reuptake inhibitors block reuptake and are used to treat depression, anxiety and OCD.
   Odansentron (Zofran) is a 5-HT_3 antagonist and potent antiemetic.

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Serotonin syndrome occurs when too much serotonin is released. It can lead to mental status changes: confusion, agitation, restlessness. It can also cause motor symptoms such as myoclonus, rigidity, and hyperreflexia. Patients often suffer from autonomic symptoms such as shivering, flushing, fever, and diaphoresis as well as gastrointestinal symptoms such as nausea and diarrhea.

Acetylcholine

Acetylcholine (ACh) is an important neurotransmitter in both the central and peripheral nervous systems- it is involved in memory and attention, the induction of REM sleep, the regulation of behavior, motor function, and the autonomic nervous system.

Main Cell Bodies

The primary cell bodies for ACh cells in the CNS are found in the patchy forebrain nuclei of the **nucleus basalis of Meynert** and **septal nuclei** (Figure 3-9). These cell bodies have rich connections to the hippocampus and amygdala. In addition, acetylcholine is the primary neurotransmitter at the neuromuscular junction and in the autonomic nervous system.

Figure 3-9

28
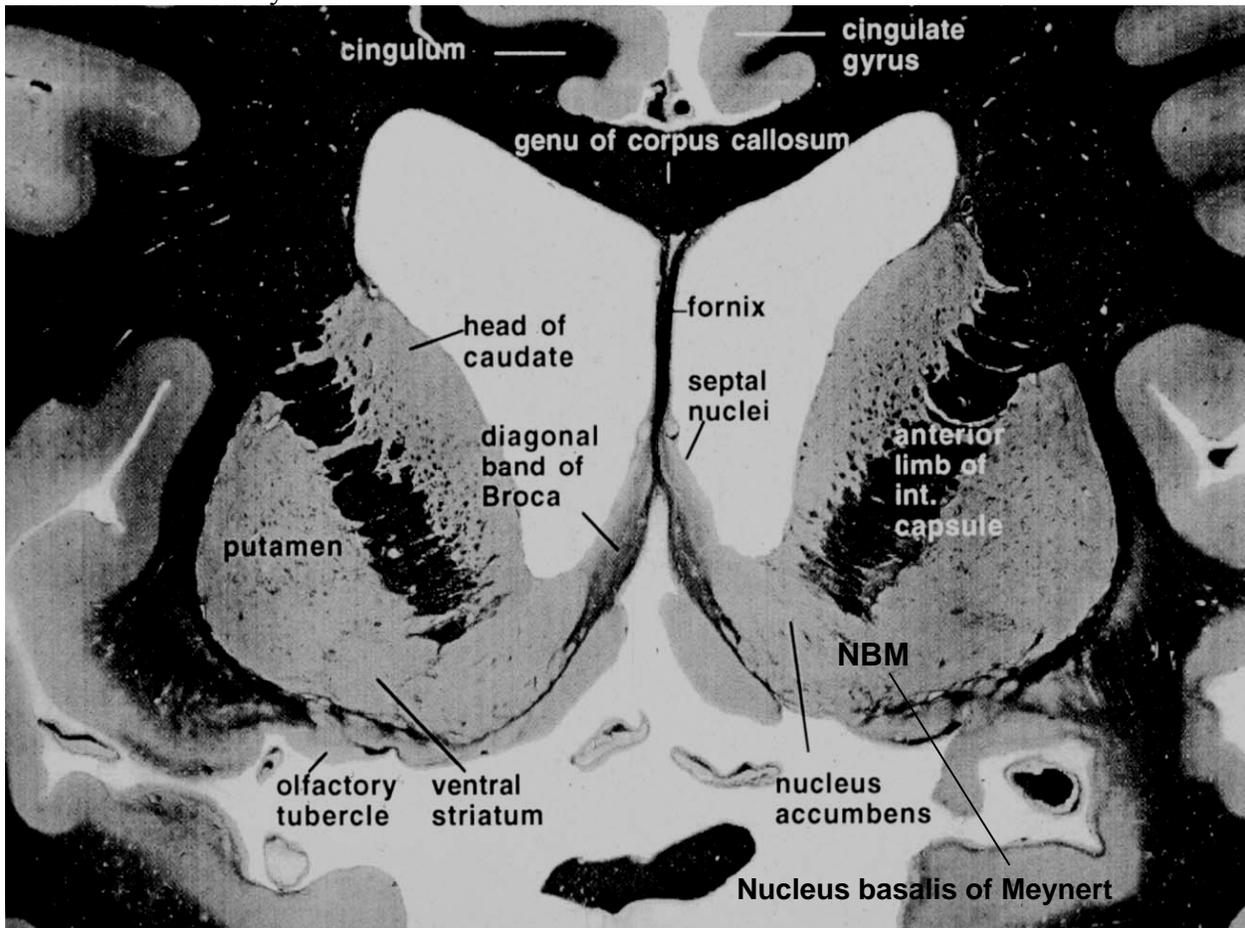
Synthesis And Degradation

Acetylcholine is formed from acetyl-coA + choline by choline acetyltransferase (CAT). *In Alzheimer's disease, CAT decreases.*

ACh is metabolized in the synapse by **acetylcholinesterases.**

Receptor Subtypes

There are two primary types of ACh receptors: **nicotinic** and **muscarinic**. Nicotinic receptors occur at the neuromuscular junction and the autonomic nervous system. (Antibodies formed against the NMJ nicotinic receptors cause *myasthenia gravis*.) Muscarinic receptors M_{1-5} occur in the brain, along with nicotinic receptors. M_2 and M_4 act by decreasing cAMP, and $M_{1,3,5}$ work via PI system.

Pharmacology
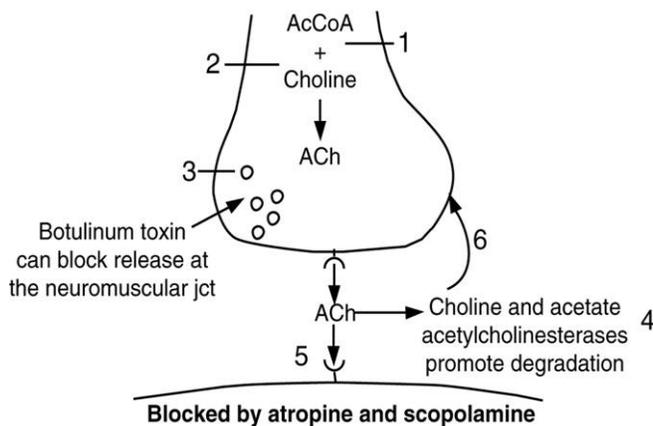
Figure 3-10
Botulinum toxin inhibits release of ACh and is useful for the treatment of focal dystonia. Lambert-Eaton syndrome, a paraneoplastic disorder, leads to decreased release of ACh.

ACh-esterase inhibitors such as **donezepil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl)** are approved for the treatment of mild-moderate Alzheimer's disease. Reminyl also modulates presynaptic nicotinic receptors. In addition to ACh-esterases, Exelon inhibits butyrylcholinesterase.

Pyridostigmine (Mestinon), a peripheral cholinesterase inhibitor, improves motor symptoms in myasthenia gravis.

Section 1. Basic Principles

Atropine and **scopolamine** block muscarinic receptors. Atropine increases heart rate, slows gastrointenstinal motility, and dilates the pupils. Scopolamine can cause memory disturbance. **Urecholine,** an autonomic agonist, promotes bladder emptying. **Ditropan**, an autonomic antagonist promotes retention of urine.

GABA

GABA is the major inhibitory neurotransmitter of the brain. Increasing GABA function can decrease anxiety, seizures, and muscle spasms. A decrease in GABA in the striatum is associated with Huntington's disease.

Main Cell Bodies

GABA neurons are ubiquitously distributed in the brain, with high concentrations in the striatum, hypothalamus, spinal cord, colliculi, and medial temporal lobe.

Synthesis And Degradation
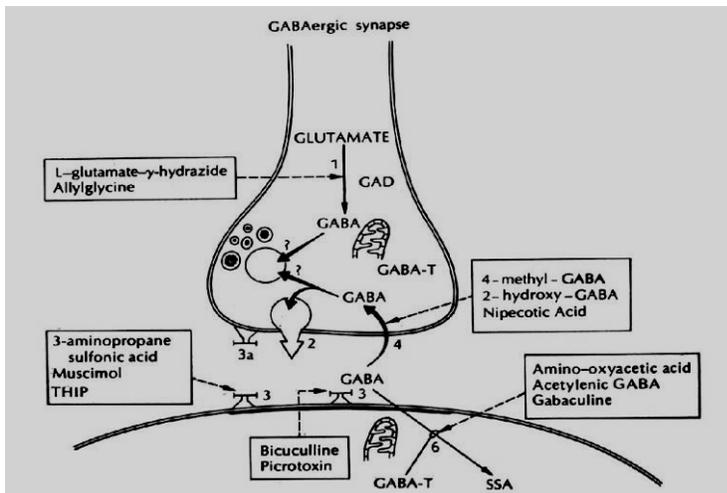
Figure 3-11.
GABA is synthesized from glutamate (an amino acid) by glutamic acid decarboxylase (GAD).

The main mechanism of termination is reuptake.

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Section 1. Basic Principles

Receptor Subtypes
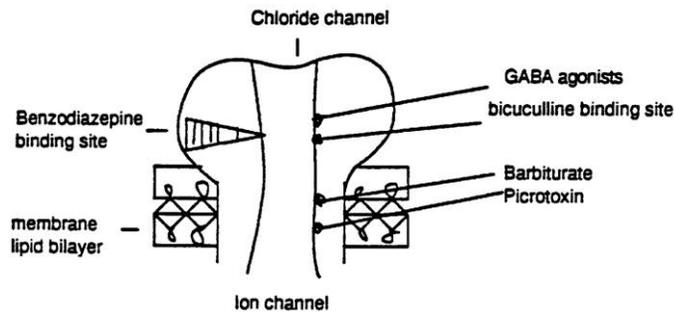
Figure 3-12.
GABA receptors are associated with ion-channels in the membrane lipid bilayer of cells. When GABA binds to the GABA-A receptor, a chloride channel opens, hyperpolarizing the cell.

Pharmacology

Benzodiazepines (BZD) (**diazepam, midazolam**, etc.) enhance GABA affinity and activity. **Flumazenil**, a benzodiazepine receptor antagonist, is used to counteract the sedative effects of benzodiazepines given for medical procedures and for overdose with BZDs.

Bicuculline is a receptor antagonist and induces seizures.

Barbiturates and alcohol help open the chloride channel at another site in the receptor.

Picrotoxin inhibits the chloride channel and produces seizures.

Anticonvulsants such as **topiramate (Topimax), divalproex (Depakote), gabapentin (Neurontin)** modulate GABA. **Vigabatrin** is a GABA transaminase inhibitor used in Europe to treat epilepsy.

Tiagabine (Gabatril) blocks the reuptake of GABA.

Glutamate

Glutamate is the most common excitatory neurotransmitter in the CNS. Glutamate neurons are dispersed widely. It is involved in excitotoxic injury, seizures, learning, memory, anxiety, depression, and psychosis.

Synthesis And Degradation

Glutamate is an amino acid, and the actions are terminated primarily by reuptake at the synapse, which is tightly regulated.

Receptor Subtypes
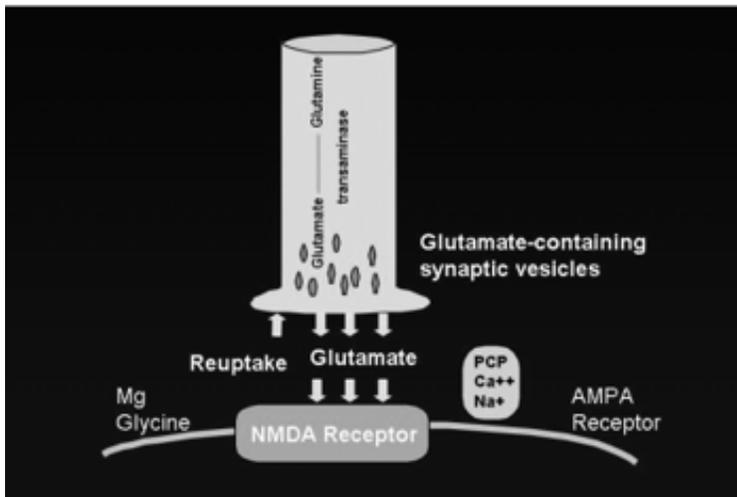
Figure 3-13.
At NMDA receptors, the binding of glutamate leads to opening of an ion channel and the influx of Ca and Na.
  The voltage dependent block of Mg is removed by activation of an AMPA receptor.
  Glycine must also bind to its receptor to allow Ca and Na influx.
  Some glutamate receptors are metabotropic and use second messengers.

Pharmacology

Blockade of glutamate receptors may have a protective role for tissue at risk in acute stroke and for TBI (traumatic brain injury).

MK801 and **PCP** are NMDA agonists and both can limit excitotoxic injury but can produce psychotic symptoms.

Riduzole for ALS and **lamotrigine** for epilepsy decrease glutaminergic transmission. **Memantine** is an NMDA antagonist and is approved for treatment of moderate to severe Alzheimer's disease.

Comments About People And Pills

One distinguishing characteristic that separates humans from lower animals is the desire and willingness to take medication. Despite this remarkable trait, taking medications for a neurological and especially a psychiatric disorder often carries with it significant meaning for the patient and family and exposure to potential stigma from members of one's community. Taking medication for a psychiatric problem is often viewed differently than taking medications for a medical illness and patients and families frequently have ambivalent feelings about taking these medications. Understanding the meaning and impact that taking a particular medication has for the patient is an important part of the art of medicine and can help improve patient compliance and quality of life. Some examples include:

Negative Stigma
- Fear of being labeled as "crazy"
- Taking the medication may be a sign of weakness of character or personality defect.
- Denial or lack of awareness
    - AD patient: "I don't need a pill for memory loss because I don't have any trouble with my memory." A patient with schizophrenia may think their delusions are real and cannot see how a pill would be helpful.

Fear Of Negative Side Effects
- Families may have erroneous ideas about the side effects of medication and unrealistic expectations about the benefits of natural treatments.
    - "My mother shouldn't take Aricept for AD, it is bad for her, phosphatidylserine is natural and much more effective."
- Medicines frequently have many more effects than the intended therapeutic benefit. Know the side effects as well as the intended effects of medication.
- Many psychotropic medications can cause weight gain, often 10-20 pounds and sometimes as much as 50-100 pounds.
- Some psychoactive medicines can cause weight loss. The daughter of a 72-year-old woman with Alzheimer's disease took her mother to the family doctor because of loss of appetite, a 12-pound weight loss, and loose stools. The doctor initiated an extensive GI work-up looking for an occult malignancy. The patient had started Aricept 4 weeks ago and the doctor was not aware that Aricept could cause early satiety and weight loss. The problem resolved when the Aricept dose was cut in half.

Medications May Have Practical Negative Consequences
- Taking an anticonvulsant could jeopardize one's ability to drive.

Compliance Is Never As Good As You Think
People rarely take medications as they are prescribed, usually missing doses, sometimes taking too many pills. The simpler the regimen, the better the compliance.

Overdoing It
- Some patients have multiple somatic complaints and visit many physicians seeking a variety of treatments, many of which may be unnecessary or harmful.

Cultural Differences
One culture may view the taking of medicine very differently from another.

Chapter 4. The Neurobiology Of Memory

Memory Systems

"…memory is, per se, a biological fact – by accident, a psychological fact… The disorders and maladies of this faculty, when classified and properly interpreted, are no longer to be regarded as a collection of amusing anecdotes of only passing interest. They will be found to be regulated by certain laws which constitute the very basis of memory, and from which its mechanism is easily laid bare."

<div align="right">Th. Ribot, 1882.</div>

A Taxonomy Of Memory

One of the most important developments in understanding the neurological basis of memory has been the recognition that memory is not a single, homogeneous entity, but rather is comprised of several relatively distinct yet mutually interacting systems that differ from one another in the type of information stored and/or in the processes acting upon that information.

One fundamental distinction has been made between long-term memory and short-term or working memory. **Working memory** is a limited-capacity (i.e. able to hold only about seven recognizable items) system that is capable of storing and manipulating information for short periods of time (i.e. about 20 to 30 seconds) without rehearsal. With rehearsal, information can be maintained in working memory indefinitely. In contrast, **long-term memory** appears to be virtually unlimited in capacity, and capable of storing the experiences, factual knowledge and skills over an entire lifetime.

Working memory can be subjectively viewed as the information one is immediately thinking about or working on, and more formally viewed as the currently active subset of long-term memory. Working memory consists primarily of a *central executive system* (or supervisory attentional system) that is aided by two subsidiary *slave buffer systems*: one (the *visuospatial scratchpad*) for holding visuospatial information and the other (*the phonological loop)* for holding speech-based information.

Further distinctions have been made between different long-term memory systems, each with its own special functions and organization. One memory system dichotomy that has generated considerable theoretical and empirical interest is the distinction between declarative and procedural memory. **Declarative memory** refers to knowledge of episodes and facts that can be consciously recalled and related (i.e., declared) by the rememberer. It has been characterized as *knowing that* and includes such things as memory for the words on a recently presented list and knowledge that a cat is an animal.

Procedural memory, in contrast, is described as *knowing how* and pertains to an unconscious form of remembering that is expressed only through the performance of the specific operations comprising a particular task. The use of procedural memory is indicated by the performance of newly acquired motor, perceptual, or cognitive skills.

Declarative memory can be further divided into episodic and semantic forms. **Episodic memory** refers to information that is remembered within a particular temporal and/or spatial context. For example, remembering what you had for breakfast this morning or when you last saw a physician would require retrieval from episodic memory. Most of the traditional verbal learning techniques used in cognitive psychology involve retrieval from episodic memory. For instance, when you read a list of words to a subject and then ask him or her to recall the words a minute later, the patient must retrieve a specific list of words presented in a specific temporal (1 minute previously) and spatial (same examining room) context. Recall of any list words encountered during his or her lifetime would not be appropriate or correct. (e.g., remembering a list of words presented 10 minutes ago).

Semantic memory, on the other hand, refers to one's fund of general knowledge that is not dependent upon contextual cues for its retrieval (e.g., knowing that a cat is an animal with four legs). For example, asking how many feet are in a yard, the name of the first president of the United States, or the capital of California would all involve retrieval from semantic memory. In each case, the specific information can be retrieved without recalling the particular episode in which that information was acquired. Semantic memory has been proposed to exist as a representation of knowledge based on an organized network of inter-related categories, concepts, and attributes.

The Neuropsychology Of Memory

Studies of memory in brain-damaged populations have generally validated this psychological model of memory, and have served to identify the neuroanatomical structures associated with different memory systems (Figure 4-1).
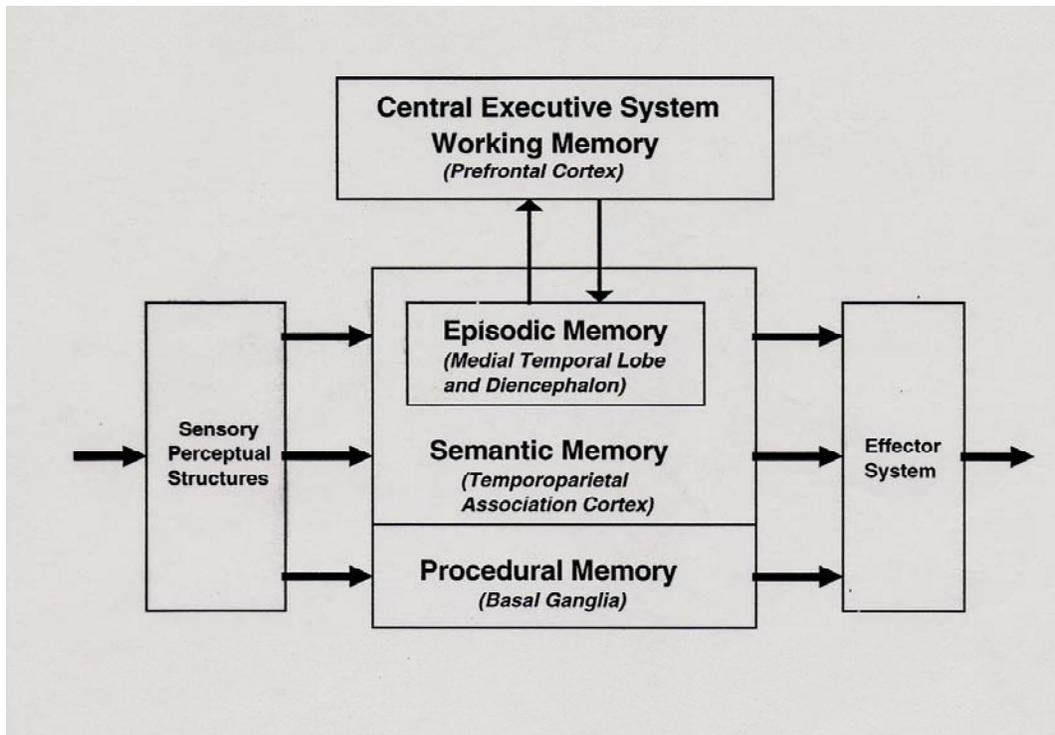
Figure 4-1. Medial Temporal Lobe System: Consolidation of Episodic Memories

Support for the distinction between declarative and procedural memory has primarily come from patients with circumscribed amnesia arising from damage to medial temporal lobe or midline diencephalic brain structures.

The most striking feature of amnesic patients' severe memory impairment is their **anterograde amnesia**, or their inability to acquire new verbal and nonverbal information. This profound memory impairment occurs despite a relative preservation of all other intellectual capacities. An amnesic patient:

"…gives the impression of a person in complete possession of his faculties; he reasons about everything perfectly well, draws deductions from given premises, makes witty

remarks, plays chess or a game of cards, in a word, comports himself as a mentally sound person. Only after a long conversation with the patient, [you] may note that at times he utterly confuses events and that he remembers absolutely nothing of what goes on around him; he does not remember whether he had his dinner, whether he was out of bed. On occasion the patient forgets what happened to him just an instant ago; you came in, conversed with him, and stepped out for one minute; then you come in again and the patient has absolutely no recollection that you had already been with him. [The patient] may read the same page over and over again sometimes for hours, because he is absolutely unable to remember what [he has] read. In conversation he may repeat the same thing 20 times, remaining wholly unaware that he is repeating the same thing."

Korsakoff, 1889.

Despite their severe anterograde memory deficits, however, amnesic patients demonstrate normal working memory and procedural memory (i.e., an intact ability to acquire and retain skills), along with a preservation of premorbid semantic memory (i.e., an intact general fund of knowledge).

In addition to their anterograde amnesia, amnesic patients also display a variable degree of **retrograde amnesia**, or impairment of memory for events that were acquired normally prior to the onset of amnesia. Regardless of the temporal extent (i.e., months, years, or decades) of their retrograde amnesia, however, most amnesic patients demonstrate a temporal gradient, with recent memories more impaired than remote memories. Although the reasons for the existence of a temporal gradient are not entirely clear, one possibility is that older memories, through repeated re-activation and rehearsal, become over-learned and consequently become increasingly a part of semantic memory. More recent memories, in contrast, will remain almost entirely as episodic memory. In this view, the temporally graded retrograde amnesia can be seen as an extension of amnesic patients' impaired episodic but intact semantic memory.

Taken together, studies with amnesic patients suggest that the acquisition and retention of episodic memories are critically dependent upon the medial temporal lobe (i.e., hippocampus, amygdala, entorhinal cortex, and parahippocampal cortex) and related diencephalic (i.e. the dorsomedial nucleus of thalamus and the mammillary bodies of the hypothalamus) regions damaged in these patients.

In this view, actual memory representations are established and maintained in the neocortex. The medial temporal lobe system, damaged in amnesics, directs consolidation of episodic memories within neocortex by gradually binding together the multiple, geographically separate cortical regions that together store memory for a whole event. This binding or integration is achieved through the reciprocal pathways connecting the hippocampus via the entorhinal cortex to the cortical modules.

Section 1. Basic Principles

Prefrontal Cortex: Central Executive System And Working Memory

A number of recent studies have indicated that damage to the prefrontal cortex in humans can produce impairments in memory that are distinguishable from the memory deficits that are classically observed following medial temporal lobe damage. While amnesic patients with medial temporal lobe damage are characterized by an inability to acquire and retain new information and experiences, patients with frontal lobe damage appear to be able to store new information in a normal fashion, but have difficulty manipulating both new and old memories in a strategic manner. Thus, frontal patients can perform normally on recognition memory tests for previously presented items, yet display significant impairments in their ability to: 1) make judgments about the temporal presentation of these items; 2) make metamemory judgments about their ability to successfully identify these items on a subsequent recognition test, and 3) identify the source from which these items were acquired.

Taken together, these studies suggest that the prefrontal cortex may be part of the central executive or working memory system that is responsible for the coordination of planning, elaborative and organizational processes which facilitate encoding and retrieval of information within the medial temporal lobe system (Figure 4-2).

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                        ┌─────────────┐
                        │ Hippocampal │
                        │ Region      │
                        └─────────────┘
                              ↕
                        ┌─────────────┐
                        │ Entorhinal  │
                        │ Cortex      │
                        └─────────────┘
                              ↕
┌─────────┐  ┌──────────────┐  ┌──────────────────────┐  ┌─────────────┐
│ Primary │↔ │ Higher-Order │↔ │ Perirhinal/          │↔ │ Prefrontal  │
│ Sensory │  │ Sensory Areas│  │ Parahippocampal Cortex│ │ Cortex      │
│ Areas   │  └──────────────┘  └──────────────────────┘  └─────────────┘
└─────────┘         ↘                                    ↙
                        ┌──────────────┐
                        │ Midline      │
                        │ Diencephalon │
                        └──────────────┘
```
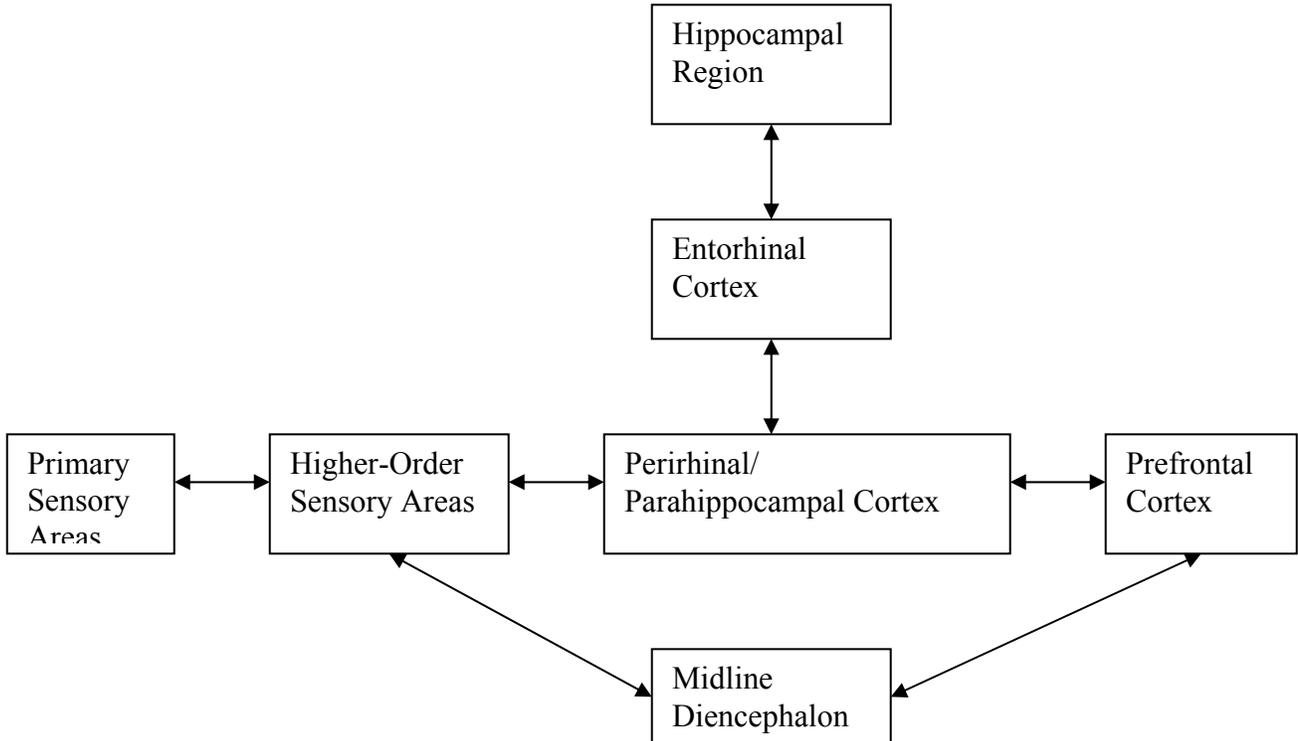
Figure 4-2. Schematic of the Profrontal Cortex and its relation to other memory structures.

Neocortical Association Areas And Semantic Memory

The observation that amnesic patients with severe episodic memory impairment often have normal semantic memory suggests that semantic memory is mediated by neurobiological systems that are distinct from the medial temporal lobe system mediating episodic memory. Indeed, recent functional imaging studies as well as studies of patients with focal brain lesions indicate that semantic knowledge may be stored in a distributed fashion in neocortical association areas, particularly in the lateral temporal lobes.

A number of studies have reported patients suffering from progressive degenerative brain disease who present primarily with semantic memory impairments. These "semantic dementia" patients typically display prominent loss of semantic memory knowledge while other aspects of language (e.g. syntax, phonology), episodic memory, and other cognitive functions are relatively preserved. The neuropathological changes seen in semantic dementia are focused in the temporal lobes, often affecting the left more than the right.

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In addition to generalized impairments of semantic memory, specific aspects of semantic memory (such as particular semantic categories) can also be selectively impaired. For example, patients have been observed who display selective impairments in knowledge about animate but not inanimate objects, while other patients have displayed the opposite pattern of impairment. One possible explanation for these striking dissociations is that semantic memory is not stored in discrete brain regions that are separate from the various sensorimotor modalities used in perception and action, but may in fact consist of distributed representations within the sensorimotor systems themselves. In this view, animate and inanimate objects may differ from one another in their reliance on knowledge from different sensorimotor modalities, with animate objects being known predominantly by their visual and other sensory attributes and inanimate objects being known predominantly by their function (i.e., abstract motoric representations). Thus, selective impairments in animate or inanimate objects may be attributable to selective damage of those brain regions mediating visual or motoric processes, respectively.

Basal Ganglia And Procedural Memory

The demonstration that amnesic patients can acquire and retain motor, perceptual and cognitive skills despite their severe episodic memory deficits provides strong evidence that procedural memory is not critically dependent upon the medial temporal lobe and midline diencephalic structures damaged in amnesia. Rather, a number of recent studies with patients with basal ganglia dysfunction (e.g. Huntington's disease and Parkinson's disease patients) have indicated that procedural memory is mediated, at least in part, by a corticostriatal system involving reciprocal connections between neocortex and basal ganglia, in particular, damage to the perceptuomotor skill learning and other tasks which involve the generation and refinement (i.e., learning) of motor programs to guide behavior. Moreover, Huntington's and Parkinson's disease patients have also recently been found to be severely impaired on a probability classification learning task analogous to habit learning tasks used in animal studies. Taken together, these findings indicate that the corticostriatal system is critically involved not only in the learning of motor skills and central motor programs, but can more generally be thought of as a procedural or habit learning system even when motor skill learning is not required.
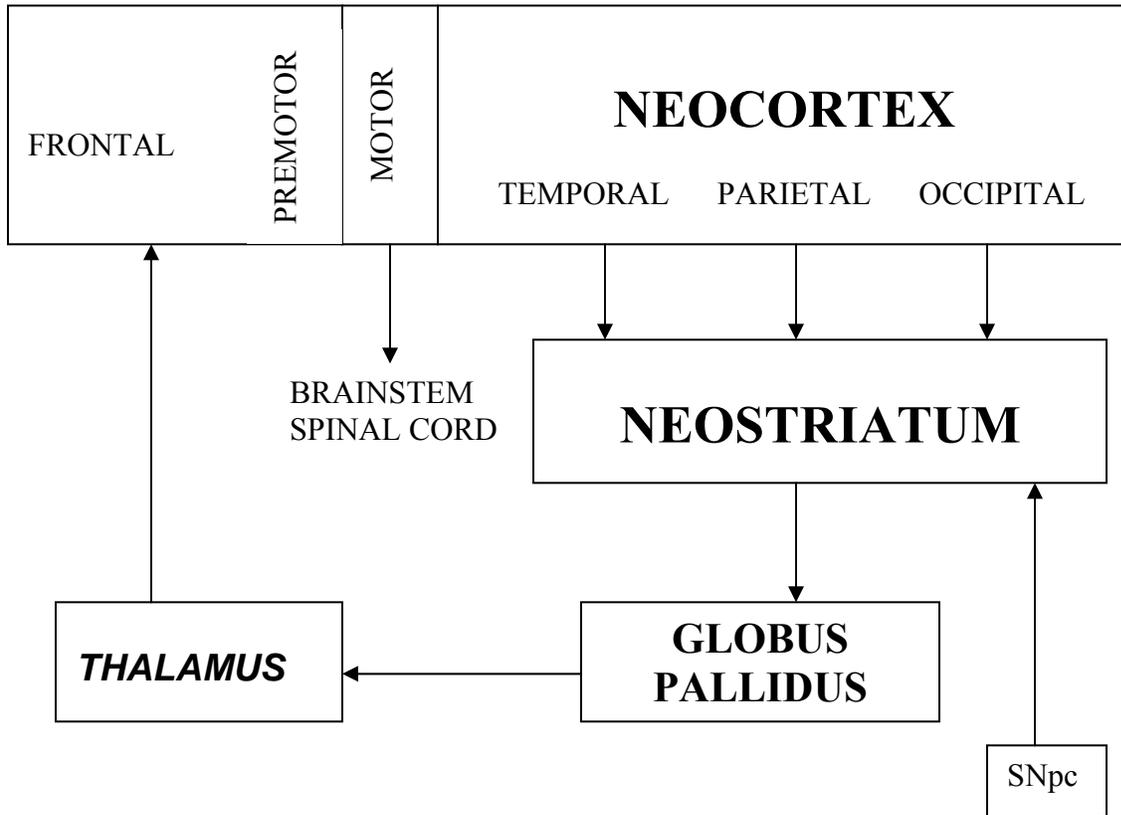
Figure 4-3. Schematic of basal ganglia and it relationship to the neocortex and other memory related structures.

Section 1. Basic Principles

Damage To Memory Systems

The Amnesic Syndrome

Medial temporal lobe (e.g. hippocampal) or midline diencephalic damage

Can have a varied etiology:
- Hypoxic ischemia
- Vascular accident
- Alcoholic Korsakoff's disease

Status Of Memory Systems: Behavioral Presentation:

Impaired episodic memory: severe anterograde amnesia
- Consolidation deficit
- Rapid forgetting
- Temporally-graded retrograde amnesia
- Intact semantic memory: intact fund of knowledge
- Intact procedural memory: intact skill learning

Frontal Lobe Amnesia

Status Of Memory Systems: Behavioral Presentation

Impaired central executive system: mild anterograde amnesia
- Impaired retrieval
- Impaired temporal order judgments – impaired source judgments
- Impaired metamemory judgments
- Intact semantic memory: intact fund of knowledge
- Intact procedural memory: intact skill learning

Alzheimer's Disease

Progressive dementia
Cortical atrophy and neuronal loss
- Medial temporal lobe structures
- Temporoparietal association cortices
Neurofibrillary tangles and neuritic plaques
Cholinergic and noradrenergic deficits

Status Of Memory Systems: Behavioral Presentation

Impaired episodic memory: severe anterograde amnesia
- Consolidation deficit
- Rapid forgetting

Temporally-graded retrograde amnesia
Impaired semantic memory: impaired fund of knowledge
Intact procedural memory: intact skill learning

Huntington's Disease

Involuntary choreiform movements
Progressive dementia
Atrophy of neostriatum

Status Of Memory Systems: Behavioral Presentation

Impaired central executive system: moderate anterograde amnesia
- Impaired retrieval
- Impaired temporal order judgments – impaired source judgments
- Impaired metamemory judgments

Moderate, flat retrograde amnesia

Intact semantic memory: intact fund of knowledge

Impaired procedural memory: impaired skill learning

(Note: Alzheimer's disease and Huntington's disease were covered in this chapter in relation to memory deficits; more comprehensive descriptions of these diseases can be found in the Cognitive Disorders chapter.)

Chapter 5. The Control Of Feeding Behavior

Long Term Regulation Of Feeding And Body Weight

While it is natural to think that body weight is under the control of feeding behavior, it is becoming increasingly clear that the causal relationship is actually the reverse. Feeding behavior over long periods is controlled by body weight. An organism's weight normally does not stray far from a certain value. For instance, Davidson, Passmore and Brock (*Human Nutrition and Dietetics*, 1972) point out that an average woman gains 24 pounds between the ages of 25 and 65. This corresponds to an excess daily energy intake of .025% of her total needs. Put another way, this represents an average excess energy intake equivalent to 350 mg of food per day over 40 years, a period during which she consumes 20 tons. If one considers the tremendous variety of eating patterns that occur over such a period, the long-term stability of weight is remarkable.

Experimental animals deprived of food (or force-fed) will eat (or starve) their way back to "normal" weight, if allowed *ad lib* access to food. Thus, body weight can be forcibly perturbed, but if the normal regulatory mechanisms are allowed to function, it tends to return to some "normal" value. *This regulatory process can be permanently altered by lesions of the hypothalamus.* A lesion of the ventromedial nucleus of the hypothalamus (VMH) results in hyperphagia and obesity in laboratory animals. A similar picture is sometimes seen in humans with hypothalamic or third ventricle tumors. This is often called the **ventromedial hypothalamic syndrome**. A lesion in the lateral hypothalamus will cause an animal to cease eating and drinking, often to the point that it dies of starvation and dehydration. This is called the **lateral hypothalamic syndrome**.

In contrast, if a rat is force-fed until it is very obese, and then given a bilateral lesion of the VMH and free access to food, instead of overeating it will avoid food until it attains a weight that is below its weight at the time of the lesion, but above its original normal weight. If a rat is food-deprived so that its body weight becomes quite low, and then given a lateral hypothalamic lesion and free access to food, instead of becoming **aphagic** it will eat steadily until it attains a body weight above that at the time of the lesion, but lower than normal.

These results led to the idea that the hypothalamic lesions disturb some kind of **set-point** at which an animal regulates body weight. This abstract set-point is the expression of neural mechanisms in the hypothalamus and the signals to which they are sensitive. When signals reflecting body weight are higher than the set-point, feeding behavior is inhibited. When they drop below the set-point, feeding behavior is initiated to "defend" the normal body weight. There is evidence that a variety of factors can affect the hypothetical set-point mechanisms, and it is not clear that there is just one signal upon which long-term regulation of body weight depends.

When weight is gained or lost, a major component of the change is in adipose tissue mass. Thus, it has long been assumed that some humoral element signals the size of the

body's fat mass and the brain regulates feeding to keep this signal constant. This is the so-called **lipostatic hypothesis** of feeding control. The search for such a substance has gone on for years and several candidate substances, such as glycerol, have been examined but set aside. **Insulin** has long been suspected of having a role in body weight regulation because its blood levels increase in proportion to body weight in certain kinds of diabetes. In recent years, evidence has developed that a protein called **leptin** is a circulating signal linking fat mass to the brain's control of energy balance. This protein is missing in certain genetically obese mice and was isolated in experiments designed to find the responsible gene, now known as the *ob* gene. Leptin itself is sometimes referred to as **OB protein**. Circulating leptin concentration in humans is proportional to body weight.

Leptin injection into the cerebral ventricles of normal and genetically obese mice causes a long-lasting decline in feeding and leads to a reduction in body weight. Circulating leptin in mice varies diurnally and is lowest during periods of active food consumption. Leptin receptors have been identified in the choroid plexus and hypothalamus. Its major hypothalamic target appears to be the **arcuate nucleus** where it has an inhibitory effect.

The effects of leptin are thought to be mediated, in part at least, through **neuropeptide Y**, a powerful stimulant of food intake when injected into the cerebral ventricles. Hypothalamic neuropeptide Y concentrations and messenger RNA increase in starvation and return to normal with injection of leptin. Leptin inhibits the feeding stimulation induced by neuropeptide Y. Receptors for neuropeptide Y (which occurs in a number of forms) are found in the hippocampus, cingulated cortex, amygdala, and in many hypothalamic regions including the lateral hypothalamic area that is known to be involved in feeding. **Melanocyte Stimulating Hormone (MSH)** and its receptor also appear to be part of the mechanism by which leptin has its **anorectic** effects.

Leptin has been studied in both humans and rodents carrying genes causing obesity. It appears that the normal function of this protein can be interrupted in at least three ways: (1) failure of the *ob* gene to produce a normal form of leptin; (2) failure of transport of leptin into the CNS; and (3) abnormalities in the receptor for leptin on neuronal cell membranes in the brain. It should be noted that leptin may have functions other than weight regulation because individuals with leptin abnormalities often experience developmental and reproductive abnormalities as well.

Recent research has unearthed another class of hypothalamic peptides that stimulate feeding when injected into the cerebral ventricles. **Orexin**, also called **hypocretin**, comes in at least two forms and activates cells in the arcuate nucleus of the hypothalamus that are inhibited by leptin. Of considerable interest is the fact that orexin may have a major role in the regulation of arousal and sleep and in the major sleep disorder narcolepsy. Some narcoleptic animals appear to have a defective brain receptor for orexin. Many humans with narcolepsy have been found to have no or abnormally low circulating levels of orexin associated with an increased level of the major

histocompatibility complex class II antigens in microglia, suggesting that their narcolepsy may be an autoimmune disorder.

Other substances have been found to have large effects on feeding behavior when injected into the brain. One of these is **cholecystokinin (CCK)**. This peptide is normally present in the brain in addition to being secreted in the gut, where it regulates emptying of the gall bladder. Tiny amounts injected into the brain will inhibit feeding. In addition, genetically obese mice have lower levels of CCK in their brains than do non-obese littermates and normals. Their sensitivity to CCK is normal.

How all of this ties together in the control of body weight (and sleeping/waking) is the subject of intense research. In the set-point model of Figure 1, body weight, as signaled through levels of various peptides (such as leptin, orexin, insulin, etc.) is compared with some "set point" for the levels of these substances, and feeding behavior is regulated to sustain them at normal levels. Deviations result in the appropriate corrective behavior, either feeding or fasting. The conceptual "set point" is a complex interaction of the sensitivities of hypothalamic cells that trigger feeding (or represent hunger and satiety) with the effects of the various substances on these same cells.

Short Term Regulation Of Feeding: Control Of Meal Size And Frequency

Acute changes in the blood levels of various nutrient substances can initiate or inhibit feeding. These include certain amino acids, glycerol, and glucose. The one most thoroughly investigated is glucose. The brain needs glucose for its normal function, so one might expect blood glucose to be maintained within narrow limits by ingestion, as well as by glycogenolysis. It has long been established that infusion of intravenous glucose inhibits feeding, while infusion of insulin initiates feeding. Infusion of glucagons, which elevates blood glucose, inhibits feeding. Infusion of 2-DG, a non-metabolized glucose analog, interferes with the access of glucose to cells and increases feeding in the face of normal blood glucose levels. Injection of gold thioglucose destroys the VMH and causes hyperphagia and obesity, suggesting the presence of glucose receptors in the hypothalamus that sense blood glucose levels and initiate or terminate feeding. Such findings led to the hypothesis that the brain uses feeding behavior to control its supply of glucose within normal limits. This is the so-called **glucostatic hypothesis**.

This theory faces the difficulty that changes in blood glucose have to be rather heroic to evoke or inhibit feeding; the behaviors are sensitive to glucose levels, but not that sensitive. Careful studies of monkeys eating a variety of diets show that minute-to-minute control of feeding is relatively independent of blood glucose levels. The available data indicate that a glucostatic mechanism is certainly present, that it is critical

in certain situations, but that normally it probably does not play a central role in the regulation of feeding.

In addition to changes in blood levels of various substances, other changes occurring as a direct result of the ingestion of food exert short-term control on meal size. Some of these have been shown to have a significant effect on when the animal will cease to eat. Taste and smell are obviously important in the initiation of feeding. More will be said about them below. The introduction of food into the mouth causes blood glucose to rise, even before any of the nutrients can be absorbed. It is not known if this rise has a control function, but it could serve as a kind of anticipatory negative feedback through the glucostatic mechanisms discussed above. Feeding can be inhibited by using a balloon to acutely dilate the esophagus, stomach or bowel. Factors, such as CCK, secreted by the gut in response to ingestion may also act via the sensory fibers in the vagus nerve to regulate meal size by inducing satiation.

The control of meal size involves a large number of possible factors operating over a time span on the order of minutes. Leptin is not thought to have this kind of role in feeding behavior, but rather participates in a regulatory process that integrates over weeks or months.

Recent studies lend support to the idea that under normal circumstances, taste and smell are important factors in the regulation of ingestive behavior and that these sensations are themselves manipulated after a fashion. An early suggestion of this came from studies of animals with hypothalamic lesions. It was found that these animals are extraordinarily fussy about the palatability of the food presented to them. The aphagic animal with a lateral hypothalamic lesion can be made to eat if the food is very tasty. Similarly the VMH lesioned animal is also very picky about the food it will eat to become obese. Such studies led to the idea that the lesions were having a large effect on the capacity of various foods to reinforce eating behavior (positively or negatively).

That such a mechanism might actually be operating is suggested by the effects of intracranial electrical stimulation. If a rat is allowed to stimulate certain areas in and around the hypothalamus, it will do so continuously until it drops of hunger, dehydration or exhaustion. A male rat will do this in the presence of a receptive female and will cross an electrified grid to reach the lever controlling the stimulation. In contrast, there are other sites that the animal will only stimulate once and then never again. These observations have given rise to the idea that there are "pure" reinforcement systems in the brain, systems which when activated will increase (or decrease) the probability of recurrence of whatever behavior led to their activation. Presumably, behaviors that are good for the organism activate the positive reinforcement mechanism, and those that are harmful activate the negative mechanism. Addictive behaviors may be traceable to the effects of addictive substances on these systems.

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Recent work indicates that behaviors classified as "foraging" (seeking, wanting) may be different from those classified as "consummatory" (liking). This makes sense because an animal has to forage in the absence of food reinforcement, so the foraging itself must be "its own reward," so to speak. The "wanting" system appears to do this. The dopaminergic projection from the ventral tegmental area to the nucleus accumbens appears to be essential to "wanting" but not to "liking." Thus, lesions here will decrease the probability that an animal will seek out food, but will not decrease the amount of food eaten when it is made available. The role of such systems in addiction is under intense study.

The basic idea of a control system based on hedonic mechanisms reveals what Walter B. Cannon called the "wisdom of the body." Pleasure and pain, or better, comfort and discomfort, are experiences that can be decoupled from the physiological regulatory mechanisms that maintain such vital parameters as blood pressure, body temperature, fluid balance and energy stores. By allowing hedonic factors to regulate behaviors related to these vital parameters, the parameters themselves never drift into the danger zone that requires emergency action. Consider how we keep our body temperatures within normal limits by anticipating and thwarting a cold threat. When we feel chilly, we use clothing, shelter, and fire to ensure that we do not have to shiver, vasoconstrict, and piloerect.

The same strategy appears to operate in one of the mechanisms regulating meal size. When appropriate food is available, its taste and smell "reward" feeding behavior and sustain consumption up to a point. After some quantity of the food has been consumed, the brain appears to modify the reinforcing properties of taste and smell, presumably by switching these sensory inputs into circuits that "punish" the feeding behavior. This mechanism will clearly regulate meal size without there ever being a threat to, say, blood sugar levels or the capacity of the gastrointestinal tract to contain and process the food. It will ensure that eating stops before the animal compromises its digestive system or is so full that it cannot flee predators.
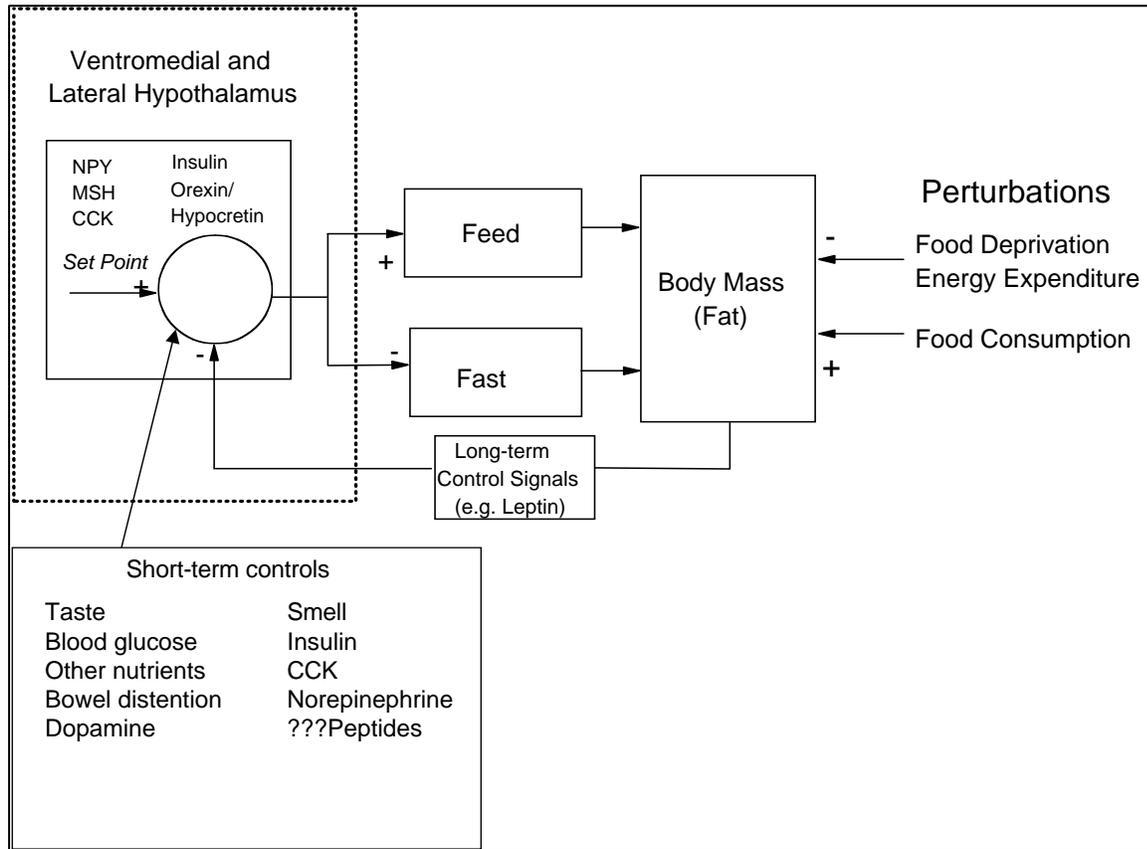
FIGURE 5-1: Schematic diagram of feedback system for the control of feeding behavior. The effects of a variety of substances acting on hypothalamic neurons, including insulin, leptin, MSH, CCK, Neuropeptide Y, and the orexins, may be thought of as regulating a "set point" for body weight. Changes in the levels of these substances or in their receptors can cause increases or decreases in body weight.

Chapter 6. Principles Of Pharmacology.

A Pharmacological View Of The Brain.

The main interest is centered upon the **nerve terminal** and the **synaptic cleft.** If you can find a pharmacological means of altering the function of the transmitter in this region, you may have a therapeutic agent that can be used to treat a brain disorder.   So the first question becomes*: In what direction do you would want to alter transmitter functioning* (e.g., increase, decrease?). The second question is: *How can you achieve this goal* (i.e., what tools are available?--and by tools, we are usually thinking of **drugs**).

Some General Points To Consider When Using Psychopharmacological Drugs

Does the drug get into the central nervous system (CNS)? In general, because of the blood-brain barrier, to get into the brain a drug would have to either be **lipophilic**, or be a user of a **transport system**.

       Many drugs of abuse are lipophilic (e.g., stimulant drugs such as amphetamine, opiate drugs such as heroin, hallucinogenic drugs such as LSD and cannabinoids).

       Some CNS-acting drugs can make use of transporters. L-DOPA, for example, used in the treatment of Parkinson's disease, is an amino acid, and can use an amino acid transport system to get into the brain

With Which Neurotransmitter System Do You Want To Interact?

The total number of transmitter systems in the brain is quite large, with additional transmitters discovered every year. Right now, we can say that there are probably over 50 different transmitters used in the brain. Some of these transmitters are familiar from study of the peripheral nervous system (acetylcholine, norepinephrine).

       The brain transmitters can be divided into *3 main categories*: **biogenic amines**, **amino acids** and **peptides**. The *biogenic amines* (or classical neurotransmitters), include the neurotransmitters **acetylcholine, dopamine, norepinephrine, epinephrine, serotonin and histamine**. The *amino acids* include **glutamic acid (glutamate), aspartic acid (aspartate), GABA (gamma-aminobutyric acid) and glycine**. The *peptide neurotransmitters* include **endogenous opiate peptides**, often referred to as **opioids** (**enkephalins** and **endorphins**) and **substance P**. The peptides have the largest number of members, since there can be so much diversity in peptide structure, however, *the category that is probably used the most in the brain is the amino acid category*. It has been estimated that at least half of all of our synaptic connections make use of an amino acid transmitter, particularly glutamate and GABA, which have been called the workhorses of the brain

For many transmitters, the effect on target tissue can be either *excitatory* or *inhibitory*. For amino acids, we can generalize: *glutamate and aspartate are usually excitatory, whereas GABA and glycine are usually inhibitory*. This stems from their general effects on ion permeability. The excitatory amino acid transmitters increase sodium permeability. This drives the neuron towards the threshold potential (about -40 mv), at which point an action potential is generated. The inhibitory amino acid transmitters increase chloride permeability. This either hyperpolarizes the neuron, or at least tends to keep it at the resting potential, making it harder to generate an action potential.

How Specific Is The Drug Action?

Drug side effects can come about in one of two general ways: *through action at the site you are aiming for*, or *through an action at a site different from the one you are aiming for*. The former problem may simply mean you are achieving your goal too well—for examine, if you are trying to achieve some receptor blockade, perhaps you are producing too much. This might be corrected simply by lowering the drug dosage. When side effects are the result of an unintended action, this implies that the drug is blocking another receptor in addition to the one you are aiming. Such drugs are considered to be less specific (i.e., for their intended action). Side effects may be even more indirect: perhaps the drug (or one of its metabolites) is causing damage to an organ, such as the liver.

Overview Of Drug Action In The Brain

In using psychopharmacological agents, we want to be able to manipulate transmitter systems. It can be useful to think of the 5 stages of the life cycle of all transmitters as providing possible targets: synthesis, storage**, release, receptor interaction, transmitter inactivation.**

Synthesis. For biogenic amines and amino acid transmitters, most of the synthesis occurs in the nerve terminal. The synthetic enzymes are made in the cell body and transported to the terminal. We can target transmitter synthetic enzymes to either inhibit or activate synthesis (example: the use of L-DOPA to increase dopamine formation in the brains of Parkinson's patients). However, this strategy can be a problem if you are dealing with a neurodegenerative disorder where the neurons are being destroyed

Storage. Most transmitters are taken up and stored in **synaptic vesicles** after they are synthesized. Some drugs can interfere with storage. For example, amphetamine can displace catecholamines and serotonin from their synaptic vesicles. The buildup of transmitter in the cytoplasm of the nerve terminal can aid in producing an egress of the transmitter into the synaptic cleft. In the periphery, this will cause an

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increased norepinephrine concentration in the synaptic cleft, which will mimic the effect of sympathetic nerve stimulation.

Release. Many nerve terminals possess receptors that can inhibit release of their transmitter. Sometimes these inhibitor receptors are activated by the same transmitter that they release. This would be called **autoinhibition** and the receptors would be designated as **autoreceptors**. This would be a form of **feedback inhibition**. Receptors can exist on the pre-synaptic terminals for transmitters other than the ones released from that terminal. For instance, if a terminal has receptors on it for opiates, occupation of the opiate receptor will produce an inhibition of transmitter release via inhibition of calcium entry. This is known as **pre-synaptic inhibition**

Receptor interaction. This is a major site for CNS drug action. We can use drugs to activate the receptors (**agonists**) or inhibit the receptors (**antagonists**). An example of an agonist is bromocriptine, which activates dopamine receptors in Parkinson's patients. An example of an antagonist is haloperidol, which blocks dopamine receptors in schizophrenic patients.

Transmitter inactivation. This is another important site of action of CNS drugs. The two main routes of inactivation *are reuptake back into the nerve terminal* (seen for catecholamines, serotonin, glutamate and GABA), and *enzymatic metabolism* (seen for seen for acetylcholine and peptide transmitters). An example of a reuptake inhibitor is fluoxetine (Prozac) which blocks the reuptake of serotonin, and thus potentiates the action of the transmitter in the synaptic cleft. An example of a drug that works on enzymatic metabolism is donepezil (Aricept), which is an acetylcholinesterase inhibitor, used in the treatment of Alzheimer's disease.

Summary point to keep in mind when studying: Many of the drugs used for their CNS action can be understood better with regard to mechanism of action and side effects, when considered with regard to their effects on the life cycle of the neurotransmitters in the brain.

Chapter 7. Principles Of Neuroimaging.

Computed Tomography (CT) Scanning provides important diagnostic information about the brain or spinal cord. With CT, x-rays are passed through the head from many different angles, and the attenuation at each point is determined by computer. High-density materials (such as bone and calcium) stop the x-rays from passing through to the detector. Structures that block x-ray transmission appear white on CT images, while structures that readily permit the passage of x-rays appear dark. The results are displayed as cross-sectional layers through the brain, usually at an angle perpendicular to the axis of the body and spaced at 0.5- to 1.0-cm intervals. CT scans are useful for diagnosing a wide variety of conditions, including subarachnoid and intracerebral hemorrhage, stroke, hydrocephalus, and brain atrophy, as well as abnormalities of the skull. Often the scan is performed after intravenous infusion of an iodinated contrast agent. In regions where the blood-brain barrier is disrupted, the contrast agent enters the brain and causes increased x-ray attenuation. Thus, contrast agent infusion increases the sensitivity of CT for detection of tumors and inflammatory conditions.

Magnetic Resonance (MR) Imaging employs a strong magnetic field and radiofrequency (RF) waves. The magnetic field orients the spin of protons (hydrogen nuclei) parallel to the magnetic field. MR scanners with strong magnets (1.5 Tesla and above) can generate higher resolution images. A brief RF current disturbs the orientation of the protons, but after the RF current stops, the protons reorient to the magnetic field and emit radio signals that can be detected. Different tissues (for instance white and gray matter) emit different radio signals because the physical behavior of protons varies in different tissue types. The result is an image of the anatomy of the structures under study. MR imaging portrays greater detail in the brain than CT and is superior for the diagnosis of certain conditions, including multiple sclerosis. It has the advantage of being free of exposure to hazardous radiation, but is more expensive and less readily available than CT is.

Typical CT and MR procedures generate *static* images that provide information only on the physical structure of the brain. Functional neuroimaging, on the other hand, is capable of assessing changes in neuronal activity or blood flow. While these techniques can track changes over the course of time, spatial resolution is usually relatively poor. **Single photon emission computed tomography (SPECT)** is a functional neuroimaging technique that can measure cerebral blood flow. This is useful because diseased or damaged brain regions (in Alzheimer's Disease, for instance) may exhibit abnormally low perfusion. Another technique used for imaging of brain function is **positron emission tomography (PET)**, which can measure cerebral blood flow, metabolism, and neuroreceptors. Both PET and SPECT require that patients receive infusions of radioactive isotopes that emit signals by undergoing decay within the brain.

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Clinical Brain Imaging

Objectives:
- Learn about the use of CT, MRI and SPECT scanning in clinical practice
- Recognize key anatomical landmarks and begin to recognize and describe the appearance of common disorders
- *Please look at the scans on your patients.*

	CT	MRI
Obtained	X-ray beam	Magnetic field
Bone	Bright	Dark
Cost	$330	$900
Plane	Axial	3-D
Technique	Adjust window	T1, T2, Pd
Length	10-20 minutes	30-60 minutes
Opening	Wide doughnut	Long, narrow

Advantages to CT
- Costs less than MRI
- Better access
- Shows up acute bleed
- A good quick screen
- Good visualization of bony structures and calcified lesions

Disadvantages to CT
- Resolution
- Beam-hardening artifact
- Limited views of the posterior fossa and poor visualization of white-matter disease
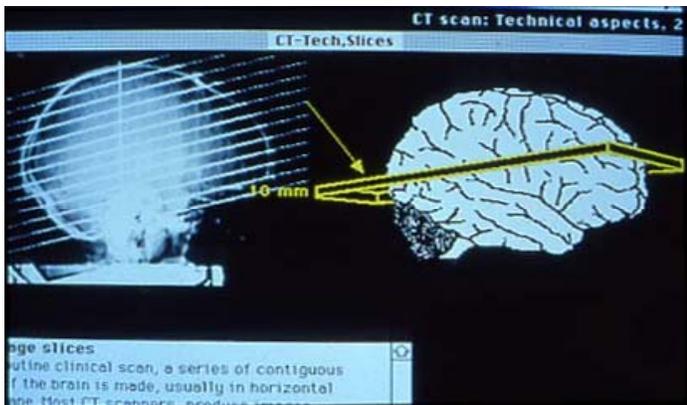
Figure 7-2: CT images

Figure 7-1: CT slices

Advantages To Mri

- Good resolution—excellent view of brain structure
- 3 dimensions
- Good gray-white differentiation
- Adjust settings based on characteristics of the lesion
- Good view of the posterior fossa
- No radiation exposure
- Gadolinium contrast is relatively nontoxic
- Capacity for quantitative imaging, 3-D reconstruction, angiography, spectroscopy

Disadvantages To Mri

- Cost
- Some patients ineligible because of pacemakers, other metal
- Claustrophobia
- Long exam
- Access
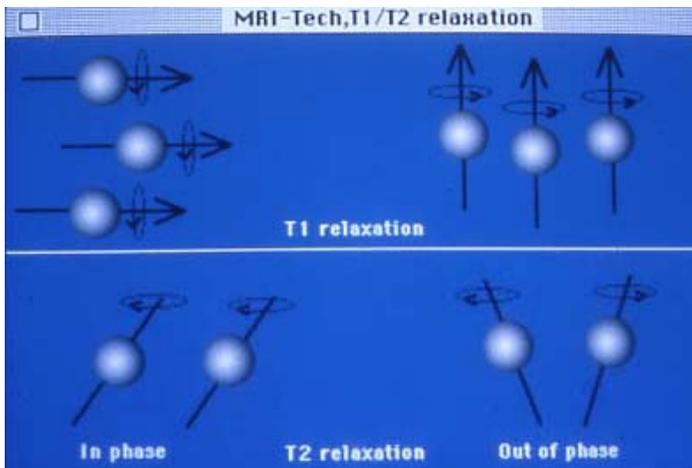
Figure 7-3: MRI - T1/T2 relaxation
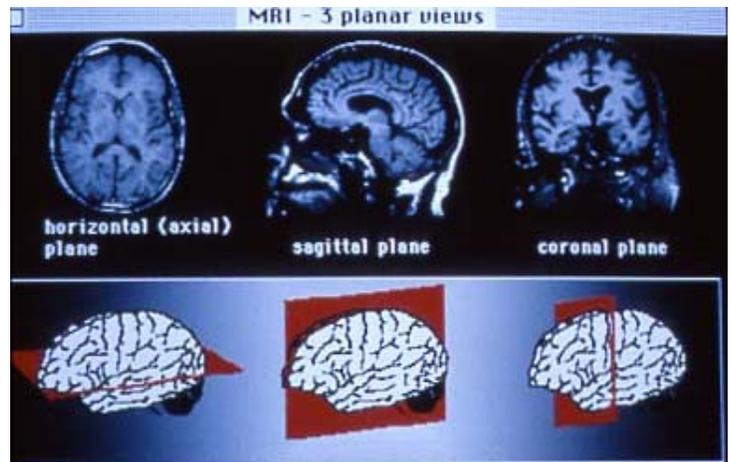
Figure 7-4: MRI - 3 planar views

MRI is the test of choice in evaluating:
- Most lesions causing epilepsy— temporal lobe glioma, mesial temporal sclerosis
- White-matter disease—subcortical dementia, HIV, MS
- Lesions in the posterior fossa
- TBI—axonal injury
- Extent of anoxic injury, herpes encephalitis
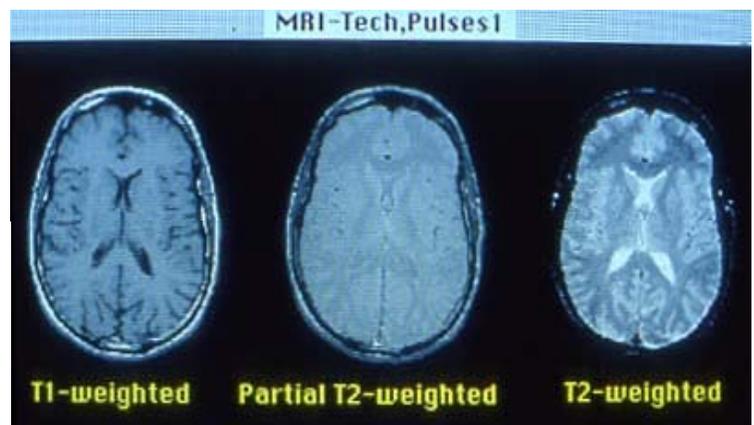
Figure 7-5: MRI – different weightings

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- Frontal atrophy, NPH
- *Other—brain anomalies, SLE, vasculitis, sagittal sinus thrombosis, pituitary lesions, AVM*
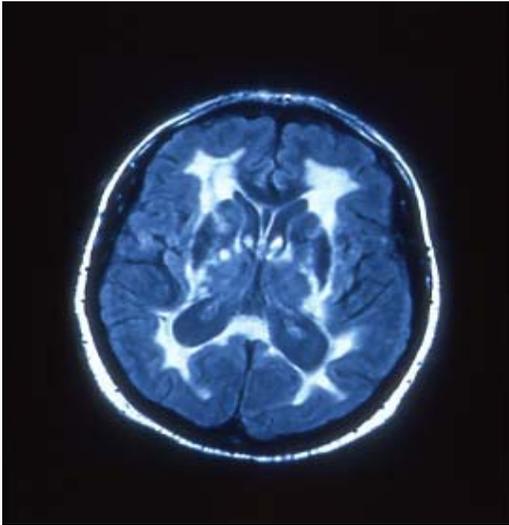
Figure 7-6: FLAIR image
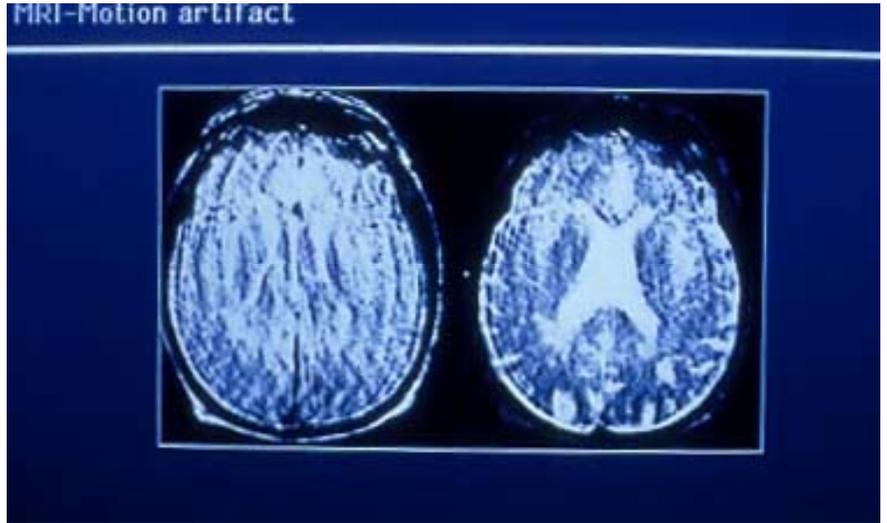
Figure 7-7: Motion artifact on MRI

What is bright on CT?
- Blood, Contrast, Bone, Calcium, Metal

What is dark on CT?
- Air, CSF/H20

Artifacts on CT?
- Beam hardening, Bone, Foreign body, Motion

Figure 7-9: foreign body/metallic artifact
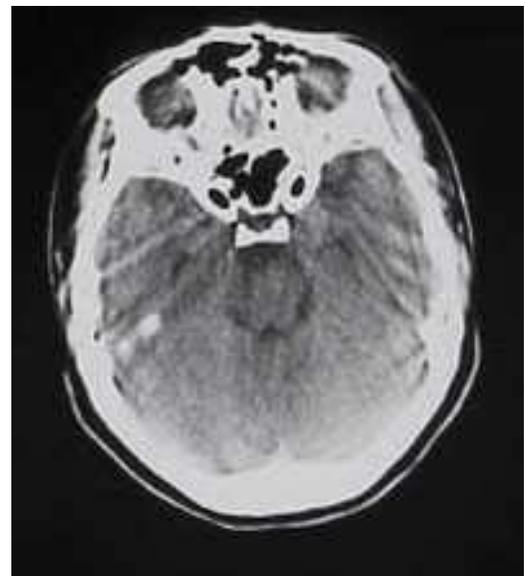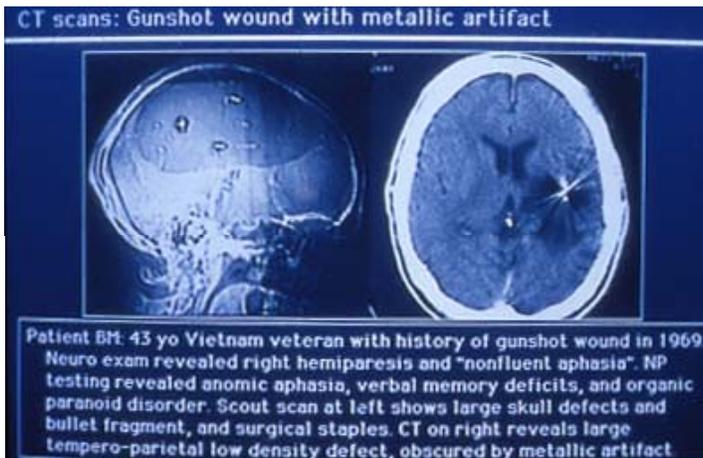
Figure 7-8: beam hardening artifact

Uses for SPECT and PET
- Acute stroke
- Identify a seizure focus-increased flow during sz and decreased interictal flow
- Dementia-frontal pattern in FTLD, temporo-parietal pattern in AD
- Ligand imaging in PD, others
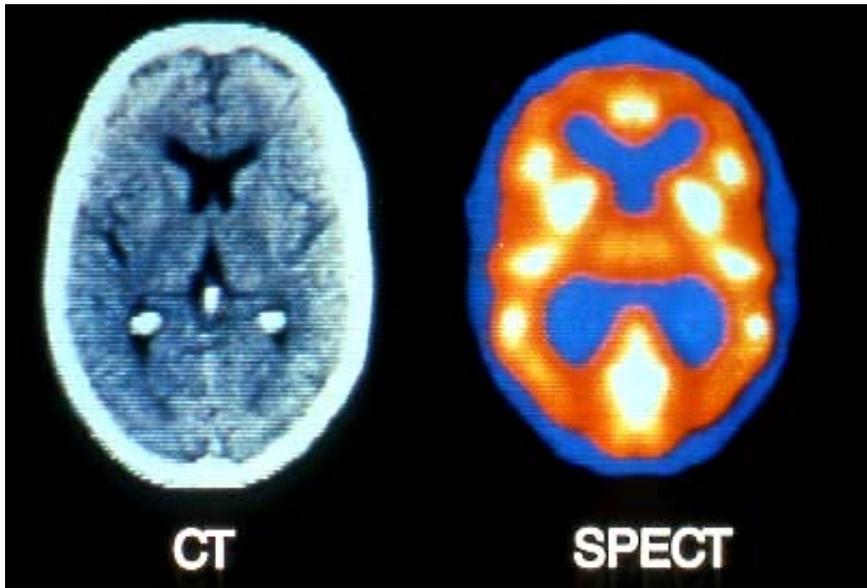
Figure 7-10: CT and SPECT images
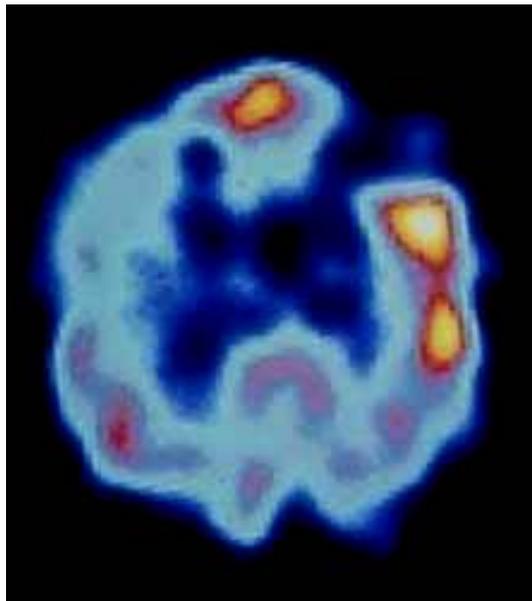
Figure 7-11: Wedge-shaped left ACA infarct (SPECT)
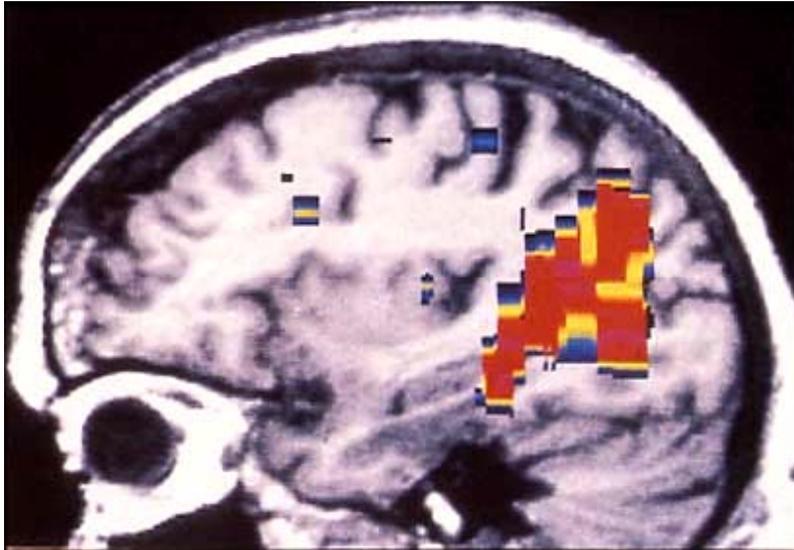
Figure 7-12: Decreased perfusion of temporal-parietal cortices; Alzheimer's
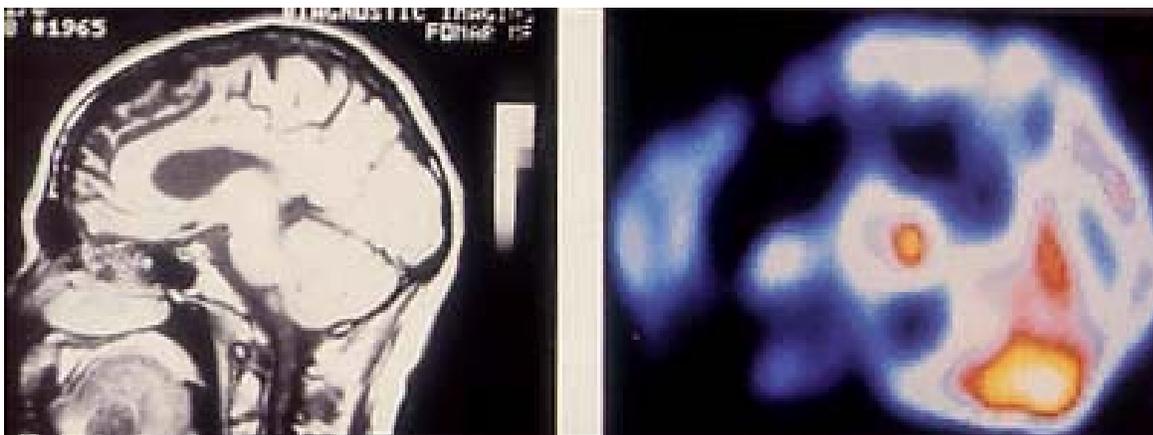
Figure 7-13: MRI (left) showing frontal atrophy, SPECT (right) showing decreased perfusion of the frontal lobes

Landmarks
- Axial views
  - Fourth ventricle
  - Petrous bone and sphenoid ridge
  - Aqueduct
  - Third ventricle
  - Lateral ventricles
  - Frontal horns
  - Calcifications in the choroid plexus, pineal, basal ganglia and falx
  - Caudate, putamen and globus pallidus
  - Internal capsule—anterior and posterior limbs
  - Thalami
  - Sylvian fissures
- Sagittal views
  - Severity of cortical atrophy
  - Corpus callosum and cingulate gyrus
  - Pituitary
- Coronal views
  - Hippocampus and amygdala
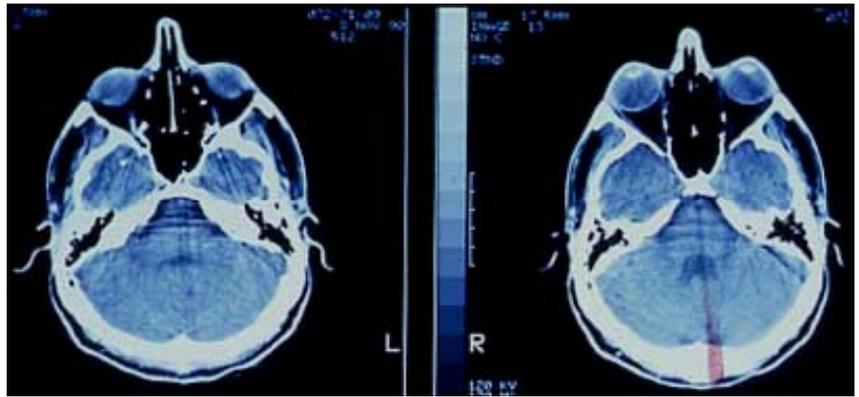
Figure 7-14: Landmarks include the fourth ventricle, bones, and sinuses
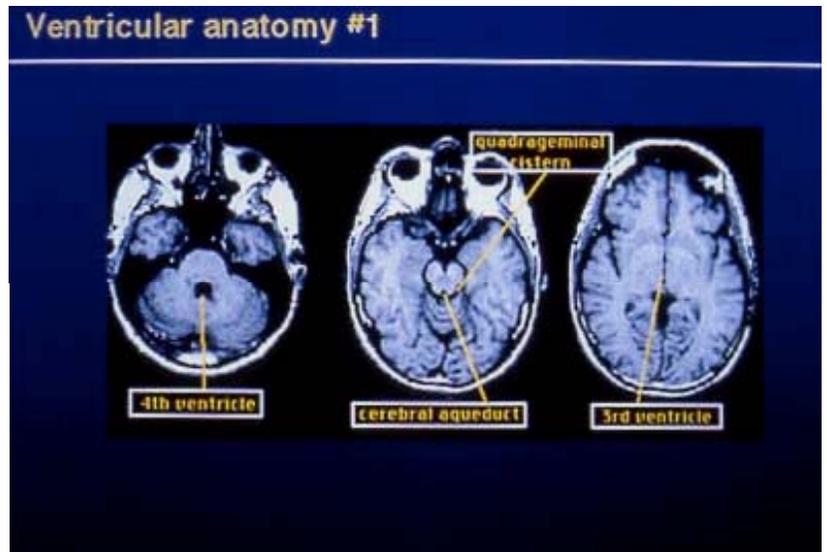
Figure 7-15: The ventricular system

Ventricular anatomy #1

quadrageminal cistern

4th ventricle   cerebral aqueduct   3rd ventricle

Ventricular anatomy #2

frontal horns
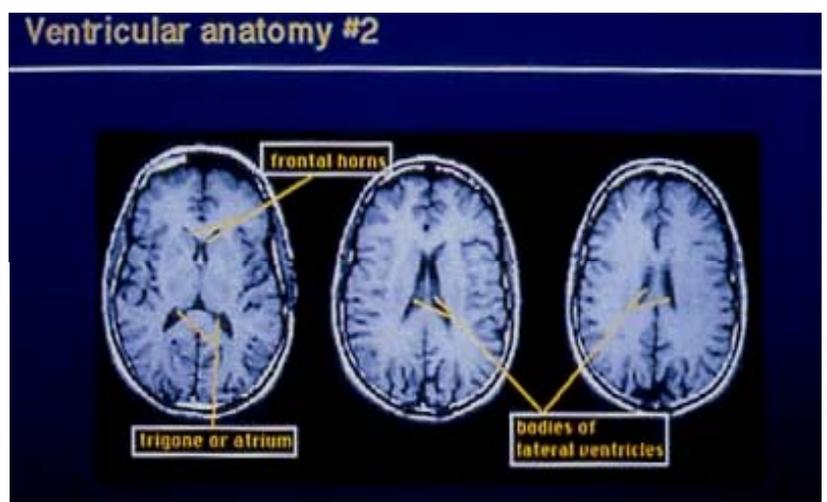
trigone or atrium   bodies of lateral ventricles

Figure 7-16: 65 year old man with right carotid occlusion, left hemiparesis, apathy, and depression. What is wrong with his scan?
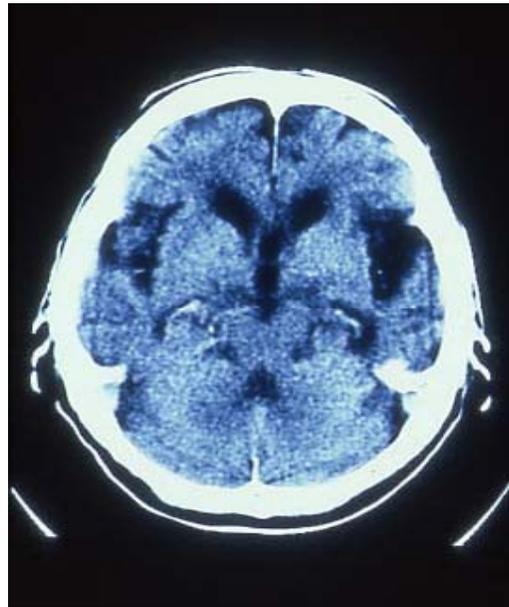
Figure 7-17: 72 year old woman with gradually progressive memory loss and word finding difficulty. Can you find the Sylvian fissure? What is wrong with this scan?
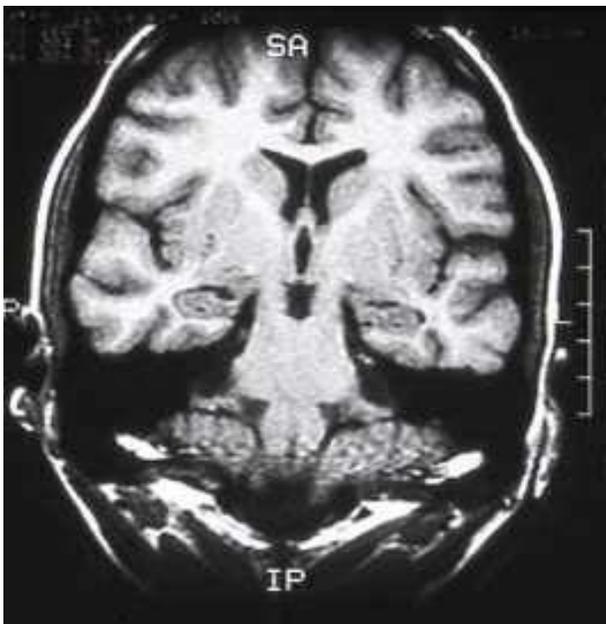
Figure 7-18: T1 coronal MRI of normal hippocampus
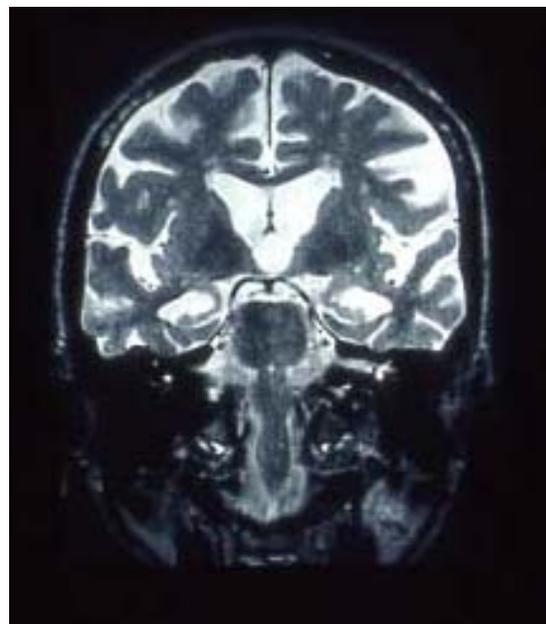
Figure 7-19: 62 year old woman with rapid progression of memory loss. T2 coronal MRI demonstrating atrophic hippocampus in probable Alzheimer's disease
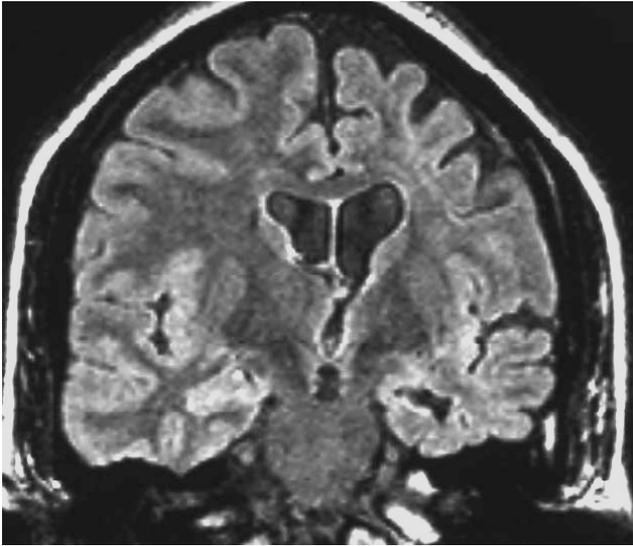
Figure 7-20: Mesial Temporal Sclerosis
31 year old woman from Africa with frequent complex partial seizures and mild developmental delay. Can you find the hippocampi? What is wrong with her scan?
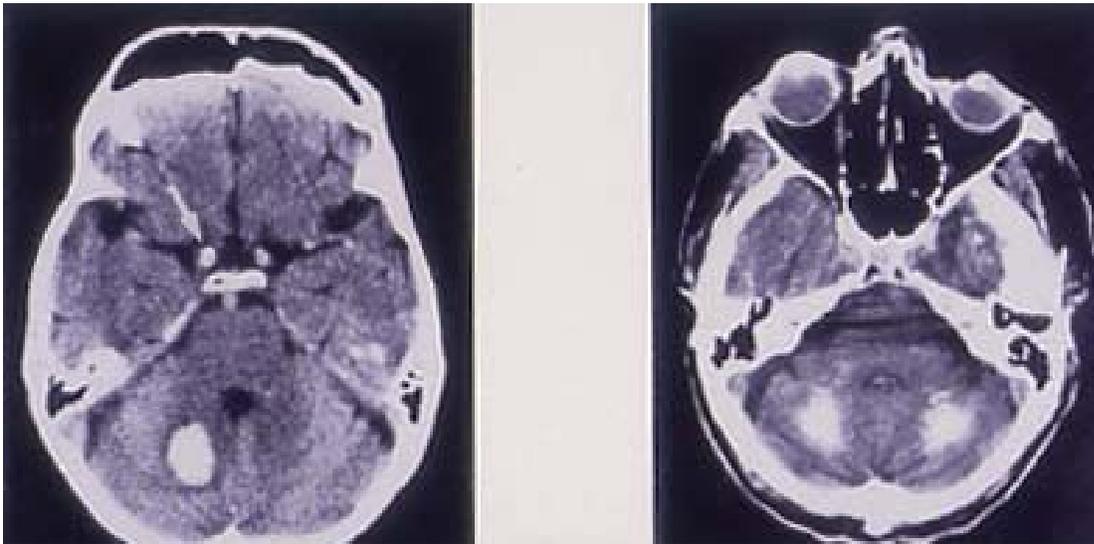
Figure 7-21: Which scan is normal variant? What is the abnormality in the other scan?

Introduction To Scan Interpretation

- Is the scan
  - Contrast or noncontrast?

Section 1. Basic Principles

        – Good quality?
- Describe the abnormality
  - Size—small, punctate, medium, large
  - Shape—round, well circumscribed, ovoid, irregular, patchy
- Signal intensity
  - High signal, hyperdense
  - Low signal, hypodense
  - Isointense, isodense
  - Mixed signal

- Location
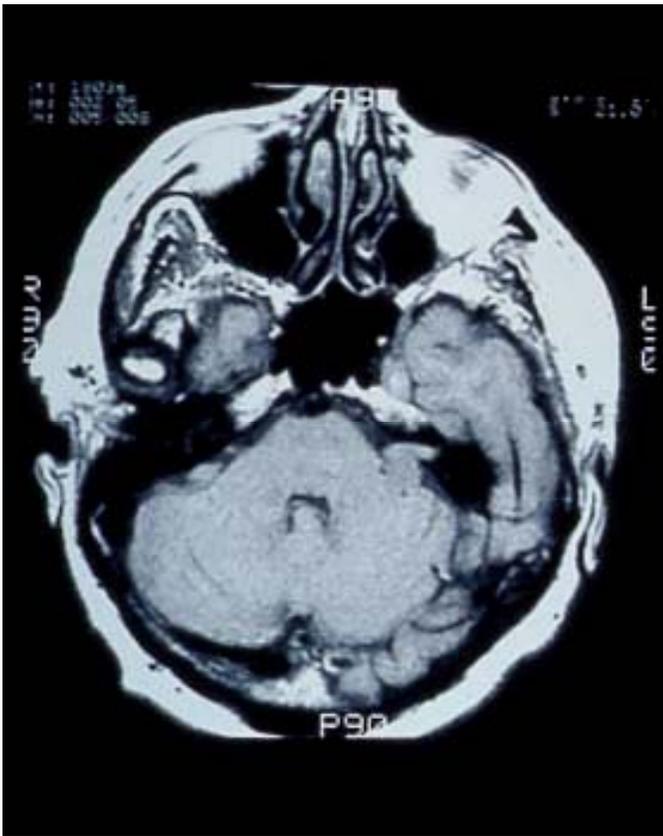
Figure 7-22: 65 year old with dizziness, mild hearing loss, and mild tinnitus on the left. Can you detect the subtle abnormality on the scan?

Figure 7-23: 66 year old admitted to the hospital with the abrupt onset of expressive aphasia and mild right hand weakness. Describe the abnormality on the CT and on hospital day 2.
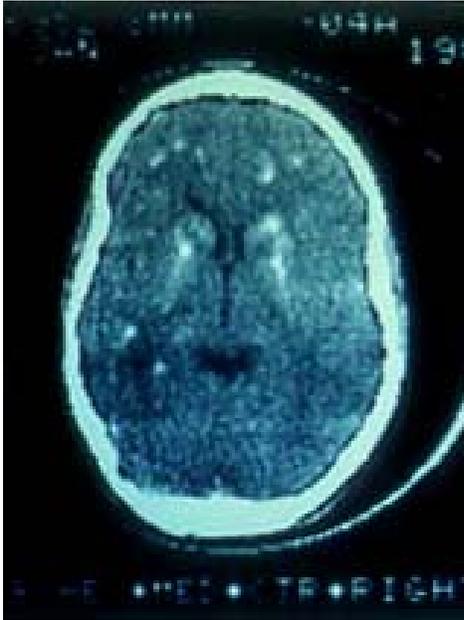
Figure 7-24: 3 year old boy with mild developmental delay. What does this scan show?
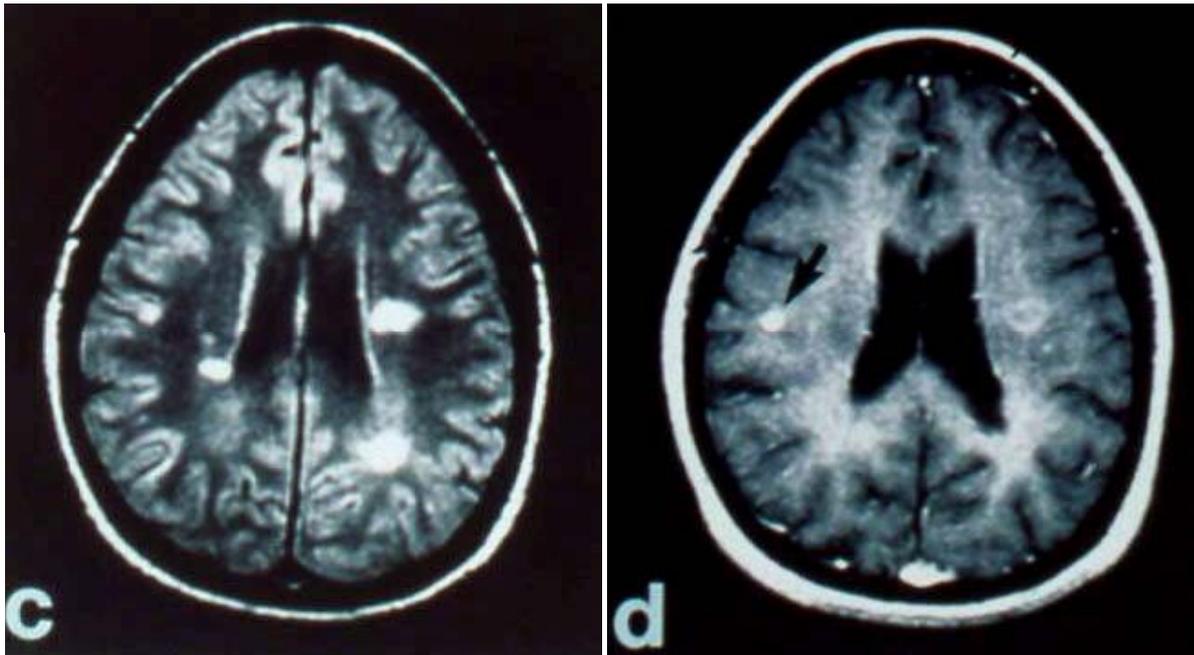
Figure 7-25: 30 year old woman with right-sided numbness for 2 weeks. MRI on left is non-contrast. MRI on right is enhanced with gadolinium. Describe the abnormalities. What is the most likely diagnosis?

Figure 7-26: 55 year old with new onset of seizure discovered to have a small bleed from a communicating artery aneurysm. Describe the abnormality on the CT scan 2 days after aneurysm surgery.
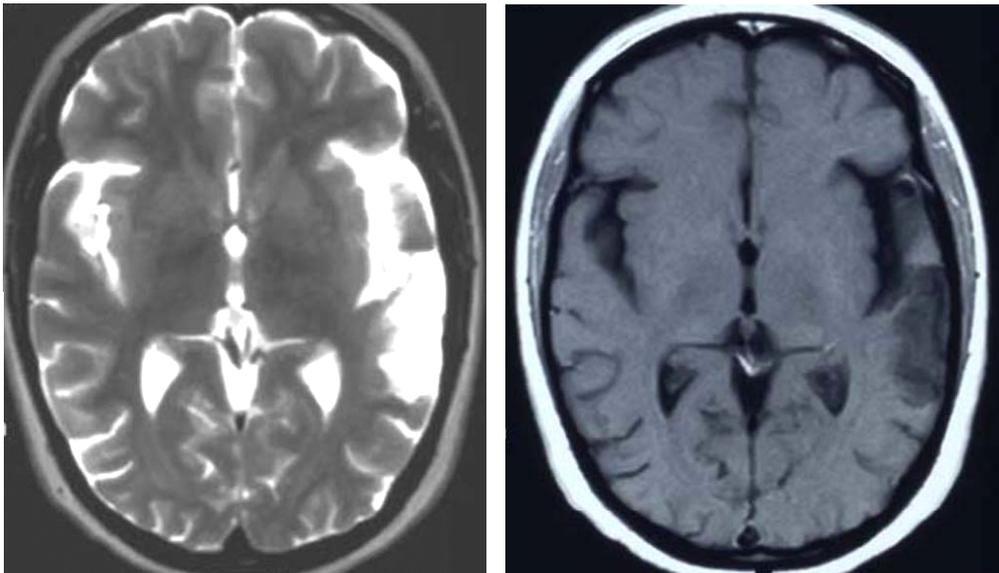
Figure 7-27: 45 year old with left subclavian occlusion developed Wernicke's aphasia following a revascularization procedure. Describe the abnormality on the MRI 7 days after the surgery.

Figure 7-28: 50 year old with new onset seizure. What the contrast-enhanced CT show?

Figure 7-29: A 32 year old woman with anticardiolipin antibody syndrome on Coumadin for stroke prophylaxis was admitted to the hospital for confusion. What does her admission CT scan show?

Figure 7-30: 72 year old man with short-term memory loss and trouble recalling people's names. He is driving without difficulty and exercises at the gym three times a week. What does the MRI show?

Figure 7-31: 30 year old IV drug abuser admitted to the hospital with headache, confusion, and fever. What does the contrast CT scan show? How many different types of abnormal signal do you see?

VASCULAR DEMENTIA – 3 Types
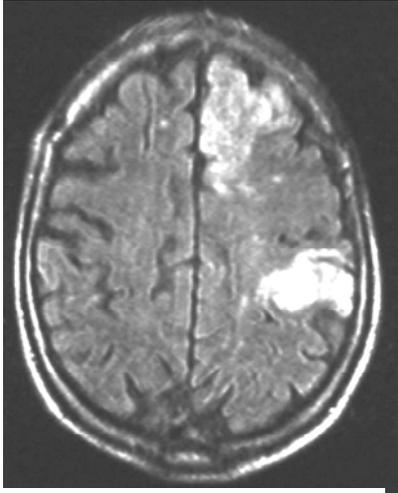
Figure 7-32: Multiple large-vessel infarctions
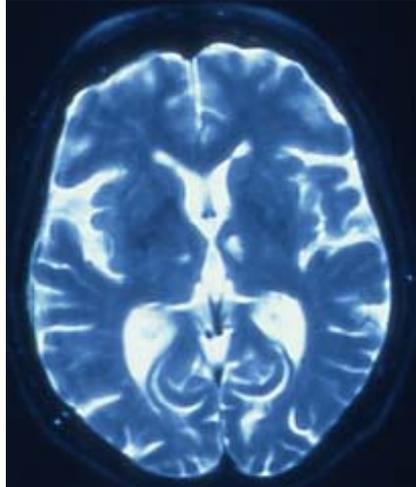
Figure 7-33: Bilateral strategic thalamic infarcts
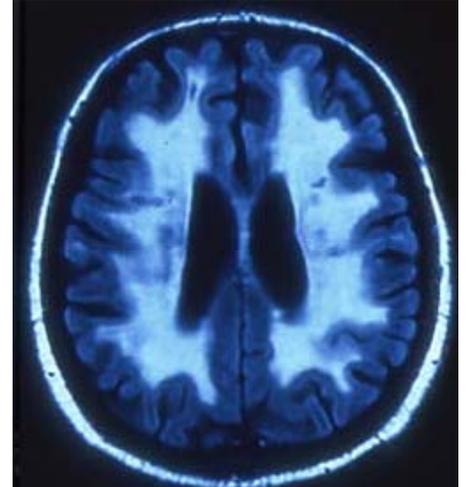
Figure 7-34: Binswanger's disease

Normal Pressure Hydrocephalus (NPH)

Normal Pressure Hydrocephalus
- Cognitive Impairment, Gait Disturbance, Bladder Control
- May Have: Behavior Problems, Parkinsonism

MRI findings:
- Ventricular enlargement disproportionate to the amount of atrophy
- Bowing of the corpus callosum
- Smooth rimming of high signal around the ventricles due to transependymal flow of CSF
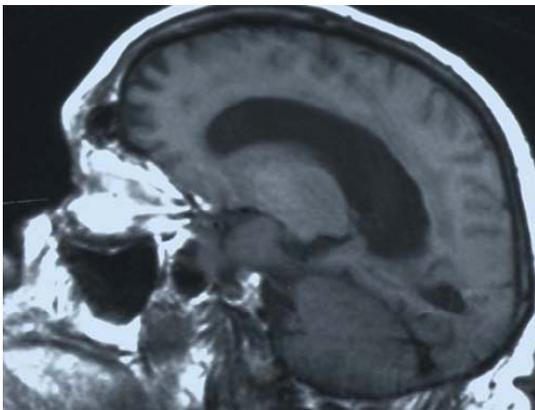
Figure 7-35: sagittal MRI of NPH
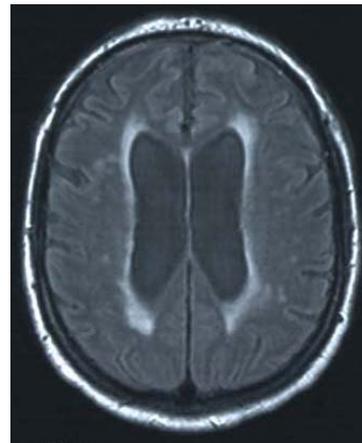
Figure 7-36: axial MRI of NPH
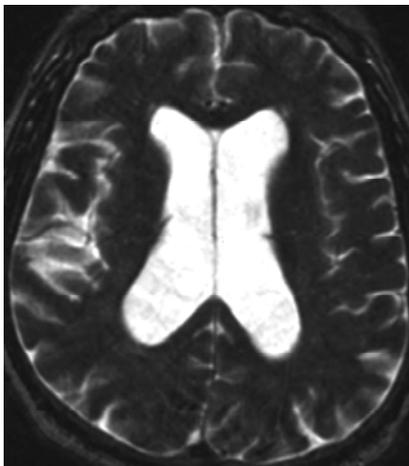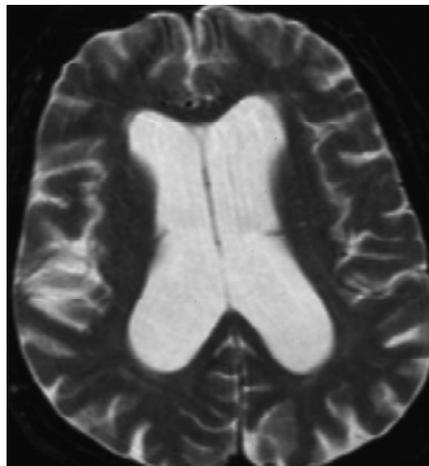
1994   2001

Figure 7-37: 72 year old man with progressive gait disturbance, bladder urgency, and memory loss beginning in 1994. Excellent response to shunt placement in 2002. The initial scan was read as normal. Please try to look at the scans in your patients.

NPH Advanced Imaging
- Flow void in the aqueduct
- Third ventricle increased in size pushing down the mammillary body

Figure 7-38: NPH, arrow pointing to flow void in third ventricle
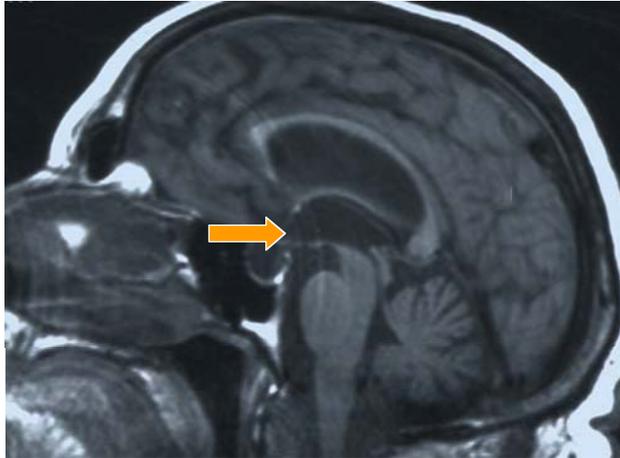
Figure 7-39: NPH, arrow pointing to large third ventricle

Types Of FMRI:

- BOLD-fMRI which measures regional differences in oxygenated blood
- Diffusion-weighted fMRI which measures random movement of water molecules. Diffusion tensor imaging (DTI) measures diffusion of water in different directions and is a good test for studying white matter tracts.
- MRI spectroscopy which can measure certain cerebral metabolites non-invasively
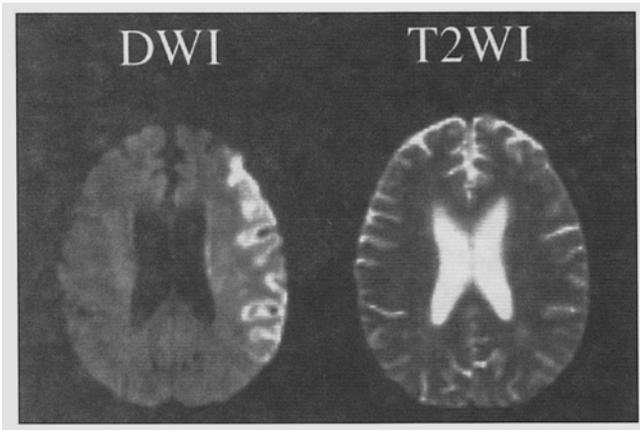
Figure 7-40: Diffusion-weighted fMRI (left) compared to a T2-weighted image (right).

Diffusion-weighted imaging show abnormalities before structural changes are apparent.
MR Spectroscopy--
MR spectroscopy of N-acetyl aspartate (NAA) showing decline of NAA over time in patients with Alzheimer's disease (lower line) compared to age-matched controls.
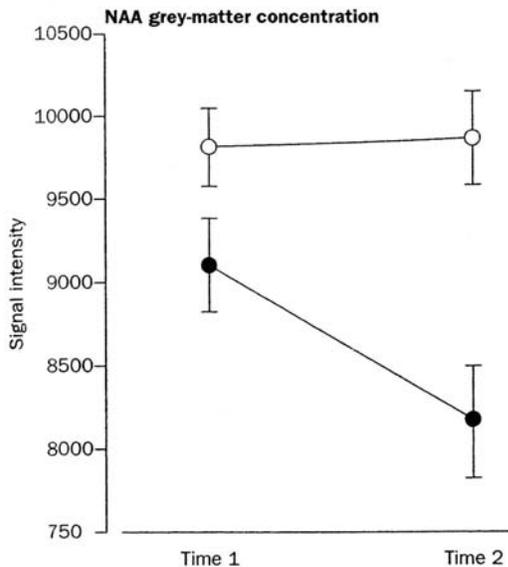
Figure 7-41: MR spectroscopy of NAA in patients with Alzheimer's disease (lower line) compared to age-matched controls
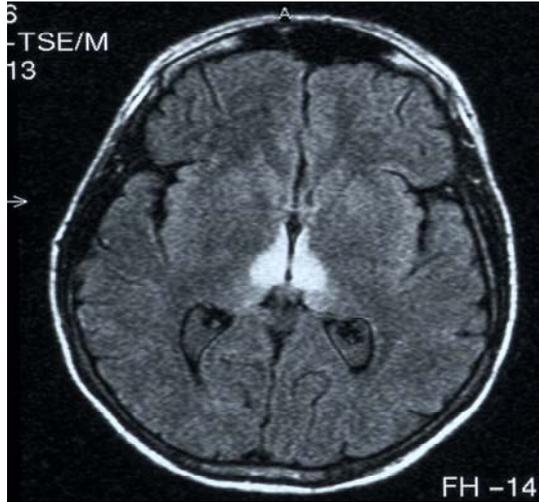
Figure 7-42: 30 year old schizophrenic admitted to the hospital with florid psychosis after stopping his neuroleptics 3 months earlier. He had stopped eating regular meals and lost 45 pounds. He was hydrated with D5 NS in the ER and admitted to the Psychiatry Unit. 6 days after admission he developed ataxia and delirium. What does this FLAIR, non-contrast MRI show? What caused this abnormality?

Chapter 7.   Neuroimaging

Chapter 8. The Mental Status Examination

This is the primary type of examination used in psychiatry. Though psychiatrists do not use many of the more intrusive physical examination techniques (such palpation, auscultation, etc.), psychiatrists are expected to be expert observers, both of significant positive and negative findings on examinations. This observation should take place throughout the patient encounter; it is not limited to any one point. However, the observations are then recorded into a specific structured format that is labeled the Mental Status Examination (MSE). When properly done, the MSE should give a detailed "snapshot" of the patient as he presented during the interview.

Often beginners become confused about the difference between this and other parts of the history. A simple way to keep it apart is to remember that this is, as the title says, an *examination*, therefore it should be limited to what is observed. The rest should go in the history. As an example, if a patient reports that they have been hearing voices throughout the day, but deny hearing them during the interview and do not seem to be responding to internal stimuli, one would not report the hallucinations as part of the MSE, but rather include it earlier in the history.   Conversely, if the patient denies any history of hallucination, but seems to be responding to internal stimuli throughout the examination, one would report the phenomenon on the MSE.

The MSE can be divided into the following major categories: (1) General Appearance, (2) Emotions, (3) Thoughts, (4) Cognition, (5) Judgment and Insight.   These are described in more detail in the following sections.

General Description

As implied, this is a general description of the patient's appearance. Being detailed and accurate is important, and such observations can be of great use to the next examiner. Imagine, for example, if a patient presents looking disheveled, poorly groomed with poor hygiene to an emergency department, but a note from only a month ago reports the same patient to have been well dressed and groomed. Something is going on!

Some of the areas that might be commented on, particularly if they have significant negative or positive findings include:

Appearance

One should describe the prominent physical features of an individual. At least one writer on the subject has suggested this should be detailed enough "such that a portrait of the person could be painted that highlights his or her unique aspects" but that is probably asking a lot. Some aspects of appearance once might note include a description of a patient's facial features, general grooming, hair color texture or styling, and grooming, skin texture, scar formation, tattoos, body shape, height and weight, cleanliness and neatness, posture and bearing, clothing (type, appropriateness) or jewelry.

Motor Behavior

The examination should incorporate any observation of movement or behavior.
Some aspects of motor behavior that might be commented on include gait, freedom of movement, firmness and strength of handshake, any involuntary or abnormal movements, tremors, tics, mannerisms, lip smacking or akathisias

Speech

This in not an evaluation of language or thought (save that for later), but a behavioral/mechanical evaluation of speech. Items that might be commented on include the rate of speech, the spontaneity of verbalizations, the range of voice intonation patterns, the volume of speech, and any defects with verbalizations (stammering or stuttering).

Attitudes

One should comment on how the patient related to the examiner. This usually includes a discussion of the patient's degree of cooperativeness with the examiner. When appropriate, a recording of the evaluator's attitude toward the patient might be appropriate, as we believe such reactions ("countertransference") may be useful information. Such discussions should be done with the understanding that the patient has a legal right to read the record, and any strong emotions or reactions should be recorded in a diplomatic manner.

Emotions

For the sake of consistency, the observation of a patient's emotions is divided into a discussion of *mood* and *affect*.

Mood is usually defined as the sustained feeling tone that prevails over time for a patient. At times, the patient will be able to describe their mood. Otherwise, evaluator must inquire about a patient's mood, or infer it from the rest of the interview. Qualities of mood that may be commented on include the depth of the mood, the length of time that it prevails, and the degree of fluctuation. Common words used to describe a mood include the following: Anxious, panicky, terrified, sad, depressed, angry, enraged, euphoric, and guilty. Once should be as specific as possible in describing a mood, and vague terms such as "upset" or "agitated" should be avoided.

Affect is usually defined as the behavioral/observable manifestation of mood. Some aspects of a mood that we might comment on include the following: the *appropriateness* of the affect to the described mood (does the person look the way they say they feel?); the intensity of the affect during the examination (is their too much--*heightened* or *dramatic*--or too little *blunted* or *flat*); the *mobility* of the affect (does the affect change at an appropriate rate, or does there seem to be too much variation–a *labile affect*-- or too little--*constricted* or *fixed*; the *range* of the affect (is there an expected range of affect–usually interview will have light and heavier moments–or does the affect seem *restricted* to a limited range; and the *reactivity* of the patient (is the response to external factors, and topics as would be expected for the situation. Alternatively, is there too little change--*nonreactive* or *nonresponsive?*).

Thought

Usually, a description of a patient's thoughts during the interview is subdivided into (at least) 2 categories: a description of the patient's *thought process*, and the *content* of their thoughts.

Thought process describes the manner of organization and formulation of thought.   Coherent thought is clear, easy to follow, and logical. A disorder of thinking tends to impair this coherence, and any disorder of thinking that affects language, communication or the content of thought is termed a *formal thought disorder*.

Some aspects of thought process that are usually commented on include the *stream of thought* and the *goal directedness* of a thought.   A discussion of the stream of thought might include a discussion of the *quantity* of thought: does there seem to be a *paucity of thoughts*, or conversely, a *flooding of thoughts*? Also, it might include a discussion of the *rate* of thought: do the thoughts seem to be *racing*? *Retarded*?

Most commonly, examiners comment on the **goal directedness** or **continuity of thoughts.** In normal thought, a speaker presents a series an ideas or propositions that form a logical progression from an initial point, to the conclusion, or goal of the thought. Disorders of continuity tend to distract from this goal or series, and the relatedness of a series of thoughts become less clear. As the thought disorder gets more serious, the logical connectedness of different thoughts becomes weaker. Some examples of disorders of thought process include: **Circumstantial thought:** a lack of goal directedness, incorporating tedious and unnecessary details, with difficulty in arriving at an end point; **Tangential thought:** a digression from the subject, introducing thoughts that seem unrelated, oblique, and irrelevant; **Thought blocking:** a sudden cessation in the middle of a sentence at which point a patient cannot recover what has been said; and **Loose associations**: a jumping from one topic to another with no apparent connection between the topics. In the other direction, a **perseveration** refers the patient's repeating the same response to a variety of questions and topics, with an inability to change his or her responses or to change the topic.

Other less common abnormalities of thought process include the following: **Neologisms:** words that patients make up and are often a condensation of several words that are unintelligible to another person. **Word salad:** incomprehensible mixing of meaningless words and phrases. **Clang associations:** the connections between thoughts become tenuous, and the patient uses rhyming and punning.

Disturbances of thought content include such abnormalities as **Perceptual Disturbances** and **Delusions**.

The most common perceptual disturbances are **Hallucinations**, which are *perceptual experiences that have no external stimuli.* Hallucinations can be auditory (i.e., hearing noises or voices that nobody else hears); visual (i.e., seeing objects that are not present); tactile (i.e., feeling sensations when there is no stimulus for them); gustatory (i.e., tasting sensations when there is no stimulus for them); or olfactory (i.e., smelling odors that are not present). They are not necessarily pathonogmonic of any specific disorder. For example **hypnagogic** (i.e., the drowsy state preceding sleep) and **hypnopompic** (i.e., the semiconscious state preceding awakening) hallucinations are experiences associated with normal sleep and with narcolepsy.

Another disorder of perception is an **Illusion**, which is a false impression that results from a real stimulus. Other examples of abnormal perceptions include **Depersonalization,** which is a patients' feelings that he is not himself, that he is strange, or that there is something different about himself that he cannot account for, and **Derealization,** which expresses a patients' feeling that the environment is somehow different or strange but she cannot account for these changes.

Delusions can be defined as false fixed beliefs that have no rational basis in reality, being deemed unacceptable by the patient's culture. **Primary delusions** are unrelated to other disorders. Examples include thought insertion, thought broadcasting, and beliefs about world destruction. **Secondary delusions** are based on other psychological experiences. These include delusions derived from hallucinations, other delusions, and morbid affective states.

Types of delusions include those of persecution, of jealousy, of guilt, of love, of poverty, and of nihilism. The most common are **persecutory delusions**, in which one believes, erroneously, that another person or group of persons it trying to do harm to oneself. Note that this is often referred to as a **paranoid** delusion, but that is a misuse of the word *paranoid*, which is a more generic in meaning and does not imply a specific type of delusion.   Other abnormal thoughts sometimes found as part of a delusion include ideas of reference and ideas of influence. **Ideas of reference** are erroneous beliefs that an unrelated event in fact pertains to an individual.   Thus, if a patient observes a car on a street make a sudden turn, and assumes that it is because the driver is following the patient, that would be an idea of reference.   Such ideas can become even more improbable, such as a belief that something an announcer is saying on the television is actually a coded message intended for the patient. **Ideas of influence** are similar in that the patient may believe that somehow they caused an unrelated event to happen (for example, believing that through one's will one was able to cause an accident, even though one was not directly involved in any way).

In addition to describing the type of delusion a patient has, one wants to comment on other aspects of the delusion, such as the quality of the delusion, or the degrees of organization of the delusion.

There are other types of abnormal thoughts. Examples include obsessions and compulsions, which, though irrational, are not as severe a disorder as hallucinations or delusions. **Obsessions** are repetitive, unwelcome, irrational thoughts that impose themselves on the patient's consciousness over which he or she has no apparent control. They are accompanied by feelings of anxious dread and are thought to be *ego alien* (coming from "outside" one's normal self or desires), unacceptable, and undesirable. They are often resisted by the patient. **Compulsions** are repetitive stereotyped behaviors that the patient feels impelled to perform ritualistically, even though he or she recognizes the irrationality and absurdity of the behaviors. Although no pleasure is derived from performing the act, there is a temporary sense of relief of tension when it is completed. These are usually associated with obsessions.

Some other specific thoughts to ask about, which may be of great practical concern, suicidal and homicidal. These should be inquired about on any examination, as patients with such thoughts commonly present to medical settings, but often do not spontaneously reveal these thoughts.

The Cognitive Exam

Cognition refers to the ability to use the higher cortical functions: thinking, logic, reasoning, and to communicate these thoughts to others. Unlike the rest of the mental status examination, examinations of cognition often involve the administering of specific tests of cognitive abilities. However, much can also be deduced from the whole of the examination.   The cognitive examination is usually divided into the following domains:

1. Consciousness
2. Orientation
3. Attention and Concentration
4. Memory
5. Visuospatial ability
6. Abstractions and conceptualization.

Consciousness should be assessed early on. Consciousness may range from normal alertness to stupor and coma. Obviously, this affects the rest of the examination and should be noted early on.

Orientation refers to the ability to understand one's situation in space and time. Generally, orientation to place and time is tested. Place may include asking about the building and floor a person is in, as well as the city and state. Orientation to time is tested by asking a person to give the day and date.   Though an ill person who has spent a good deal of time convalescing may not be clear on the exact date, a cognitively intact person generally can give an approximate date, and it would be unusual for a cognitively intact person to not know the month or year, or what part of the month they are in.   Orientation to person generally remains intact except in the most severe of cognitive disorders. In fact, a patient who presents disoriented to person, but otherwise cognitively intact almost assuredly is almost never displaying a cognitive disorder, but is most likely suffering from some other problem (for example a dissociative disorder, or perhaps malingering).

Attention and Concentration. Attention refers to the ability to focus and direct one's cognitive in a physiologically aroused state. Concentration refers to the ability to maintain attention for a period. They need not go together: one can imagine a person who is attentive, but cannot concentrate on any one thing: for example a patient with early Alzheimer's disease who is easily distracted. The patient's attention and concentration during the interview should be noted. Most screening tests for dementia include a test of these items. For example, on the Folstein Mini-Mental Status Examination (below), a patient is asked to do serial seven's (described below). Though this does involve some mathematical skill (about a 3rd grade level), the ability to sustain the task over time implies a reasonable degree of attention and concentration.

An example of a specific attentional task is the digit span, in which a patient is asked to repeat increasing lengths of numbers forwards, and then backwards. A normal person should be able to recite about 7 numbers forwards. A person usually can recite a reverse series that is 2 less than their forward series (thus, 5 for most people). It is important to recite the numbers in a relatively monotone way, put an equal interval between the numbers to avoid potential cues.

A simple test of concentration is to ask a person to count backwards starting at 65 and stopping at 49. The instructions should be given only once, with no cuing during the task. Another example is the **serial sevens** task, in when a patient is asked to start at 100 and subtract 7, then keep subtracting 7 from each answer. Usually a person is asked to perform 5 subtractions, and each correct interval of 7 scores 1 point.

Memory. Though variously defined, for the purposes here, memory will refer to *the process of learning involving the registering of information, the storage of that information, and the ability to retrieve the information later.* Thus, there are separate component of memory, and the boundaries between them are somewhat controversial. A simple approach to testing will be used here, and memory will be divided into **registration**, **short-term memory**, and **long-term memory**.

Registration refers to the ability to repeat information immediately. It is usually limited in capacity to about seven bits of information. Registration is usually tested by asking a patient to repeat a series of items (for example, three unrelated words). If the patient cannot do on the first try, the words should be repeated until the patient can do it, and the number of tries should be recorded (more than 2 trials for 3 words would be abnormal). Registration should always be ascertained before testing other parts of memory: an inattentive patient who cannot register properly may appear to have a deficit of short or long-term memory, when in fact the memory items were never incorporated properly for information storage.

Short-term memory refers to the storage of information beyond the immediate (registration) period, but prior to the consolidation of memory into long-term memory. Practically speaking, it lasts from a few seconds to a few minutes, and may or may not

be temporary (depending on the purpose of the memory).   It is limited in capacity, though the specific limits are very individual.   Short-term memory can be tested by asking a patient to recall 3 or 4 words after a five-minute delay. After the initial test, a patient can be cued, or given multiple changes, which subsequent performance being recorded (although if the patient were being scored, these correct answers would not add to the score).   Other typical tests of short-term memory include reading a paragraph to a patient and asking them to recall as much information from the story as possible in 5 minutes.

Long-term memory is usually divided into procedural and declarative memory. **Procedural memory** refers to the ability to remember a specific set of skills. As one thinks of any task one has learned–say, driving a car–it is clear that there is a point at which one no longer has to think about the specific steps in the task—it has become unconscious and automatic. Procedural memory is generally not assessed during a standard mental status examination, but can be specifically tested when indicated. For example, a person may be asked to act out a specific task ("show me how you brush your teeth").

Declarative memory refers to the retention of data or facts, which can be verbal or nonverbal (i.e., sounds, images). In contrast to short-term memory, it is not temporary (though it can decay over time), and it has no known limit.

Long-term (declarative) memory is usually tested by asking a patient to recall past details. These details may be personal (wedding dates, graduations, past medical history–all of which would have to then be independently confirmed), or historical (important historical dates that a patient would reasonably be expected to know, based on their own upbringing and culture). Typically, a patient is asked to name past presidents, but some patients (ex. recent immigrants) may now know politics. One can usually assess appropriate questions after learning of a patient's background. Some events are fairly universal: Pearl Harbor, for example, at least for people living in the US who are old enough to have been old enough in 1941. Similarly, one can expect, at least in this general area, that asking when the Red Sox won the World Series will be pretty reliable, at least for a while.

Constructional Ability refers to the ability to recognize the relationship of different objects in the world. Though occasionally neglected during cognitive testing, it is of great practical significance, particularly if a person wishes to drive, or live alone. Constructional tasks require reasonable vision, motor coordination, strength, praxis and tactile sensation, and in cases in which patient's appear to have a deficit in this ability, these other domains should be tested as well. Usually, constructional ability is tested by having a person copy a design, such as a transparent cube, or a clock. The Folstein Mini Mental Status examination includes a constructional task in which a person is

asked to draw intersecting pentagrams: a patient is expected both to draw the correct number of sides on both polygons as well as the two intersection points.

Abstraction and Conceptualization refer to higher intellectual functions. Abstraction involves the ability to understand the meanings of words beyond the literal interpretation. Conceptualization involves a number of intellectual functions, including the ability to be self-aware: of one's existence, one's thoughts, and one's behaviors. Deficits in these areas may be inferred during an examination, especially from overly concrete answers to questions (example: doctor: "what brought you to the hospital" patient: "an ambulance.").   These abilities can be tested through such tasks as asking a patient to identify similarities between objects (example: "how are an apple and an orange both alike." One would expect an abstract answer such as "fruit", as opposed to a concrete answer such as that they are both round). Often, patients are asked to interpret proverbs as a test of abstract reasoning. Examples of proverbs typically used including "The grass is greener on the other side" and "Don't count your chicken's before they hatch." Harder ones include "People who live in glass houses shouldn't throw stones" and "A rolling stone gathers no moss." In each case, it should first be explained what a proverb is ("a saying that has a broader meaning") and an example might be given. A number of things can impair proverb interpretations besides deficits in abstract functioning: lower education (usually at least 8 years of education is expected for proverb interpretations), or a lack of cultural applicability, and these should be investigated as possibilities in a person who is having trouble with proverbs.

Standardized tests. There are a number of tests designed to examine various domains of cognitive ability. An example of a commonly used one is the Folstein Mini-Mental Status exam, and this is shown below.

Figure 8-1. The Mini-Mental State Examination (MMSE)

Maximum	Score	
		ORIENTATION
5	( )	What is the (year) (season) (date) (month)?
5	( )	Where are we (state) (country) (town or city) (hospital) (floor)?
		REGISTRATION
3	( )	Name 3 common objects (e.g. "apple", "table", "penny"). Take 1 second to say each. Then ask the patient to repeat all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until they lean all 3. Count trials and record. Trials:
		ATTENTION AND CALCULATION
5	( )	Ask patient to count back by sevens, starting at 100. Alternately, spell "world" backwards. The score is the number of numbers or words in the correct order. (93___86___79___72___65___) (D____L___R____O___W____)
		RECALL
3	( )	Ask for the 3 objects repeated above. Give 1 point for each correct answer. (Note: Recall cannot be tested if all 3 objects were not remembered during registration.
		LANGUAGE
2	( )	Name a "pencil" and "watch"
1	( )	Repeat the following: "No ifs, ands, or buts."

3	( )	Follow a 3-stage command:
		        "Take a paper in your right hand,
		         Fold it in half, and
		         Put it on the floor."

1	( )	Read and obey the following Close our eyes.
1	( )	Write a sentence.
1	( )	Copy the following design.
Total Score	_____	compare this score against norms for education and age.
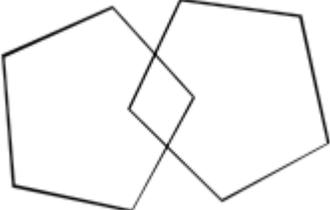
Figure 8-2. Normative Data for MMSE.

	Age													
Education	**18-24**	**25-29**	**30-34**	**35-39**	**40-44**	**45-49**	**50-54**	**55-59**	**60-64**	**65-69**	**70-74**	**75-79**	**80-84**	**>84**
4th grade	22	25	25	23	23	23	23	22	23	22	22	21	20	19
8th grade	27	27	26	26	27	26	27	26	26	26	25	25	25	23
High School	29	29	29	28	28	28	28	28	28	28	27	27	25	26
College	29	29	29	29	29	29	29	29	29	29	28	28	27	27

These numbers can be used to compare a patient's performance on the MMSE against norms for their age and education.

Insight And Judgment.

Insight and Judgment refer to complex tasks that require a good deal of cognitive functioning (including conceptual thinking and abstract ability), though intact cognitive functioning alone is not adequate for good judgment and insight. One could spend a good deal of time debating what these terms really mean. For the purposes here, suffice it to say that these concepts are much more approachable when seen in specific circumstances. Thus, rather than discussion these are overarching functions ("Judgment and insight: intact"), it is more useful to discuss them as they relate to a particular activity or question. In context, one can specifically discuss a patient's insight into a particular problem, or their ability to use judgment to arrive at a particular decision. For example, a patient's ability to make a particular medical decision requires both insight into their specific malady, as well as the judgment to weigh alternatives in the service of arriving at an appropriate decision.

Insight (in the medical context) refers to the capacity of the patient to understand that he or she has a problem or illness and to be able to review its probable causes and arrive at tenable solutions.   Self-observation alone is insufficient for insight. In assessing a patient's insight into their medical situation, the examiner should determine whether patients recognizes that they are ill, whether they understand that the problems they have are not normal, and whether they understand that treatment might be helpful. In some situations, it may also be important determine whether a patient realizes how their behaviors affect other people.

Judgment (in the medical context) refers to the patient's capacity to make appropriate decisions and appropriately act on them in social situations. The assessment of this function is best made in the course of obtaining the patient's history, and formal testing is rarely helpful. An example of testing would be to ask the patient, "What would you do if you saw smoke in a theater? Clearly, a meaningful judgment first requires appropriate insight into one's situation.   There is no necessary correlation between intelligence and judgment.

Reliability

Upon completion of an interview, the psychiatrist assesses the reliability of the information that has been obtained. Factors affecting reliability include the patient's intellectual endowment, his or her (perceived) honesty and motivations, the presence of psychosis or organic defects and the patient's tendency to magnify or understate his or her problems. In cases in which there is a strong reason to question a patient's reliability (ex. significant dementia), the assessment of reliability should be discussed early in the examination, rather than waiting to the end to reveal that much of the information reported already is unreliable!

Figure 8-3. The Mental Status Exam			
Appearance: Attitude		Normal	Cooperative
		Abnormal	Uncooperative, Hostile, Guarded, Suspicious
Mood		Euthymic	calm, comfortable, euthymic, friendly, pleasant, unremarkable
		Angry	angry, bellicose, belligerent, confrontational, frustrated, hostile, impatient, irascible, irate, irritable, oppositional, outraged, sullen
		Euphoric	cheerful, ecstatic, elated, euphoric, giddy, happy, jovial
		Apathetic	apathetic, bland, dull, flat
		Dysphoric	despondent, distraught, dysphoric, grieving, hopeless, lugubrious, overwhelmed, remorseful, sad
		Apprehensive	anxious, apprehensive, fearful, frightened, high-stung, nervous, overwhelmed, panicked, tense, terrified, worried.
Affect	Appropriateness	normal	appropriate, congruent
		abnormal	inappropriate incongruent
	Intensity	normal	normal
		abnormal	blunted, exaggerated, flat, heightened, overly dramatic
	Variability/ Mobility	normal	mobile
		abnormal	constricted, fixed, immobile, labile.
	Range	normal	full
		abnormal	restricted range
	Reactivity	normal	reactive, responsive
		abnormal	nonreactive, nonresponsive
Speech		Fluency, repetition, comprehension, naming, writing, reading, prosody, quality of speech.	Comment specifically
Thought	Process	Disorders of Connectedness	circumstantiality, flight of ideas, loose associations, tangentiality, word salad

		Other	clanging, echolalia, neologisms, perseveration, thought blocking
	Content	thoughts	delusions, homicidal ideation, magical thinking, obsessions, overvalued ideas, paranoia, phobia, poverty of speech, preoccupations, ruminations, suicidal ideation, suspiciousness.
		perceptions	autoscopy, déjà vu, depersonalization, derealization, hallucinations, illusion, jamais vu.
Cognition	See description in text		
Judgment and Insight			
Reliability			

Section 2. The Clinical Disorders.

Chapter 9. Anxiety Disorders

Phenomenology

Fear can be a normal, appropriate reaction to a known source of danger. "Anxiety" can be defined as a "warning signal," functioning to make us aware of present or potential danger.

With an anxiety disorder, an individual is frightened, but the source of the danger is not known, not recognized, or inadequate to account for the symptoms. That is to say, the anxiety response is inappropriate to the situation.

The physiologic manifestations of anxiety are similar to the manifestations fear. They include symptoms such as shakiness and sweating, palpitations, tingling in the extremities, numbness around the mouth, dizziness and syncope, mydriasis, and GI or urinary disturbances.

By definition, the anxiety disorders (see Diagnosis section of this chapter for complete list) are primarily disorders of emotion.
However, like other mental disorders, anxiety can affect all areas of the mental status exam. (see Table to right).

Mental status exam		Anxiety Disorders
General		Various physical manifestations: restless-appearing, psychomotor agitation, shortness of breath, hyperventilation, stomach upset, chest pain, diaphoresis. May be ill kempt, or meticulously groomed (OCD). May display odd, ritualistic behaviors.
Emotional	Mood	Anxious, fearful
	Affect	Frightened-appearing, can be very intense
Thought	Process	Can involve obsessive, perseverative thoughts
	Content	Delusions, hallucinations

Epidemiology

Anxiety disorders are the most prevalent of psychiatric disorders. Community samples have shown surprisingly high lifetime prevalences. The ECA study demonstrated the following lifetime prevalences:

- ***Anxiety Disorders Overall: 15%***
- *Generalized anxiety disorder: 8.5%*
- *Phobias: 12.5%*
- *Panic disorder: 1.6%*
- *OCD: 2.5%*

Similar rates were found by the National Comorbidity Survey, which demonstrated the following lifetime prevalences:
- *Any anxiety disorder: 25%*
- *Generalized anxiety disorder: 5%*
- *Agoraphobia without panic: 5%*
- *Social phobia: 13%*
- *Panic disorder: 3.5%*

Additionally, one-month prevalence rates were determined by the ECA study as follows:
- *All anxiety disorders: 7.3%, distributed fairly equally across age groups though somewhat lower in 65+*
- *Phobias: 6%, distributed fairly equally across age groups, but women tended to have higher in young adulthood*
- *Panic: 0.5% overall, distributed fairly equally across age groups, but women tended to have higher in young adulthood*
- *OCD: 1.3% overall, tended to have higher in late adolescence and young adulthood*

Clinical samples have shown anxiety disorders to be a very common reason for presentation to primary care doctors, ER, etc. In terms of gender effects, anxiety disorders seem more common in women. They may decrease with age, and can present differently at different ages. In children, an anxiety disorder can manifest as separation anxiety ("school phobia"). Elderly patients may tend towards somatic presentations ("stomach problems," headaches, sleep problems).

Etiology/Pathology

Genetic influences are a factor. There is a high incidence of anxiety disorders passed to subsequent generations, as evidenced by family studies. In these studies, generally all the disorders are more common in first-degree relatives of affected individuals than the general public. Panic disorder has a 4-7X greater incidence in first-degree relatives. Specific phobias may aggregate by type within families. In addition, twin studies show strong genetic contribution to Panic Disorder. For example, in OCD concordance is higher for monozygotic than dizygotic twins.

The key neurotransmitters seem to be **catecholamines** ("fight or flight reaction") and **serotonin** modulation. In addition, the **GABA receptor**, the primary inhibitory transmitter in the brain, plays an important role in the modulation of arousal and anxiety. Specific structures important in the etiology of anxiety disorders include the **Reticular Activation System (RAS)** and the so-called **"suffocation response."** The **locus coeruleus** (site of noradrenergic neurons), **raphe nucleus** (site of serotonergic neurons), caudate nucleus (particularly in OCD), temporal cortex, and frontal cortex are brain areas likely to be involved in anxiety disorders.

Cortical modulation plays an important role; key to this is the role of learning (classical and operant conditioning), as well as the role of stress, conflict and neuroses (psychoanalytic theory).

Diagnostic tests have been used to explore the pathogenesis of anxiety disorders. For example, **lactic acid infusion** and **carbon dioxide inhalation** bring out panic disorder. This, along with some tentative data, gives some credence to the suggestion that panic disorder is a "suffocation response" gone awry.

Diagnosis

The Syndromes

Syndromes are defined not as disorders, but rather "building blocks for disorders" (like the "episodes" in mood disorders). The Syndromes include **panic attacks** and **agoraphobia**.

DSM-IV DIAGNOSES AND CRITERIA FOR PANIC ATTACKS:

Panic attacks must include **4 or more** of the following symptoms:

- *Palpitations, pounding heart, or increased heart rate*
- *Sweating*
- *Trembling or shaking*
- *Sensations of shortness of breath or smothering*
- *Feeling of choking*
- *Chest pain*
- *Nausea*
- *Dizziness*
- *Derealization (feelings of unreality) or depersonalization*
- *Feeling of losing control/going crazy*
- *Fear of dying*
- *Paresthesias*
- *Chills*

A panic attack starts abruptly and peaks in about 10 minutes.

DSM-IV CRITERIA FOR AGORAPHOBIA:

Anxiety about being a place or situation from which either:
- escape is difficult or embarrassing, or
- if a panic attack occurred, help might not be available

The situation:
- Is avoided (restricting travel), or
- Is endured, but with marked distress or anxiety about having a panic attack, or
- Requires a companion

Other mental disorders don't explain the symptoms better.

The Disorders

The anxiety disorders are:
- **Panic Disorder with Agoraphobia**
- **Panic Disorder without Agoraphobia**
- **Agoraphobia without a History of Panic Disorder**
- **Specific Phobia**
- **Social Phobia**
- **Obsessive-Compulsive Disorder**
- **Posttraumatic Stress Disorder**

- **Acute Stress Disorder**
- **Generalized Anxiety Disorder**
- **Anxiety Disorder due to a General Medical Condition**
- **Substance-Induced Anxiety Disorder**
- **Anxiety Disorder Not Otherwise Specified (NOS)**

DSM-IV CRITERIA FOR PANIC DISORDER (WITH OR W/O AGORAPHOBIA):

Recurrent unexpected panic attacks, and

At least 1 attack has been followed by 1 month+ of:
- Concern about having additional attacks
- Worry about the implications or consequences of the attack
- Significant change in behavior relating to the attack

Specify presence or absence of agoraphobia

Panic attacks are not caused by substance or general medical condition.

Panic attacks are not part of another Anxiety or Mental Disorder.

DSM-IV CRITERIA FOR AGORAPHOBIA WITHOUT PANIC DISORDER

The presence of **agoraphobia.**

No history of **Panic Disorder.** (The focus of the fear is on the occurrence of incapacitating or extremely embarrassing panic-like symptoms or limited-symptom attacks rather than full Panic Attacks.)

The disturbance is not caused by a general medical condition or by substances.

If an associated general medical condition exists, the symptoms are in excess of that expected for the medical condition.

DSM-IV CRITERIA FOR SOCIAL PHOBIA

Marked and persistent fear of one or more social or performance situations. The fear is of possible humiliation or embarrassment.

The phobic stimulus almost always causes anxiety.

The fear is recognized as excessive or unreasonable.

The feared situation is avoided or endured with intense distress or anxiety.

The Global Criteria

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DSM-IV CRITERIA FOR SPECIFIC PHOBIA

Marked persistent fear that is excessive or unreasonable, cued by the presence or anticipation of a specific object or situation.

The phobic stimulus almost invariably provokes an immediate anxiety response.

The fear is recognized as excessive or unreasonable (not needed in children).

The phobic stimulus is avoided or endured with intense anxiety or distress.

Persons under age 18 must have the symptoms for 6 months+.

The Global Criteria.

SPECIFIC TYPES OF SPECIFIC PHOBIAS

- Animal type
- Natural environment type (e.g. heights, storms, water, etc.)
- Blood-Injection-Injury type
- Situational type (e.g. public transportation, tunnels, elevators, flying, driving, enclosed spaces, etc.)
- Other type (e.g. choking, vomiting, contracting an illness, children's fears of loud sounds or costumed characters, etc.)

DSM-IV CRITERIA FOR OBSESSIVE COMPULSIVE DISORDER (OCD)

Either obsessions or compulsions:

Obsessions: Recurrent, persistent thoughts or impulses, experiences (sometimes) as intrusive and inappropriate, and cause distress.

The thoughts aren't realistic worries about real problems.
Person tries to ignore or suppress the obsessions.
The obsessive thoughts are recognized as such.

Compulsions: Repetitive behaviors or mental acts that are done in response to an obsession.

The behaviors are meant to reduce distress, or prevent a feared event, but are not realistic.

At some point, the person had good insight into the unrealistic nature of these.

The Global Criteria.

DSM-IV CRITERIA FOR POSTTRAUMATIC STRESS DISORDER

The person experienced/witnessed/was confronted by an unusually traumatic event, which:
- Involved actual or threatened death/serious injury to the person or other, and
- Caused intense fear, horror or helplessness

The event is reexperienced through (1 or more of following):
- Intrusive, recurrent recollections
- Recurrent nightmares
- Flashbacks
- Intense distress in reaction to internal or external cues symbolizing/resembling the event
- Physiological reactivity in response to these cues

Avoidance of the stimuli and numbing of general responsiveness shown by (3+):
- Efforts to avoid thoughts, feelings or conversations about the trauma
- Efforts to avoid activities, people or places associated with the event
- Inability to recall important aspects of the event
- Loss of interest/participation in significant activities
- Feeling of detachment or estrangement from others
- Restricted range of affect
- Sense of foreshortened future

Persistent symptoms of hyperarousal:
- Insomnia
- Irritability
- Difficulty concentrating
- Hypervigilance
- Exaggerated startle response

The above symptoms have lasted longer than one month.
The Global Criteria.

DSM-IV CRITERIA FOR GENERALIZED ANXIETY DISORDER

Excessive anxiety and worry occurring more days than not for at least 6 months, in regard to work, school or other activities.

It is difficult to control these worries.

The anxiety and worry are associated with 3+ of the following:
Restlessness, or feeling keyed up
Easy fatigue
Difficulty concentrating
Irritability
Muscle tension
Insomnia or restless, unrefreshing sleep

Aspects of another Axis I disorder do not provide the focus of the anxiety and worry.

The Global Criteria.

Other Anxiety Disorders:

Acute Stress Disorder is like PTSD, but less than 1 month.

Anxiety Disorder Due to a General Medical Condition and **Substance-Induced Anxiety Disorder** can demonstrate as generalized anxiety, panic attacks, OCD symptoms, or phobic symptoms in the case of substances.

Anxiety Disorder NOS is a "wastebasket diagnosis" for anxiety symptoms not meeting the criteria for any specific disorder.

Differential Diagnosis

Important medical disorders that should be considered in the differential for anxiety disorders include **endocrine disorders**, **cardiopulmonary disorders**, and **neurologic disorders**. **Substance-induced disorders** mistaken for anxiety disorders include *withdrawal syndromes* (alcohol or tranquilizers), and *intoxication/therapeutic syndromes* (stimulants or others). Some specific organic causes of symptoms of anxiety include excessive caffeine intake, hyperthyroidism, vitamin B12 deficiency, hypo- or hyperglycemia, cardiac arrhythmias, anemia, pulmonary disease, and pheochromocytoma (an adrenal medullary tumor).

Other psychiatric syndromes in the differential include mood disorders (anxiety can be misdiagnosed as, or comorbid with depression), psychotic disorders, sleep disorders, somatoform disorders, and eating disorders.

Adjustment disorder often must be distinguished from post-traumatic stress disorder. Adjustment disorder is characterized by emotional symptoms (e.g. anxiety, depression, conduct problems) that cause social, school, or work impairment occurring within 3 months and lasting less than 6 months after a serious (but usually not life-threatening) life event (e.g. divorce, bankruptcy, changing residence). Generally, adjustments disorders are understandable, even seemingly "normal" reactions to unusual circumstances. PTSD is an abnormal reaction to an abnormal trauma, and though the reaction may be understandable, it is grossly maladaptive.

Comorbid Disorders

Commonly, mood disorders like depression can present comorbidly with anxiety, bringing to question genetic linkage or different forms of the same disorder. Some medical disorders are commonly comorbid with anxiety disorders: for example, mitral valve prolapse and Panic Disorder. .

Course

Most anxiety disorders tend to be chronic disorders. **Panic disorder** tends to present in late adolescence to early adulthood. It has perhaps a bimodal distribution (late adolescence and mid-30's). It can be chronic, but waxing and waning. At 6-10 years follow-up, 1/3 patients appear to be well, about 1/2 have improved but are still symptomatic, and 1/5 – 1/3 feel the same or worse. There is a high risk of relapse after (somatic) treatment. **Agoraphobia** may or may not improve if panic improves; it can become a "learned behavior."

Specific Phobia tends to begin in childhood. The situation type has a second peak in mid-20's (bimodal). It may spontaneously remit, but if it persists until adulthood, it becomes very chronic (perhaps 80% of those persisting to adulthood will be chronic). For **Social Phobia**, the onset is in the mid-teens. Patients may exhibit a premorbid history of shyness. Usually, social phobia is chronic, but it can fluctuate in severity. The onset of **OCD** is in adolescence or early adulthood. It presents earlier in males, who may begin in childhood. The course is a chronic waxing and waning one. 15% have deterioration, and 5% have episodes with interepisode recovery. **PTSD** can present for the first time at any age. Half of patients with PTSD recover in 3 months; the rest may persist for long duration. The most important predictor is the severity of trauma. Other factors which may mitigate severity/duration include social support, family history, premorbid personality and psychological health. **Generalized Anxiety Disorder** has an onset from childhood to early adulthood. It is, by definition, very chronic.

Treatment

Somatic Treatment For Anxiety Disorders: The Psychopharmacology Of Anxiety

Categories Of Anxiolytic Drugs
- Antidepressants (Selective Serotonin Reuptake Inhibitors)
- Benzodiazepines
- 5-HT1A agonists
- Beta antagonists
- Barbiturates (historical in this context; have been supplanted by other drugs)

The most common medications used for anxiety are the antidepressants and/or sedative hypnotics.

Antidepressants have gradually replaced sedative hypnotics for the first line of treatment of many anxiety disorders. Several studies show antidepressants to be as effective as benzodiazepines for a variety of anxiety disorders (e.g., fluoxetine [Prozac] compared favorably against alprazolam [Xanax] for panic disorder). Their mechanism of action in treating anxiety is presumed to be similar to that for their antidepressant effect. This presumption is reasonable, as monoamines exert a modulatory influence on most other neurotransmitters in the brain, including GABA. However, antidepressants are used preventively, on an every day basis. They are not effective in "as needed" dosing, and thus are not appropriate for short-term anxiety, or for quick relief of acute anxiety.

For more on antidepressants, see their description under Mood Disorders.

Sedative Hypnotics: Benzodiazepines
Benzodiazepines have multiple properties, which lend the drugs to multiple clinical applications:

Property Of Benzodiazepines → Clinical Application
- Anticonvulsant → treatment of epilepsy
- Muscle relaxant → treatment of spasticity (multiple sclerosis and cerebral palsy)
- Sedating → sleep induction
- Anxiolytic → treatment of anxiety

(This last property and application are what we are focusing on in this chapter.)

The mechanism of action for benzodiazepines is potentiation of GABA action at GABA-A receptors in the CNS. Benzodiazepines increase the affinity of GABA for its receptor, and can potentiate the increase in chloride permeability (and hyperpolarization) of the target neurons normally produced by GABA.

There are three classes of benzodiazepines: 2-keto, 3-hydroxy, and triazolo. 2-keto drugs include chlordiazepoxide, diazepam, prazepam, clorazepate, halazepam, clonazepam, and flurazepam. Many of these are pro-drugs; they are oxidized in the liver (usually to active metabolites). They therefore tend to have long half-lives and are more susceptible to drug interactions and age effects. The 3-hydroxy drugs include oxazepam, lorazepam, and temezepam. These are conjugated in the liver (to inactive substances); thus, they have shorter half-lives, and are less affected by age and other drugs. The triazolo class includes alprazolam, triazolam and adinazolam. These are oxidized, but with more limited active metabolites. Thus, they are somewhat shorter-acting than the 2-keto drugs. The mechanism of action relates to specific receptors on GABA receptors.

Indications for these medications include panic, generalized anxiety, specific and social phobias, mixed anxiety syndromes, insomnia, muscle tension, seizures, anesthesia, and alcohol withdrawal.

Side effects and risks include abuse potential, tolerance, withdrawal, dependence, and addiction. There is also an overdose potential, with rare deaths as single agents. Other side effects are of the sedative variety – namely, sedation, dizziness, weakness, ataxia, decreased motoric performance, and falls in the elderly. In addition, anterograde amnesia, nausea, hypotension (slight), and possibly dyscontrol have been shown in patients taking these drugs.

Although benzodiazepines can impair motor coordination, they don't have the acute toxic effects (respiratory depression) of barbiturates. However, benzodiazepines *can* produce respiratory depression if combined with other sedatives, such as alcohol. These acute effects can be antagonized by **flumazenil**, a competitive GABA antagonist.

Of most concern are the side effects of tolerance and withdrawal, and the related (but not identical) fear of addiction in patients who take benzodiazepines regularly. Though perhaps overstated by some, a risk does exist. The best predictor of a likelihood of developing a problem like addiction with these drugs is a previous history of addiction to other substances.

A related concern is the possibility of rebound anxiety once these drugs are stopped, which can be as serious as the original anxiety the drugs were meant to treat.

Because of these worries, benzodiazepines are often reserved either for short-term treatment of time-limited anxiety (e.g. worried preceding an upcoming surgery) or for intermittent anxiety (e.g. if a person gets infrequent panic attacks, say, less than once a month). In both of these cases, they may be preferable to antidepressants, in that antidepressants take weeks to work, and cannot be used intermittently (and it seems inappropriate to give daily antidepressants for an event that only happens once in a while).

5-HT1A Agonists
Buspirone is a novel agent, in the class of drugs called azaspirones. Buspirone's mechanism of action is very complex and, so far, it is not totally elucidated. Several different neuropharmacologic processes can be involved. Buspirone has an affinity for 5-HT_{1A} -receptors, moderate affinity for DA_2-receptors, and weak affinity for 5-HT_2-receptors but no affinity for the benzodiazepine receptor complex (on the GABA receptor) in vitro.   It is not useful for panic or other acute anxiety syndromes, but it may be **useful for generalized anxiety disorder**. It works like an antidepressant; in other words, it requires regular dosing and takes several weeks to work. There is little abuse potential and few side effects. Buspirone lacks the benzodiazepines' sedative, muscle relaxant, or anticonvulsant actions, and has no ability to affect benzodiazepine withdrawal symptoms. It is also surprisingly free of significant drug-drug interactions. However, it is not widely used; this means either that the drug isn't as effective in clinical situation than in "ideal" drug marketing studies, or that the patients who are most likely to benefit may not be the complicated anxiety disorders seen by psychiatrists. Thus, there is a bias against the drug.

Other novel treatments include β *antagonists ("beta blockers")* for social phobias and *neurosurgery* for OCD.

β antagonists (e.g. propranolol) are used especially for treatment of physical symptoms such as tremor and tachycardia. (Note: epinephrine can cause skeletal muscle twitch via $β_2$ agonist effects; this would be blocked by propranolol).

For more on **neurosurgery**, see the chapter on OCD.

Psychosocial/Behavioral Treatments For Anxiety Disorders:

Psychotherapies have been greatly successful for many of the anxiety disorders, sometimes more so than somatic treatments. An example of a well-studied effective treatment for anxiety is **cognitive behavioral treatment (CBT)**. CBT is based on learning theory; the idea is that people learn to develop automatic responses of fear or dread in relation to a stimulus. What is learned can be unlearned, and much of CBT is spent teaching the patient to tolerate the triggers of anxiety. In the case of phobias, the triggers are clear; in the case of panic disorder, the trigger is, in a sense, the anxiety itself, and the patient learns to tolerate their anxiety. This treatment may be the only thing that helps agoraphobia if it is associated with the panic (which, otherwise, often persists long after medications have prevented the panic).

Other examples of psychotherapy for anxiety include desensitization techniques for phobias. Often these are much more effective than any medication, and can truly cure the disorder, whereas medication will only provide symptomatic relief.

Other therapies may be more general, e.g. group support is also offered for PTSD patients. However, again this can be very effective in a complicated disease that often doesn't respond well to medication alone.

Some drugs commonly used for anxiety, sedation or for sleep

Name	Type	Approved for	Equivalent Dose (for benzos)	Half-life	Onset	Metabolism
Diazepam (Valium)	Benzodiazepine	anxiety, EtOH withdrawal, muscle spasm, preop sedation, seizures	5 mg/day	long	very fast	oxidation
Chlordiazepoxide (Librium)		anxiety, alcohol withdrawal, preop sedation	10	long	fast	N-dealkylation
Oxazepam (Serax)		anxiety, alcohol withdrawal	15	short	slow	conjugation
Lorazepam (Ativan)		anxiety, preop sedation	1	short	fast	conjugation
Clonazepam (Klonopin)		seizures, panic disorder	0.25	long	fast	reduction
Alprazolam (Xanax)		anxiety disorders, panic disorder	0.5	medium	fast	oxidation
Flurazepam (Dalmane)		sleep	15	very long	fast	oxidation
Temezepam (Restoril)		sleep	15	medium	medium	conjugation
Triazolam (Halcion)		sleep	0.5	short	fast	oxidation
Zolpidem (Ambien)	Benzodiazepine omega-1 receptor agonists	sleep		2 hrs	1/2 -1 hr	
Zaleplon (Sonata)		sleep		1 hr	1/2 -1 hr	
Buspirone	azapirone (5-HT$_{1A}$ agonist)	anxiety		N/A, usually given TID	1/2 -1.5 hr	N/A
Diphenhydramine (Benadryl)	Antihistamine	various: allergies, cold remedy.		3-10 hr	?	
Hydroxyzine (Vistaril, Atarax)		anxiety, pruritus, preop and postop sedation		?	2 hr	?
Antidepressants	*see the antidepressant table*					

Chapter 10. Obsessive-Compulsive Disorder

Phenomenology

Obsessive-compulsive disorder (OCD) is an **anxiety disorder** characterized by intrusive obsessions and repetitive compulsions, which cause distress or are a significant burden to the patient. ***Obsessions*** are *recurrent and persistent thoughts that are experienced as intrusive and inappropriate, causing marked anxiety.* ***Compulsions***, on the other hand, are *repetitive behaviors or mental acts carried out in response to an obsession and are aimed at preventing or reducing anxiety.* At some point during the course of the disorder, a patient has recognized that the obsessions or compulsions are excessive or unreasonable. These characteristic symptoms of OCD often interfere with a person's normal routine, occupation, or social activities and relationships.

Typical obsessions:
- Fear of getting dirty or contaminated by people or the environment
- Fear of infection, including AIDS or other illness
- Disgust with bodily waste or secretions
- Recurring thoughts of harming oneself or others
- Fear that a disaster will occur
- Fear of committing a crime
- Recurring distressing sexual thoughts or images
- Fear of thinking sinful or blasphemous thoughts
- Fear of blurting out obscenities or insults
- Extreme concern with order, symmetry or exactness
- Recurrent intrusive thoughts of certain sounds, images, words, or numbers
- Intense need to know or remember
- Fear of losing/discarding something important

Typical compulsions:
- Excessive or ritualized hand washing
- Prolonged or ritualized showering, brushing teeth, or toilet routine
- Repeated dressing and undressing
- Repeated cleaning of household objects
- Intense need to order or arrange things in a particular way
- Repeatedly checking locks, switches, faucets, appliances
- Checking to see no one has been harmed by the patient's actions
- Need to tell, ask, confess
- Repeating certain actions (e.g. going through doors)
- Checking that the patient did not make a mistake
- Constant seeking of approval or reassurance
- Touching certain objects in a particular way
- Repeated counting to a certain number or a multiple of that number
- Hoarding useless objects

Epidemiology

OCD has a lifetime prevalence of 2-3% in the United States. There is a bimodal pattern of onset of OCD, occurring in childhood and late adolescence/early adulthood. Two-thirds of cases have their onset earlier than age 25, and only 15% occur after age 35. About one-third of cases have onset in childhood or early adolescence. Males tend to have earlier onset.

Etiology/Pathology

Familial/Genetic Theories: Twin studies have shown that concordance rates for monozygotic twins are higher than that of dizygotic twins. OCD prevalence is higher if a 1st degree relative has OCD or Tourette's syndrome. There is also evidence that in some families with Tourette's, rates of both OCD and Tourette's are increased in biological relatives, which suggests that in these families, OCD and Tourette's may be alternative phenotypic expressions of the same underlying genetic defect.

Behavioral Theories: Two-stage classical instrumental conditioning model of OCD: Obsessions result from pairing mental stimuli with anxiety-provoking thoughts. Compulsions are neutral behaviors that have been associated with anxiety reduction and therefore reinforced.

Neurobiological Theories: Converging evidence from imaging, pharmacological and behavioral studies implicates **hyperactivity in frontal-subcortical thalamic circuits in the pathogenesis of OCD**. This theory holds that hyperactivity in these circuits leads to excess activity in frontal-subcortical systems giving rise to the behavioral disturbance in OCD.

Prefrontal cortex (orbitofrontal and anterior cingulate) → basal ganglia → globus pallidus → thalamus → prefrontal cortex

A series of functional imaging studies (PET, SPECT, fMRI) have demonstrated **increased perfusion and metabolism in the orbital frontal cortex, anterior cingulate gyrus, and head of the caudate nucleus in patients with active OCD**. Some studies have suggested that the hypermetabolism may have a right-sided predominance. **The hypermetabolism in these circuits can be reversed following successful medication, behavioral or surgical treatment of the OC symptoms**.

Cognitive Functions Of Frontal-Subcortical Structures Involved In The Development Of A "Worry Circuit" In Ocd:

- *Prefrontal cortex*: response inhibition, planning, error detection and mood regulation
- *Paralimbic cortex, orbitofrontal cortex, and amygdala*: integrating external stimuli with emotional states and modulation of arousal and intense emotion
- *Basal ganglia*: automatic filtering of stimuli and mediation of stereotyped behaviors
- *Thalamus*: gating of transmission of stimuli and refined information back to the cortex

Several finding implicate the serotonergic system in modulation of OCD symptoms:
- Serotonin Reuptake Inhibitors (SRIs) are uniquely effective in OCD.
- Serotonin partial agonists (mCPP) can acutely worsen OCD.
- Serotonin antagonists (metergoline, ritanserin) can provoke OCD symptoms in SRI responders.
- There is a tentative association between some variants in genes coding for serotonin system components and OCD.

Diagnosis

DSM-IV CRITERIA FOR OBSESSIVE COMPULSIVE DISORDER (OCD)

Either obsessions or compulsions:

Obsessions: Recurrent, persistent thoughts or impulses, experiences (sometimes) as intrusive and inappropriate, and cause distress.

The thoughts aren't realistic worries about real problems.
Person tries to ignore or suppress the obsessions.
The obsessive thoughts are recognized as such.

Compulsions: Repetitive behaviors or mental acts that are done in response to an obsession.

The behaviors are meant to reduce distress, or prevent a feared event, but are not realistic.

Differential Diagnosis And Comorbidity

OCD is often associated with other disorders such as depression (>50%), dysthymia, anxiety disorders such as social phobia and panic disorder, hypochondriasis, and eating disorders. Obsessive-compulsive symptoms are often seen in schizophrenia as well. There is a great deal of overlap with other repetitive behaviors such as **Tourette's Syndrome** (<50% have OCD, but 25% with OCD have tics).

Obsessive-Compulsive Personality Disorder (OCPD) is a personality disorder (see chapter on personality disorders) characterized by rigid overconcern with rules, sometimes so much that individuals lose the point of an activity. OCPD is usually seen without OCD in individuals and vice-versa, but OCD and OCPD may run together in families.

Course

Symptoms may be present for years before treatment is sought and those affected often suffer in silence. The disease follows a chronic waxing and waning course where 15% of patients have deterioration and 5% have episodes with interepisode recovery. Males tend to undergo a more malignant course than females.

Treatment

OCD can be treated with medication, behavioral therapy, and even surgical procedures. **Selective serotonin reuptake inhibitors (SSRIs) are the only medications currently approved for the treatment of OCD.** These include the Tricyclic antidepressant Clomipramine, and all of the SSRIs (see a fuller discussion of these in the Mood Disorders chapter).

Benzodiazepines may help blunt initial anxiety problems and insomnia. These are most often used in combination with antidepressants.

In general, combining medications and behavior therapy may work best, especially for patients who are unable to tolerate behavioral therapy due to severe anxiety (more than 25% in some series). Behavioral therapy involves exposing the patient to symptom-triggering situations and not allowing them to perform compulsive or avoidance responses. This gradual desensitization allows the patient to build up the ability to handle everyday situations.

Neurosurgery (anterior cingulotomy, capsulotomy, limbic leucotomy) should be considered a last resort. Recent analysis from Massachusetts General Hospital found about 30% of patients with severe, refractory OCD benefited from cingulotomy. Anterior capsulotomy, especially with the "double-shot" gamma-knife technique looks promising for patients with intractable and disabling OCD. 40% of patients were very much improved on the clinical global impression scale at 12 months after the procedure. There is often a delay after the procedure before symptoms improve.

Deep brain stimulation is a new approach described in a recent Lancet article (Nuttin et al., 1999), which is still early in development. It has markedly improved symptoms in a small number of severely affected patients who would otherwise be candidates for neurosurgery. Potential advantages over neurosurgery are that no brain tissue is destroyed, it can be titrated for maximum individual benefit, and it is reversible.

Chapter 11. Mood Disorders

What Is A Mood?

Mood is the **sustained tone of feeling** that prevails over time for a patient. A normal mood is defined as **euthymia** (literally "feeling normal"). However, euthymia can be disturbed if a patient feels a prevailing and generalized sense of anxiety, panic, terror, sadness, depression, anger, rage, euphoria, or guilt. At times, the patient will describe this mood. Otherwise, the clinician must inquire or use cues from the **mental status exam** to infer the patient's mood by evaluating affect. **Affect is generally defined as the observable manifestations of emotion, whereas mood refers to the subjective experience of emotion**. Particular attention should also be given to the quality of mood, noting its depth, length of time it prevails, and the degree of fluctuation.

What Is A Mood Disorder?

A **mood disorder** refers to a **sustained abnormality of a person's mood**. Most often, the abnormal mood can be thought of in levels: when the mood is too high, a person is **manic** and when the mood is too low a person is **depressed**. Mood disorders can also cause both physical changes as well as changes in the process and content of thought. One must be careful to distinguish transient deviations from euthymia and actual mood disorders. Most people experience highs and lows but maintain a general balance of mood; it is only when these highs and lows persist for certain durations, meet a certain level of severity and meet the global criteria of causing dysfunction in a person's life that they become mood <u>disorders</u>.

Depression

Phenomenology

"Feeling down, blah, blue, apathetic, sad, irritable, hopeless…depressed." This is how a patient experiencing a major depressive episode might describe his or her mood. Depression is one of the most common psychiatric disorders worldwide. A **major depressive episode** consists of a period of **at least 2 weeks** during which the patient has experienced a depressed mood or **anhedonia**, which is the loss of interest in formerly pleasurable activities. In addition, a major depressive episode is characterized by **suicidal ideation**, **changes in sleep and/or appetite**, **feelings of guilt**, **decreases in concentration**, **energy and/or psychomotor**

		Depression
General		Signs of poor self care, soft, slow speech, psychomotor retardation
Emotional	Mood	Dysphoric, angry or apathetic
	Affect	Blunted, sad, constricted
Thought	Process	Slowed process, though blocking
	Content	Guilty, self-deprecating, suicidal ideation
Cognition		Poor attention, concentration, registration, poor effort

activity. In the United States, it is estimated that depression costs $43 billion due to treatments, loss of productivity and work missed. Depression is associated with approximately 80% of suicides. Clearly, a major depressive episode extends beyond simply "feeling blue." It includes psychological and physical changes which decrease a person's ability to carry out and enjoy his or her life.

Despite the impairments caused by depression, not all patients will describe their depressed mood. A clinician can use the examination to identify patients who may be experiencing a major depressive episode. The depressed patient may present to the doctor with signs of **poor self care**. During the interview, the depressed patient may show **psychomotor changes** which can range from agitation, such as fidgeting, to retardation, such as slow, soft, monotonous speech or lack of speech.   The depressed patient may have experienced significant gain or loss of weight due to **appetite changes**. Patients with major depression may perform poorly on the **mental status exam** due to their decreased ability to concentrate, process information and/or due to a lack of effort. Older and younger patients will often complain of **physical ailments or irritability**. Patients who work or go to school might report a **drop in their performance**.   Many depressed patients report **decreased amounts of sleep**, however, others patients may **sleep too much**. The majority of depressed patients experience both a decrease in their energy level and a **lack of motivation**. Some patients will express a sense of hopelessness, the feeling that life is not worth living. When working with a depressed patient, it is important to inquire regarding any **suicidal intentions**, including the intensity and lethality of these thoughts. Once major depression disorder is identified, the clinician has a range of effective methods to treat this disorder.

Epidemiology

The Epidemiologic Catchment Area (ECA) study reports the following statistics on depression:
- *5% lifetime prevalence of depression*
- *2:1 female to male ratio*
- *socioeconomic factors not clear*

The National Comorbidity Study reported:
- *17% lifetime prevalence*
- *12% male, 21% female*

This study attributed its higher lifetime prevalence to more comprehensive questions. Of note, only people under 55 were surveyed. They proposed that their questions increased recall of major depressive episodes which may not otherwise have been easily remembered.

Etiology

The **limbic system** has been identified as playing a central role in the **mediation of emotional processes**. Thus, dysfunction of this system contributes to the etiology of depression. The limbic system consists of a number of highly interconnected structures that function to integrate internal and external inputs relevant to the **coordination of major neurobehavioral processes** (emotional, cognitive, vegetative, autonomic, and motor). The maintenance of euthymia depends on the interactions of a widely distributed network of **cortical-limbic** and **cortical-striatal pathways**.

It is possible to organize limbic and other related brain structures on a regional basis that also reflects discrete neurobehavioral functions:

- **Dorsal Compartment**

Functions subserved by the dorsal compartment are **attentional**, **cognitive**, and **psychomotor** in nature. The dorsal compartment consists of the **dorsolateral prefrontal cortex**, the **dorsal anterior cingulate**, the **inferior parietal cortex**, and the **striatum** (including the caudate, the putamen, and the nucleus accumbens). Some authorities would also include the **mediodorsal thalamus** in this compartment.

- **Ventral Compartment**

Functions subserved by the ventral compartment are **vegetative**, **autonomic**, and **somatic** in nature. This consists of the **hypothalamus** (including the hypothalamic-pitituary-adrenal [HPA] and hypothalamic-pitituary-thyroid [HPT] axes), the **insula**, the **subgenual cingulate**, the **hippocampus**, and the **brainstem** (including the midbrain and pons). Some authorities would include in this grouping the **anterior thalamus**.

- **Rostral Compartment**

This compartment is responsible for the **subjective experience** and **understanding of internal mood states** as well as the facilitation of **interactions between the dorsal and ventral compartments**. This compartment consists of the **rostral anterior cingulate**.

- **Indeterminate compartment**

Responsible for mediating several more **elemental emotional states**, such as **fear** and **anxiety**. This compartment is comprised of the **amygdala**.

Clinically significant depressive syndromes consist of abnormalities in emotional, cognitive, vegetative, autonomic, and motor functions. Based on a recognition of these clinical features, the compartmental approach articulated above can be used to formulate hypotheses about the neuroanatomy of depressive illness. Specifically, we can speculate that:

- **sadness and depression** are associated with functional **decreases in dorsal limbic (**anterior and posterior cingulate) and **neocortical** (prefrontal, premotor, and parietal) regions, causing **decreases in attention and cognition and the psychomotor retardation** seen in depressed patients.

- depression can be associated with functional **increases in ventral paralimbic** (subgenual cingulate, anterior insula, hypothalamus, and caudate) regions, which **increases the vegetative, autonomic and somatic functions** of this compartment.

Extrapolating from this, it is reasonable to hypothesize that effective treatment for depression must involve (a) the disinhibition of underactive dorsal regions and (b) the inhibition of the overactive ventral regions. It is important to note that this disinhibition of the dorsal regions may result from the therapeutic inhibition of the ventral regions.

Depression And Neurotransmitters

However, categorizing the dorsal and ventral compartment activities in depressed patients does not answer the fundamental question of what is causing this imbalance in activity. Most research on depression is currently focused on the role of neurotransmitters. Neurotransmitters can affect mood by binding at a postsynaptic receptor, resulting in a process of transduction, amplification and activation of an effector mechanism. Their ultimate consequence is some biological or behavioral response. Depression is known to be tied to levels of specific neurotransmitters. For example, depression can be induced by reserpine treatment, which depletes serotonin. In addition, most currently accepted antidepressant drugs act to increase monoamine neurotransmitter function in the brain. In the mid-1960's, investigators in the United States hypothesized that **depression was characterized by a deficit of norepinephrine (NE) function**. At about the same time, investigators in the United Kingdom posited **a similar role for serotonin (5-hydroxytryptamine, 5-HT)**. Over the past 35 years, the great preponderance of neurochemical research in depression has focused on these two neurotransmitters. The **catecholamine hypothesis of mood regulations** suggests that there is a **decrease in the catecholamines in depression and an increase in mania**. While it has not been possible to directly measure concentrations of these neurochemicals in the brains of depressed patients, many studies have measured decreased norepinephrine and serotonin metabolite concentrations in urine, plasma, and cerebrospinal fluid. There is also some evidence that pre-treatment levels of norepinephrine metabolites may predict response to medication. Moreover, animal models have also proven useful in identifying changes in these neurotransmitters associated with specific behavioral states. What is clear is that **many of the symptoms associated with depression appear to be mediated by serotonin** (e.g., poor impulse control, diminished sex drive, decreased appetite, irritability) **and norepinephrine** (poor attention and memory, diminished concentration, decreased socialization, altered states of arousal).

Other neurotransmitter systems have also been implicated in the pathogenesis of depression. For example, **dopamine (DA) appears to be critically involved in the mediation of reward and arousal**, and both of these functions are severely compromised in depression. Indeed, some drugs which increase dopamine function (e.g., cocaine and amphetamine) are well known to have elevating (euphorigenic) effects on mood, although these drugs are generally not effective in treating clinical depression. **Excessive acetylcholine (Ach) activity has also been associated with depressive symptoms**, but anticholinergic drugs have little beneficial effect on mood (acetylcholine

appears to be more centrally involved in the maintenance of normal memory processing). **Gamma aminobutyric acid (GABA)** is one of the most common neurotransmitters, and decreased plasma levels of GABA have been demonstrated in some depressed patients; in general, however, drugs which act to promote GABA function appear to have more beneficial effects on anxiety than on depression.

While an imbalance of neurotransmitter functions clearly plays a role in the etiology of depression, the original deficit theories have not been confirmed. In fact, a good deal of evidence suggests that the story goes way beyond neurotransmitters. **The receptor hypothesis suggests that a defect in the regulation of receptors for neurotransmitters causes depression.** This hypothesis is supported by evidence that medications for depression and mania induce changes in pre- and post-synaptic density of receptors. Although **antidepressants** quickly increase synaptic neurotransmitter levels, the **lag time of up to 6 weeks** before the drug's full effects take hold also suggests the drugs work via **regulation at the receptor level**, not at the neurotransmitter level. The **post-receptor hypothesis** implicates **changes in second messenger systems** in the etiology and pharmacological treatment of mood disorders. Antidepressant treatments have been shown to modify activity of the **G-protein** and **cyclic adenosine monophosphate (cAMP)** signal transduction cascades. Because certain alleles of G-proteins have been shown to correlate with responsiveness to antidepressants, antidepressants are hypothesized to work by modifying G-protein activity. Many antidepressants stimulate the cAMP cascade, which is located downstream of the G-protein. This results in increased production of **brain-derived neurotrophic factor (BDNF)**, which exerts a trophic effect upon cholinergic and dopaminergic neurons.

Depression And Neuropeptides

Changes in the function of specific **neuroendocrine systems** also have been consistently associated with depression. The largest body of literature documents abnormalities in the **hypothalamic-pituitary-adrenal (HPA) axis**, which includes **corticotropin-releasing hormone (CRH)** and **glucocorticoids** (specifically **cortisol**, the "stress hormone" which mediates metabolic and immune function). Numerous studies have demonstrated that **depressed patients have elevated CRH and free cortisol levels**. The **dexamethasone suppression test (DST)** introduces an exogenous source of glucocorticoids into the body and tests the regulation of cortisol levels. In normal physiology, the excess glucocorticoids work via negative feedback to reduce the level of CRH and thus lower cortisol output. However, many depressed patients maintain high CRH levels when given the DST. Stimulation of CRH receptors in the cerebral cortex, amygdala and locus coeruleus causes appetite suppression, sleep disturbances, behavioral problems and increased vegetative function, symptoms often evident in depressed patients. Interestingly, CRH is also under the regulation of various neurotransmitters (e.g., serotonin, norepinephrine, acetylcholine) which themselves have been implicated in depression.

Another large body of data has demonstrated abnormalities in the **hypothalamic-pituitary- thyroid (HPT) axis**, which includes **thyrotrophin releasing hormone (TRH)**, **thyroid stimulating hormone (TSH)** and the **thyroid hormones thyroxine**

(T4) and triiodothyronine (T3). Just as with CRF, several studies have demonstrated **increased levels of TRH in the cerebrospinal fluid of depressed patients** compared with age- and sex-matched healthy controls. The comorbidity between **hypothyroidism** and **major depressive disorder** provides another link between the HPT axis abnormalities and depression.

Other neuropeptides have also been implicated in depression. Numerous investigators have shown decreased levels of, and responsiveness to, **growth hormone (GH)**. Some studies have demonstrated abnormal responsiveness to **gonadotropins** (e.g., estrogen, progesterone, and progesterone metabolites), particularly in women with premenstrual mood syndromes. A few studies have suggested abnormalities in the regulation of posterior pituitary hormones **vasopressin and oxytocin** in depression, as well as in the **endogenous opioids** (endorphins and enkephalins), although these findings are less consistent.

Depression And Genetic Factors

A familial basis for depression has been well established for about 40 years. The concordance of depression supports a genetic link:

- *30% in dizygotic twins*
- *50% in monozygotic twins.*
- *Twin studies also suggest that the heritability of depression is similar to, or slightly greater than, the heritability for many other common medical conditions (e.g., adult-onset diabetes, hypertension).*
- *In general, an individual with a first-degree relative having depression is at approximately 3 times greater risk than the general population for developing depression him/herself.*

To date, a specific gene predisposing to depression has not been identified, although the gene which codes for the serotonin transporter has been implicated in several studies. Recent research suggests that the inheritance of **depression is likely to be polygenic** (i.e., reflecting the inheritance of several genes), rather than reflecting an abnormality at a single major locus.

Depression And Experiential Factors

It has long been recognized that **sustained or severe stress** can precipitate depressive episodes. Stressors which entail diminished self-esteem or personal loss are particularly depressogenic. Extensive research has now shown that individuals vary in their susceptibility to such stressors, reflecting characteristics of the individual as well as characteristics of the stressor itself. Interestingly, the identification of a precipitating stressor is of relatively little value in determining whether or not a given patient with depression will respond to antidepressant medication.

Pathology

There is no single clear pathologic finding that correlates with clinical findings, but there are many associated findings that give hints to the etiology of depression.

- Depressed patients display **alterations in circadian rhythms**, often demonstrating early morning awakening, early fatigue during the day and more REM sleep early on.
- Changes in **sleep EEGs**, including decreased total sleep and decreased REM and stage 4 sleep.
- **Strokes** in certain areas of the brain such as lesions in the dominant frontal or basal ganglia areas have been shown to predispose to depression
- As already noted, depressed patients do not show normal feedback of **HPA axis** with the dexamethasone suppression test.
- Functional imaging in depressed patients shows **hypometabolism** in certain areas, especially in the **prefrontal areas** (orbital cortex, basal ganglia).
- **Volume reductions** in the **prefrontal cortex** and **hippocampus** occur in depressed patients.
- **Reductions in neuronal and glial cells** in the **dorsolateral** and **orbital prefrontal cortex**, especially in the areas that receive the greatest amount of monoamine input.

Diagnoses And Criteria (DSM-IV)

Episodes versus disorders: Episodes should not be equated with disorders, but rather comprise clusters of symptoms that will be used in defining the actual disorders.

The Episode

> ### Major depressive episode
>
> 1. Depressive symptoms represent a change from previous functioning
> 2. Symptoms must occur for at least 2 weeks
> 3. Symptom list (5 or more, 1 has to be depressed mood or anhedonia)
> -mnemonic: "SIG E CAPS":
> - Sleep
> - Interest
> - Guilt
> - Energy
> - Concentration
> - Appetite
> - Psychomotor Retardation
> - Suicidal ideation
> 4. The Global Criteria (i.e. must "cause clinically significant distress or impairment in social, occupational or other important areas of functioning")

The Disorder

> ### Major depressive disorder
>
> Conceptually: this is the "classical" depressive diagnosis and requires the presence of a Major Depressive Episode (see above).
> Specifiers for Major Depression:
> - Level of Severity
> - Course Specifiers
> - Special types:
>   - Catatonic
>   - Melancholic
>   - Atypical
>   - Postpartum
> - Rule out:
>   - some other psychiatric disorder
>   - history of manic, mixed or hypomanic episode

Important Differential Diagnoses

- **Adjustment Disorders**

Adjustment disorders cover the concept of a response to a psychosocial/environmental stress. This disorder usually manifests as some emotional symptoms, but these do not cover the full spectrum of a mood disorder. If the response to the stressor meets criteria for another psychiatric disorder (like major depression or bipolar disorder), then one would diagnose that disorder instead of adjustment disorder.

- **Bereavement (Grief)**

 Similar rationale to the Adjustment Disorders.

- **Dysthymia**

This is a chronic depressed mood lasting 2 years in adults the symptoms of which fall short of the DSM definition of a major depressive episode.

- **Bipolar Disorder**

Absence of a manic or hypomanic episode differentiates major depressive disorder from the bipolar disorders.

- **Anxiety disorders**

Anxiety can share symptoms with depression, such as racing thoughts, sleep disturbance and irritability. Anxiety itself can actually be a symptom of depression. The primary difference is the prominence of the moods of dysphoria and anhedonia in depression. Anxiety and depression are commonly comorbid, however, so both may occur.

- **Psychotic disorders**

Schizoaffective disorder shares features of both schizophrenia and mood disorders. Schizoaffective patients have persistent psychotic symptoms with intermittent periods of mood symptoms. Although psychotic symptoms can occur in depressed patients, these symptoms are usually congruent with a depressed mood, i.e. hearing voices saying you are a failure. In major depressive disorder, once the depressed mood has lifted, patients will no longer experience these psychotic symptoms. However, with psychotic disorders, the patient will still experience psychotic symptoms even when they are not depressed or manic.

- **Substance Abuse disorders**

 Many substances can cause depressive symptoms either through use or as a result of withdrawal. However, depression should cease after 3-4 weeks of alcohol abstinence and 1 week after stimulant abstinence. Substance abuse disorders and depression are commonly comorbid.

- **Personality disorders**

Some patients with personality disorders frequently show depressive symptoms, especially patients with type B personality disorders such as borderline personality.   The difference between a patient with major depressive disorder and a patient with a

personality disorder is in the timing of depressive symptoms--major depressive episodes are stable over the course of days to weeks, whereas mood lability as a part of a personality disorder tends to vary rapidly throughout the day. There is a high incidence of comorbidity between depressive disorders and personality disorders.

- **Mood Disorder Due to a General Medical Condition**

In this condition, the mood disorder is judged to be directly related to the medical condition (not just a "reaction" to a disorder). Many medical illnesses can mimic mood disorders. It must be emphasized that diagnosis of a secondary mood disorders implies direct causation of a mood disorder by a physical phenomenon. For example, cerebrovascular accidents, particularly those occurring in the dominant fronto-parietal area, can cause the onset of depression. Quite often medical disorders feature one or more depressive symptoms, but generally not enough to meet criteria for a major mood disorder. Some medical illnesses in which depression-like symptoms are evident include:

  - **Cancer**: Adenocarcinoma of the pancreas can present with depression-type symptoms such as fatigue and poor appetite.
  - **Dementias**: Can present with social withdrawal and emotional distress that may be misperceived as a mood problem.
  - **Parkinson's Disease**: Associated bradykinesia can be misinterpreted as the psychomotor retardation of depression.
  - **Obsessive-Compulsive Disorder**: Some suggest that OCD is better included as a mood disorder.
  - **Multiple Sclerosis**: Patients display emotional lability as part of a pseudobulbar palsy. This can be misinterpreted as depression, but tends to be transient and to lack much emotional content.
  - **Hypothyroidism**: Can cause a depression-like condition that is unlikely to resolve unless the primary disorder is corrected.
  - **Adrenal problems**: Have been associated with both depressive- and manic-like conditions, for example Cushing's syndrome.

- **Substance-induced disorders**

In addition to the substance use disorders mentioned above, a wide variety of substances have been listed as having effects on mood. Some had been implicated in causing "true" mood disorders (ex. Reserpine causing depression). More often, they cause some symptoms associated with depression. Diagnosis of substance induced mood disorders can only be made when mood symptoms are directly due to the substance, are in excess of what would be expected for that substance, and are bad enough to warrant independent attention. To treat substance-induced disorders, try to remove the offending substance. In some cases, this cannot be done (i.e. a patient requiring high dose steroids). In that case, treatment with an antidepressant may help.

Comorbid Disorders

- **Anxiety**

Twin studies suggest a common genetic origin between anxiety and depression, with the differentiation of the two disorders determined by environmental factors. Anxiety is so frequently comorbid with depression that some question whether the two can really be considered distinct disorders at all. An example is panic disorder. As many as 50% of patients with panic disorder have comorbid depression. The presence of mixed anxiety and depression may predict a poorer prognosis and response to treatment.

> **Mixed Anxiety-Depression:** Observations of the common overlap between anxiety and depressive symptoms lead to the addition of this category to the DSM-IV. The presence of this common syndrome may predict a poorer course of illness.

- **Dysthymia**

The concurrent presence of both dysthymia and major depressive disorder is called **double depression**. By definition, dysthymia and major depression can only be recognized as coexistent if the dysthymia precedes the episode of major depression, or if there has been remission from major depression for at least two months. In double depression, the episodes of major depression appear to be superimposed upon a more chronic depression. Studies suggest that a person with double depression recovers more easily from a major depressive episode than a person with major depression alone. However, recovery is not to a state of euthymia and relapse is more likely.

Substance Abuse

The ECA study found that about 13% of those with substance abuse or dependence also have a lifetime diagnosis of a mood disorder. Similar results have been found in other countries. Alcoholism predicts a worse outcome for a mood disorder. When compared with non-alcoholics, alcoholics may be half as likely to recover from an episode of major depression after even 10 years. Some theories regarding the relationship

> **Self-medication:** Perhaps alcoholics are "medicating" their mood disorder. There is little data to support this theory and it is mostly based on clinical observation.
>
> **Forme frustre:** Perhaps alcoholism is part of a depressive spectrum of disorders. Twin studies suggest that the substantial comorbidity between major depression and alcoholism results primarily from genetic factors influencing the risk to both disorders. This does not mean, however, that major depression and alcoholism are manifestations of the same disorder. The two disorders appear to have both common and separate genetic factors that independently influence the susceptibility to either disorder.
>
> **Secondary mood disorders:** Perhaps alcohol causes depression. The strongest support exists for this theory. Investigators at a NYC VA Hospital withdrew depressed alcoholics, and observed depressive symptoms improve over the next 4 weeks without specific treatment of depression.

between mood disorders and alcoholism include the self-medication medication, alcoholism as a forme fruste, and the idea of secondary mood disorders. Other substance use disorders include nicotine dependence, cocaine and opioids. There is a high prevalence of depression in smokers, and this may negatively influence attempts to quit.

- **Psychotic Disorders**

It is difficult to judge comorbidity, as one can have psychotic depression, and an understanding of the longitudinal course is usually needed to differentiate the two. Psychotic symptoms that mirror the course of a mood disorder are likely secondary to the mood disorder, whereas symptoms that predate or outlast mood symptoms are more likely to be a comorbid disorder: Schizophrenic patients can often have comorbid mood symptoms. By definition, s**chizoaffective disorder** includes mood symptoms, however both the mood and psychotic symptoms would be accounted for in that single diagnosis.   The presence of psychotic features, whether as a symptoms of the mood disorder, or independently of it, has an adverse affect on the prognosis for the mood disorder.

> Other Psychiatric Disorders where depression is common:
> - **Somatoform Disorders:** particularly hypochondria and somatization disorder.
> - **Eating Disorders:** particularly anorexia nervosa.
> - **Attention Deficit Disorders:** perhaps a third of children with ADD will also have a mood disorder (usually major depression).

- **Depression in the Medically Ill**

Depression is common in medical patients. 2-4 percent of medical patients in the community, 5-10 percent of primary care patients, and 10-14 percent of medical inpatients are depressed. It is often unrecognized and untreated in the medical population. Such inadequate treatment may in part reflect the obsolete view that depressive symptoms triggered by medical illness are not the same as "clinical depression." Comorbid medical illnesses predispose an individual to a worse course of major depression.

> **Medical Outcomes Study (Wells et al.,1989)**
> Studied more than 22,000 patients receiving care from 523 clinicians. Focused on five specific diseases: myocardial infarction, congestive heart failure, hypertension, diabetes and depression.
>
> An additive effect on patient's functioning was observed between depression and other chronic medical illnesses, suggesting a worse course for the medically co-morbid depressed patients.
>
> In a 2-year follow-up, they found that certain medical disorders predicted a worse course of depression, whereas others did not. The most adverse association was between myocardial infarction and depression: depressed patients with a history of myocardial infarction had more frequent spells and worse symptoms of depression during the period of follow-up.

- **Personality Disorders**
  There are high rates of comorbidity between personality disorders and major depression, with a range from 30% to almost 90%. Inpatient samples typically see comorbidity in the **dramatic types of personality disorders** (cluster B: histrionic, narcissistic, borderline, and antisocial) because the impulsive behaviors associated with these personality disorders are likely to lead to hospitalization. Outpatient samples are more likely to show **anxious/fearful types of personality disorders** (cluster C). It is generally believed that depressed patients with a comorbid personality disorder are less likely to respond to somatic treatments. Few controlled studies have tested this belief; naturalistic studies, however, tend to support this assumption. This poorer response to treatment may, in part, reflect a greater severity of illness that results from the combination of major depression and a personality disorder. Some studies also suggest that depressed patients with borderline personality features may preferentially respond to monoamine oxidase inhibitors. A number of investigators have reported a relationship between comorbid borderline personality disorder, depression, and increased risk of suicide.

Course and Prognosis

The first major depressive episode **typically occurs in the mid-20's**, although there is a wide distribution ranging from childhood to old age. Depression has usually been characterized as a self-limited disease, with an average duration of six to nine months. Newer studies suggest, however, that a significant number of patients recover more slowly or do not ever fully recover. The greatest probability of recovery was early in the course of the illness, while chances of recovery diminish greatly if the patient hadn't yet recovered in the 1st year.

A number of studies suggest that depression, for many, may be a lifetime illness. Significant numbers of patients experience multiple episodes of depression.   Others never fully recover from their illness, but may stabilize at a level of dysthymia or sub-syndromal depression. **The risk of relapse for depressed patients is high**. At least 60% of patients with a single major depressive disorder will have a second episode, 70% of individuals with 2 episodes will have a third, and 90% of individuals who have had three episodes will have a fourth. Comorbid disorders can modify the course of major depression disorder. Up to 15% of depressed patients die from suicide.

The **Collaborative Depression Study (CDS),** a multi-center naturalistic study of the course of depression.

- 54% of the patients recovered within the first six months of the study.
- Approximately 70% recovered within one year.
- 81% were recovered after two years, 87% after 4 years and 88% after five.
- Thus, many of the patients who were still depressed after one years had not recovered by year five.
- In the CDS study, 22% of recovered patients relapsed within 1 year. Relapse was quicker if the patient had a history of recurrent episodes.

Predictors of **poor recovery/relapse** included:
- Long duration of illness
- Married status
- Inpatient hospital status at the time of intake
- Low family income
- Presence of other psychiatric disorders

Treatment

Antidepressant classes include tricyclics, monoamine oxidase inhibitors ("**First Generation Antidepressants**"), serotonin reuptake inhibitors and bupropion ("**Second Generation Antidepressants**") and others ("**Third Generation Antidepressants**"). Overall, there is a **70-80% response rate** to these drugs when used to treat major depression. They are also used for treatment of anxiety disorders and other disorders. When considering pharmacological treatment, it is important to consider the following clinical principles: target symptoms, response time to medications, the option of psychotherapy. Side effects and risks must also be considered, including the predictable effects, drug interactions, idiosyncratic effects, and allergic reactions. **A full response to antidepressants can take up to 6 weeks, although an initial response is commonly observable in approximately 2 weeks**. Due to receptor interaction, antidepressants can have anticholinergic effects, adrenergic effects and serotonergic effects.

- **Selective Serotonin Reuptake Inhibitors (SSRIs)**

SSRIs are the **first line treatment** for depression. SSRIs **inhibit serotonin reuptake**, which is the primary mechanism of serotonin termination. The main advantage may lie in **reduced side effects** compared to classical tricyclics. **Fluoxetine** (Prozac) is an example of an SSRI.

Side effects

SSRIs can cause **nausea**, **vomiting**, **headache** and **sexual dysfunction** for both males and females.

> **Serotonin Syndrome**.
> Combining several serotonin enhancing drugs can cause serotonin syndrome, characterized by euphoria, drowsiness, sustained rapid eye movement, overreaction of the reflexes, rapid muscle contraction and relaxation in the ankle causing abnormal movements of the foot, clumsiness, restlessness, feeling drunk and dizzy, muscle contraction and relaxation in the jaw, sweating, intoxication, muscle twitching, rigidity, high body temperature, mental status changes were frequent (including confusion and hypomania - a "happy drunk" state), shivering, diarrhea, loss of consciousness and death.

- **Tricyclic Antidepressants (TCAs)**

Tricyclics inhibit biogenic amine reuptake, and, depending on their structure, can be good **inhibitors of NE and/or 5-HT reuptake**. Most are not good inhibitors of DA reuptake. Secondary amines (**desipramine**) are more effective for NE neurons. Tertiary amines (**amitriptyline**) are more effective for 5-HT neurons. This is consistent with theories of

amine function and mood, although these compounds do not cause mood elevation in non-depressed subjects

Side effects

Tricyclic antidepressants can produce **antimuscarinic effects** (dry mouth, constipation, visual effects, sedation, drowsiness), α_1 blockade resulting in **postural hypotension** and can produce a **switch to mania in bipolar patients**.

- **MAO inhibitors**

The mitochondrial enzyme Monoamine Oxidase (MAO) degrades catecholamines. MAO inhibitors **decrease the degradation of NE, 5-HT and DA** to prolong their action. MAO inhibitors are **used when tricyclics and/or SSRIs are ineffective**. The drugs **phenelzine** and tranycypromine are examples of MAO inhibitors.

Side effects

MAO inhibitors can cause a **hypertensive crisis**, especially when one consumes foods with excess tyramine such as wine and cheese (hence "the wine and cheese effect" of MAO inhibitors). This is because tyramine, a metabolite of tyrosine, increases blood pressure. Usually tyramine is broken down by MAO, but this degradation does not occur with use of MAO inhibitors.

- **Newer Antidepressants**

The original first generation antidepressants were discovered serendipitously. Subsequent first generation antidepressants were attempts to copy the effects of these first agents. This group includes the TCAs and MAOIs.   Second generation agents were an attempt to isolate the likely therapeutic effects of antidepressants—hence make them more "selective."   These include the SSRIs. Unfortunately, this group turned out to be no more effective than the first group, although they were more tolerable (which can be of great practical significance). The next, or **Third Generation**, have largely been an attempt to combine effects in the hope of producing a more effective antidepressant. Examples of third generation antidepressants are the combination Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)   **venlafaxine** and **duloxetine**. **Nefazodone**, another third generation agent, combines both serotonin and norepinephrine transporter inhibition with antagonism of the 5-HT_{2A} and α_1-receptors.   **Mirtazapine**, a Mixed Serotonin/Noradrenaline Antagonist appears to have a direct effect on receptor sites, blocking both the noradrenergiç 2-autoreceptors as well as antagonizing 5-HT_2 and 5-HT_3 receptors, the latter effect which may help concentrate the action of serotonin on the therapeutically important 5-HT_{1A} receptors.

- **ECT**

First used in the 1930s for schizophrenia, this was found to be more effective for depression. It is used in conjunction with a muscle relaxant to avoid fractures. The mechanism by which ECT works is not known. It has been suggested that down regulation of β receptors in the CNS is a common feature of most antidepressant treatments. It has also been suggest that down regulation of α_2 presynaptic receptors

occurs, which would increase NE release receptor (or other protein) alterations, and would fit better with the time dependency for clinical effect. **ECT is used for refractory, life-threatening depression**.

- **Psychotherapy**

Cognitive-Behavioral Therapy (CBT) is based on learning theory. Learning theory suggests that behaviors are learned (i.e., made more likely to occur), usually through some sort of reinforcement. CBT applies learning theory to depression by suggesting that thoughts can also be learned, and that we learn to think a certain way and develop automatic thoughts and responses to situations. Depressive ways of thinking can become habitual. However, what we learn can be unlearned through practice, hence the rationale for CBT. CBT is an active therapy with lots of homework and assignments. **Interpersonal Therapy (IPT)** is based on the notion that depression is a response to loss or perceived loss in social network. It is also very active and practice based. Other psychotherapies shown to be effective include Psychodynamic Therapy and Marital/Family Therapy.

When To Choose Meds Versus Psychotherapy?

The weight of data supports the following conclusions:
- Medication is superior to therapy for severe depression.
- Medication and therapy are probably equal for mild to moderate depression.
- Combination of medication and therapy likely confer an advantage over either alone, perhaps a strong advantage.
- Psychotherapy may confer some protection against episodes, even after the therapy is over.

Antidepressants: Special Populations And Concerns:

Children And Adolescents

Much concern has been raised over the use of antidepressants after the U.S. Food and Drug Administration (FDA) raised concerns over a **possible link between antidepressants and suicide in children and adolescents**. As of October 2004, the FDA began requiring manufacturers of antidepressants to include a **black box warning** that the medications "increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) or other psychiatric disorders."   The basis of this warning was a pooled analysis of 24 short-term (4 to 16 weeks) placebo-controlled trials involving over 4,400 patients. The studies included a variety of antidepressants (mostly SSRIs) and childhood disorders (mostly depression). The analysis found an increased risk (4%) of suicidal thinking or behavior compared with placebo (2%). It should be noted that this increased risk remains low compared to the risk of suicide in patients with depression, and that no actual suicides occurred in any of the trials.

The warning has generated a good deal of controversy, given the nature of the analysis, the high rate of depression in children and adolescents, and the fear that depression will not be appropriately treated in light of this warning.   The American Academy of Child and Adolescent Psychiatry currently opposes the black box warning. They recommend continuing to use antidepressants, including SSRIs, for childhood and adolescent depression, along with appropriate education of the family regarding suicidal risk, and signs of behavioral toxicity, and appropriate patient monitoring (their full recommendations are available on their web site at www.acap.org).

Pregnant And Postpartum Patients

The commonly used antidepressants show **no compelling evidence of teratogenicity**, however definitive data are lacking.   SSRIs are most commonly used in pregnancy, largely for reasons of tolerability.   Fluoxetine has been reported to have low teratogenicity in pregnancy, however the data are limited to open, uncontrolled reports (Pastuszak et al, 1993). All antidepressants are secreted in breast milk, and though there are isolated reports of adverse behavioral effects associated with antidepressants systematic investigations are lacking.

Geriatric Patients

Elderly patients have a decreased muscle to fat ratio and have decreased efficiency of the hepatic microoxidase system. The result of both effects is that **antidepressants can have increased plasma levels and half-lives in the elderly**, which can exacerbate the side effects from antidepressants in elderly patients versus younger patients. We therefore hear the oft repeated adage to **"start low and go slow"** in elderly patients. Though this is prudent, many elderly patients have normal metabolisms and will require normal doses of antidepressants. There is support for the efficacy of virtually all antidepressants in the elderly depressed patient, though the majority of data is in the healthy elderly.

Suicidal Patients.

Similar to the discussion of child and adolescent data, there remains a concern in adults that antidepressants may raise the risk of suicide. Metanalyses (Mann and Kapur, 1991; Kapur et al, 1992) and one prospective study (Leon et al, 1999) suggest that if any pro-suicide effect exists, it is extremely rare, and not unique to any one antidepressant. At least one study suggests that fluoxetine may have a protective effect in some suicidal patients (Sachetti et al, 1991). **Though some concerns about potentiating suicidal behavior may remain, these should be balanced over the clear risk of suicide in patients with untreated depression**. As many suicidal patients choose to overdose on their medication, in patients considered at high risk for suicide, antidepressants with wide safety margins should be chosen. For this reason, **tricyclic antidepressants are often avoided**: doses of only 3-5 times the therapeutic dose can be lethal in adults (and the ratio is lower in children: doses of 5 mg/kg can be toxic). Most of the second and third generation agents are relatively safe in overdose, though bupropion can cause seizures in about 1/3 of overdoses.

Table 1. **Commonly used drugs for treating depression**				
	Class	$t_{1/2}$	Metabolism	Side Effects
Fluoxetine (Prozac, others)	Selective Serotonin Reuptake inhibitors (SSRI)	2-3 days (+ active metabolite, 7-10 days)	95% protein bound, liver met.: P-450 2D6 inhibition	nausea, vomiting, diarrhea, anorexia
Paroxetine (Paxil)		@ 1 day	95% protein bound, less affinity for p-450 inhibition.	
Sertraline (Zoloft)				
Citalopram (Celexa)				
Fluvoxamine (Luvox)		15 hours	80% protein bound, little P-450 2D6 inhibition, but does inhibit 1A2, 2C9, 3A4.	
Venlafaxine (Effexor)	Serotonin (5HT) and Norepinephrine (NE) Reuptake inhibitor	5 hours	25% protein bound, inhibits P450 2 D6.	SSRI side effects, + increased BP.
Duloxetine (Cymbalta)		12 hours	>90% protein bound. Inhibits both P450 2D6 and 1A2	Anticholinergic and SSRI side effects
Mirtazapine (Remeron)	?Antagonism of presynaptic receptors: increases 5HT and NE	20-40 hr	85% protein bound. Extensively metabolized in the liver; excreted in both the urine (75%) and feces (15%).	Sedation, weight gain, postural hypotension.
Nefazodone (Serzone)	SSRI + $5HT_2$ postsynaptic blockade	2-4 hours	99% protein bound, inhibits P-450 3A4	Nausea, vomiting, sedation.
Trazodone		6 hours	90% protein bound.	Sedation, postural hypotension
Bupropion (Wellbutrin)	dopamine agonism, ? Norepinephrine effect?	6-24 hours	80% protein bound	anxiety, agitation, insomnia.
Amitriptyline, Doxepin, imipramine, desipramine	Tricyclic antidepressants: inhibit reuptake of norepinephrine,	15-20 hours	liver metabolized, high individual variation	sedation, anticholinergic effects, weight gain, orthostatic hypotension.
nortriptyline, maprotiline		1-2 days		
protriptyline		3 days		
phenelzine, tranycypromine	monoamine oxidase inhibition	3 hours	liver metabolism, lots of drug interactions	orthostasis, dizziness, anticholinergic effects. Tyramine-cheese reaction.

Bipolar Disorder

Phenomenology

There are two recognized types of bipolar disorders: bipolar I disorder and bipolar II disorder. The diagnosis of **bipolar I disorder** is defined by a **single manic episode lasting for at least a week (or less if hospitalization is required)**, but generally the course of the disorder involves a cycling between mania and depression. During manic episodes, patients experience a heightening of mood. Patients may feel a sense of **euphoria** and **invincibility** or they may experience **dysphoria**, **irritability** and **delusions of persecution**. Manic episodes affect more than mood; a manic episode is characterized by symptoms other than heightened mood including **inflated self-esteem** or **grandiosity**, **decreased sleep requirement**, **flight of ideas**, **distractibility**, **increased activity level**, **psychomotor agitation and/or excessive involvement in pleasurable but risky activities**.

		Mania
General		Flamboyant appearance, rapid, pressured speech, agitation or increased movement
Emotional	Mood	Euphoric, irritable
Emotional	Affect	Heightened, dramatic, labile
Thought	Process	Flight of ideas, loose associations
Thought	Content	Grandiosity, delusions
Cognition		Distractible, poor concentration

A typical manic patient might appear well groomed, possibly displaying a dramatic change in appearance (e.g. a drastic change in wardrobe, make-up, or hairstyle). The manic patient will probably be very talkative and may initially appear more clever or entertaining; however, conversation will become tangential with puzzling jumps from one subject to another. Often a manic patient has an inflated sense of self-confidence and feels invincible. This often leads the patient to take on unrealizable projects, engage in risky sexual activities, spend too much money, and get in trouble with the law. After the manic episode has passed, the bipolar patient will often come to regret actions carried out during the manic episode. **The majority of bipolar I disorder patients also cycle into major depressive episodes**.

In **bipolar disorder type II**, the patient has experienced **at least one major depressive episode and at least one hypomanic episode** (see below for definition). The **hypomania** seen in bipolar disorder type II is of **shorter duration** and causes **less impairment** in the patient's life than the mania seen in bipolar disorder type I. Hypomanic episodes may actually result in increased productivity due to the person's

increased energy level. This contrasts with mania where the individual is too disorganized to accomplish much, despite a greatly augmented energy level.

While a genetic component to bipolar disorder has been identified, little is understood about the etiology of the disease. Still, there are effective methods of mood stabilization that are used to treat both types of this disorder.

Epidemiology

- *0.4% to 1.6% lifetime prevalence of bipolar I disorder*
- *1:1 male to female ratio*

Adoption and twin studies show a strong genetic component. In some families, bipolar disorder type I linkage has been established to a locus on chromosome 18.

- *0.5% lifetime prevalence of bipolar II disorder*
- *More common in women than men*

First-degree relatives of bipolar II disorder patients have higher rates of bipolar II disorder, bipolar I disorder and major depressive disorder, suggesting a genetic link between these disorders.

Etiology

The etiology of mania is unclear; however, **disturbances in biogenic amines** have been implicated. While norepinephrine metabolite levels are normal during mania, other neurotransmitters such as **dopamine**, **acetylcholine** and **serotonin** have all been implicated in manic and hypomanic episodes, as well as in the depressive symptoms that follow. The administration of alpha-methyltyrosine, which blockades DA synthesis, and/or antipsychotics, which block DA receptors can shorten the duration of a manic episode. L-DOPA administration can induce hypomania in patients. Physostigmine, which increases cholinergic activity in the brain, decreases mania. From data regarding dopamine and acetylcholine during manic episodes, it has been suggested that **mania can result from DA overactivity relative to acetylcholine**. Some studies have associated **serotonin receptor polymorphisms** with bipolar disorder and it is known that serotonin agonists used as anti-depressants can induce a switch to mania in bipolar patients.

Studies suggest that **alterations in GABA receptor subunits** and **decreased GABA neuron density** are involved in bipolar disorder. **Increased glutamate activity** may be associated with bipolar disorder, and antidepressants that increase glutamate receptor density can trigger a manic episode. Many of the anticonvulsants used to treat mania act to increase GABA and decrease glutamate functions.

Mania can be induced in predisposed patients in a variety of ways. As noted above, some drugs can trigger a manic episode, particularly antidepressants.   Sleep deprivation has been known to cause mania.   Light exposure, as with light therapy (for seasonal

depression) has also been reported to trigger manic episodes.   Several neurological injuries (see below) can also cause bipolar type symptoms.

The mechanism of depression in bipolar patients is presumably similar to the mechanism in major depressive disorder; however, this presumption has not been intensively studied. Some indirect data, particularly treatment studies, makes one wonder whether the depression in bipolar disorders is a different entity altogether.

Pathology

Some laboratory findings are abnormal in individuals with manic episodes versus normal individuals, although these are not diagnostic:

- Increased cortisol secretion
- Polysomnographic abnormalities
- Abnormalities in monoamine neurotransmitter systems

Diagnoses and Criteria (DSM-IV)

Episodes

Manic Episode

1. Symptoms must occur for 1 week (any duration if hospitalization is necessary)
2. Symptom list (3 or more--four if the mood is only irritable):
- grandiosity
- decreased need for sleep
- pressured speech
- flight of ideas
- increased distractibility
- increased activity/agitation
- increased engagement in risky activities
3. The Global Criteria (i.e. "sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features")

Hypomanic Episode

Basically the same as Manic Episode, except:
1. Symptoms can last only 4 days
2. The episode is not severe enough to cause marked social or occupational dysfunction.

Mixed Episode

Symptoms of both Major Depressive Episode and Manic Episode, meeting criteria for both

Disorders:

> ## Bipolar I Disorder
>
> The "classic" Manic Depressive Disorder
> 1. Has to have had at least one Manic or Mixed episode at least once.
> 2. Defined by the current or most recent episode

> ## Bipolar II Disorder
>
> 1. Must have had one or more Major Depressive Episodes, and
> 2. At least one Hypomanic Episode
> 3. But never have had a Manic Episode

> ## Cyclothymic Disorder
> 1. Essentially "a little bipolar", with milder mood fluctuations and episodes of hypomania
> 2. But never have had true Manic, Major Depressive or Mixed Episodes.

Differential Diagnosis

- **Mood disorder due to a General Medical Condition**

Secondary mania is directly traceable to a medical condition. For example, mania has been associated with injury to limbic areas on the right side of the brain, stroke, tumors and multiple sclerosis.

- **Substance Induced Mood Disorder**

Stimulant drugs can also cause euphoric mood, pressured speech, irritability, agitation and delusions. Antidepressant therapy can induce mania directly in a patient with a history of only unipolar depression, and corticosteroids can induce secondary mania.

- **Psychotic Disorders**

Many psychotic disorders also share delusions, irritability and agitation. However, psychotic patients have psychotic symptoms independent of mood symptoms, whereas bipolar patients do not.

Comorbidity

- **Personality disorders**
While many bipolar patients have personality disorders, the diagnosis of personality disorder in the bipolar patient can be influenced by the patient's mood at the time and by other comorbid conditions. In addition, many of the symptoms of personality disorders, such as narcissism, anxiety and paranoia overlap with the symptoms of mania.

- **Anxiety disorders**
 Studies have shown high comorbidity between bipolar disorder and anxiety disorders such as panic disorder, OCD, social phobia, and post-traumatic stress disorder.

- **Substance Abuse**
It is estimated that 60% of people with bipolar disorder also have a substance abuse problem.

Course of Bipolar Disorder

Onset of bipolar disorder usually occurs in the **late teens or early 20's**. In a little greater than half of bipolar patients, the first episode is a depressive episode. At least 10% of those who experience a first lifetime event of major depression will eventually become bipolar, so it is important to monitor any patient with major depressive disorder for later onset of mania. Manic episodes begin with a rapid onset and can last weeks to months. Manic episodes occur in three stages:

- **Stage I, or hypomania**
Stage I is defined by heightened mood, grandiosity, pressured speech, a rapid flow of ideas, decreased concentration, increased distractability, hyperactivity, more energy and less need for sleep.

- **Stage II, or acute mania**
In Stage II all of the symptoms of Stage I are present and intensified, in addition, the patient experiences either delusions of grandeur or paranoia.

- **Stage III, or delirious mania**
In Stage III, all of the symptoms of Stage II are exacerbated, and the patient also presents with hallucinations, incoherence and bizarre behavior.

While all manic episodes display Stage I and a majority progress to Stage II, only some reach Stage III. Recovery from an episode of mania is usually thought to be around 4 months, with great variance.

Predictors of **recovery** include:
- Symptoms: Patients with "pure" mania seem to recover faster and more completely than patients with mixed or cycling symptoms.
- History of previous mood episodes (both depressive and manic episodes): In one long-term study (20 years), 85% of bipolar patients relapsed. The number of symptom free intervals tends to decrease over time (see below).

The predictors of **relapse** are not clear, however, some proposed predictors include:
- low vocational advancement at illness onset
- depression
- number of previous episodes
- mixed symptoms
- comorbidity (especially with alcoholism)
- psychotic features when manic
- interepisode features

Bipolar disorder cannot only be debilitating, but it can be deadly. Approximately 10 to 15 percent of Bipolar I patients complete suicide.

There is some evidence that episode severity increases as a function of the number of episodes a person has had-i.e., for each recurrent episode to be more severe and to occur in closer succession than the previous one. This may represent a "kindling" phenomenon as has been seen in some models of epilepsy. This putative tendency for each affective episode to exacerbate the course of the disease is another reason for the emphasis that is placed on prophylactic treatment.

Treatment

Treatment for bipolar disorder is much more pharmacologically based than major depression. The treatment of acute mania and the prevention of future episodes may require different pharmacological approaches.

Lithium

Lithium was first used in 1949 by John Cade following lethargy production in guinea pigs. The mechanism of action is poorly understood, but probably at the level of the **second messenger systems involving adenylate cyclase and phosphatidylinositol**. Lithium has been shown to inhibit phosphatidylinositol creation and turnover, dampening this second messenger system, and possibly leading to mood stabilization. Lithium is a **first line treatment for acute mania** and is also used for **long-term (prophylactic) bipolar treatment**. Lithium may also prove useful for recurring unipolar depression. There is a **narrow range between the therapeutic and toxic doses of lithium**, so blood level monitoring for lithium toxicity is critical. Additionally, there is wide variability of lithium pharmacokinetics among different individuals; thus, optimum doses for an individual patient cannot be based on the dosage administered. While there is a 60% response rate overall, Lithium's efficacy is slow-- it **works in about 7-14 days**.

Side Effects of Lithium

At therapeutic doses, lithium can cause an **inflammatory response in the kidney**. Toxic doses, which are not too much higher than therapeutic doses, can damage kidney function. **Nausea, vomiting, abdominal pain, diarrhea, tremor, coma, death are all associated with increasing toxicity**. Diuretics and NSAIDS may increase lithium levels in the blood. Lithium use with antipsychotics may increase risk for neuroleptic malignant syndrome.

Anticonvulsants

Anti-epileptic drugs have shown some success in treating mania. **Carbamazepine**, which blocks the sodium channel opened by glutamate, slows the rate of neuronal recovery from the inactivated state. The mechanism of action of carbamazapine may relate to the process of "kindling," an idea derived from seizures in which repetitive subthreshold electrical stimulation of the brain eventually may lead to either a behavioral or a convulsive response. In this model of affective illness, repeated biochemical or psychological stresses would result in abnormal limbic neuronal sensitization.   Overall, efficacy of carbamazapine is 25-50%; it may be especially effective for dysphoric-type or mixed symptom mania.

Side Effects of Carbamazepine
The most common side effect is **sedation**; the most serious side effect is **agranulocytosis**. Patients should be warned of symptoms of bone marrow suppression (e.g., fever, sore throat, petechiae). Carbamazapine induces its own metabolism through induction of liver enzymes; thus, what is initially an effective dose may have to be increased later due to a drop in effective serum level following the induction of increased metabolism of the drug. Drug interactions are common with carbamazepine due to this same tendency to induce enzymes. Some drugs are metabolized faster in the presence of carbamazapine and many substances (such as erythromycin, ketoconazole and grapefruit juice) can raise carbamazepine levels, often drastically.

Though of interest, Carbamazepine is rarely used as a first line treatment for bipolar disorder, owing to its side effects. However, newer anticonvulsants are overtaking Lithium as a first line treatment for bipolar disorder. Among these, the strongest evidence is for the use of **Valproic Acid**, usually in the form of a sodium salt, (divalproex sodium) for the treatment of bipolar disorder. Valproate's mechanism of action is presumably similar to carbamazepine. Evidence of equal efficacy against mania for valproate and lithium has been shown in several studies, including a large placebo controlled study. Valproate may be particularly effective for bipolar patients who display rapid mood cycling.

Side Effects of Valproate
The most common side effect is **sedation**; the most dangerous side effect is **hepatotoxicity**. Valproate can cause **neural tube defects** (spina bifida, anencephaly) in pregnancy.

Other Anticonvulsants

Gabapentin has had several positive studies in bipolar patients, but they have generally been open studies will small populations. Gabapentin's mechanism of action is unknown. Its elimination half-life is 5 to 7 hours, and is primarily renally excreted. Gabapentin does not bind to plasma proteins and seems to be safe in overdose.

Lamotrigine is reported to possess moderate to marked efficacy in bipolar depression, hypomania, and mixed states; however, its efficacy in hospitalized mania is not clear. This is on the basis of 14 clinical reports involving 207 patients with bipolar disorder (66 with rapid cycling).   In practice, it is developing a reputation of being a preferred drug for bipolar depression: an entity considered hard to treat as standard antidepressants can be problematic in bipolar patients.

Newer anticonvulsants, such as **topiramate** and **oxcarbazapine** are promising for maintenance treatment of bipolar disorder, but more studies must be done. **Oxcarbazapine** is of interest as it is similar to Carbamazepine in structure.

Antipsychotics

Antipsychotics (formerly haloperidol, now more likely atypical antipsychotics such as olanzapine) have **rapid effects** and are also used to treat mania. Antidepressants appear to have both an **acute effect on mania** (which is likely a sedative effect), as well as a **prophylactic effect**. Thus antipsychotics can be used both as an acute intervention for a manic patient as well as a maintenance drug for bipolar disorder. Generally, typical antipsychotics such as **haloperidol** are only used only to treat acute mania, but the atypical antipsychotics are becoming more common in maintenance therapy, either alone or in combination with another mood stabilizer. **Olanzapine** is now generally considered a "first line" treatment for bipolar disorder.

Side Effects of Antipsychotics

Haloperidol has high **extrapyramidal side effects** and can cause **tardive dyskinesia** and **neuroleptic malignant syndrome** after long-term use. **Olanzapine** has **anti-muscarinic effects** such as sedation and dry mouth. While olanzapine long-term use can cause tardive dyskinesia and neuroleptic malignant syndrome, the risk is reportedly smaller with olanzapine versus haloperidol.

Sedatives

Sedatives such as **Lorazepam (Ativan)** and **Clonazepam (Klonopin)** may be as effective, and possibly faster and safer than antipsychotics for **treatment of acute mania**. Clonazepam is sometimes used also for maintenance, but is probably not as effective as other choices. Usually, high doses are used.

Antidepressants

Lithium, anti-psychotics and anticonvulsants can be effective to treat depressive episodes in bipolar patients, and these mood stabilizers should be used as the primary treatment. **Antidepressants can be used if the mood stabilizers are not effective; however, there is the danger that antidepressants will induce mania in the bipolar patient.** Therefore, if antidepressants are used with the bipolar patient, it is important to quickly taper down and discontinue their use once the depressive episode has been treated.

Commonly used drugs for treating bipolar disorder				
Class	T½	Metabolism	Common Side Effects	Serious Side Effects
Lithium	24 hours	4-6 days	nausea, tremor, increased urination and thirst.	CNS toxicity, renal toxicity
Valproate (Depakene, Depakote)	5-13 hours	2-5 days	nausea, vomiting, drowsiness, tremor, dizziness.	Thrombocytopenia, liver toxicity, pancreatitis
Carbamazepine (Tegretol)	12-17 hours	3-5 weeks	Drowsiness, dizziness, ataxia, nausea.	Thrombocytopenia, neutropenia
Haldoperidol (Haldol)			Very high extrapyramidal side effects	Tardive dyskinesia, neuroleptic malignant syndrome
Olanzapine (Zyprexa)	21-54 hours	1-2 weeks	Sedation, dry mouth.	Tardive dyskinesia, neuroleptic malignant syndrome (but risk is lower than with haloperidol)
Benzodiazepines (Lorazepam, Clonazepam)	Short for lorazepam, longer for clonazepam		Sedation, dizziness, weakness, ataxia, decreased motoric performance	Tolerance, withdrawal (with long term usage), addiction, paradoxical excitement

Chapter 12. Psychotic Disorders

Psychotic disorders can be described as the loss of contact with reality. A person with a psychotic disorder is unable to evaluate properly what is or is not real. Psychotic disorders represent the failure of normal thought and, hence, they can be categorized as "disorders of cognition" or "thought disorders". **Thought disorders** can be divided into different types. Most commonly, they are divided into **disorders of process** versus **disorders of content**.

Disorders of thought process involve a disturbance in the way one formulates thought. Thought disorders are inferred from speech, and often referred to as "disorganized speech." Historically, thought disorders have included **associative loosening**, **illogical thinking**, **over inclusive thinking**, and **loss of the ability to engage in abstract thinking**. Associative loosening includes **circumstantial thought** and **tangential thought**. Other types of formal thought disorder have been identified, including perseveration, distractibility, clanging, neologisms, echolalia, thought blocking and word salad.

> **Disorders of thought include:**
> **Perseveration:** the patient gets stuck on one idea or one thing and cannot move on from there
> **Clanging:** the connections between thoughts may be tenuous, and the patient uses rhyming and punning
> **Neologisms:** words that patients make up; often a condensation of several words that are unintelligible to another person
> **Echolalia:** the patient repeats back the words of other people, "parrots" people's speech
> **Blocking:** stopping mid-thought and being unable to continue with the thought
> **Word salad:** an incomprehensible mixing of meaningless words and phrases

Disorders of thought content include hallucinations and delusions. **Hallucinations** are perceptions without external stimuli. They are most commonly auditory, but may be any type. Auditory hallucinations are often voices, mumbled or distinct. Visual hallucinations can be simple or complex, in or outside the field of vision (ex. "in head") and are usually of normal color rather than black and white. Olfactory and gustatory hallucinations generally occur together as unpleasant tastes and smells. Tactile or haptic hallucinations may include any sensation—for example, an electrical sensation or the feeling of bugs on skin (formication).

Delusions are fixed, false beliefs, not amendable by logic or experience. There are a variety of types. Delusions are most commonly persecutory, but may be somatic, grandiose, religious or nihilistic. No one type of delusion is specific to any particular disorder (such as schizophrenia). Hallucinations and delusions are common across all cultures and backgrounds; however, culture may influence their content.

> Culture and religion must be considered when evaluating whether an event is a delusion or hallucination. In this context, a good rule of thumb is that if other people endorse it, it may not be a delusion or hallucination.

Another disorder of cognition is **lack of insight**. Truly psychotic persons have a breakdown in the ability to analyze their own thoughts rationally. This may best distinguish psychotic disorders (like schizophrenia) from "normal" hallucinations and delusions. Most psychotic patients thus have poor insight into their own illness, which can make compliance with treatment difficult.

Schizophrenia

Phenomenology

Schizophrenia is a chronic and often progressively deteriorating disorder of thought, affect, behavior and perception. The signs and symptoms of schizophrenia are divided into two categories:

- **Positive** or **Type 1 symptoms** consisting of the production of abnormal behaviors; and

- **Negative** or **Type II symptoms** which represent a deficiency of normal behavior.

Positive symptoms are disorders of commission, including things patients do or think. Examples are hallucinations, delusions, marked positive formal thought disorder (manifested by marked incoherence, derailment, tangentiality, or illogicality), and bizarre or disorganized behavior. **Negative symptoms** are disorders of omission, or things patients do not do. Negative symptoms include alogia (i.e., marked poverty of speech, or poverty of content of speech), affective flattening, anhedonia or asociality (i.e., inability to experience pleasure, few social contacts), avolition or apathy (i.e., anergia, lack of persistence at work or school), and attentional impairment. The exact significance of these symptoms is unclear. Perhaps they represent independent subtypes of schizophrenia? Probably not. Different stages of disease? Maybe-- positive symptoms tend to occur early on, negative symptoms later. Most patients have a mix of symptoms.

	Schizophrenia
General	Poor grooming and hygiene. Poor eye contact. Motor disturbances such as catatonia, stereotypy, mannerisms. Behavioral problems. Poor social function.
Mood	Anxious, angry or apathetic.
Affect	Affective flattening. Blunted, constricted, inappropriate.
Process	Tangential and/or circumstantial thinking. Loosening of associations.
Content	Delusions, hallucinations.
Cognition	May feature subtle deficits, such as difficulty with abstractions.
Insight and Judgement	May be lacking

Other symptoms associated with psychosis include **motor disturbances**, **disorders of behavior** and **disorders of mood and affect**.

Motor disturbances include disorders of mobility, activity and volition. Schizophrenic patients can exhibit either too little or too much movement. **Catatonia** (from Greek *katatonos*, "stretching tight") is a broad term used to describe a variety of movement disorders thought to have a psychiatric cause, usually (but not always) schizophrenia. For example, **Catatonic stupor** is a state in which (usually schizophrenic) patients are immobile, mute, yet conscious. They may exhibit waxy flexibility, so one can move their limbs into postures and the patient will retain these postures, like a wax doll. **Catatonic excitement** is uncontrolled and aimless motor activity.

Disorders of behavior may involve **deterioration of social functioning**-- social withdrawal, self-neglect, neglect of environment (i.e. deterioration of housing) or socially inappropriate behaviors (talking to oneself in public, obscene language, exposing self). **Substance abuse** is another disorder of behavior. Patients may abuse cigarettes, alcohol or other substances; substance abuse is associated with poor treatment compliance, and may be a form of "self-medication" for negative symptoms or medication effects.

> **Other disorders of movement include:**
> **Stereotypy:** repeated but non-goal-directed movement such as rocking.
> **Mannerisms:** normal goal-directed activities that appear to have social significance but are either odd in appearance or out of context, such as repeatedly running one's hand through one's hair or grimacing.
> **Mitgehen:** moving a limb in response to slight pressure on it despite being told to resist the pressure.
> **Echopraxia:** imitating the movements of another person.
> **Automatic obedience:** carrying out simple commands in a robot-like fashion.
> **Negativism:** refusing to cooperate with simple requests for no apparent reason.

Disorders of mood and affect include **affective flattening**, which is a reduced intensity of emotional expression and responsivity that leaves patients indifferent and apathetic. Typically, one sees unchanging facial expression, decreased spontaneous movements, poverty of expressive gestures, poor eye contact, lack of vocal inflections, and slowed speech. **Anhedonia**, or the inability to experience pleasure, is also common, as is emotional emptiness. Patients may also exhibit inappropriate affect, such as laughing at a funeral.

Epidemiology

The Epidemiologic Catchment Area (ECA) study reports the following statistics on schizophrenia:
- *1% lifetime prevalence of schizophrenia*
- *Relatively lower incidence rate of 1/10,000/year indicates this is a chronic illness*
- *1:1 male to female ratio*
- *However women have later onset and better psychosocial functioning*

The National Comorbidity Study reported
- *0.7% incidence of "Nonaffective Psychosis"*
- *This study included schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder and atypical psychosis.*

Etiology

Neurotransmitter Theories: The Dopamine Theory
Stated briefly, **the dopamine theory** suggests that **psychosis is caused by dysregulation of dopamine in the brain**. Two dopamine pathways are implicated in the etiology of schizophrenia:

- **Mesolimbic System:** This system is composed of the **dopamine neurons** from the **ventral tegmental area** that release dopamine to the **nucleus accumbens**. This system regulates **reward pathways** and **emotional processes** and is associated with the **positive symptoms** of schizophrenia.

- **Mesocortical System**: This system is composed of the **dopamine neurons** from the **ventral tegmental area** and the **substantia nigra**. The ventral tegmental area neurons included in the mesocortical system release dopamine to the **prefrontal cortex** and regulate **areas involved in cognitive processing** (i.e. the dorsal lateral prefrontal cortex that regulates executive function). The neurons in the substantia nigra release dopamine to the **basal ganglia** and regulate **areas involved with motor control**. The mesocortical system is associated with the **negative symptoms** of schizophrenia.

It is hypothesized that **hyperactivity of mesolimbic dopamine neurons and hypoactivity of mesocortical dopamine neurons are responsible for positive and negative symptoms, respectively**. There exists quite a lot of evidence for this theory:
- All available medications used to treat psychosis are dopamine blockers.
- A number of dopamine agonists (ex. L-DOPA, amphetamine) can cause psychosis.
- Use of amphetamine produces hyperactivity of mesolimbic dopaminergic neurons and is characterized by paranoid delusions, ideas of reference, hallucinations and agitation, all of which are positive symptoms of schizophrenia. Most normal subjects will develop psychotic symptoms if administered high doses of amphetamine over several days.
- Patients with schizophrenia will often experience exacerbation of psychotic symptoms following relatively low doses of amphetamine.
- Hypoactivity of mesocortical dopamine neurons has been correlated with severity of negative symptoms and impairment in performance on tests of prefrontal cortical function.

There are, however, problems with the dopamine neurotransmitter theory. Studies measuring dopamine metabolites in cerebrospinal fluid are inconclusive. Also, the theory does not account for the time lag until antipsychotics exert their effect: most of the

dopamine blockers start blocking dopamine immediately, yet it takes about 2 weeks for psychosis to resolve. Even if the theory is true, it probably represents a final common pathway for psychotic episodes, and does not tell us enough about individual causes of psychosis. Dopamine blockers used to treat schizophrenia are equally effective in treating, say, an LSD-induced psychosis. Refinements of neurotransmitter theories have come to pinpoint specific dopamine receptors.

Receptor Theories of Schizophrenia

Modulation of cortical function can be achieved via the **D1**, **D2**, **D3** and **D4 dopamine receptors**, leading to the "fine tuning" of information processing. D1 and D2 are high in the striatum, D3 is located in the nucleus accumbens and D4 is high in the frontal cortex and limbic areas. Evidence supporting this theory includes:

- The **downregulation of D1 receptors** in the **frontal cortex** may contribute to the hypoactivity of the mesocortical dopamine system and thus the negative symptoms of schizophrenia. In schizophrenics, there is a correlation between fewer cortical D1 receptors with the severity of negative symptoms and with poor function in frontal executive tasks.
- The expression of cortical D1 receptors is increased by the chronic antipsychotic treatment.
- Both **typical** and **atypical antipsychotics** exert their effects mainly via D_2 **receptor blockade** by reducing the regional dopamine hyperactivity associated with the positive symptoms of schizophrenia. There is a significant correlation between the D_2 receptor blockade and the clinical efficacy of antipsychotics in treating positive symptoms.
- **Atypical antipsychotics** also block the **D4 receptor**, and may block the D_3 receptor.

In addition to the dopamine receptors, the **serotonin 5-HT$_{2A}$ receptor** is also of relevance for the pathophysiology and treatment of psychosis. Hallucinogens, e.g. LSD, act as agonists at the 5-HT$_{2A}$ receptor and several antipsychotic compounds, especially the atypical neuroleptics, block the activity of the 5-HT$_{2A}$ receptor. Because LSD produces positive symptoms this suggests a possible role for serotonin in schizophrenia. Several postmortem studies have reported a decrease of 5-HT$_{2A}$ receptors in schizophrenia, but others have not. **Atypical antipsychotics act as 5-HT$_{2A}$ antagonists**.

Neurotransmitter Theories: The Glutamate Model

Alterations of the **cortical glutamatergic system** have also been implicated in schizophrenia. The glutamate model complements the dopamine model in presenting a hypothesis that explains the etiology of both the **positive** and **negative symptoms** of schizophrenia. Prolonged exposure to NMDA receptor antagonists such as phencyclidine (PCP) has been associated with chronic, severe psychotic illness displaying both the positive and negative symptoms of schizophrenia. Ketamine, which is also an NMDA antagonist drug, produces transient, mild psychotic symptoms, negative symptoms, and cognitive deficits in normal subjects, mimicking schizophrenia. When administered to patients with schizophrenia, ketamine produces transient exacerbations of psychotic symptoms.

Glutamate can bind to dopamine neurons and is hypothesized to produce regional hyperactivity and hypoactivity in dopamine neuron release. Chronic NMDA antagonist administration results in persistent elevation of dopamine release in the nucleus accumbens (mesolimbic system) and decreases in dopamine release in prefrontal cortex (mesocortical system). Because NMDA antagonists produce schizophrenic symptoms, schizophrenia may be a result of hypoactivity of the glutamatergic system. It is hypothesized that **a lesion in the hippocampal or frontal cortical glutamatergic circuits develops in schizophrenia.** This lesion then produces dopaminergic hyperactivity in the nucleus accumbens and hypoactivity in the frontal cortex contributing to both the positive and negative symptoms of schizophrenia.

Neural circuitry in schizophrenia
There is a focus on neurotransmitters and their receptors in schizophrenia since most treatments are based here. However, the etiology of the neurotransmitter imbalances may result from **structural brain abnormalities** in schizophrenics with changes in the brain architecture leading to **dysregulation of neurotransmitters and their receptors**. Specific areas of brain abnormalities are located in the **association cortex**, **medial temporal lobe**, **hippocampus**, **thalamus** and **basal ganglia**.

Schizophrenics are not properly able to "sort" or "filter" information from the external world to create a correct mental representation of an experience. Normally, incoming sensory information is processed by the **thalamus**, which sorts out what sensory information should be sent to different cortical areas for processing. After the **primary sensory cortex areas** receive the appropriate sensory information from the thalamus and process this information, it is sent to the association cortex. The **association cortex** integrates information from the primary cortices, subcortical structures, and brain areas serving memory (such as the medial temporal lobe) to create the representation of the sensory experience. Schizophrenics have been shown to **lack the ability to sort out what sensory information is or is not relevant and to filter and process the relevant information**. Dysfunction in such information processing areas of the brain may explain the disordered thought associated with schizophrenia.

The **association cortex** is composed of the cortical areas of the brain excluding the primary sensory cortices; the association cortex is of special interest in schizophrenia research because it includes the **dorsal lateral prefrontal cortex**, which modulates executive functioning. The association cortex of the human brain is a six-layered isocortex. Cortical layers 2 and 4 are defined by a high density of small interneurons. In contrast, layers 3 and 5 are defined by a high density of pyramidal cells that collect input through their dendrites and project to other cortical or subcortical areas. Interneurons are GABAergic cells and exert an inhibitory influence on their targets whereas pyramidal cells are glutamatergic and have an excitatory influence. Normal cortical function depends on an intricate balance of GABAergic inhibition and glutamatergic excitation, however, glutamatergic function is abnormal in schizophrenics. **Volume reduction of the association cortex** in schizophrenia has been reported in several postmortem and neuroimaging studies. Sulci are widened, indicating decreased brain tissue. Regional cerebral blood flow (rCBF) and glucose metabolism were found to be abnormal in the

frontal cortex at rest as well as during the performance of cognitive tasks.
Hypofrontality, a phenomenon in which patients cannot activate prefrontal cortex, has also been observed. This may explain the cognitive insufficiency and deficits in attention, alerting, memory, learning and shifting sets that schizophrenic patients display even before their first psychotic episode.   In normal patients asked to play a game where the sets of rules constantly change (as in the Wisconsin Card Sort Test), the prefrontal area would light up on a SPECT or PET scans, denoting increased executive function activity. However, schizophrenics do not show increased prefrontal areas activity on SPECT or PET scans, and thus do not perform well on such tasks.

Medial Temporal Lobe and Hippocampus
The **medial temporal lobe** serves two major functions in the brain: to integrate multimodal sensory information for storage into and retrieval from memory, and to attach limbic valence to sensory information. In schizophrenia, **mild cortical atrophy** has been reported in the **medial temporal lobe** along with **cortical neuronal disarray**. Focal abnormalities indicating abnormal alignment of neurons have been observed in medial temporal lobe structures such as the amygdala, entorhinal cortex, and especially the hippocampus.

There is evidence for the contribution of **hippocampal dysfunction** to the pathogenesis of schizophrenia. The serial circuitry of glutamatergic pyramidal and nonpyramidal neurons provides the structural basis for the formation of long-term memories. The hippocampus is also closely connected with the limbic system. The hippocampal formation is recruited via these connections to regulate emotion or to modulate information with respect to emotions. Most studies have found no change in the number of hippocampal pyramidal neurons but nonpyramidal cells in the hippocampus seem to be reduced by nearly half. Synaptic organization is changed, possibly indicating altered plasticity of the hippocampus in schizophrenia. The metabolism and blood flow of the hippocampus are increased at baseline in schizophrenia. Furthermore, **hippocampal and parahippocampal rCBF is increased during the experience of psychotic symptoms and correlates with positive symptoms (delusions, hallucinations)**.   As stated previously, a lesion in the hippocampal glutamergic circuit is hypothesized to produce regional variations in dopamine in the schizophrenic.

Thalamus
The **thalamus** is the gateway to cortical processing for all incoming sensory information, here represented by the three major systems: somatosensory, auditory, and visual. Two abnormalities of thalamic function have been proposed in schizophrenia. First, a **decrease in the total thalamic volume** might signify a breakdown of its sensory filtering capabilities, leading to increased stimulation of primary sensory cortical areas. Second, **dysfunction of the medial dorsal nucleus of the thalamus** leads to impairments of cortical association areas, especially the dorsal lateral prefrontal cortex.

Basal ganglia
The **basal ganglia** are primarily involved in the integration of input from cortical areas, particularly from the motor cortex. Post-mortem studies have provided evidence for an

overall **increased number of striatal neurons** and for a **change in the synaptic organization of the striatum** along with a **decreased number of nucleus accumbens neurons** in schizophrenics. Antipsychotic medicines act as D_2 receptor blockers, and thus act predominantly in the striatum where D_2 is most abundant. The volume of basal ganglia structures is increased in medicated schizophrenic patients.

Genetic Insights
Concordance rates for relatives of schizophrenics are remarkably high.
- *50% monozygotic twins*
- *40% 2 parents*
- *12-15% dizygotic twins*
- *12% 1 parent*
- *8% non-twin siblings*
- *10 times increased risk for schizophrenia with a schizophrenic first-degree relative*

These rates suggest that the disorder is inherited (strong concordance), but either is incompletely penetrant or that it is multifactorial, involving a gene that makes one vulnerable to some environmental trigger that must occur to actually result in the disease. Prenatal exposure to the flu or famine, obstetric complications or CNS infections in early childhood have all been theorized to contribute to a genetic predisposition towards schizophrenia.

Psychosocial Theories
It has been noted that schizophrenics often have **low socioeconomic status**. Social theories have been developed regarding the possible effects of environmental stressors on brain development. However, it appears that the correlation between socioeconomic status and schizophrenia may be better explained by the **"downward drift" theory**. This theory holds that because schizophrenics cannot hold a job or function well in society, they "drift" down to a lower status. Few people nowadays believe that schizophrenia and other psychotic disorders are other than biological disorders. Psychological factors such as stress, however, may mitigate the presentation (time of onset, degree of social impairment) and response to treatment.

Pathology

Certain **brain structure abnormalities** are consistently found in schizophrenics. These abnormalities may actually be related either to a congenital cause of the disease or to the degenerative process of the disease.
- Schizophrenics show **widened ventricles** on neuroimaging. This has been shown even early in their disease.
- Other **areas of the brain are decreased in size**, for example the anteromedial temporal lobe.
- A **reduced neuronal density** has also been found in the **prefrontal region, thalamus and cingulate gyrus**. In the areas of low neuronal density, there is no

gliosis or inflammation, both which are normally seen in degenerative processes. This suggests a possible developmental abnormality.

A substantial proportion of schizophrenic patients display non-localizing neurological signs called "**soft signs**." They may reflect defects in the integration of proprioceptive and other sensory information. They may represent a biological marker for schizophrenia.

Neurological soft signs include:
- abnormalities in **stereognosis** (the ability to determine what an object is through touch alone)
- abnormalities in **graphesthesia** (the ability to identify characters written on the skin using a dull pointed probe through touch alone, i.e. with patients' eyes closed)
- problems with balance
- decreased **proprioception** (the ability to sense the position, location, orientation and movement of the body and its parts)
- disorders of **smooth pursuit eye movement**
- sleep disturbance
- usually IQ is less than normal population for their age; it does not tend to decline over time
- poor accommodation to stimulus (this phenomenon is also present in relatives of schizophrenics)

Smooth eye pursuit movements are abnormal is 50 to 85% of schizophrenic patients. It is also abnormal in 45% of their relatives, even if they don't have schizophrenia. However, this phenomeneon is non-specific. It occurs in other disorders such as mood disorders.

Diagnostic Criteria (DSM-IV)

Schizophrenia

1. Patients have to have been psychotic at some time. This is referred to as the "A" Criteria of Schizophrenia.
2. Additionally, two or more of the following (1 if the delusions or hallucinations are severe) are required:
- delusions
- hallucinations
- disorganized speech
- disorganized behavior or catatonia
- negative symptoms
3. Symptoms must persist for 1 month (less if treated).
4. Finally, during the overall course of the disorder the patient must show some signs of disturbance (psychotic episode + prodromal or residual symptoms) for at least 6 months.
5. The Global Criteria (i.e. "for a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic or interpersonal achievement))

Subtypes of Schizophrenia
The purpose of subtyping is to improve prediction of likely effective treatment and/or course of illness. The types are listed as follows:

- **Catatonic subtype**

Dominated by *at least* two of the following: *motoric immobility* as evidenced by catalepsy or stupor, *excessive motor activity*, *extreme negativism* or *mutism peculiarities of voluntary movement* (e.g., stereotypies, mannerisms, grimacing), and *echolalia* or *echopraxia.*   (Thus, catatonia can be, broadly speaking, any disorder of abnormal motoric activity thought to be caused by a psychiatric disorder).

- **Disorganized subtype**

Characterized by disorganized speech and behavior, and flat or inappropriate affect and not meeting the criteria for catatonic schizophrenia.

- **Paranoid subtype**

Preoccupation with one or more delusions or frequent auditory hallucinations. Disorganized speech/behavior, catatonic behavior, and flat or inappropriate affect are *not* prominent in this subtype.

- **Undifferentiated subtype**

A residual category for patients meeting criteria for schizophrenia but not meeting criteria for the paranoid, disorganized, or catatonic subtypes.

- **Residual subtype**

Used for patients who no longer have prominent psychotic symptoms but who once met criteria for schizophrenia and have continuing evidence of illness.

Important Differential Diagnoses

- **Delusional Disorder**

Patients present with persistent delusions in this disorder, however the delusions are nonbizarre, i.e., they could seem plausible, thus differentiating this from schizophrenia. Hallucinations are not prominent. Generally, psychosocial functioning is okay, except for the direct impact of the delusions. For example, patients with delusional disorder might not take the bus because they think people are talking about them but might still be able to hold down a job.

Delusional disorder subtypes include:
- **Erotomanic type:** believes someone else is in love with the person. The other person may be famous or otherwise unobtainable.
- **Grandiose:** great but unrecognized talent or insight.
- **Jealous:** spouse/lover is unfaithful. This is often based on small bits of misinterpreted "evidence."
- **Persecutory:** most common subtype. The patient feels conspired against or cheated and often seeks legal/government action.
- **Somatic type:** the delusion centers around bodily function or sensation. For example, emitting foul odor or being infested with parasites.

- **Brief Psychotic Disorder**

This disorder is different in that the psychotic symptoms last for less than a month and there is full remission by one month.

- **Schizophreniform disorder**

This disorder shares the characteristic symptoms of schizophrenia except the duration is less than six months (but more than one month) including prodrome + episode + residual phase. Impaired psychosocial functioning is not required for the diagnosis; probably about 2/3 go on to become schizophrenics.

- **Schizoaffective Disorder**

Schizoaffective disorder has symptoms of both schizophrenia and of a mood episode. It must fulfill symptoms of "Criterion A" of schizophrenia. For diagnosis, at some point psychotic symptoms have to occur independently of abnormal mood (for at least 2 weeks). The mood episode may include either manic, depressed or mixed symptoms. These have to occur for a "substantial" amount of time; otherwise, a patient might more accurately be diagnosed as depressed or agitated schizophrenic.

- **Shared Psychotic Disorder**

Also called Folie à Deux, this disorder has two components. The inducer or "primary case" is a person who already has some psychotic disorder. There is a second person who is in close relationship with the inducer and who does not have a psychotic disorder. The inducer (with the psychotic disorder) convinces the second person (without the psychotic disorder) that a delusion is true. The non-psychotic second person is usually in a dependent relationship with the inducer. This second person rarely seeks treatment; rather, shared psychotic disorder comes to attention when the inducer is treated. Treatment is to separate the second person from the inducer.

- **Psychotic Disorder Due to a General Medical Condition**

There is a long list of medical conditions that can cause psychotic symptoms and thus justify a diagnosis of Psychotic Disorder Due to a General Medical Condition. You would not want to make the diagnosis of, say schizophrenia, without ruling these diagnoses out. Some examples of medical conditions with schizophrenia-like symptoms include:

  - **Delirium**: This is an acute confusional state with multiple possible etiologies that can cause delusions and hallucinations. Usually delirious delusions and hallucinations are poorly formed, not very elaborate, and they occur in a setting of "clouding of consciousness."
  - **Dementia**: Disorders such as Alzheimer's can cause delusions and hallucinations. Typically these are persecutory delusions--after losing a wallet, an Alzheimer's patient might accuse a loved one of stealing it. Delusions and hallucinations again tend to be poorly formed, not elaborate, and thus would not justify a second diagnosis of a psychotic disorder.

- o **Neurological Disorders**: Such as temporal lobe epilepsy, tumor, stoke and brain trauma
- o **General Medical disorders**: Such as endocrine and metabolic disorders (like porphyria), vitamin deficiency, infections, autoimmune disorders (like systemic lupus erythematosus) or toxins (like heavy metal poisoning)

- **Substance-induced disorders**

Medications and drugs that can cause psychotic symptoms may include stimulants (amphetamines, cocaine), hallucinogens (PCP), and anticholinergic medications. Alcohol withdrawal (delirium tremens), and barbiturate withdrawal can also manifest with psychotic symptoms. Because antipsychotic medicines can produce extrapyramidal side effects, it is important to differentiate schizophrenic catatonic behavior from antipsychotic induced movement disorders.

- **Mood Disorders**

Mania and depression may cause delusions or hallucinations, but these only occur within the context of the mood disorder and will cease upon treatment of the mood disorder.

- **Anxiety Disorders**

Patients with anxiety disorders share some symptoms with schizophrenics. Patients who experience panic attacks may report they feel they are "going crazy." Patients with obsessive-compulsive disorder may have obsessions that are so severe they reach the point where they seem like delusions. However, classically speaking, these symptoms experienced by patients with anxiety are ego-dystonic, meaning that the patient has good insight into the abnormality of their behavior.

- **Personality Disorders**

Especially Cluster B patients (Borderline Personality Disorder, for example) can show elements of psychosis as well as delusions. However, symptoms tend to be short lived, as opposed to the chronic symptoms of schizophrenia.

Comorbid Disorders

Comorbidity is very common. In one study of new-onset psychosis, about 50% of patients had some other medical or psychiatric disorder. The most common of these are **substance abuse** and **mood disorders**.

- **Substance abuse**

Substance abuse is more common in schizophrenics versus in the general population. Substance abuse is associated with poorer outcome. Eighty to ninety percent of schizophrenics smoke cigarettes and a high percentage abuse alcohol.

- **Mood disorders**

60% of Schizophrenics are reported to have depressive symptoms. However, depression is difficult to diagnose, as it overlaps with (negative) symptoms of schizophrenia and medication side effects.

- **Medical disorders**

Medical problems are also more common in psychotic individuals than in the general population (17% in one study). These patients tend to be older. They have a higher incidence of diabetes. In chronic medical disorders, schizophrenia is associated with a poorer outcome.

- **Anxiety disorders**

Obsessive compulsive disorder and panic disorder are common in schizophrenic patients.

Course And Prognosis

Schizophrenia tends to be a chronic disease with a **variable course**. It most commonly starts in **late adolescence/early adulthood**. It rarely occurs in children. Women are more likely to have a later onset and generally tend to have better psychosocial functioning. Schizophrenia occurs throughout the world, regardless of site or culture. Schizophrenia has three stages of disease:

(1)   Prodromal phase
The prodromal phase precedes the active phase of illness by many years. It is characterized by **negative symptoms** such as social withdrawal, deteriorating grooming, unusual behavior, outbursts of anger and other subtle changes in behavior and emotional responsiveness.

(2)   Active phase
Psychotic symptoms ("Criterion A") predominate in the active phase. Onset of the active phase generally occurs between the late teens and early thirties. Onset can be acute, occurring over weeks, or gradual, occurring over years. A particular stressor (such as moving away to college) may precipitate onset. The age of onset has prognostic significance.

(3)   Residual phase
Negative symptoms predominate in the residual phase (similar to the prodromal phase) although affective flattening and role impairment may be worse. Psychotic symptoms may persist, but at a lower level of intensity, and they may not be as troublesome to the patient.

There are **four possible outcomes** to psychotic episodes:
- **Complete resolution**, with or without treatment.

Complete resolution of psychosis is typical of brief reactive psychosis, and medical/substance related causes of psychosis. It can also be associated with mood disorders with psychotic features.

- **Repeated recurrences with full recovery every time.**

These are more typical of mood disorders with psychotic features (ex. Bipolar Disorder).

- **Repeated recurrences in which recovery is incomplete.**

In this outcome a persistent defect state develops. This is typical of delusional disorder as well as schizophrenia.

- **Progressive deterioration.**

Progressive deterioration is typical of schizophrenia, where symptoms may alternate between positive and negative but become worse with the course of the disease.

> One review suggested that after a first admission for a psychotic episode:
> - 1/4 of patients had no hospital readmission during follow-up
> - 1/4 had continuous hospitalization during follow-up with moderate to severe intellectual or social impairment
> - 1/2 had an outcome intermediate to those.

Predictors of a **good outcome** include:
- acute onset
- short duration of active phase
- good premorbid functioning
- affective symptoms
- good social functioning
- higher social class

Predictors of a **poor outcome** include:
- insidious onset
- long duration (chronic)
- personal and/or family history of psychiatric illness
- obsessions or compulsions
- assaultive behavior
- poor premorbid functioning
- poor psychosocial functioning
- neurological soft signs
- indications of brain structural abnormalities
- lower social class
- family history of schizophrenia

Treatment

Antipsychotics, also known as **neuroleptics**, are used to treat schizophrenia. The goals of treatment include **managing acute symptomatic disturbances**, **maintenance therapy** and **prophylactic therapy** to decrease future psychotic episodes. Current pharmacological treatments for schizophrenia all possess dopamine **D2 receptor antagonism**. Initially, dopamine antagonists increase firing rates of dopamine neurons in the substantia nigra and ventral tegmental area, presumably acting via presynaptic D2 autoreceptors. **Two to four weeks after initiation of treatment** with dopamine antagonists, a substantial proportion of dopamine neurons become electrically silent. **The depolarization blockade of mesolimbic ventral tegmental neurons is thought to play a role in antipsychotic efficacy.**   In addition to altering firing patterns of dopamine neurons, subchronic treatment with D2 receptor antagonists increases postsynaptic D2 receptor density, which is associated with behavioral "supersensitivity" to dopamine agonists such as amphetamines.

There are **two major classes** of antipsychotic drugs:

Typical Antipsychotic Drugs (I.E. Haloperidol)

These are relatively **selective D2 antagonists**. They are moderately effective for **positive symptoms** in approximately 70% of patients. **Negative symptoms** generally show little to no response to the D2 blockade. Cognitive deficits also exhibit minimal to no response to conventional antipsychotics. The link between dopamine D2 receptor blockade and antipsychotic efficacy is strengthened by the highly significant correlation between D2 receptor affinity and clinical potency of the conventional antipsychotic agents. Similarly, striatal D2 receptor occupancy of 65% or greater has been associated with clinical response in vivo using PET ligand binding studies.

Side Effects of Typical Antipsychotics:
Because D2 receptors are located primarily in the striatum, **extrapyramidal side effects** are typically observed with the typical antipsychotics, which have an occupancy greater than 80%. Extrapyramidal side effects can include:
- o Parkinsonian- like rigidity
- o Bradykinesia
- o Tremor or akathisia, which presents as physical restlessness or a subjective feeling of restlessness

Treatment with typical antipsychotics can also cause **neuroleptic malignant syndrome**, which manifests as delirium, fever, rigidity and autonomic instability (tachycardia, diaphoresis, and labile blood pressure). Approximately 2 to 3% of schizophrenic patients who are treated chronically with neuroleptics develop tardive dyskinesia. **Tardive dyskinesia** most commonly manifests as choreiform movements of the face, including tongue thrusting, lip smacking, grimacing, blinking and puckering. Unfortunately, tardive dyskinesia is frequently chronic; discontinuation of neuroleptic treatment often

does not offer relief. Neuroleptics can also produce increased levels of prolactin since dopamine usually inhibits release of this hormone.

Atypical Antipsychotic Drugs

Atypicals differ from classical dopamine antagonists in possessing (perhaps) greater efficacy for both positive and negative symptoms while producing fewer neurological side effects than the classical agents possess. The atypical antipsychotic clozapine was found to exert superior antipsychotic efficacy at doses producing only 20%-40% D_2 receptor occupancy.   Clozapine has a **higher D_4/D_2 blocking ratio** than classical neuroleptics. The increased ratio of D_4/D_2 is hypothesized to **decrease motor side effects** in the atypicals versus the typical antipsychotics. Clozapine also acts at serotonin $5\text{-}HT_2$, $5\text{-}HT_6$ and $5\text{-}HT_7$ receptors, alpha-adrenergic receptors, histaminic receptors and muscarinic receptors, which could relate to its clinical profile. Clozapine has a relatively **higher 5-HT2$_A$ blockade versus D_2 blockade**, which has been shown to reduce extrapyramidal side effects and contribute to increased efficacy for negative symptoms. This combination of relatively higher $5\text{-}HT_{2A}$ over D_2 affinity has been the cornerstone for development of the family of atypical antipsychotic agents, which have followed clozapine, including **olanzapine** and **risperidone**.

Side Effects Of Atypical Antipsychotics:

The atypical antipsychotics do not produce tardive dyskinesia as often as the typical antipsychotics due to the lower D_2 receptor blockade. While clozapine is thought to be clinically superior to other antipsychotics, it has so many non-neurological side effects that it is not often prescribed. A very serious side effect of clozapine is **agranulocytosis**, a large decrease in white blood cells that leaves patients susceptible to infections. Any patient on clozapine must have white blood cell counts frequently. Olanzapine and risperidone are antipsychotics that do not cause agranulocytosis, and thus are more frequently prescribed. Patients on atypical antipsychotics may experience a significant **weight gain** and have increased risk for developing **diabetes**.

Other Somatic Treatments

These include electroshock therapy and benzodiazepines. **Electroshock therapy** may be useful for catatonia, but is otherwise of little use in schizophrenia. **Benzodiazepines** are used for controlling agitation associated with psychosis. They may be as useful as antipsychotics in the acute setting if your main goal is to calm a patient down. These are safer (particularly in younger patients) than antipsychotics, but are not for long term management. **Frontal lobotomy** was at one time popular as a treatment for schizophrenia because it made patients more docile, however, it is no longer utilized.

Psychosocial Treatments

Psychosocial treatments are rarely used as a primary therapy. There is good data to suggest that psychosocial treatments can help schizophrenic patients improve

functioning, particularly social functioning. Therapy tends to be educational and supportive rather than "insight oriented." It is focused on the practical needs of the patient. Therapy with family members is thought to be useful, both in helping them to cope with an ill relative, as well as educating them in useful approaches to the patient. One study has been influential in showing that family therapy together with medication is more effective than medication alone in preventing relapse.

Hospitalization.

In the past, long term institutionalization was the treatment for schizophrenia. Since the 1960's however, and the rise of the Community Mental Health Movement, great efforts have been made to keep chronic psychiatric patients in the community. Nowadays, most schizophrenics are hospitalized only acutely for specific problems (e.g. exacerbation of their psychosis).

Drugs used to treat psychosis					
	Class	*Relative Potency*	*Kinetics*	*Common Side Effects*	*Serious Side Effects*
Chlorpromazine (Thorazine)	Phenothiazine	100 mg	$t_{1/2}$=12 hrs, liver metabolized	Orthostatic hypotension, high anticholinergic disorder effects, low to moderate extrapyramidal side effects (EPS)	Tardive dyskinesia, neuroleptic malignant syndrome
Thioridazine (Mellaril)		100 mg	little known, t½ @ 10-30 hours, metabolized in liver		
Fluphenazine (Prolixin)		2 mg		high EPS, low anticholinergic	
Perphenazine (Trilafon)		8 mg			
Trifluoperazine (Stelazine)		5 mg			
Thiothixene (Navane)	Thioxanthine	4 mg			
Haloperidol (Haldol)	Butyrophenone	2 mg	probably no active metabolites.	Very high EPS, very low anticholinergic	
Clozapine (Clozaril)	Atypical Antipsychotic	50 mg	12 hours with large range	high anticholinergic, high sedation, hypotension, rare EPS. Rare but reported agranulocytosis sialorrhea, weight gain glucose intolerance	agranulocytosis (requires blood monitoring)
Quetiapine (Seroquel)		N/A		rare EPS and anticholinergic, moderate sedation and hypotension weight gain glucose intolerance	tardive dyskinesia and neuroleptic malignant syndrome possible, but much more rare than above agents.
Olanzapine (Zyprexa)				very low EPS and anticholinergic, moderate sedation weight gain glucose intolerance	
Ziprasidone (Geodon)				Rare arrhythmia (QT prolongation).	
Aripiprazole (Abilify)				Similar to other atypicals, somewhat less sedation.	
Risperidone (Risperdal)				low EPS, very low anticholinergic, low sedation, moderate hypotension glucose intolerance	

Chapter 13. The Cognitive Disorders.

Phenomenology

Dementia is a disorder of cognitive function that can affect attention, concentration, language function, memory, visuospatial ability, perceptual ability, emotion, personality, cognition (conceptualization, abstract reasoning, calculation, and judgment) and general intelligence.

You should be able to distinguish between **cortical** and **subcortical** dementias.

CORTICAL DEMENTIAS
reflect dysfunction of the cerebral cortex, and are characterized by *amnesia, aphasia, apraxia*, and *agnosia*. Classic example is Alzheimer's disease.

SUBCORTICAL DEMENTIAS
reflect dysfunction of the deep gray and deep white matter structures, including the basal ganglia, thalamus, brain-stem nuclei, and the frontal lobe projections of these structures. They are characterized by *disorders of arousal, attention, motivation,* and *the rate of information processing*; this manifests clinically as psychomotor retardation, defective recall, poor abstraction and strategy formation, and mood and personality alterations such as depression and apathy. Classic example is Parkinson's disease. Other examples include HIV dementia and Huntington's disease.

Classic examples of dementia:

Cortical = Alzheimer's
Subcortical = Parkinson's

Some definitions:
Amnesia = a loss of memory
Aphasia = impairment of the ability to communicate through speech, writings or signs because of brain dysfunction
Apraxia = the inability to perform purposive movements although there is no sensory or motor impairment
Agnosia = loss of comprehension of auditory, visual, or other sensations although the sensory sphere is intact

Epidemiology

Dementia affects between 2-4 million Americans.
5-7% of those over 65
20% of those over 80

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Different types:

	Percent of Dementias
Alzheimer's	50%
Mixed	15-20%
Vascular	17-29%
Pick's	13-16%
Alcoholic Dementia	7%

Dementia accounts for at least 1/2 of all nursing home beds.

Financial impact: present cost is estimated to be around 12 billion dollars. Estimated to be 30 billion by 2030.

Etiology/Pathology

ALZHEIMER'S DISEASE
Pathology is characterized by **neuritic plaques**, **neurofibrillary tangles**, and **granulovacuolar** degeneration.

Etiology is unknown. Some hypotheses include:

Acetylcholine (Ach)
Decrease in Ach
Selective degeneration of the basal nuclei of Meynert, which control central cholinergic innervation.

Genetic

About 10% of Alzheimer's patients report other affected family members. There is conflicting data from molecular genetics; marker on chromosome 21 has been claimed and challenged.

Microtubule And Other Cellular Damage Hypotheses--

Aluminum

Most popular environmental candidate
Seems to be associated with senile plaques

Glutaminergic

Degeneration of glutaminergic nerve terminals

Neuritic Plaques are clusters of granular or filamentous materials with dense argrophylic core. They are composed of amyloid and mucopolysaccharides and located throughout the cortex, but especially in the frontal, hippocampal and parahippocampal areas.

Neurofibrillary tangles are normally present in the elderly, the difference is in the number of neurofibrillary tangles. They are composed of masses of paired helical filaments.

There is a familial variety of Alzheimer's. It is a rare form of Alzheimer's, with an early onset (mid 50s) and an autosomal dominant transmission.

Philothermal

Migration of white blood cells towards warmer temperatures impaired.

Autoimmune

Abnormal proteins (amyloid, for example).

Infectious Agent

Shown in other dementias (Creutzfeldt-Jakob, kuru, for example).
None identified, despite numerous attempts.

Head-Injury Hypothesis

Many patients with Alzheimer's have had history of head injury.

Blood-Flow Hypothesis

Decreased blood flow and decreased oxygen consumption in Alzheimer's patients
demonstrated on PET and SPECT. Not clear if this is a cause or effect of disease.

Other

Minerals, toxins, alcohol, drugs

VASCULAR DEMENTIA
Can be due to a variety of vascular insults:
- Large-vessel occlusion, usually due to cerebrovascular accidents
- Small-vessel occlusions, including multiple lacunar infarcts
- Sclerosis of the recurrent arteries penetrating subcortical white matter from the cortex, probably due to chronic hypertension.
- Border-zone infarctions, resulting from episodes of ischemia and/or hypotension.

PICK'S DISEASE
Pathology features preferential degeneration of the frontal and anterior lobes
Pick bodies (a cellular pathological finding) = ballooning of nerve cells with inclusions
stained by silver compounds.

PARKINSON'S DISEASE
Destruction of dopaminergic cells originating from the
substantia nigra in the midbrain.

Lewy bodies: found in some Parkinson's dementias. *They occur in the cytoplasm of the remaining nigral neurons, and likely represent an early marker for neuronal cell degeneration*

HUNTINGTON'S DISEASE

Hypometabolism, and then degeneration of the caudate nucleus
Autosomal dominant transmission with high penetrance
Gene localized to chromosome 4
Premorbid determination of risk is available

CREUTZFELDT-JAKOB DISEASE
Spongiform encephalopathy
Multiple extracellular vacuoles seen microscopically in brain tissue.
Usually due to direct brain tissue inoculation of a unique proteinaceous material ("prion")
Ex: recipients of human growth hormone, which is harvested from cadavers, corneal transplant patients.
May be genetically transmitted (rare).

Diagnosis

ALZHEIMER'S
Ultimately a pathological diagnosis, made on the observation of the (above) pathological findings.

Clinical assessments:
Look for course typical of Alzheimer's (see "Typical course and prognosis of Alzheimer's disease" chart)
Accuracy can reach 80-90% if standard criteria (such as that in the DSM) are used

Typical diagnostic work-up for Alzheimer's:
Screening tests, e.g. Mini-Mental State Exam
Neuropsychological assessment
Tests to rule out other causes of cognitive decline (see Delirium section)

Diagnostic criteria for Dementia of the Alzheimer's Type.

1. Has to have Memory Impairment, and one (or more) of the following cognitive disturbances:

aphasia
apraxia
impaired motor performance despite intact motor function
agnosia
failure to recognize or identify objects despite intact sensory function
disturbance in executive functioning e.g. planning, organizing, sequencing, abstracting

2. Behavioral dysfunction (occupational, interpersonal or self-care dysfunction).

VASCULAR DEMENTIA
Look for evidence of sudden changes ("step-wise progression"), patchy deficits (very good at some things, while very bad at others, in a manner atypical of Alzheimer's).

DSM-IV criteria for vascular dementia:
Same as Alzheimer's, with addition of focal neurological signs and symptoms or laboratory evidence indicative of cerebrovascular disease that are judged to be etiologically related to the disturbance.
Focal signs: exaggeration of deep tendon reflexes, extensor-plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity.

Laboratory evidence: multiple infarctions involving cortex and underlying white matter.

Other Dementias:

PICK'S DISEASE
Characterized by signs of frontal lobe disease
Personality change, usually disinhibition, and socially inappropriate behavior
Personality change usually precedes memory and other cognitive problems
Functional brain imaging (ex. PET, SPECT) often helpful in localizing the frontal hypometabolism.

PARKINSON'S DISEASE
Characterized by typical symptoms of Parkinson's disease
A subcortical dementia

HUNTINGTON'S DISEASE
Triad of **dementia**, **psychosis**, and **choreiform movements**
Dementia symptoms
Personality changes
Judgment deficits
Relative preservation of other cognitive functions

CREUTZFELDT-JAKOB DISEASE
Global dementia, usually with marked confusion
Generalized myoclonus, with exaggerated startle response
EEG shows characteristic periodic discharges

HIV DEMENTIA
Usually a subcortical-type dementia
Correlates with degree of HIV disease
Be careful to rule out opportunistic infections, and other treatable causes of cognitive change

Differential Diagnosis

Important differential diagnoses to consider include:
- Benign senescent forgetfulness
  - Same as Stage 2 of Alzheimer's (see below), but does not progress.
- Mild Cognitive Dysfunction
  - Early cognitive deficits, not sufficient to cause significant dysfunction (therefore, not a dementia). May or may not progress to dementia.
- Delirium
- Depression

- o Depression can cause cognitive deficits, often through the patient's lack of motivation and tendency to overestimate deficits.
- o May answer "I don't know" to most cognitive questions
- o Course of cognitive deficits tend to mirror course of the mood disorder; should therefore improve with treatment
- o Term "pseudodementia" often used to describe cognitive deficits caused by depression, that are reversible with treatment of the depression
    - ▪ Probably a misnomer; in actuality, depression and progressive dementia are probably comorbid, and cognitive deficits often persist beyond resolution of the depression.
- Other psychiatric illnesses
    - o Amnesia: only memory, not other cognitive functions affected; often progresses to a dementia
- Malingering
    - o Most malingerers are not good at replicating neuropsychological deficits typical of true dementias.

Common Comorbid Disorders

- Depression
- Anxiety
- Psychosis

(See corresponding discussions for each disorder.)

Course

Dementia may be progressive, static, or remitting, depending on the underlying pathology.

Typical course and prognosis of Alzheimer's disease

Stage of Cognitive Decline	Forgets	Remembers	Functioning	Behavior	Psychological
1: None	not significant				
2: Very Mild	aware of some forgetfulness: names, losing items	most important things	normal	normal	appropriate concern
3: Mild	may remember little of what they read Trouble with word finding, names	most important things	coworkers becoming aware of poor performance		Anxiety, Denial
4: Moderate	Obvious memory deficits, including recent events Concentration problems	oriented to time, recognizes familiar people and places	Trouble traveling alone or handling finances	Withdrawal from challenging situations	Denial
5: Moderately Severe	address, telephone number, familiar people, disoriented to time or place	own name, spouse and children	Cannot survive without assistance, cannot clothe self. Can eat and toilet		May be personality and emotional changes
6: Severe	spouses name, unaware of recent events	sketchy knowledge of past life		Disturbed sleep pattern. Loss of initiative.	Often Personality and emotional changes. Delusion. Hallucinations. Anxiety, agitation, even violent behavior. Repetitive behaviors.
7: Very Severe	Cannot communicate		Incontinent, needs assistance with all functions, may be unable to walk		agitation

VASCULAR DEMENTIA
Varies. Usually progresses in step-wise progression.

PICK'S
Progression: personality changes early, then cognitive disturbances. Motor disturbances occur late.

PARKINSON'S
Dementia may improve with treatment by anti-Parkinson's drugs. However, the same treatment can also make the patient psychotic (think about why).

HUNTINGTON'S
Insidious onset; suicide and other psychiatric morbidity common.

CREUTZFELDT-JAKOB
Rapidly progresses.

Treatment

Treat all possible causes, but probably only <10% of dementias are reversible.

PHARMACOLOGICAL TREATMENTS FOR ALZHEIMER'S

Treating Alzheimer's:
No definitive treatment, a lot of interesting ongoing research.

Acetylcholinesterase inhibitors = the most common only drugs approved for Alzheimer's, they restore lost ACh by inhibiting the enzyme that breaks down Ach

NMDA receptor antagonists. May slow calcium influx and subsequent nerve damage.

Potentially treatable causes of cognitive impairment:
- Drugs and alcohol
- Tumors
- Nutritional: B12, folate
- Infections: syphilis, abscess, encephalitis
- Metabolic
- Electrolytes
- Hepatic
- Renal
- Inflammatory: lupus
- Endocrine: thyroid
- Trauma: subdural
- Neurologic: normal pressure hydrocephalus
- Psychiatric: depression

Drugs Approved for Alzheimer's Disease			
	Approved	mechanism	side effects
tacrine (Cognex)	1993	cholinesterase inhibitor (CI)	nausea, vomiting, loss of appetite, and increased frequency of bowel movements (also liver effects in tacrine)
donepezil (Aricept)	1996	CI	
rivastigmine (Exelon)	2000	CI	
galantamine (Reminyl)	2001	CI and ACh stimulation	
memantine (Namenda)	2003	NMDA receptor antagonist	Dizziness, confusion, somnolence, nausea.

OTHER TREATMENTS FOR ALZHEIMER'S

Antioxidants

Free radicals produced through oxidation may be produced by beta-amyloid (a major component of the senile plaques). Antioxidants prevent or lessen free radical production.

Some interesting preliminary studies:
Czech researchers gave the antioxidant drug selegiline to 173 people with mild to moderate Alzheimer's disease. After six months, their memory improved significantly. In another study, selegiline enhanced the benefits of tacrine.

Non-Steroidals

Some years ago, researchers noticed that people with severe arthritis have strikingly low rates of Alzheimer's disease.

More recently, Japanese researchers noted a similar, usually low rate of Alzheimer's disease in people being treated for leprosy. Treatment of both leprosy and arthritis involves large doses of non-steroidal anti-inflammatory drugs (NSAIDS).

Meanwhile, researchers discovered that inflammation of brain tissue plays a key role in the development of neurofibrillary tangles and beta-amyloid plaques, the anatomical hallmarks of Alzheimer's disease.

These observations strongly suggested that NSAIDS might prevent, or at least delay, Alzheimer's disease, or help treat it. Several studies have corroborated this speculation.

Estrogen

Several studies show that women who take estrogen after menopause have an unexpectedly low incidence of Alzheimer's disease.

Among women with Alzheimer's, those taking estrogen suffer less severe symptoms and slower mental deterioration.

Animal studies show that estrogen improves blood circulation through the brain, and stimulates nerve cell growth in areas of the brain affected by Alzheimer's.

Possible reasons estrogen might help treat Alzheimer's disease:
- Estrogen boosts the production of ACh
- Estrogen also impedes the deposition of beta-amyloid
- Estrogen improves blood flow through the brain, and enhances verbal abilities of postmenopausal women who take hormone replacement therapy
- Estrogen also helps maintain the integrity of the hippocampus

Ampakines

New class of drugs that improve memory.
Increase levels of AMPA-glutamate.
Improved memory in animal studies.
Only human studies done in young adults with normal brain function. Showed improvement in memory.

Calcium Channel Blockers

As nerve cells die, they lose their ability to regulate the flow of calcium across their cell membranes. Some researchers speculate that calcium channel blockers, drugs that affect this mineral's flow in and out of cells, may prolong nerve cell life.

Nerve Growth Factor

This hormone stimulates the growth of the nerve cells that release ACh.
Some researchers believe that by introducing nerve growth factor—or a similar compound—into the brains of people with early Alzheimer's, they may be able to slow or reverse cognitive deterioration.
Unfortunately, nerve growth factor does not cross the blood-brain barrier, so the hormone cannot be given orally or by injection.

Treating Symptoms Associated With The Disease

Similar reasoning to section under delirium.

Psychosocial Treatments

Attention to the care-givers.
Find local support (ex. Alzheimer's association)
Encourage family to keep up with activities
Encourage family to educate themselves
          e.g. book called <u>The 36 Hour Day</u>
Education for family
Management
Structured environment at home
Regular scheduling
Attention to their own lives
Avoid confrontation
Distraction best tactic when patient wants to do something they can't (drive, leave)

Treat Complications Of Illness

Ex. Incontinence—look for urinary tract infections

Chapter 14. Substance Abuse

Phenomenology

Definitions

- **Intoxication:** reversible, substance-specific physiological and behavioral changes due to recent exposure to a psychoactive substance.
- **Addiction:** compulsion to use a drug, usually for its psychic, rather than therapeutic, effects.
- **Tolerance:** the decline in potency of a drug experienced with continued use, so that higher doses are needed to achieve the same effect. This is a receptor-mediated effect, typical of many psychoactive drugs.
- **Physical Dependence:** the development of withdrawal symptoms once a drug is stopped.
- **Withdrawal:** a physiological state that follows cessation or reduction in the amount of a drug used. Generally these effects are the opposite of the drug's normal effects.
- **Substance Dependence:** according to DSM-IV, this is "a maladaptive pattern of substance use with adverse clinical consequences."
- **Substance Abuse:** according to DSM-IV, this is "a maladaptive pattern of use that causes clinically significant impairment."   Symptoms of substance abuse have not met the criteria for substance dependence and do not include tolerance and withdrawal (which can, but do not have to be, features of substance dependence).
- **Alcohol intoxication:** the physiological and behavioral response to alcohol use that includes disinhibition, emotional lability, impaired coordination, slurred speech, ataxia, coma, and/or blackouts.
- **Alcohol withdrawal:** the physiological state that results following cessation of alcohol use; it may be uncomplicated (causing tremulousness, anxiety, and/or increased heart rate) or cause potentially serious complications such as seizures and/or delirium tremens (all of which are discussed further below).
- **Alcoholism:** A repetitive, but inconsistent and sometimes unpredictable loss of control of drinking which produces symptoms of serious dysfunction or disability.

Clearly, there is a wide range of findings possible on the mental status exam; however, any exam should look for typical signs of regular substance use (discussed further below).

Epidemiology

Use of psychoactive substances is common in society, and is often socially acceptable, or at least tolerated. Historically, psychoactive substances have served a variety of

purposes, including medicinal, social, recreational and religious. In the US, 90% of people report some alcohol use, 80% report some caffeine use, 25% report use of tobacco products, and 37% report having used illicit substances (at least once in their lives). **Dependence and Abuse** are also very common (13.6% in ECA).

Alcohol

Over 10 million Americans are alcoholics, over 8 million are "problem drinkers." Only 3% of alcoholics are on skid row. Alcoholism is reportedly more common in rural areas and in the undereducated. It is more common in males than females, and more common in adults than teens/kids. However, teenage alcoholism studies show that 15% of high school students are reported to have 5 or more drinks per occasion at least once a week, and 31% of high school students were intoxicated 6 or more times in the past year.

> *The lifetime prevalence of abuse for substances other than alcohol are as follows:*
> - Amphetamines: 2%
> - Cannabis: 4%
> - Cocaine 0.2% (1981 data, probably higher now)
> - Hallucinogens: 0.3%
> - Opioids: 0.7%
> - Sedative hypnotics: 1.1%

Social/economic factors are considerable in that people in low socioeconomic status are less likely to drink, but more likely to misuse if they do. Drinking is associated with unstable work and family circumstances. Additionally, one should not forget the effect of substance abuse on families. 43% of US adults report exposure to alcoholism in their families. Divorced or separated adults are 3 times as likely as married people to report having been married to an alcoholic or problem drinker. Additionally, the cost to society is of great importance; alcohol-related deaths are the 3rd leading cause of death in the US, after cancer and heart disease. There are 98,000 alcohol-related deaths per year, and an estimated $86 billion in costs due to alcohol abuse (along with $58 billion in costs from other substances). Alcoholism is also a major cause of other medical illnesses and injuries. Alcohol may be involved in 20-50% of hospital admissions, though these often go unrecognized. It contributes to 18-20% of ER visits, causes 80% of liver cirrhosis, and 33% of suicides are alcohol-related.

Cultural differences are also apparent in that alcoholism rates vary in different countries. Countries with high rates include Russia, France, Scandinavia, Ireland, and Korea. Those with low rates include China, Islamic countries, and Mediterranean countries

Etiology

The reward pathway and addiction

There is considerable research interest in the notion of a common "reward pathway" in the human brain that may be responsible for the pleasurable feelings experienced by humans in response to both natural stimuli (i.e. food, water, sex) and artificial (i.e. drugs). The major structures of this postulated reward pathway include the ventral tegmental area (VTA), the nucleus accumbens, and the prefrontal cortex. The VTA consists of

dopamine-containing neurons that project to both the nucleus accumbens and prefrontal cortex. Thus, it is believed that dopamine has a considerable role in addiction, and indeed, a number of illicit drugs cause increased release of dopamine at these synapses. The most recent research indicates that the reward pathway may be important in both obtaining a reward, and in the associated craving. Opioids, cocaine, and nicotine have been shown to potentiate dopamine release in the reward pathway, and alcohol has been shown to indirectly activate this pathway through potentiation of neural activity in the globus pallidus (which in turn connects to components of the reward pathway).

Patterns of cigarette smoking provide an interesting perspective on addiction. It is believed that smokers work, consciously or unconsciously, to maintain blood nicotine levels within the "therapeutic window" by a process referred to as nicotine regulation. For example, the smoker can manipulate the dose of nicotine on a puff-by-puff basis ("finger tip control"). Evidence for this comes from studies of low tar, low nicotine cigarettes. Research has convincingly demonstrated that smokers will compensate for low nicotine yields by smoking more effectively—blocking filter holes to prevent ventilation of smoke; smoking more of the cigarette; inhaling more rapidly and deeply; and smoking a larger total number of cigarettes.

The route of delivery also has implications for addictive potential. For example, with cocaine use, smoking the drug causes an increased rate of its delivery to the brain compared to snorting; hence the greater addictive potential of freebase and crack in patients with cocaine dependence. For nicotine, compared to other forms of its administration, cigarettes offer the most efficient delivery and the fastest spike in blood nicotine levels. Likewise, the subjective effects of smoking a cigarette are greater than the subjective effects after nicotine exposure to the nicotine gum or transdermal patch (types of nicotine replacement therapy to be discussed later).

Alcoholism and genetics

While 51% of cases of alcoholism are non-familial, genetics has been well established in alcoholism, particularly among young male alcoholics. Any drinking carries with it a 5-10% risk of becoming alcoholic. For children of alcoholics, having 1 parent with alcoholism is associated with a 20% risk of alcoholism in the child. With 2 parents, the risk is 20-50%. Sons of father are at greater risk, at 50%. If the father is a severe alcoholic and criminal, there is a 90% risk in his son. Children of alcoholics are also at risk for other substance use disorders.

Adoption studies and twin studies have shown that alcoholism concordance among identical twins is twice that of fraternal. The Danish Adoption Study (1974), in which adopted sons of alcoholics were raised by non-alcoholic foster parents, showed that these children still had increased risk of alcoholism.

Sons of alcoholics show a number of physiological abnormalities, including abnormal EEG's associated with drinking compared with normal subjects and other abnormal brain wave studies (such as evoked potentials). In addition, there exist abnormal hormonal response patterns in sons of alcoholics.

Some genetic differences may relate to inherited variations in the rate of metabolism. For example, decreased gastric oxidation of alcohol

in women causes a higher blood alcohol level (BAL) in woman than in men. There has also been report of an association with a mutation on the D_2 dopamine receptor gene on chromosome 11. This likely acts not as "causer," but rather a modifier.

Pathology

Psychoactive effects relate to the direct effect of drug on receptors in the central nervous system. Thus, it is important to understand the pharmacokinetics of a drug: its routes of administration, absorption, metabolism, binding capacity, and excretion. Receptors have been identified for a number of substances—caffeine and cannabis, for example. Others substances act more nonspecifically—alcohol and inhalants, for example, act by dissolving into cell membranes, particularly in the central nervous system.

Pharmacodynamics: the following substances are listed with their receptors:
- Caffeine—adenosine
- Cannabis—THC receptor
- Hallucinogens—serotonin, NMDA
- Nicotine—nicotinic cholinergic receptors
- Opioids—opioid receptors
- Phencyclidine—NMDA
- Sedatives—chloride channel, GABA receptor

Alcohol

Alcohol is generally thought to act by dissolving into cell membranes, specifically in the central nervous system. There is also some evidence that alcohol may potentiate the effects at neural synapses with $GABA_A$ receptors, similar to drugs such as benzodiazepines. Compared to benzodiazepines and other similar sedative drugs, however, alcohol use requires higher blood concentrations to achieve a comparable level of intoxication. Blood alcohol levels represent the concentration of alcohol in the blood and are typically measured in acutely intoxicated patients presenting for medical care (such as in emergency departments). The rate of increase in BAL is inversely related to the rate of gastric emptying; hence the reason for not drinking on an empty stomach. Generally speaking, about 90% of patients with a BAL greater than 0.15% will show gross intoxication (with symptoms involving speech and gait), loss of consciousness can occur at 0.30%, and respiratory depression may be seen at about 0.45% (potentially resulting in death). Other acute effects of alcohol at the cellular level include ADH antagonism (the "happy hour diuresis"), potentiation of gastric acid secretion (increasing the risk for gastritis), increased peripheral vasodilation and flushing (a centrally-mediated effect), and increased levels of HDL, triglycerides, and uric acid.

Alcohol metabolism follows zero-order kinetics, meaning that a constant amount of the substance is metabolized per unit of time. The steps involved in hepatic alcohol metabolism are as follows:

Ethanol → acetaldehyde → acetate

The enzymes involved in this reaction are alcohol dehydrogenase (1[st] step) and acetaldehyde dehydrogenase (2[nd] step). As noted above, in women the rate of activity of alcohol dehydrogenase is lower, thus causing increased BAL levels. Alcohol metabolism can also be modified by hepatic microsomal enzymes that use NADPH. Acutely, alcohol

use can inhibit hepatic p450 enzymes, thus transiently increasing the levels of concurrently taken drugs such as diazepam. With chronic use, however, alcohol can induce hepatic p450 enzymes, thus causing an increase in its own metabolism along with other drugs eliminated by this route. This may provide one cellular-based mechanism of tolerance that occurs with long-term users.

Cocaine

Cocaine acts in the brain by inhibiting catecholamine reuptake, thus increasing the availability of DA and NE in the synaptic cleft. As described above, the potentiation of DA activity in regions of the brain such as the nucleus accumbens may be responsible for cocaine's addictive properties as well as its euphoriant effects. Dopaminergic activity is thought to also underlie the hallucinations (often tactile) sometimes seen during cocaine intoxication. Additionally, increased NE activity in the brain may cause symptoms of psychomotor agitation, including stereotypic or repetitive behaviors such as pacing, nail-biting, and scratching. This may be related to the binding of cocaine in areas such as the caudate nucleus. In addition, cocaine has peripheral effects on the body, augmenting sympathetic nervous system activity and causing tachycardia, pupillary dilation, and hypertension. Cocaine-mediated vasoconstriction can also produce angina, and in rarer instances, sudden cardiac death. Note that the effects of other substances on the body, particularly amphetamines, can mimic cocaine intoxication. Amphetamines enhance the release of NE and DA from the axon terminal, thus working similar to cocaine by increasing their availability in the synaptic cleft.

Nicotine

Receptors: Nicotine in tobacco exerts its actions on physiology and behavior by binding to nicotinic acetylcholine receptors (nAChRs), ion-gated channels that are normally responsive to endogenous acetylcholine. These receptors are found in the central nervous system and in the periphery (ANS, neuromuscular junction), and they are all involved in the physiological responses to tobacco. Each class of receptors generally contains different subunits, and experiments using gene knockout mice have indicated that certain subunits are specifically implicated in nicotine dependence. In time, this information may help to understand individual differences in response to nicotine and therefore nicotine dependence (e.g., those smokers with more or less of the specific nicotinic receptors), and it might help in tailoring new pharmacologic treatments which specifically target these receptors (e.g., by blocking or antagonizing their function, making nicotine less reinforcing).

It is also important to understand the dynamics of receptor function in relation to smoking and blood/brain nicotine levels. Neuroreceptors can become more sensitive for various reasons and they can also proliferate, both of which can be referred to as **upregulation**. Typically, one observes upregulation of receptors as a compensatory response to low levels of a neurotransmitter. **Downregulation** refers to the opposite, reduced sensitivity or fewer receptors, which in turn serves to compensate for excess levels of a neurotransmitter.

In the case of nicotinic receptors, the story is a little more complicated, and can be explained as follows (after Dani & Heinemann, '96): upon smoking a cigarette, a small pulse of nicotine activates nAChRs that directly or indirectly induce dopamine release, thus providing a pleasurable effect. With continued use, nicotine builds up to a slow steady-state concentration that causes significant nAChR desensitization and, over time, inactivation. There is evidence that nicotinic receptor turnover decreases following inactivation, leading to an increased number of nAChRs. In between cigarettes, during sleep, or under conditions of abstinence while attempting to stop smoking, nicotine levels drop and a portion of the inactive nAChRs recover to a responsive state. Because of the increased number of nAChRs that have now become responsive, some cholinergic systems become hyperexcitable to acetylcholine, contributing to the drive for the next cigarette. Thus, smokers may medicate themselves with nicotine to regulate the number of functional nAChRs. Note that this is still only a theoretical model, but it explains the powerful reinforcement experienced when smoking after a period of abstinence, even overnight. Understanding receptor function can also explain the rapid development of tolerance to nicotine's effects, which would drive continued smoking.
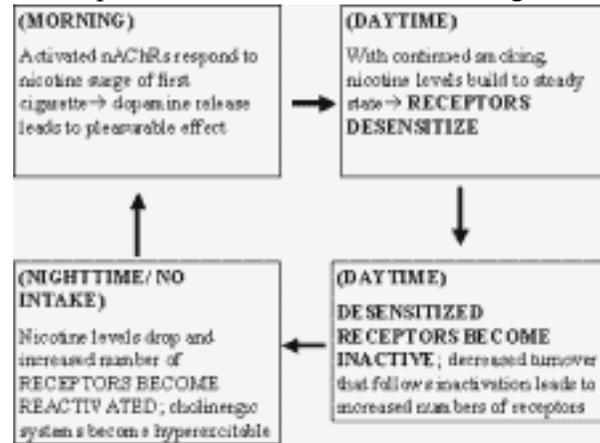
Effects on the body: The effects of nicotine on the body are widespread. In the CNS, nicotine causes direct activation of ACh receptors, which when activated in regions such as the hippocampus can improve short-term memory and cognition/attention. Additionally, via activation of ACh receptors, nicotine can potentiate the release of dopamine (promoting its addictive properties, as described above), NE (promoting stimulation and arousal), and endogenous opioids (promoting stress-reducing and analgesic effects). There is also evidence that a component of tobacco (not nicotine) may inhibit the enzyme monoamine oxidase (MAO), which normally breaks down neurotransmitters such as dopamine, serotonin, and norepinephrine. Peripheral effects of nicotine are considerable and include increased heart rate, increased blood pressure, vasoconstriction, increased metabolic rate and lipolysis, skeletal muscle relaxation, and increased ACTH release and adrenal steroid production. Nicotine is rapidly cleared from the brain, and has a short half-life in the blood (with p450 liver metabolism to cotinine, the active metabolite), both which are factors that could partially account for the need for constant dosing.

Diagnosis

Classes of psychoactive substances recognized in DSM-IV include alcohol,

amphetamines and related drugs, caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine and related drugs, and sedatives. Polysubstance abuse occurs in which three or more categories of drug are abused (not including nicotine). Other drugs of abuse can include steroids, nitrates, and anticholinergics, to name a few. The criteria for diagnosis are as follows:

DSM-IV defined **Substance Dependence** is a maladaptive pattern of substance use. Criteria for diagnosis include three of following over a 1 year period: -Tolerance -Withdrawal -Use in larger amounts than intended -Persistent desire or unsuccessful attempts to cut down -Time spent in activities necessary to get substance, taking substance or recovering from its effects. -Social, occupational or recreational activities given up as a result of the substance -Continued substance use despite knowledge of having a problem Note that these patients don't need to have physical dependence. The definition of substance dependence is basically equivalent to "addiction," which is not used in DSM.	DSM-IV **Substance Abuse** is a maladaptive pattern of substance use leading to impairment. Criteria include one or more of following over 12 months: -recurrent substance use resulting in a failure to fulfill role obligations (work, school, home) -hazardous use (driving while intoxicated) -related legal problems -continued use despite persistent problems relating to the substance It is important in the case of substance abuse to rule out substance dependence (which takes precedence).
DSM-IV **Substance Intoxication** is a reversible substance-specific syndrome due to recent exposure to a substance. Maladaptive behaviors or psychological changes can develop due to the substance and are not due to another medical/mental condition.	DSM-IV **Substance Withdrawal** is a substance-specific syndrome due to cessation or reduction in substance use that has been heavy and prolonged. Withdrawal causes distress/impairment, and is not due to another medical/mental condition.

Alcohol

Aside from classification according to DSM-IV criteria, other schemas of substance use/abuse exist as well. One such schema includes alcohol patterns. The so-called "alpha" pattern is one of continual excessive use when under stress, with no dependence and no loss of control. The "beta" pattern is one of heavy social drinking with physical complications, such as cirrhosis, but no dependence. The "delta" pattern is that of heavy daily drinking, but no loss of control. This is the more common type in Europe, for

example in France. The "epsilon" pattern is defined as binge drinking, and the "gamma" pattern is that of physical dependence with loss of control. This is a more common type in the US.

Diagnostic tools for detecting alcoholism include administering the **CAGE Questionnaire**, and collecting other relevant historical data. Some historical "red flags" might include (1) a pattern of unexplained job changes; (2) vague, defensive or evasive responses to alcohol-related questions; (3) DUI convictions; or (4) multiple unexplained traffic accidents. In addition, patients with alcoholism may have a history of impulsive behavior, fighting, or falls and scrapes, blackouts, binge drinking, or delirium tremens (DT's). A history of drinking to relax or sleep is significant, as is a history of family chaos and instability. Relevant physical data to collect include the obvious stigmata of alcohol or drug use. For alcohol use, this may include spider angiomas, ruddy nose and face, peripheral neuropathies, liver disease, or cerebellar dysfunction. Additionally, patients may experience symptoms of gastric irritation related to acute or chronic alcohol use. For other drugs, this may be cutaneous abscesses and track marks (in IV drug abusers), or nasal lesions (cocaine).

> *The CAGE Questionnaire:*
> 1. Have you ever felt the need to **Cut** down on your drinking?
> 2. Have you ever felt **Annoyed** by criticisms of your drinking?
> 3. Have you ever had **Guilty** feelings about your drinking?
> 4. Have you ever taken a morning **Eye** opener?

Relevant laboratory data to collect for diagnostic purposes in alcoholism include a complete blood count and liver enzymes. Lab abnormalities may relate to malnutrition and organ damage, and may be expressed as leukopenia, macrocytic anemia, target cells (liver damage), thrombocytopenia, and bone marrow suppression. CAMP (cyclic adenosine monophosphate) levels in white blood cells of alcoholics are 3 times normal. Liver enzymes are abnormal in chronic alcoholism. Substance use can be easily detected via toxicology screens, in which urinary metabolites of several drugs are measured. It is important to observe directly the sample collection process. In addition, it is important to note the risk of false positives. One needs to confirm findings with a second test on the same sample using different analytic method (for example, poppy seed ingestion can cause false positive screens for opiates). Informed consent is crucial in toxicity screens.

Differential

"Normal use" is the main component in the differential of substance abuse. However, this brings up the question of what is normal. Perhaps the most important differential is between those patients who are addicted to drugs, and those who are merely physically dependent. The difference lies in the definition of addiction. For example, a patient with chronic pain, who is using regular opioids to alleviate pain, is probably physically dependent on the opioids, in the sense that the patient is probably tolerant to opioids, and would likely go into withdrawal if the opioids were suddenly stopped. However, such a patient does not necessarily show

> Remember–to confuse things, DSM-IV's use of the term substance dependence is really describing a syndrome more like addiction, than like dependence in the way everyone uses the word (i.e., physical dependence). To clarify, I generally use an adjective to keep it straight (**physical dependence** versus **DSM-IV-defined dependence**).

the compulsive behaviors associated with addiction. Furthermore, if the patient is taking the opioids for their analgesic, rather than euphoriant effects, then one cannot really say that the patient is addicted to antidepressants. Other differentials to consider in a patient with suspected substance abuse includes delirium along with other Axis I psychiatric conditions (which are often comorbid).

Comorbid Disorders And Complications

Medical Comorbidities

Alcohol

Withdrawal: Though generally uncomplicated, alcohol withdrawal can progress to delirium tremens (DTs), 10% of which are fatal. It is important to understand the differences between uncomplicated withdrawal and delirium tremens. Also, note that the hallucinations found in both of the above conditions are typically visual or tactile in nature, which may be distinguished from the auditory hallucinations of a distinct entity termed alcohol hallucinosis (described later).

	Early Withdrawal	Late Withdrawal (DT's)
Onset after drinking	8-9 hours	48-96 hours
Symptoms	seating, flushed face, insomnia	tremor, increased psychomotor activity, increased autonomic activity, fever
Hallucinations	25%, relatively less intense	common, vivid
Seizures	Grand Mal ("Rum Fits")	Uncommon
Orientation	Normal or mildly abnormal	Profoundly abnormal

Seizures: Seizures are common with high levels of alcohol use, independent of withdrawal.

Alcoholic Hallucinosis: Hallucinations can occur after drinking cessation in patients with alcohol dependence. These occur in a clear sensorium, and are not part of DTs. They are usually auditory hallucinations with persecutory content, and they can become chronic.

Wernicke's encephalopathy: An acute neurological syndrome associated with long term alcohol abuse, the condition consists of delirium and the following triad of symptoms: ataxia, nystagmus and opthalmoplegia. It is thought to result from the thiamine deficiency that can result from chronic alcoholism. The treatment is, of course, to give thiamine (typically, it is given with folate).

Dementia: Dementia is common in patients with alcoholism. Most classic is the Korsakoff's Dementia (sometimes called Korsakoff's Psychosis, but that is a misnomer). This is characterized by an extremely poor short term memory--much worse than with Alzheimer's. Often associated with the memory losses are confabulations, though this is nonspecific to any dementia. More common is a more "run of the mill" type of dementia, usual called simply alcohol dementia, or dementia due to alcohol dependence. There remains some debate as to whether the dementia associated with alcoholism is due to a neurotoxic effect of alcohol itself, or to accessory problems (e.g., malnutrition, vitamin deficiencies).

The dementia associated with alcoholism is most likely irreversible. In the case of Korsakoff's, the thiamine and folate are usually given, which do generally improve the Wernicke's syndrome, but the memory disorder generally remains.

Fetal Alcohol Syndrome: FAS is due to heavy alcohol use during pregnancy. There is a high incidence in alcoholic mothers. 17% of births to alcoholic mothers are stillborn or die shortly after birth. 20% have some defects, and 32% show fetal alcohol syndrome. Of those children with fetal alcohol syndrome, less than 6% are able to function normally in schools, and most never hold a job.

Withdrawal from other drugs

Unlike alcohol withdrawal, the course of withdrawal is generally not life-threatening in most of the other drugs of abuse described above. However, withdrawal in these instances may be very uncomfortable for the patient. Nicotine, for example, causes symptoms of irritability, headache, anxiety, increased heart rate, cravings, and (most concerning for many) weight gain. Women tend to gain more weight than men do during withdrawal. Most symptoms send to subside within two weeks on average, with considerable variability, but cravings and appetite increases may persist for much longer periods of time. Cocaine withdrawal also produces a number of symptoms, including hypersomnolence, fatigue, depression, intense cravings, and in some cases, suicidality.   Note that the course of benzodiazepine withdrawal can mimic that of alcohol withdrawal (including seizures, DTs, or death), as both substances utilize biochemical mechanisms of action. Thus, benzodiazepine detoxification is approached with the same vigilance as in patients withdrawing from alcohol.

Signs/Symptoms of Fetal Alcohol Syndrome:
- Small length and weight
- Microcephalic: usually below 3^{rd} percentile for head circumference
- Palpebral fissures and epicanthal folds
- Maxillary hypoplasia
- Associated with thinned upper lip, micrognathia, cleft palate, dislocation of hips, flexion deformities of the fingers, limited range of motion of other joints, cardiac abnormalities (usually septal defects), abnormal external genitalia, and capillary hemangiomata
- Often irritable, hyperactive and tremulous

Children with FAS often go on to have learning disabilities and other behavioral abnormalities in later life. 44% have IQs of 79.

Psychiatric Comorbidities

ECA data suggested that 53% of those with a substance disorder had a comorbid mental disorder. Some of these mental disorders include antisocial personality disorder (11x higher than the general public), anxiety disorders (panic disorder, generalized anxiety disorder, and phobias), and depression. Most often, depression is secondary to alcoholism. It generally improves with abstinence, though some dysphoria may remain. Depression affects 13% of female alcoholics. Alcoholism is also more common in patients with schizophrenia and bipolar disorder. Attention Deficit Disorder may predispose to alcoholism, but this is a controversial topic.

Course

General principles dictate that alcoholism is often worse if familial. There are probably high incidences of (unreported) spontaneous remission. This complicates evaluation of different treatments. Drug abuse patterns are influenced by social and cultural factors and, compared with alcohol abuse, fluctuate more with time.

Alcoholism typically has an exacerbating and remitting course, with periods of relative or complete abstinence. 2-3% of alcohol dependents become abstinent per year. Onset of alcoholism rarely begins after 45. 30% of college problem drinkers are alcohol dependent 20 years later. First hospitalization for alcohol tends to be earlier in men (30's-40's). Abuse of cocaine and stimulants has a rapidly progressing course, from use to abuse and dependence, particularly by more potent routes (injection, inhaled). Oral and intranasal routes of ingestion show slower progression. Cannabis use rarely progresses to abuse and dependence if used alone. Hallucinogens very rarely progress to dependence. Opioid dependence represents a lifelong, chronic pattern. Abuse of sedative hypnotics can remit, either spontaneously or with treatment.

Treatment

Alcohol

Acute treatment for alcoholics includes management of withdrawal. This may be accomplished non-pharmacologically: less than 5% of detoxifications are severe. Pharmacologically, benzodiazepines (such as chlordiazepoxide) are the treatment of choice. Lorazepam (Ativan) is given to patients with evidence of liver damage, as there is less of a risk for systemic benzodiazepine toxicity with this drug. *Thiamine should be given to all alcoholics to prevent Wernicke's encephalopathy.* Also important is supportive care and replacement of nutritional deficits.

Efficacy data on treatment plans include the following:
NIAAA data: followup on Federal Programs
- 70% recovery after 18 months
- 50% needed only minimal intervention
- Abstinence was more related to intensity rather than length of treatment.

AA data:
- 40% retention in 12 months.
- 43% chance of remaining sober after 1 year

Secondary treatment involves confrontation of the alcoholic/substance abuser. One must confront the patient with the consequences of their behavior. Involve the family. It is important not to argue over definitions, labels (whether or not an "alcoholic"), or the quantity consumed. Focus on the need to do something about a "problem." Negotiate a treatment contract or referral. On the question of controlled drinking, data is very mixed. Probably only 1-3% of alcohol dependents ever attain stable controlled drinking. Possible good predictors of return to "normal" drinking include being female and having less severe alcoholism to begin with.

The primary goal of long-term treatment involves maintaining abstinence. There is some debate whether "normal" drinking can be a goal. Modalities for this include group treatment, family therapy and medications. Group treatment is usually peer support (ex. AA). This form of treatment usually quotes high success rates, though little objective data actually exists. Family therapy is also important, as family is always involved, both in the pathology (denial, chaotic dynamics) and as primary motivation for treatment. Support groups exist as well, including Al-Anon.

Medications include disulfiram for alcoholism and naltrexone. **Disulfiram** inhibits acetaldehyde dehydrogenase. It acts as deterrent to drinking, as the result of a drink will be tachycardia, dyspnea, nausea and vomiting. It is probably most useful as an adjunct to, not a substitute, for other treatments. **Naltrexone** acts as a μ-receptor antagonist. It is thought to decrease cravings and has been used to maintain abstinence both for opioid dependent individuals and, more recently, for alcoholism. Several recent studies report longer periods of abstinence when patients are given this drug. **Acamprosate** has been used in Europe, and may soon be available in the US. It has favorable data for enhancing alcohol abstinence. It is believed to act through GABA agonism, but does not appear to have the unfavorable side effects (tolerance, dependence) associated with benzodiazepines (though beware, that has been said before...) Other medications have been tried, most with initial enthusiasm but no consistent data. Some examples include antidepressants, lithium carbonate, and anticonvulsants. *It is important that benzodiazepines not be used as a "substitute" for alcohol.*

General rules of management of alcohol abuse include supportive care to build defenses and avoiding raining anxiety. Sobriety is the primary goal, even in patients with other psychiatric problems. It is important to work with (rather than compete with) AA. For relapse prevention, one must identify specific triggers/factors. Management of chronic alcoholism must include anticipating lapses and relapses, encouraging prompt return to treatment, negotiating new treatment contracts, and setting reasonable goals. In other words, do not get upset when they fail and begin drinking or drugging again—relapses are part of the disease, to be expected, and not proof that the patient is a "hopeless case."

Drugs commonly used to treat alcohol abuse/dependence				
	Mechanism	Half life	common side effects	serious side effects
Disulfiram (Antabuse)	acetaldehyde dehydrogenase inhibition	1-2 days	dizziness, palpitations, blurred vision, hypotension, and nausea.	Neuropathies, exacerbation of psychosis. Potential drug-drug interactions
Naltrexone (ReVia)	Opioid Antagonist	4-10 hours	nausea, vomiting, dysphoria	Opioid withdrawal, Elevation of liver transaminases.
Acamprosate (Campral)*	GABA agonist	13-28 hours	diarrhea, nausea, abdominal pain	renal and hepatic dysfunction

*not yet available in the US

Nicotine

Several strategies for nicotine cessation exist. Non-pharmacologic therapies are aimed at providing an organized manner in which to taper cigarette smoking so as to minimize withdrawal symptoms. Generally, the goal is to decrease nicotine intake to 25% of the original level over a 2-4 week period. Other strategies for quitting include pharmacologic means, described further below.

Nicotine replacement therapy:
There are currently four approved types of nicotine replacement therapy (NRT), including the patch, inhaler, nasal spray, and gum. It is believed that NRT works by blocking nicotine withdrawal symptoms, including cravings, through the maintenance of a certain nicotine blood level. The most popular form of NRT is the nicotine patch.
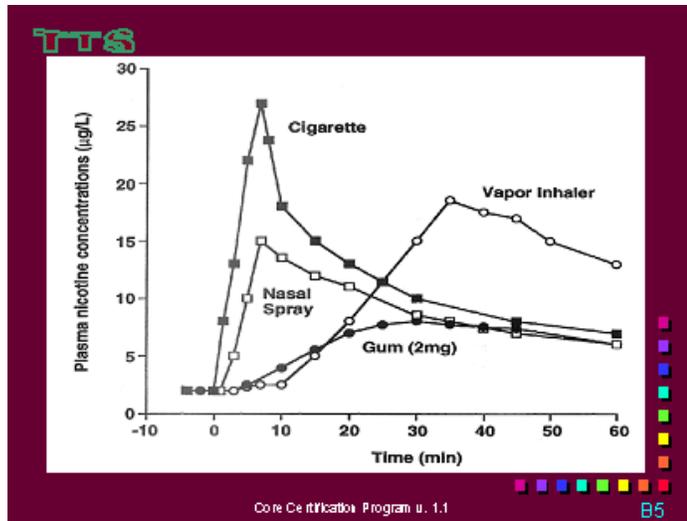
Patches differ in their construction and use different mechanisms to regulate nicotine dosage, but all transdermal systems provide relatively similar dosing in terms of pharmacokinetic profiles. Compared to smoking, nicotine absorbed by the skin patch provides a much slower rise time, but much

steadier and stable levels throughout the day. Nicotine provided by the patch replaces about half of that provided by cigarettes, which contributes to its safety. Among the more common side effects are abnormal or vivid dreams, believed to be the result of nicotine absorption during sleep. While one could simply discontinue use of the patch before bedtime to prevent this effect, the downside is that severe cravings may result in the morning since blood nicotine levels will have decreased.

Pharmacokinetics of other forms of replacement show the inhaler and gum to have relatively slow rise times (although faster than the patch). This has to do with absorption of nicotine through the lining of the mouth and tissue in the throat, not the lungs. The gum produces lower blood levels than the patch, and the inhaler is roughly equivalent to the patch. The advantage of the inhaler and gum is that dosing is flexible and controlled by the patient, so higher blood levels could be achieved if needed. In addition, products which require constant dosing may help the smoker cope with habitual aspects of smoking related to oral and handling behaviors. Side effects related to the inhaler and gum are negligible. The nasal spray is a prescription product that allows for a more rapid rise in nicotine levels than any other NRT, therefore most closely approximating the smoking of a cigarette. However, a deterrent to the spray's popularity includes its side effect profile, which commonly includes nasal and throat irritation, rhinitis, coughing, sneezing, and watery eyes.

Other pharmacotherapies: Bupropion (Zyban) is a heterocyclic antidepressant that was initially found to be effective in smoking cessation in patients being treated for depression. Recent studies have suggested that bupropion used in combination with the nicotine patch results in greater quit rates than either therapy alone. Another therapy used is clonidine, an antihypertensive (alpha-2 antagonist) which is also used as an adjunctive agent in alcohol and opiate addiction. It is thought that clonidine is most effective as a second-line agent in nicotine cessation to reduce withdrawal symptoms associated with craving, irritability, anxiety, and restlessness. Its side effect profile (dry mouth, sedation, rebound hypertension) can potentially limit its use.

Results from meta-analyses have compared nicotine cessation rates for different forms of therapy. The least efficacious therapy according to these studies is the nicotine gum, which increases quit rates about 60-70% compared to placebo. In comparison, the nicotine nasal spray and inhaler improve quit rates to almost 2.5 times placebo rates. The patch has the greatest efficacy, with quit rates ranging from 2-3 times that of placebo. Additionally, bupropion has also been shown to increase smoking cessation at a rate of 2.6 times greater than placebo. It should be noted that very few studies of bupropion, nasal spray, and inhaler exist relative to the patch and gum, so these numbers may fluctuate as more research trials are conducted.

Chapter 15. Obesity

Introduction

An estimated 97 million adults in the United States are overweight or obese, a condition that substantially raises their risk of morbidity from hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and endometrial, breast, prostate, and colon cancers. Higher body weights are also associated with increases in all-cause mortality. Obese individuals may also suffer from social stigmatization and discrimination. As a major contributor to preventive death in the United States today, overweight and obesity pose a major public health challenge.

Overweight is here defined as a body mass index (BMI) of 25 to 29.9 kg/m2 and obesity as a BMI of ≥30 kg/m2. However, overweight and obesity are not mutually exclusive, since obese persons are also overweight. A BMI of 30 is about 30 lb overweight and equivalent to 221 lb in a 6'0"person and to 186 lb in one 5'6". The number of overweight and obese men and women has risen since 1960; in the last decade the percentage of people in these categories has increased to 54.9 percent of adults age 20 years or older. Overweight and obesity are especially evident in some minority groups, as well as in those with lower incomes and less education.

Obesity is a complex multifactorial chronic disease that develops from an interaction of genotype and the environment. Our understanding of how and why obesity develops is incomplete, but involves the integration of social, behavioral, cultural, physiological, metabolic and genetic factors.

While there is agreement about the health risks of overweight and obesity, there is less agreement about their management. Some have argued against treating obesity because of the difficulty in maintaining long-term weight loss and of potentially negative consequences of the frequently seen pattern of weight cycling in obese subjects. Others argue that the potential hazards of treatment do not outweigh the known hazards of being obese. The intent of these guidelines is to provide evidence for the effects of treatment on overweight and obesity. The guidelines focus on the role of the primary care practitioner in treating overweight and obesity.

Evidence-Based Guidelines

To evaluate published information and to determine the most appropriate treatment strategies that would constitute evidence-based clinical guidelines on overweight and obesity for physicians and associated health professionals in clinical practice, health care policy makers, and clinical investigators, the National Heart, Lung, and Blood Institute's Obesity Education Initiative in cooperation with the National Institute of Diabetes and Digestive and Kidney Diseases convened the Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults in May 1995. The guidelines are based on a systematic review of the published scientific literature found in MEDLINE from January 1980 to September 1997 of topics identified by the panel as key to extrapolating the data related to the obesity evidence model.

Evidence from approximately 394 randomized controlled trials (RCTs) was considered by the panel.

The panel is comprised of 24 members, 8 ex-officio members, and a methodologist consultant. Areas of expertise contributed to by panel members included primary care, epidemiology, clinical nutrition, exercise physiology, psychology, physiology, and pulmonary disease. There were five meetings of the full panel and two additional meetings of the executive committee comprised of the panel chair and four panel members.

The San Antonio Cochrane Center assisted the panel in the literature abstraction and in organizing the data into appropriate evidence tables. The center pretested and used a standardized 25-page form or "Critical Review Status Sheet" for the literature abstraction. Ultimately, 236 RCT articles were abstracted and the data were then compiled into individual evidence tables developed for each RCT. The data from these RCTs served as the basis for many of the recommendations contained in the guidelines.

The panel determined the criteria for deciding on the appropriateness of an article. At a minimum, studies had to have a time frame from start to finish of at least 4 months. The only exceptions were a few 3-month studies related to dietary therapy and pharmacotherapy. To consider the question of long-term maintenance, studies with outcome data provided at approximately1 year or longer were examined. Excluded were studies in which self-reported weights by subjects were the only indicators used to measure weight loss. No exclusions of studies were made by study size. The panel weighed the evidence based on a thorough examination of the threshold or magnitude of the treatment effect. Each evidence statement (other than those with no available evidence) and each recommendation is categorized by a level of evidence which ranges from A to D. Table ES-1 summarizes the categories of evidence by their source and provides a definition for each category.

• **Who is at Risk?** All overweight and obese adults (age 18 years of age or older) with a BMI of ≥25 are considered at risk for developing associated morbidities or diseases such as hypertension, high blood cholesterol, type2 diabetes, coronary heart disease, and other diseases. Individuals with a BMI of 25 to29.9 are considered overweight, while individuals with a BMI ≥30 are considered obese. Treatment of overweight is recommended only when patients have two or more risk factors or a high waist circumference. It should focus on altering dietary and physical activity patterns to prevent development of obesity and to produce moderate weight loss. Treatment of obesity should focus on producing substantial weight loss over a prolonged period. The presence of comorbidities in overweight and obese patients should be considered when deciding on treatment options.

• **Why Treat Overweight and Obesity?** Obesity is clearly associated with increased morbidity and mortality. There is strong evidence that weight loss in overweight and obese individuals reduces risk factors for diabetes and cardiovascular disease (CVD). Strong evidence exists that weight loss reduces blood pressure in both overweight hypertensive and nonhypertensive individuals; reduces serum triglycerides and increases high-density lipoprotein(HDL)-cholesterol; and generally produces some reduction in total serum cholesterol and low-density

lipoprotein (LDL)-cholesterol. Weight loss reduces blood glucose levels in overweight and obese persons without diabetes; and weight loss also reduces blood glucose levels and HbA1c in some patients with type 2 diabetes. Although there have been no prospective trials to show changes in mortality with weight loss in obese patients, reductions in risk factors would suggest that development of type 2 diabetes and CVD would be reduced with weight loss.

Table ES-1: EVIDENCE CATEGORIES

Evidence Category	*Sources Of Evidence*	Definition
A	Randomized controlled trials (rich body of data)	Evidence is from endpoints of well-designed RCTs (or trials that depart only minimally from randomization) that provide a consistent pattern of findings in the population for which the recommendation is made. Category A therefore requires substantial numbers of studies involving substantial numbers of participants.
B	Randomized controlled trials (limited body of data)	Evidence is from endpoints of intervention studies that include only a limited number of RCTs, post hoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, and the trial results are somewhat inconsistent, or the trials were undertaken in a population that differs from the target population of the recommendation.
C	Nonrandomized trials Observational studies	Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.
D	Panel Consensus Judgment	Expert judgment is based on the panel's synthesis of evidence from experimental research described in the literature and/or derived from the consensus of panel members based on clinical experience or knowledge that does not meet the above-listed criteria. This category is used only in cases where the provision of some guidance was deemed valuable but an adequately compelling clinical literature addressing the subject of the recommendation was deemed insufficient to justify placement in one of the other categories (A through C).

● **What Treatments Are Effective?** A variety of effective options exist for the management of overweight and obese patients, including dietary therapy approaches such as low-calorie diets and lower-fat diets; altering physical activity patterns; behavior therapy techniques;

pharmacotherapy*[*]; surgery; and combinations of these techniques.

Clinical Guidelines

Treatment of the overweight or obese patient is a two-step process: assessment and treatment management. Assessment requires determination of the degree of overweight and overall risk status. Management includes both reducing excess bodyweight and instituting other measures to control accompanying risk factors.

Assessment: When assessing a patient for risk status and as a candidate for weight loss therapy, consider the patient's BMI, waist circumference, and overall risk status. Consideration also needs to be given to the patient's motivation to lose weight.

● **Body Mass Index.** The BMI, which describes relative weight for height, is significantly correlated with total body fat content. The BMI should be used to assess overweight and obesity and to monitor changes in body weight. In addition, measurements of body weight alone can be used to determine efficacy of weight loss therapy. BMI is calculated as weight(kg)/height squared (m^2). To estimate BMI using pounds and inches, use: [weight (pounds)/height (inches)^2] x 703. Weight classifications by BMI, selected for use in this report, are shown in Table ES-2. A conversion table of heights and weights resulting in selected BMI units is provided in Table ES-3.

TABLE ES-2: CLASSIFICATION OF OVERWEIGHT AND OBESITY BY BMI

	Obesity Class	**BMI (kg/m2)**
Underweight		< 18.5
Normal		18.5 – 24.9
Overweight		25.0 – 29.9
Obesity	I	30.0 – 34.9
	II	35.0 – 39.9
Extreme Obesity	III	≥40

● **Waist Circumference.** The presence of excess fat in the abdomen out of proportion to total body fat is an independent predictor of risk factors and morbidity. Waist circumference is positively correlated with abdominal fat content. It provides a clinically acceptable measurement for assessing a patient's abdominal fat content before and during weight loss treatment. The sex-specific cutoffs noted on the next page can be used to identify increased relative risk for the development of obesity-associated risk factors in most adults with a BMI of 25 to 34.9 kg/m^2:

These waist circumference cutpoints lose their incremental predictive power in patients with a BMI ≥35 kg/m^2 because these patients will exceed the cutpoints noted above. Table ES-4 adds the disease risk of increased abdominal fat to the disease risk of BMI. These categories denote

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[*] As of September 1997, the Food and Drug Administration (FDA) requested the voluntary withdrawal from the market of dexfenfluramine and fenfluramine due to a reported association between valvular heart disease and the use of dexfenfluramine or fenfluramine alone or combined with phentermine. The use of these drugs for weight reduction, therefore, is not recommended in this report. Sibutramine is approved by FDA for long-term use. It has limited but definite effects on weight loss and can facilitate weight loss maintenance (Note: FDA approval for orlistat is pending a resolution of labeling issues and results of Phase III trials.)

relative risk, not *absolute* risk; that is, relative to risk at normal weight. They should not be equated with absolute risk, which is determined by a summation of risk factors. They relate to the need to institute weight loss therapy and do not directly define the required intensity of modification of risk factors associated with obesity.

● **Risk Status.** Assessment of a patient's absolute risk status requires examination for the presence of:

Disease conditions: established coronary heart disease (CHD), other atherosclerotic diseases, type 2 diabetes, and sleep apnea; patients with these conditions are classified as being at very high risk for disease complications and mortality.

Other obesity-associated diseases: gynecological abnormalities, osteoarthritis, gallstones and their complications, and stress incontinence.

Cardiovascular risk factors: cigarette smoking, hypertension (systolic blood pressure ≥140mm Hg or diastolic blood pressure ≥90 mmHg, or the patient is taking antihypertensive agents), high-risk LDL-cholesterol (≥160mg/dL), low HDL-cholesterol (< 35 mg/dL), impaired fasting glucose (fasting plasma glucose of 110 to 125 mg/dL), family history of premature CHD (definite myocardial infarction or sudden death at or before 55 years of age in father or other male first-degree relative, or at or before 65 years of age in mother or other female first-degree relative), and age (men ≥45 years and women ≥55 years or postmenopausal). Patients can be classified as being at high absolute risk if they have three of the aforementioned risk factors. Patients at high absolute risk usually require clinical management of risk factors to reduce risk.

Patients who are overweight or obese often have other cardiovascular risk factors. Methods for estimating *absolute risk* status for developing cardiovascular disease based on these risk factors are described in detail in the National Cholesterol Education Program's *Second Report of the Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults* (NCEP's ATP II)and the *Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC VI). The intensity of intervention for cholesterol disorders or hypertension is adjusted according to the absolute risk status estimated from multiple risk correlates. These include both the risk factors listed above and evidence of end-organ damage present in hypertensive patients. Approaches to therapy for cholesterol disorders and hypertension are described in ATP II and JNC VI, respectively. In overweight patients, control of cardiovascular risk factors deserves equal emphasis as weight reduction therapy. Reduction of risk factors will reduce the risk for cardiovascular disease whether or not efforts at weight loss are successful.

Other risk factors: physical inactivity and high serum triglycerides (> 200 mg/dL).When these factors are present, patients can be considered to have incremental absolute risk above that estimated from the preceding risk factors. Quantitative risk contribution is not available for these risk factors, but their presence heightens the need for weight reduction in obese persons.

HIGH RISK

Men > 102 cm (> 40 in)
Women > 88 cm (> 35 in)

Table ES-3: SELECTED BMI UNITS CATEGORIZED BY INCHES (CM) AND POUNDS (KG)

	Body weight in pounds (kg)		
Height in inches(cm)	BMI 25 kg/m^2	BMI 27 kg/m^2	BMI 30 kg/m^2
58 (147.32)	119 (53.98)	129 (58.51)	143 (64.86)
59 (149.86)	124 (56.25)	133 (60.33)	148 (67.13)
60 (152.40)	128 (58.06)	138 (62.60)	153 (69.40)
61 (154.94)	132 (59.87)	143 (64.86)	158 (71.67)
62 (157.48)	136 (61.69)	147 (66.68)	164 (74.39)
63 (160.02)	141 (63.96)	152 (68.95)	169 (76.66)
64 (162.56)	145 (65.77)	157 (71.21)	174 (78.93)
65 (165.10)	150 (68.04)	162 (73.48)	180 (81.65)
66 (167.64)	155 (70.31)	167 (75.75)	186 (84.37)
67 (170.18)	159 (72.12)	172 (78.02)	191 (86.64)
68 (172.72)	164 (74.39)	177 (80.29)	197 (89.36)
69 (175.26)	169 (76.66)	182 (82.56)	203 (92.08)
70 (177.80)	174 (78.93)	188 (85.28)	207 (93.89)
71 (180.34)	179 (81.19)	193 (87.54)	215 (97.52)
72 (182.88)	184 (83.46)	199 (90.27)	221 (100.25)
73 (185.42)	189 (85.73)	204 (92.53)	227 (102.97)
74 (187.96)	194 (88.00)	210 (95.26)	233 (105.69)
75 (190.50)	200 (90.72)	216 (97.98)	240 (108.86)
76 (193.04)	205 (92.99)	221(100.25)	246 (111.58)

Metric conversion formula = **weight (kg)/height (m)^2**	**Non-metric conversion formula =** **[weight (pounds)/height (inches)^2] x 703**
Example of BMI calculation: A person who weighs 78.93 kilograms and is 177 centimeters tall has a BMI of 25:	Example of BMI calculation: A person who weighs 164 pounds and is 68 inches (or 5' 8") tall has a BMI of 25:
weight (78.93 kg)/height (1.77 m)2 = 25	**[**weight (164 pounds)/height (68 inches)2**]** x703 = 25

Table ES-4: CLASSIFICATION OF OVERWEIGHT AND OBESITY BY BMI, WAIST CIRCUMFERENCE AND ASSOCIATED DISEASE RISK*

	BMI (kg/m^2)	Obesity Class	Disease Risk* Relative to Normal Weight and Waist Circumference Obesity	
			Men ≤ 102 cm (≤ 40 in) Women ≤ 88 cm (≤ 35 in)	> 102 cm (> 40 in) > 88 cm (> 35 in)
Underweight	<18.5		—	—
Normal+	18.5 –24.9		—	—
Overweight	25.0 – 29.9		Increased	High
Obesity	30.0 – 34.9	I	High	Very High
	35.0 – 39.9	II	Very High	Very High
Extreme Obesity	≥40	III	Extremely High	Extremely High

● **Patient Motivation.** When assessing the patient's motivation to enter weight loss therapy, the following factors should be evaluated: reasons and motivation for weight reduction; previous history of successful and unsuccessful weight loss attempts; family, friends, and work-site support; the patient's understanding of the causes of obesity and how obesity contributes to several diseases; attitude toward physical activity; capacity to engage in physical activity; time availability for weight loss intervention; and financial considerations. In addition to considering these issues, the health care practitioner needs to heighten a patient's motivation for weight loss and prepare the patient for treatment. This can be done by enumerating the dangers accompanying persistent obesity and by describing the strategy for clinically assisted weight reduction. Reviewing the patients' past attempts at weight loss and explaining how the new treatment plan will be different can encourage patients and provide hope for successful weight loss.

Evaluation and Treatment: The general goals of weight loss and management are: (1) at a minimum, to prevent further weight gain; (2) to reduce body weight; and (3) to maintain a lower body weight over the long term. The overall strategy for the evaluation and treatment of overweight and obese patients is presented in the Treatment Algorithm on the next page. This algorithm applies only to the assessment for overweight and obesity and subsequent decisions based on that assessment. It does not include any initial overall assessment for cardiovascular risk factors or diseases that are indicated.

Goals Of Weight Loss And Management.

The *initial goal* of weight loss therapy is to reduce body weight by approximately 10 percent from baseline. If this goal is achieved, further weight loss can be attempted, if indicated through further evaluation.

A *reasonable time line* for a 10 percent reduction in body weight is 6 months of therapy. For overweight patients with BMIs in the typical range of 27 to 35, a decrease of 300 to 500 kcal/day will result in weight losses of about 1.2 to 1 lb/week and a 10 percent loss in 6 months. For more

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* Disease risk for type 2 diabetes, hypertension, and CVD.

+ Increased waist circumference can also be a marker for increased risk even in persons of normal weight.

severely obese patients with BMIs > 35, deficits of up to 500 to1,000 kcal/day will lead to weight losses of about 1 to 2 lb/week and a 10 percent weight loss in 6 months. Weight loss at the rate of 1to 2 lb/week (calorie deficit of 500 to 1,000kcal/day) commonly occurs for up to 6 months. After 6 months, the rate of weight loss usually declines and weight plateaus because of a lesser energy expenditure at the lower weight.

Experience reveals that lost weight usually will be regained unless a weight maintenance program consisting of dietary therapy, physical activity, and behavior therapy is continued indefinitely.

After 6 months of weight loss treatment, efforts to maintain weight loss should be put in place. If more weight loss is needed, another attempt at weight reduction can be made. This will require further adjustment of the diet and physical activity prescriptions.

For patients unable to achieve significant weight reduction, prevention of further weight gain is an important goal; such patients may also need to participate in a weight management program.

Strategies For Weight Loss And Weight Maintenance.

Dietary Therapy: A diet that is individually planned and takes into account the patient's overweight status in order to help create a deficit of 500 to 1,000 kcal/day should be an integral part of any weight loss program. A patient may choose a diet of 1,000 to 1,200kcal/day for women and 1,200 to 1,500kcal/day for men. Depending on the patient's risk status, the low-calorie diet (LCD) recommended should be consistent with the NCEP's Step I or Step II Diet (see page 74 of the guidelines). Besides decreasing saturated fat, total fats should be 30 percent or less of total calories. Reducing the percentage of dietary fat alone will not produce weight loss unless total calories are also reduced. Isocaloric replacement of fat with carbohydrates will reduce the percentage of calories from fat but will not cause weight loss. Reducing dietary fat, along with reducing dietary carbohydrates, usually will be needed to produce the caloric deficit needed for an acceptable weight loss. When fat intake is reduced, priority should be given to reducing saturated fat to enhance lowering of LDL cholesterol levels. Frequent contacts with the practitioner during dietary therapy help to promote weight loss and weight maintenance at a lower weight.

Physical Activity: An increase in physical activity is an important component of weight loss therapy, although it will not lead to substantially greater weight loss over 6 months. Most weight loss occurs because of decreased caloric intake. Sustained physical activity is most helpful in the prevention of weight regain. In addition, it has a benefit in reducing cardiovascular and diabetes risks beyond that produced by weight reduction alone. For most obese patients, exercise should be initiated slowly, and the intensity should be increased gradually. The exercise can be done all at one time or intermittently over the day. Initial activities may be walking or swimming at a slow pace. The patient can start by walking30 minutes for 3 days a week and can build to 45 minutes of more intense walking at least 5 days a week. With this regimen, an additional expenditure of 100 to 200 calories per day can be achieved. All adults should seta long-term goal to accumulate at least 30 minutes or more of moderate-intensity physical activity on most, and preferably all, days of the week. This regimen can be adapted to other forms of physical activity,

but walking is particularly attractive because of its safety and accessibility. Patients should be encouraged to increase "every day" activities such as taking the stairs instead of the elevator. With time, depending on progress and functional capacity, the patient may engage in more strenuous activities. Competitive sports, such as tennis and volleyball, can provide an enjoyable form of exercise for many, but care must be taken to avoid injury. Reducing sedentary time is another strategy to increase activity by undertaking frequent, less strenuous activities.

Behavior Therapy: Strategies, based on learning principles such as reinforcement, that provide tools for overcoming barriers to compliance with dietary therapy and/or increased physical activity are helpful in achieving weight loss and weight maintenance. Specific strategies include self-monitoring of both eating habits and physical activity, stress management, stimulus control, problem solving, contingency management, cognitive restructuring, and social support.

Combined Therapy: A combined intervention of behavior therapy, an LCD, and increased physical activity provides the most successful therapy for weight loss and weight maintenance. This type of intervention should be maintained for at least 6 months before considering pharmacotherapy.

Pharmacotherapy: In carefully selected patients, appropriate drugs can augment LCDs, physical activity, and behavior therapy in weight loss. Weight loss drugs that have been approved by the FDA for long-term use can be useful adjuncts to dietary therapy and physical activity for some patients with a BMI of $\geq$30 with no concomitant risk factors or diseases, and for patients with a BMI of $\geq$27 with concomitant risk factors or diseases. The risk factors and diseases considered important enough to warrant pharmacotherapy at a BMI of 27 to 29.9 are hypertension, dyslipidemia, CHD, type 2 diabetes, and sleep apnea. Continual assessment by the physician of drug therapy for efficacy and safety is necessary.

At the present time, sibutramine is available for long-term use. (Note: FDA approval of orlistat is pending a resolution of labeling issues and results of Phase III trials.) It enhances weight loss modestly and can help facilitate weight loss maintenance. Potential side effects with drugs, nonetheless, must be kept in mind. With sibutramine, increases in blood pressure and heart rate may occur. Sibutramine should not be used in patients with a history of hypertension, CHD, congestive heart failure, arrhythmias, or history of stroke. With orlistat, fat soluble vitamins may require replacement because of partial malabsorption. All patients should be carefully monitored for these side effects.

Weight Loss Surgery: Weight loss surgery is one option for weight reduction in a limited number of patients with clinically severe obesity, i.e., BMIs $\geq$40 or $\geq$35 with comorbid conditions. Weight loss surgery should be reserved for patients in whom efforts at medical therapy have failed and who are suffering from the complications of extreme obesity. Gastrointestinal surgery (gastric restriction[vertical gastric banding] or gastric bypass[Roux-en Y]) is an intervention weight loss option for motivated subjects with acceptable operative risks. An integrated program must be in place to provide guidance on diet, physical activity, and behavioral and social support both prior to and after the surgery.

• **Adapt Weight Loss Programs To Meet the Needs of Diverse Patients.** Standard treatment

approaches for overweight and obesity must be tailored to the needs of various patients or patient groups. Large individual variation exists within any social or cultural group; furthermore, substantial overlap among subcultures occurs within the larger society. There is, therefore, no "cookbook" or standardized set of rules to optimize weight reduction with a given type of patient. However, to be more culturally sensitive and to incorporate patient characteristics in obesity treatment programs: consider and adapt the setting and staffing for the program; consider how the obesity treatment program integrates into other aspects of patient health care and self care; and expect and allow for program modifications based on patient responses and preferences. The issues of weight reduction after age 65involve such questions as: does weight loss reduce risk factors in older adults; are there risks associated with obesity treatment that are unique to older adults; and does weight reduction prolong the lives of older adults? Although there is less certainty about the importance of treating overweight at older ages than at younger ages, a clinical decision to forgo obesity treatment in older adults should be guided by an evaluation of the potential benefit of weight reduction and the reduction of risk for future cardiovascular events. In the obese patient who smokes, smoking cessation is a major goal of risk factor management. Many well-documented health benefits accompany smoking cessation, but a major obstacle to cessation has been the attendant weight gain observed in about 80 percent of quitters. This weight gain averages 4.5 to 7 lb, but in 13 percent of women and 10 percent of men, weight gain exceeds 28 lb. Weight gain that accompanies smoking cessation has been quite resistant to most dietary, behavioral, or physical activity interventions. The weight gained with smoking cessation is less likely to produce negative health consequences than would continued smoking. For this reason, smoking cessation should be strongly advocated regardless of baseline weight. Prevention of weight gain through diet and physical activity should be stressed. For practical reasons, it may be prudent to avoid initiating smoking cessation and weight loss therapy simultaneously. If weight gain ensues after smoking cessation, it should be managed vigorously according to the guidelines outlined in this report. Although short-term weight gain is a common side effect of smoking cessation, this gain does not rule out the possibility of long-term weight control.

Summary Of Evidence-Based Recommendations

A. Advantages Of Weight Loss

The recommendation to treat overweight and obesity is based not only on evidence that relates obesity to increased mortality but also on RCT evidence that weight loss reduces risk factors for disease. Thus, weight loss may not only help control diseases worsened by obesity, it may also help decrease the likelihood of developing these diseases. The panel reviewed RCT evidence to determine the effect of weight loss on blood pressure and hypertension, serum/plasma lipid concentrations, and fasting blood glucose and fasting insulin. Recommendations focusing on these conditions underscore the advantages of weight loss.

1. Blood Pressure
To evaluate the effect of weight loss on blood pressure and hypertension, 76 articles reporting RCTs were considered for inclusion in these guidelines. Of the 45 accepted articles, 35 were

lifestyle trials and 10 were pharmacotherapy trials. There is strong and consistent evidence from these lifestyle trials in both overweight hypertensive and nonhypertensive patients that weight loss produced by lifestyle modifications reduces blood pressure levels. Limited evidence exists that decreases in abdominal fat will reduce blood pressure in overweight nonhypertensive individuals, although not independent of weight loss, and there is considerable evidence that increased aerobic activity to increase cardiorespiratory fitness reduces blood pressure (independent of weight loss). There is also suggestive evidence from randomized trials that weight loss produced by most weight loss medications, except for sibutramine, in combination with adjuvant lifestyle modifications will be accompanied by reductions in blood pressure. Based on a review of the evidence from the 45 RCT blood pressure articles, the panel makes the following recommendation:

Weight loss is recommended to lower elevated blood pressure in overweight and obese persons with high blood pressure. Evidence Category A.

2. Serum/Plasma Lipids
Sixty-five RCT articles were evaluated for the effect of weight loss on serum/plasma concentrations of total cholesterol, LDL-cholesterol, very low-density lipoprotein (VLDL)-cholesterol, triglycerides, and HDL-cholesterol. Studies were conducted on individuals over a range of obesity and lipid levels. Of the 22 articles accepted for inclusion in these guidelines, 14 RCT articles examined lifestyle trials while the remaining 8 articles reviewed pharmacotherapy trials. There is strong evidence from the 14 lifestyle trials that weight loss produced by lifestyle modifications in overweight individuals is accompanied by reductions in serum triglycerides and by increases in HDL-cholesterol. Weight loss generally produces some reductions in serum total cholesterol and LDL-cholesterol. Limited evidence exists that a decrease in abdominal fat correlates with improvements in lipids, although the effect may not be independent of weight loss, and there is strong evidence that increased aerobic activity to increase cardiorespiratory fitness favorably affects blood lipids, particularly if accompanied by weight loss. There is suggestive evidence from the eight randomized pharmacotherapy trials that weight loss produced by weight loss medications and adjuvant lifestyle modifications, including caloric restriction and physical activity, does not result in consistent effects on blood lipids. The following recommendations based on the review of the data in these 22 RCT articles:

Weight loss is recommended to lower elevated levels of total cholesterol, LDL-cholesterol, and triglycerides, and to raise low levels of HDL-cholesterol in overweight and obese persons with dyslipidemia. Evidence Category A.

3. Blood Glucose
To evaluate the effect of weight loss on fasting blood glucose and fasting insulin levels, 49 RCT articles were reviewed for inclusion in these guidelines. Of the 17 RCT articles accepted, 9 RCT articles examined lifestyle therapy trials and 8 RCT articles considered the effects of pharmacotherapy on weight loss and subsequent changes in blood glucose. There is strong evidence from the nine lifestyle therapy trials that weight loss produced by lifestyle modification reduces blood glucose levels in overweight and obese persons without diabetes, and weight loss reduces blood glucose levels and HbAlc in some patients with type 2 diabetes. There is suggestive evidence that decreases in abdominal fat will improve glucose tolerance in

overweight individuals with impaired glucose tolerance, although not independent of weight loss; and there is limited evidence that increased cardiorespiratory fitness improves glucose tolerance in overweight individuals with impaired glucose tolerance or diabetes, although not independent of weight loss. In addition, there is suggestive evidence from randomized trials that weight loss induced by weight loss medications does not appear to improve blood glucose levels any better than weight loss through lifestyle therapy in overweight persons both with and without type 2 diabetes. Based on a full review of the data in these 17 RCT articles, the panel makes the following recommendation:

Weight loss is recommended to lower elevated blood glucose levels in overweight and obese persons with type 2 diabetes. Evidence Category A.

B. Measurement Of Degree Of Overweight And Obesity

Patients should have their BMI and levels of abdominal fat measured not only for the initial assessment of the degree of overweight and obesity, but also as a guide to the efficacy of weight loss treatment. Although there are no RCTs that review measurements of overweight and obesity, the panel determined that this aspect of patient care warranted further consideration and that this guidance was deemed valuable. Therefore, the following four recommendations that are included in the Treatment Guidelines were based on nonrandomized studies as well as clinical experience.

1. BMI To Assess Overweight and Obesity
There are a number of accurate methods to assess body fat (e.g., total body water, total body potassium, bioelectrical impedance, and dual-energy X-ray absorptiometry), but no trial data exist to indicate that one measure of fatness is better than any other for following overweight and obese patients during treatment. Since measuring body fat by these techniques is often expensive and is not readily available, a more practical approach for the clinical setting is the measurement of BMI; epidemiological and observational studies have shown that BMI provides an acceptable approximation of total body fat for the majority of patients. Because there are no published studies that compare the effectiveness of different measures for evaluating changes in body fat during weight reduction, the panel bases its recommendation on expert judgment from clinical experience:

Practitioners should use the BMI to assess overweight and obesity. Body weight alone can be used to follow weight loss, and to determine efficacy of therapy. Evidence Category C.

2. BMI To Estimate Relative Risk
In epidemiological studies, BMI is the favored measure of excess weight to estimate relative risk of disease. BMI correlates both with morbidity and mortality; the relative risk for CVD risk factors and CVD incidence increases in a graded fashion with increasing BMI in all population groups. Moreover, calculating BMI is simple, rapid, and inexpensive, and can be applied generally to adults. The panel, therefore, makes this recommendation:

The BMI should be used to classify overweight and obesity and to estimate relative risk of disease compared to normal weight. Evidence Category C.

3. Assessing Abdominal Fat
For the most effective technique for assessing abdominal fat content, the panel considered measures of waist circumference, waist-to-hip ratio (WHR), magnetic resonance imaging(MRI), and computed tomography. Evidence from epidemiological studies shows waist circumference to be a better marker of abdominal fat content than WHR, and that it is the most practical anthropometric measurement for assessing a patient's abdominal fat content before and during weight loss treatment. Computed tomography and MRI are both more accurate but impractical for routine clinical use. Based on evidence that waist circumference is a better marker than WHR—and taking into account that the MRI and computed tomography techniques are expensive and not readily available for clinical practice—the panel makes the following recommendation:

The waist circumference should be used to assess abdominal fat content. Evidence Category C.

4. Sex-Specific Measurements
Evidence from epidemiological studies indicates that a high waist circumference is associated with an increased risk for type 2 diabetes, dyslipidemia, hypertension, and CVD. Therefore, the panel judged that sex-specific cutoffs for waist circumference can be used to identify increased risk associated with abdominal fat in adults with a BMI in the range of 25 to 34.9. These cutpoints can be applied to all adult ethnic or racial groups. On the other hand, if a patient is very short, or has a BMI above the 25 to 34.9 range, waist cutpoints used for the general population may not be applicable. Based on the evidence from nonrandomized studies, the panel makes this recommendation:

For adult patients with a BMI of 25 to34.9 kg/m^2, sex-specific waist circumference cutoffs should be used in conjunction with BMI to identify increased disease risks. Evidence Category C.

C. Goals For Weight Loss

The general goals of weight loss and management are to reduce body weight, to maintain a lower body weight over the long term, and to prevent further weight gain. Evidence indicates that a moderate weight loss can be maintained over time if some form of therapy continues. It is better to maintain a moderate weight loss over a prolonged period than to regain from a marked weight loss.

1. Initial Goal of Weight Loss from Baseline
There is strong and consistent evidence from randomized trials that overweight and obese patients in well-designed programs can achieve a weight loss of as much as 10 percent of baseline weight. In the diet trials, an average of 8 percent of baseline weight was lost. Since this average includes persons who did not lose weight, an individualized goal of 10 percent is reasonable. The panel, therefore, recommends that:

The initial goal of weight loss therapy should be to reduce body weight by approximately 10 percent from baseline. With success, further weight loss can be attempted if indicated through further assessment. Evidence Category A.

2. Amount of Weight Loss
Randomized trials suggest that weight loss at the rate of 1 to 2 lb/week (calorie deficit of 500 to1,000 kcal/day) commonly occurs for up to 6months.

Weight loss should be about 1 to 2 lb/week for a period of 6 months, with the subsequent strategy based on the amount of weight lost. Evidence Category B.

D. How To Achieve Weight Loss

The panel reviewed relevant treatment strategies designed for weight loss that can also be used to foster long-term weight control and prevention of weight gain. The consequent recommendations emphasize the potential effectiveness of weight control using multiple interventions and strategies, including dietary therapy, physical activity, behavior therapy, pharmacotherapy, and surgery, as well as combinations of these strategies.

1. Dietary Therapy
The panel reviewed 86 RCT articles to determine the effectiveness of diets on weight loss (including LCDs, very low-calorie diets (VLCDs), vegetarian diets, American Heart Association dietary guidelines, the NCEP's Step I diet with caloric restriction, and other low-fat regimens with varying combinations of macronutrients). Of the 86 articles reviewed, 48 were accepted for inclusion in these guidelines. These RCTs indicate strong and consistent evidence that an average weight loss of 8 percent of initial body weight can be obtained over 3 to 12 months with an LCD and that this weight loss effects a decrease in abdominal fat; and, although lower-fat diets without targeted caloric reduction help promote weight loss by producing a reduced caloric intake, lower-fat diets with targeted caloric reduction promote greater weight loss than lower-fat diets alone. Further, VLCDs produce greater initial weight losses than LCDs (over the long term of >1 year, weight loss is not different than that of the LCDs). In addition, randomized trials suggest that no improvement in cardiorespiratory fitness as measured by VO2 max appears to occur in obese adults who lose weight on LCDs alone without physical activity. The following recommendations are based on the evidence extracted from the 48 accepted articles:

LCDs are recommended for weight loss in overweight and obese persons. Evidence Category A. Reducing fat as part of an LCD is a practical way to reduce calories. Evidence Category A.

Reducing dietary fat alone without reducing calories is not sufficient for weight loss. However, reducing dietary fat, along with reducing dietary carbohydrates, can facilitate caloric reduction. Evidence Category A.

A diet that is individually planned to help create a deficit of 500 to 1,000 kcal/day should be an intregal part of any program aimed at achieving a weight loss of 1 to 2 lb/week. Evidence Category A.

2. Physical Activity
Effects of Physical Activity on Weight Loss
Twenty-three RCT articles were reviewed to determine the effect of physical activity on weight

loss, abdominal fat (measured by waist circumference), and changes in cardiorespiratory fitness (VO_2 max). Thirteen of these articles were accepted for inclusion in these guidelines. A review of these articles reveals strong evidence that physical activity alone, i.e., aerobic exercise, in obese adults results in modest weight loss and that physical activity in overweight and obese adults increases cardiorespiratory fitness, independent of weight loss. Randomized trials suggest that increased physical activity in overweight and obese adults reduces abdominal fat only modestly or not at all, and that regular physical activity independently reduces the risk for CVD. The panel's recommendation on physical activity is based on the evidence from these 13 articles:

Physical activity is recommended as part of a comprehensive weight loss therapy and weight control program because it: (1)modestly contributes to weight loss in overweight and obese adults (Evidence Category A), (2) may decrease abdominal fat (Evidence Category B), (3) increases cardiorespiratory fitness (Evidence Category A), and (4) may help with maintenance of weight loss (Evidence Category C).

Physical activity should be an integral part of weight loss therapy and weight maintenance. Initially, moderate levels of physical activity for 30 to 45 minutes, 3 to 5 days a week, should be encouraged. All adults should set a long-term goal to accumulate at least 30 minutes or more of moderate intensity physical activity on most, and preferably all, days of the week. Evidence Category B.

Effects of Physical Activity and Diet on Weight Loss (Combined Therapy)
Twenty-three RCT articles were reviewed to determine the effects on body weight of a combination of a reduced-calorie diet with increased physical activity. Fifteen of these articles were accepted for inclusion in the guidelines. These articles contain strong evidence that the combination of a reduced-calorie diet and increased physical activity produces greater weight loss than diet alone or physical activity alone, and that the combination of diet and physical activity improves cardiorespiratory fitness as measured by VO_2 max in overweight and obese adults when compared to diet alone. The combined effect of a reduced calorie diet and increased physical activity seemingly produced modestly greater reductions in abdominal fat than either diet alone or physical activity alone, although it has not been shown to be independent of weight loss. The panel's following recommendations are based on the evidence from these articles:

The combination of a reduced calorie diet and increased physical activity is recommended since it produces weight loss that may also result in decreases in abdominal fat and increases in cardiorespiratory fitness. Evidence Category A.

3. Behavior Therapy
Thirty-six RCTs were reviewed to evaluate whether behavior therapy provides additional benefit beyond other weight loss approaches, as well as to compare various behavioral techniques. Of the 36 RCTs reviewed, 22 were accepted. These RCTs strongly indicate that behavioral strategies to reinforce changes in diet and physical activity in obese adults produce weight loss in the range of 10 percent over 4 months to 1 year. In addition, no one behavior therapy appeared superior to any other in its effect on weight loss; multimodal strategies appear to work best and those interventions with the greatest intensity appear to be associated with the greatest weight loss. Long-term follow-up of patients undergoing behavior therapy shows a return to baseline

weight for the great majority of subjects in the absence of continued behavioral intervention. Randomized trials suggest that behavior therapy, when used in combination with other weight loss approaches, provides additional benefits in assisting patients to lose weight short-term, i.e., 1 year (no additional benefits are found at 3 to 5 years). The panel found little evidence on the effect of behavior therapy on cardiorespiratory fitness. Evidence from these articles provided the basis for the following recommendation:

Behavior therapy is a useful adjunct when incorporated into treatment for weight loss and weight maintenance. Evidence Category B.

There is also suggestive evidence that patient motivation is a key component for success in a weight loss program. The panel, therefore, makes the following recommendation:

Practitioners need to assess the patient's motivation to enter weight loss therapy; assess the readiness of the patient to implement the plan and then take appropriate steps to motivate the patient for treatment. Evidence Category D.

4. Summary of Lifestyle Therapy
There is strong evidence that combined interventions of an LCD, increased physical activity, and behavior therapy provide the most successful therapy for weight loss and weight maintenance. The panel makes the following recommendation:

Weight loss and weight maintenance therapy should employ the combination of LCDs, increased physical activity, and behavior therapy. Evidence Category A.

5. Pharmacotherapy
A review of 44 pharmacotherapy RCT articles provides strong evidence that pharmacological therapy (which has generally been studied along with lifestyle modification, including diet and physical activity) using dexfenfluramine, sibutramine, orlistat, or phentermine/fenfluramine results in weight loss in obese adults when used for 6 months to 1 year. Strong evidence also indicates that appropriate weight loss drugs can augment diet, physical activity, and behavior therapy in weight loss. Adverse side effects from the use of weight loss drugs have been observed in patients. As a result of the observed association of valvular heart disease in patients taking fenfluramine and dexfenfluramine alone or in combination, these drugs have been withdrawn from the market. Weight loss drugs approved by the FDA for long-term use may be useful as an adjunct to diet and physical activity for patients with a BMI of ≥30 with no concomitant obesity-related risk factors or diseases, as well as for patients with a BMI of ≥27 with concomitant risk factors or diseases; moreover, using weight loss drugs singly (not in combination) and starting with the lowest effective doses can decrease the likelihood of adverse effects. Based on this evidence, the panel makes the following recommendation:

Weight loss drugs approved by the FDA may be used as part of a comprehensive weight loss program, including dietary therapy and physical activity for patients with a BMI of ≥30 with no concomitant obesity-related risk factors or diseases, and for patients with a BMI of ≥27 with concomitant obesity-related risk factors or diseases. Weight loss drugs should never be used without concomitant lifestyle modifications. Continual assessment of drug therapy for efficacy

and safety is necessary. If the drug is efficacious in helping the patient to lose and/or maintain weight loss and there are no serious adverse effects, it can be continued. If not, it should be discontinued. Evidence Category B.

6. Weight Loss Surgery

The panel reviewed 14 RCTs that examined the effect of surgical procedures on weight loss; 8 were deemed appropriate. All of the studies included individuals who had a BMI of 40 kg/m^2 or above, or a BMI of 35 to 40 kg/m^2 with comorbidity. These trials provide strong evidence that surgical interventions in adults with clinically severe obesity, i.e., BMIs ≥40 or ≥35 with comorbid conditions, result in substantial weight loss, and suggestive evidence that lifelong medical surveillance after surgery is necessary. Therefore, the panel makes the following recommendation:

Weight loss surgery is an option for carefully selected patients with clinically severe *obesity (BMI ≥40 or ≥35 with comorbid conditions) when less invasive methods of weight loss have failed and the patient is at high risk for obesity-associated morbidity or mortality. Evidence Category B.*

E. Goals For Weight Loss Maintenance

Once the goals of weight loss have been successfully achieved, maintenance of a lower bodyweight becomes the challenge. Whereas studies have shown that weight loss is achievable, it is difficult to maintain over a long period of time(3 to 5 years). In fact, the majority of persons who lose weight, once dismissed from clinical therapy, frequently regain it—so the challenge to the patient and the practitioner is to maintain the weight loss. Successful weight reduction thus depends on continuing a maintenance program on a long-term basis. In the past, obtaining the goal of weight loss has been considered the end of weight loss therapy. Observation, monitoring, and encouragement of patients who have successfully lost weight should be continued long term. The panel's recommendations on weight loss maintenance are derived from RCT evidence as well as nonrandomized and observational studies.

1. Weight Maintenance Phase

RCTs from the Behavior Therapy section above suggest that lost weight usually will be regained unless a weight maintenance program consisting of dietary therapy, physical activity, and behavior therapy is continued indefinitely. Drug therapy in addition may be helpful during the weight maintenance phase. The panel also reviewed RCT evidence that considered the rate of weight loss and the role of weight maintenance. These RCTs suggest that after 6 months of weight loss treatment, efforts to maintain weight loss are important. Therefore, the panel recommends the following:

After successful weight loss, the likelihood of weight loss maintenance is enhanced by a program consisting of dietary therapy, physical activity, and behavior therapy which should be continued indefinitely. Drug therapy can also be used. However, drug safety and efficacy beyond 1 year of total treatment have not been established. Evidence Category B.

A weight maintenance program should be a priority after the initial 6 months of weight loss

therapy. Evidence Category B.

Strong evidence indicates that better weight loss results are achieved with dietary therapy when the duration of the intervention is at least 6 months. Suggestive evidence also indicates that during dietary therapy, frequent contacts between professional counselors and patients promote weight loss and maintenance. Therefore, the panel recommends the following:

The literature suggests that weight loss and weight maintenance therapies that provide a greater frequency of contacts between the patient and the practitioner and are provided over the long term should be utilized whenever possible. This can lead to more successful weight loss and weight maintenance. Evidence Category C.

F. Special Treatment Groups

The needs of special patient groups must be addressed when considering treatment options for overweight and obesity. The guidelines focus on three such groups including smokers, older adults, and diverse patient populations.

1. Smokers

Cigarette smoking is a major risk factor for cardiopulmonary disease. Because of its attendant high risk, smoking cessation is a major goal of risk-factor management. This aim is especially important in the overweight or obese patient, who usually carries excess risk from obesity-associated risk factors. Thus, smoking cessation in these patients becomes a high priority for risk reduction. Smoking and obesity together apparently compound cardiovascular risk, but fear of weight gain upon smoking cessation is an obstacle for many patients. Therefore, the panel recommends that:

All smokers, regardless of their weight status, should quit smoking. Evidence Category A. Prevention of weight gain should be encouraged and if weight gain does occur, it should be treated through dietary therapy, physical activity, and behavior therapy, maintaining the primary emphasis on the importance of abstinence from smoking. Evidence Category C.

2. Older Adults

The general nutritional safety of weight reduction at older ages is of concern because restrictions on overall food intake due to dieting could result in inadequate intake of protein or essential vitamins or minerals. In addition, involuntary weight loss indicative of occult disease might be mistaken for success in voluntary weight reduction. These concerns can be alleviated by providing proper nutritional counseling and regular body weight monitoring in older persons for whom weight reduction is prescribed. A review of several studies indicates that age alone should not preclude treatment for obesity in adult men and women. In fact, there is evidence from RCTs that weight reduction has similar effects in improving cardiovascular disease risk factors in older and younger adults. Therefore, in the panel's judgment:

A clinical decision to forego obesity treatment in older adults should be guided by an evaluation of the potential benefits of weight reduction for day-to-day functioning and reduction of the risk of future cardiovascular events, as well as the patient's motivation for weight reduction. Care

must be taken to ensure that any weight reduction program minimizes the likelihood of adverse effects on bone health or other aspects of nutritional status. Evidence Category D.

3. Diverse Patient Populations
Standard obesity treatment approaches should be tailored to the needs of various patients or patient groups. It is, however, difficult to determine from the literature how often this occurs, how specific programs and outcomes are influenced by tailoring, and whether it makes weight loss programs more effective. After reviewing two RCTs, four cross-sectional studies, and four intervention studies, as well as additional published literature on treatment approaches with diverse patient populations, the panel recommends the following:

The possibility that a standard approach to weight loss will work differently in diverse patient populations must be considered when setting expectations about treatment outcomes. Evidence Category B.

Chapter 16. Eating Disorders

Phenomenology

Anorexia nervosa and bulimia nervosa are common syndromes associated with disordered eating. Anorexia nervosa is characterized by a refusal to maintain body weight at or above 85% of that person's ideal body weight, and bulimia nervosa is characterized by recurrent cycles of binge eating followed by inappropriate compensatory behaviors to prevent weight gain. While anorexia and bulimia differ in their clinical manifestations and outcomes, patients afflicted with these syndromes often demonstrate *a preoccupation with weight and a desire to be thinner.*

Epidemiology

Although both men and women can be afflicted, post-pubescent females account for nearly 95% of people with eating disorders. The age of onset is most typically in the teenage and early adult years, but cases with prepubertal onset and with onset in the 40s have been reported.

Diagnosis

Anorexia nervosa is characterized by a refusal to maintain body weight at or above 85% of that person's ideal body weight. This can be secondary to either a weight loss or a failure to gain weight during the period of growth. Anorexia can further be categorized into two types: a *restricting type* where the person achieves a low weight by restricting caloric intake and does not regularly engage in binging/purging and a *binge-eating/purging type* where during the episodes of anorexia, the person engages in binge eating or purging behavior (i.e. self-induced vomiting or the misuse of laxatives, diuretics, or enemas.) Diagnostic criteria for anorexia also include the presence of an intense fear of gaining weight or becoming fat, despite the patient being underweight. The patient will also experience a disturbance in the perception of her body weight or shape, which has undue influence of body weight or shape on self-evaluation. Another criterion for anorexia nervosa is amenorrhea (the absence of at least three consecutive menstrual cycles) in post-menstrual females due to decreased levels of LH and FSH.

Bulimia nervosa is characterized by recurrent cycles of binge eating followed by inappropriate compensatory behaviors to prevent weight gain. Patients with bulimia may be underweight, normal weight, or overweight. Binge eating is consumption of a large amount of food in a discrete period of time often accompanied by a sense of "lack of control." This is followed by inappropriate behaviors aimed at preventing weight gain. These can be of the *Purging Type* (self-induced vomiting; misuse of laxatives, diuretics, enemas or other medications) or *Nonpurging Type* (fasting or excessive exercise).

Pathology/Etiology

The etiology of eating disorders is unclear.   Although psychological factors most certainly contribute to the development of eating disorders, there have been many studies investigating biologic factors which may increase the susceptibility of certain women to developing eating disorders. Anorexia has a 6% prevalence in siblings, and in one twin-study, 9 of 12 monozygotic and 1 of 14 dizygotic pairs were concordant for the disorder.

Recent studies of neurotransmitters in patients with anorexia nervosa suggest that underlying abnormalities may play a role in the pathogenesis of anorexia. The following are some theories that have been proposed regarding chemical signals in the pathogenesis of eating disorders.

Neuropeptides

Many disturbances of the hypothalamic-pituitary axis occur in anorexia and bulimia, and in general are related to the state of being under-nourished and tend to normalize after clinical recovery. Neuropeptides such as NPY and peptide YY have been found to regulate the rate, duration, and size of meals and thus it is possible that disturbances in their function may contribute to disordered eating.

NPY and PYY are endogenous stimulants of feeding behavior. Increased NPY activity may represent a homeostatic mechanism to stimulate feeding. Underweight anorexics have been shown to have elevations of CSF NPY but normal PYY. While the increase in NPY is not effectively stimulating feeding in these patients, it may be related to the obsessive and paradoxical interest in dietary intake that occurs in patients with anorexia nervosa. Animal studies have noted that intraventricular injection of NPY produces many of the physiologic and behavioral changes associated with AN, including alteration of the hypothalamic-pituitary axis and hypotension.

In addition to their known peripheral effects, vasopressin and oxytocin have also been implicated in modulating complex behavioral effects: vasopressin promotes consolidation of learning and memory function, and administration of oxytocin to rats has been shown to antagonize memory consolidation and retrieval. Some underweight patients with AN have abnormally high levels of cerebral vasopression and abnormally low levels of cerebral oxytocin which may contribute to the retention of cognitive distortions and relentless preoccupation with food intake. These levels tend to normalize with weight restoration.

Cholecystokinin (CCK)

CCK is a peptide secreted by the GI system in response to food intake. Exogenously administered CCK has been shown to reduce food intake in animals and humans. Some studies have found that elevations of basal and postprandial plasma CCK in underweight anorexics, which may play a role in the perpetuation of pathologic eating in anorexia nervosa.

Leptin

Leptin is a hormone secreted by adipose cells and has been proposed as an afferent signal of body fat stores. Malnourished and underweight people have decreased leptin concentrations, which implies a normal physiological response to starvation. However, these levels increase with weight gain but appear to precede normalization of body weight. This "premature" negative feedback may contribute to the difficulties patients suffering from anorexia nervosa experience in attaining and maintaining normal weights.

Serotonin

The central serotonergic system has been implicated in mediating satiety via its action in the ventromedial hypothalamus. Increases in serotonin function leads to reductions in food intake, and decreases lead to increased food consumption and the promotion of weight gain.

In patients with anorexia nervosa, the major serotonin metabolite 5-HIAA is found to be decreased in the CSF, suggesting decreased serotonin levels. Serotonin levels also decrease in non-anorexic women who are dieting, (A likely contributor to this decrease is the decreased availability of the dietary protein tryptophan- the precursor to serotonin.) In women who achieve long-standing recovery, however, serotonin metabolite levels rise above normal. As increased levels of serotonin have been associated with obsession with symmetry, exactness and perfection, this is consistent with the theory that *a preexisting elevation in serotonin levels may predispose some patients to an increase in rigid and obsessive behavior and suppression of the appetite center.* Regardless, underweight women with anorexia tend to have low levels of serotonin, and studies have shown that treatment of anorexics with SRI such as fluoxetine improved patient outcome with reduction of core eating disorder symptoms, depression, anxiety, and obsession and compulsions. Anorectic effects may also be mediated by dopaminergic systems, demonstrated by the appetite suppression caused by cocaine and amphetamine use.

Differential

Many medical illnesses can anorexia and weight loss, and some might be mistaken for anorexia nervosa. Some illnesses, for example some forms of cancer, may cause weight loss despite adequate intake. In differentiating these from anorexia nervosa, one should look for a distortion in body image, which is a a primary distinguishing feature found among primary anorectics: they usually see themselves as being overweight despite being obviously emaciated. In contrast, a patient with a medical disorder will usually show concern for their unexplained weight loss, particularly if it is reaching a critical degree.

Some patients with cognitive disorders may have unexplained weight loss. This may simply reflect poor eating habits. One should be suspicious of this in the case of a patient with dementia who is living independently, as they may be forgetting to eat regular meals.

An number of psychiatric disorders may also present with poor appetite or weight loss as well. Most common is major depression, for which anorexia is a common symptom. Such patients may also have some degree of body image distortion, or poor insight into their weight loss. In

such cases, however, the anorexia resolves along with the depression. Patients with a somatization disorder may complain of poor appetite, but this is accompanied by a number of other unexplained physical symptoms, which are unrelated to weight or body image. Patients with a psychotic disorder may misperceive their physical appearance, however such delusional beliefs are generally more bizarre and elaborate than that seen with an eating disorder (e.g., imagining that ones body is infested with parasites, or that one's eating habits are being externally controlled). Body dysmorphic disorder is the syndrome of imagined ugliness. In such cases, there is a distortion of body image. However, this distortion is not merely of weight, but of a perceived physical abnormality.

A number of disorders can occasionally be confused with bulimia nervosa. Patients with depression may exhibit binge eating. Such disorders as the Kluver-Bucy syndrome and the Kleine-Levin syndrome may present with hyperphagia. These disorders are generally distinguished through a good history, with an appreciation of the full spectrum of symptoms with which an individual suffers.

Common Comorbid Disorders

Anorexia nervosa and bulimia nervosa are not mutually exclusive. Approximately 50% of patients with anorexia will have accompanying bulimia nervosa.

Course

The depletion of fat and malnutrition that occurs with anorexia leads to muscle wasting, and in extreme cases, can involve cardiac muscle. Electrolyte imbalances can lead to arrhythmias. Other complications include leukopenia, increased levels of cortisol, osteoporosis, and the development of lanugo (baby fine hair covering the body).

Malnutrition and electrolyte abnormalities can occur with bulimia as well, and persistent vomiting can lead to dental erosion and enlarged salivary glands.

Treatment

Current treatments for patients with anorexia nervosa and bulimia nervosa center around psychotherapy and pharmacotherapy, with perhaps a higher rate of success in patients with bulimia over patients with anorexia. Cognitive behavioral therapy has been shown to be an effective treatment for 60-70% of individuals with bulimia nervosa. People with anorexia nervosa often respond less effectively to treatment. Often extended hospitalization is required, with psychotherapy and strict monitoring of feeding. Serotonin reuptake inhibitors have been found to alleviate some of the associated symptoms of depression and anxiety. Occasionally, tube feedings by nasogastric tube become necessary. Relapse after hospitalization has been high, and it has been reported that up to 20% of patients with anorexia nervosa die within twenty years as a result of medical complications from this disease.

Section 3. Other Subjects.

Chapter 17. Childhood And Adolescent Disorders

Attention-Deficit Hyperactivity Disorder (ADHD)

Phenomenology/Epidemiology/Etiology

ADHD is a disorder of impaired attention, hyperactivity, distractability, and/or impulsivity that results in impaired academic and social function. The disorder has a prevalence of 3-5% in the general population, is almost nine times more common in boys than girls, and has a genetic predisposition. It has been estimated that approximately 50% of patients will have persistent symptoms into adulthood. The disorder typically presents as poor performance in school in children between ages 3 and 13.

Diagnosis

A patient diagnosed with ADHD may be subclassified into the predominantly inattentive type, predominantly hyperactive-impulsive type (more common in boys), or the combined type. To meet DSM-IV criteria for ADHD, a child must have six or more symptoms of inattention or six or more symptoms of hyperactivity and impulsivity. The symptoms must be present before the age of seven and must cause clinically significant impairment in social and academic functioning. Additionally, symptoms must be present for at least six months, are not accounted for by another Axis I disorder, and must be present in at least two settings (i.e. both home and school). The symptoms are as follows:

Inattentive Symptoms	Hyperactive/Impulsive Symptoms
-Makes careless mistakes owing to inability to pay close attention to detail -Has difficulty maintaining attention in schoolwork or at play -Has difficulty listening even when spoken to directly -Fails to follow instructions or complete tasks or schoolwork -Has difficulty organizing tasks and activities -Avoids or dislikes tasks requiring concentration or sustained mental effort -Loses items necessary for completion of school tasks (e.g., pencils, papers, and books) -Is easily distracted by external stimuli -Is forgetful in daily activities	-Fidgety (e.g., squirms in seat) -Unexpectedly leaves desk in classroom -Runs about excessively in inappropriate situations -Has difficulty playing quietly -Is often "on the go" or acts as if "driven by a motor" -Talks excessively -Blurts out answers before questions have been completed -Has difficulty waiting his turn -Often interrupts or intrudes on others

Differential

The differential diagnosis for ADHD is extensive. It includes neurologic disorders, psychiatric conditions, environmental issues, and other general medical conditions. Some alternate diagnoses to consider include:

Neurologic

Learning disorders: these are deficiencies in a particular academic area such as reading, mathematics, and written expression which would place a child below the expected performance for their chronological age. They affect about 5% of school-aged children, with males affected more commonly than females (2-4x greater risk).

Mental retardation: this is globally impaired (as opposed to a specific area, as in learning disorders) intellectual functioning in a child as manifest by an IQ (mental age/chronological age) < 70. Patients must have concurrent deficiencies in multiple areas of adaptive functioning for diagnosis. MR has a prevalence of 1-2% and is twice as common in males compared to females.

Tourette's disorder: this is a disorder that occurs most commonly in boys and is characterized by the presence of multiple motor tics and one or more vocal tics, which must be present nearly every day or intermittently for at least 1 year. Eye tics such as blinking and eye rolling are the most common initial symptoms, followed by facial tics and in some cases whole-body tics. Traditionally, this disorder has been treated with high-potency neuroleptics such as haloperidol and pimozide.

Others: traumatic brain injury, seizure disorders (i.e. absence seizures)

Psychiatric

Conduct disorder: This condition refers to persistent behavior that grossly violates social norms, including aggression to other people and animals, destruction of property (e.g. fire-setting), stealing, or serious rule violations (truancy, running away from home). For diagnosis, behaviors must be present for at least a year, and the patient must be younger than 18 (if 18 or older, then the diagnosis is antisocial personality disorder).
Oppositional Defiant disorder: refers to a pattern of persistent noncompliant, hostile, and defiant behavior toward authority figures such as parents and teachers. The disorder must last at least six months, and must not meet criteria for conduct disorder.
Substance abuse
Others: OCD, anxiety disorders, depression, PTSD

General Medical Conditions

Visual/hearing impairments
Lead toxicity
Hypothyroidism
Malnutrition

Environmental Conditions

Family dysfunction/child abuse
Improper learning environment in school

Comorbidity

Evidence suggests that ADHD is frequently comorbid with conditions such as Tourette's disorder and psychiatric conditions, including OCD, other anxiety disorders, and depression. The presence of any one of these conditions may affect the course of treatment regimens (discussed further below).

Treatment

Non-pharmacologic means of treating ADHD should be attempted prior to initiating pharmacotherapy. Some considerations when first managing a child with ADHD include addressing educational concerns and associated learning disabilities along with improving maladaptive family behavior patterns. Other behavioral modification

techniques that employ a consistent system of positive rewards for appropriate behaviors may be useful as well.

Pharmacologic treatment is indicated when impairment is significant and not improved by other means. Stimulants such as methylphenidate (Ritalin, Concerta) are effective in treating approximately 70% of patients with ADHD. Other drugs in this class include dextroamphetamine (Dexedrine), and pemoline (Cylert—must check liver function tests every 2 weeks with this drug). Common side effects include insomnia, other symptoms of psychomotor stimulation, and reduced growth velocity (which returns to normal when the medication is discontinued). Modafanil, a non amphetamine stimulating drug is currently approved for the treatment of narcolepsy, but is being tested in ADHD. It seems to cause less of the unwanted stimulant side effects, such as anxiety and jitteriness.

Antidepressants have shown efficacy in treating ADHD: Tricyclic antidepressants such as nortriptyline have been shown to be as effective in treating ADHD and are useful in treating comorbid tic disorders. Bupropion also has good data attesting to its utility. Clonidine also has utility in treating ADHD, and is indicated when a patient also suffers from Tourette's disorder or OCD.

The newest kid on the block is atomoxetine (Strattera). It is a selective norepinephrine reuptake inhibitor, and appears to have little effect on dopamine reuptake. However, it does appear increase dopamine in the prefrontal cortex. Though similar to the tricyclic antidepressants both in structure and likely mechanism of action, Strattera doesn't seem to have some of the most troublesome side effects of those drugs. Most notably, it does not appear to have the anticholinergic, antihistaminic and alpha adrenergic effects typical of the tricylics. Its most common side effects are the type associated with stimulants: appetite suppression, insomnia, and irritability. It can cause nausea, and can increase blood pressure (usually only slightly). It is reported to have little abuse potential. This is commonly said of new drugs, but if true, this would give it a substantial advantage over the typical stimulants. Limited studies suggest it is as effective as Ritalin, but that it has a more gradual onset (days to weeks).

Autism And Pervasive Developmental Disorders (PDDs)

Phenomenology/Epidemiology/Etiology

PDDs are severe, persistent impairments in developmental areas such as communication, social interactions, or behaviors. PDD encompasses a spectrum of disorders, including autism, Asperger's syndrome, Rett's syndrome, and childhood disintegrative disorder. Autistic disorder involves a preoccupation with the internal world and presents with deficiencies in all three areas of development noted above, including communication,

social interaction, and behavior. It has an incidence of 2-6/10000 live births, usually presents before age four, and is 3-4 times more common in males. The disorder is believed to be organic in nature, but the exact etiology remains unknown. Autism has been associated with inherited conditions such as tuberous sclerosis and fragile X syndrome. About 75% have comorbid MR, and approximately 25% suffer from seizures.

Diagnosis

The first sign of impairment is usually social in nature, as a child may fail to develop a social smile. Later, the patient shows an impaired ability/desire to create relationships with parents and peers. Communication deficiencies include impaired language development, manifest as impaired ability to have conversations or improper speech construction/quality (echolalia, pronoun reversals). Behavioral impairments include stereotypical, repetitive actions and interests (such as preoccupation with a restricted interest or area of knowledge).

Differential

The differential diagnosis of autism is generally divided into psychiatric and neurologic conditions:

Psychiatric

Rett's disorder: this is a condition characterized by normal prenatal, perinatal, and postnatal development through the first 5 months of life, followed by a loss of social, verbal, and cognitive functioning between the ages of 5 and 48 months. The disorder is X-linked and seen only in females, and stereotyped hand-wringing movements are often a prominent feature.
Asperger's disorder: this condition is generally considered to be a mild form of autistic disorder and involves repetitive behavior and difficulties forming social relationships. However, language impairments are generally not present and intelligence is typically normal.
Childhood disintegrative disorder: a condition that resembles autism in that patients possess symptoms of social, behavioral, and language impairment, but it is differentiated by the fact that symptoms occur after a period of normal development up to the age of 3 or 4.
Others: selective mutism (refusal to speak in certain social situations but not others), OCD, childhood psychosis

Neurologic

Mental retardation
Congenital deafness/blindness

Tourette's disorder (stereotypical motor behaviors)
Congenital infection (e.g., CMV)
Inborn Errors of Metabolism (e.g., Lesch-Nyhan syndrome)

Treatment

Autism is a lifelong disorder that generally prevents people from living independently. Medications are generally not indicated in the absence a comorbid disorder, but nonpharmacologic approaches may improve coping mechanisms. For example, psychotherapy may have some use for both the patient and family. Additionally, highly structured educational settings may help communication and living skills, while behavioral approaches can reduce stereotyped actions. Instances where medications are indicated include aggressive and self-injurious behavior, where neuroleptics may be given, and a concurrent seizure disorder, where use of anticonvulsants is necessary.

Other Psychiatric Conditions In Children

Separation anxiety disorder: developmentally inappropriate and excessive anxiety concerning separation from the home or from those to whom the individual is attached. The onset of symptoms must be present for four weeks and begin prior to age 18. Patients may not like to go to school, may have repeated physical symptoms when at school, and/or may sleep in their parents' bed at night.

Reactive attachment disorder of infancy/early childhood: markedly disturbed social relatedness present in most contexts and beginning before age five.

Chapter 18. Personality Disorders.

Working Definitions

Personality Trait

A stable, recurring pattern of human behavior – e.g. a tendency to joke in serious situations, hypersensitivity to criticism, talkativeness in groups.

Personality Type

A constellation of personality traits recognizable as a frequent and familiar combination – e.g. the compulsive personality, characterized by preoccupations with work, detail, order, time, money, and cleanliness.

Personality Disorder

A constellation of personality traits that are inflexible and maladaptive, leading to difficulties in work or interpersonal relations, subjective distress, and usually both.

Neurosis

An unfashionable term for a non-psychotic mental disorder that causes the patient unpleasant feelings such as anxiety, depression, or pathological shame or guilt.

Many disorders formerly called neuroses now fit DSM-IV categories such as generalized anxiety disorder, dysthymia, adjustment disorder, obsessive-compulsive disorder, etc.

Some people have emotionally painful difficulties in living that do not easily fit discrete DSM-IV categories. Many of these patients would have been called neurotic. Often, they meet some of the criteria for a DSM-IV personality disorder, but have an insufficient number of criteria, or insufficient impairment, to warrant a personality disorder diagnosis.

Speculations on Etiology

Personality in general is formed through an interaction of genetic and developmental influences. Severe personality disorders generally imply a mood disorder, mild neurologic abnormality (such as attention deficit disorder or learning disability), or a family history of alcoholism or personality disorder, plus some kind of early loss, trauma, or abuse. If the developmental history is apparently benign, the likelihood of an affective or organic factor is even greater.

Personality traits that are maladaptive in adulthood may have been more adaptive in childhood. In some cases, it is possible to see how troublesome personality traits were reinforced by the

family environment. However, we must still understand what maintains this behavior once it is no longer adaptive. Are there critical periods for personality development, or is personality change always possible?

Appreciation of the Role of Early Trauma in Severe Personality Disorders

Several studies show increased prevalence of childhood abuse, incest, or neglect, early loss, or family alcoholism in hospitalized patients with severe personality disorders.

Chronic post-traumatic stress disorder may produce symptoms that aggravate the personality disorder. Developmental histories of patients with severe personality disorder must attend to potential trauma, abuse, and neglect. Specific therapeutic attention to traumatic events may be crucial to success of treatment.

Approaches to Describing Personality

Categorical
Specific personality disorders are defined by diagnostic criteria, as are other mental disorders.

Advantages
- Consistent with the DSM-IV approach to other mental disorders
- Convenient for follow-up studies, family studies, etc.

Disadvantages
- Draws an arbitrary line between normal and pathological
- Personality disorders overlap, so multiple diagnoses are common
- Categorically defined groups may actually be heterogeneous, so diagnosis may not have predictive value
- Many encourage destructive labeling and stigmatization
- May lead to a lack of appreciation of disorders not meeting categorical criteria

Dimensional
Personality traits, such as hostility or extroversion, are scaled. Disorder is defined in terms of statistical deviance from the norm.

Advantages
- Possibly more reliable, because it avoid arbitrary all-or-none decision
- Permits greater appreciation of individual differences

Disadvantages

- A statistical criterion for normality will depend on the normative sample
- Dimensional ratings are based on standardized tests, and are vulnerable to biases in test design
- Does not facilitate recognition of personality types

Prototypical

Patients' personalities are compared with typical examples of well-recognized personality types, such as the compulsive, the hysterical, the antisocial, etc. Diagnoses are made by "a family resemblance."

Advantages
- Models the way the way that clinicians think
- Facilitates recognition of patterns

Disadvantages
- Vulnerable to bias
- Probably poor inter-rater reliability
- Difficult to use in research

Structured Assessment Of Adaptive Strengths And Preferred Defense Mechanisms

The patient's disorder is not labeled, but psychological strengths and weaknesses are appraised in a qualitative, but structured manner.

Advantages
- Useful as a complement to other forms of diagnosis
- Helpful in planning management and treatment regardless of diagnosis

Disadvantages
- Strengths and weaknesses may fluctuate with time, and may be less stable than the personality traits assessed by other approaches
- Strength and weakness assessments may depend greatly on the clinician's interviewing skill

The Five Axes of the DSM-IV

The DSM-IV divides the evaluation of individuals into five levels or axes. Axis I identifies mental disorders, Axis II identifies personality disorders and mental retardation, Axis III identifies relevant physical diseases and conditions, Axis IV identifies the individuals psychosocial and environmental issues, and Axis V is used by the clinician to assess an individual's overall functioning.

Thus, the disorders discussed in this chapter are Axis II diagnoses.

The DSM-IV Personality Disorders

The Odd Cluster (Type A)

Paranoid personality
Mistrustful of everyone, but still able to test reality (so, not psychotic).

Schizoid personality
Lacks intimate relationships, and is frightened by closeness; virtually incapable of being warm, and anxious when others try to be close (due to the fear of the intimacy of socialization).

Schizotypal personality
Has odd and eccentric ideas that influence daily behavior, but not psychotic.

The Dramatic Cluster (Type B)

Antisocial personality
The "psychopath" – violates laws and social conventions, is dishonest, and basically unconcerned about his effect on others.

Narcissistic personality
Grandiose, needs attention, lack of empathy for others, exaggerated sense of self-importance. Acts as if he is superior or unique to others.

Borderline personality
Emotionally intense and unstable, with impulsive behavior, self-destructiveness, inner emptiness and intolerance of being alone.

Histrionic personality
Dramatic, attention-seeking behavior, often leading to a caricature of femininity or masculinity.

The Anxious Cluster (Type C)

Avoidant personality
Avoids social situations because of fears of rejection, criticism, or disappointment (in other words, fears of the challenge of socialization).

Dependent personality
Clings to a stronger person, sometimes submissively, seeks help and advice, is anxious when faced with the need for an independent decision.

Obsessive-compulsive personality
Preoccupation with orderliness, perfectionism, and mental and interpersonal control, at the expense of flexibility. (Note: obsessive-compulsive *personality disorder*, an Axis II diagnosis, is different from obsessive-compulsive *disorder*, an Axis I diagnosis. People with obsessive-compulsive personality disorder might be described as being preoccupied with work or duty, not enjoying life, and/or rigid and inflexible. Unlike OCD, OCPD people don't describe their own behaviors as being alien to themselves (in other words, people with OCPD don't ask themselves "why am I doing this??"))

How Personality Disorders Present

In Medical Settings
- Interpersonal problems in the doctor-patient relationship
- Noncompliance with medical or rehabilitative regimens
- Difficulty coping with hospitalization, disability, or medically-required restrictions on diet or activity

In The Family
- Marital conflicts
- Sexual dysfunction
- Problems with child rearing
- Domestic violence

Within The Individual
- Anxiety or Depression
- When external problems or losses result from the patient's behavior:
  - Divorce
  - Job loss
  - Legal troubles
  - Poor outcome from a medical condition
- When circumstances prevent living according to one's usual personality style:
  - The dependent personality without anyone to depend on
  - The antisocial personality in a tough, consistent therapeutic community
  - The compulsive personality on weekends or vacations

Comorbidity

Antisocial, borderline, and histrionic personalities are vulnerable to alcohol and drug abuse.

Borderline personalities are vulnerable to brief reactive psychosis and to major depression.

Schizotypal and schizoid personalities are vulnerable to schizophrenia.

Dependent personalities are vulnerable to agoraphobia.

Compulsive personalities are vulnerable to obsessive-compulsive disorder.

Making a Personality Diagnosis

Reliability is enhanced by interviewing collateral sources such as family members.

The social and development history is crucial.

Personality tests, such as the MMPI, complement the clinical interview and are a useful preventive against the clinician's biases and blind spots.

For acute management, an assessment of current strengths and weaknesses is often more pertinent than precise categorical diagnosis.

Treatment

In Medical Settings
- Identify and treat problems of pain, anxiety, and depression.
- Identify and resolve problems covering medical diagnosis or treatment.
- Tailor the management plan and patient education to the patient's personality style: ex— Give information to compulsives, but reassure dependent and histrionic patients, set firm, consistent, and unambiguous limits with antisocial and borderline patients.

In Marital/Family Therapy Settings
- In brief therapy, attempt to solve problems using strategies that do not expect or presume change in fundamental personality style.
- In longer-term therapy, get family members to reinforce more adaptive behavior by the patient.

In Individual Psychotherapy

- In *supportive treatment* – identify the patient's more effective coping mechanisms and encourage their use
- In *more definitive treatment* – work to raise the patient's consciousness of his or her maladaptive behavior patterns, to facilitate a freer choice of more adaptive strategies. This may or may not involve exploration of the past roots of the behavior.

Pharmacology of Personality Disorder – A New Frontier

Low-dose **antipsychotics** have been used for borderline and schizotypal personalities. They have been shown to be effective in symptom control in double-blind studies, though they may not help deeper problems with personal relations. The benefits of these drugs must be balanced against the risk of tardive dyskinesia.

Antidepressants are commonly used, usually for treatment of concomitant mood and anxiety disorders.

Benzodiazepines have been used as well, both for anxiety symptoms (ex. To help avoidant and schizoid individuals to better tolerate social relations) and to decrease impulsive behaviors.

A newer approach has been to view at least some of the more dramatic personality disorders as a *forme frustre* of bipolar disorders. Though there is only limited validity for this approach, it has opened up treatment options; patients are sometimes treated with medication typically used in bipolar disorder (particularly anticonvulsants).