INTRODUCTION

The Axis I psychiatric disorders - schizophrenia, bipolar disorder, the anxiety disorders, depression, and substance abuse – are the focus of thousands of new research papers each year. These articles provide new insights regarding epidemiology, clinical presentation, physical findings, and treatments for these disorders. This guide provides a readable summary of the latest information available in the professional literature.

Disclaimer:
The author is not on any pharmaceutical advisory boards and does not receive research support from the industry. Every effort has been made to assure there are no errors in this publication, but this guide should not be used as a sole source of information for diagnostic or treatment purposes.

Copyright 2011: David Mays
10th Edition

Not for reproduction in part or in whole without the express written permission of the author.
# CONTENTS

Medical Principles of Substance Abuse 3  
Addiction 3  
Genetics 4  
Smoking 4  
Alcohol 6  
Marijuana 6  
Epidemiology 7  
Gender Issues 7  
Prevention and Treatment 8  

Co-occurring Disorders 11  
Anxiety Disorders 14  
  Generalized Anxiety Disorder 15  
  Panic Disorder 17  
  Obsessive-Compulsive Disorder 19  
  Phobic Disorders 23  
  PTSD 24  

Schizophrenia/Schizoaffective Disorder 34  

Major Depression 44  
Bipolar Disorder 55  

BIBLIOGRAPHY 64
MEDICAL PRINCIPLES OF SUBSTANCE ABUSE

The most important proposal for revision for the Substance-Related Disorders in DSM-5 is an emphasis on addiction. The new category – Addiction and Related Disorders - would distinguish between addiction and the related physical phenomena of dependence, tolerance, and withdrawal, which are normal responses to a wide range of drugs, including anti-depressants, beta-blockers, and anti-anxiety medications. The category would also allow for inclusion various behavioral addictions, such as compulsive gambling and Internet addiction, if data supports it (DSM-5 website.)

Addiction

Addiction is characterized by 1) uncontrollable, sometimes compulsive drug seeking and drug use, in spite of severe aversive consequences, and 2) the experience of craving, often for years or decades after abstinence has been obtained. There is a permanent vulnerability to relapse. This vulnerability arises from an intense desire for the drug and a reduced capacity to control the desire.

It is important to distinguish tolerance (the need for increasing amounts of a substance for the same effect), habituation (the adaptation of an organism to the chronic presence of a drug, often resulting in withdrawal symptoms if the drug is removed), and addiction. All organisms naturally experience tolerance and habituation to some substances, but only some develop addiction.

Understanding the neurobiology of craving and relapse is one of the greatest challenges in the area of addiction. Four brain regions have been the focus of investigation:

1) The ventral tegmentum, where dopamine is released in response to a motivationally relevant event (danger, food, sex, etc.) Except with repeated drug administration, as the event becomes familiar by repeated exposure, dopamine is no longer released by that event. Dopamine is, however, released by anticipation of that event.
2) The amygdala establishes learned associations between motivationally relevant events and predictors of the event (a smile predicting a pleasant social interaction, for example.)
3) The nucleus accumbens where dopamine release is experienced as highly pleasurable. This is required for the drug “high.” But it also determines the motivational salience (importance) of an event and mediates behavior in response to the event through connections with the prefrontal cortex. It adds the “wanting” to the “liking.”
4) The prefrontal cortex determines what and how intense the behavioral response will be to the event. People value many goals, and the cortex is where we select among them. Activation of the prefrontal cortex is influenced by how predictable the reward will be.

Repeated use of addictive drugs reorganizes these circuits. Drug stimuli become overvalued in the prefrontal cortex and responses become more compulsive (trying to relieve an unpleasant feeling), and less impulsive (pleasure motivated.) There is reduced salience for non-drug motivational stimuli and a subsequent narrowing of goal choice to only those behaviors that are drug related. Decision making ability is reduced. There is a biased representation of the world, over-weighted toward drug-related cues and away from other choices. Addiction isn’t caused by the pleasurable response to the drug, but with pathologically enhanced motivation to procure the drug. These cellular changes endure for years (Kalivas P, Volkow N 2005.)
Multiple lines of evidence support a relationship between substance addiction and behavioral addictions. Both share common core clinical features: compulsive engagement despite adverse consequences, diminished control, craving, common comorbidities, etc. In addition, laboratory studies are beginning to show that both kinds of disorders share a common chemistry and neurophysiology (Grant J et al. 2006.)

**Genetics** (Jang K 2005)

The factors contributing to addiction risk are present before substance use begins. Substance abuse runs in families. Drug use disorders are believed to arise from multiple genes exerting small effects, gene-gene interactions, and environmental factors that contribute to the maintenance of addiction. Trait disinhibition, both inherited and developmental stage specific (adolescence), strongly contribute to the development of addiction. These traits include impulsivity, risky decision-making, and antisocial behavior (Leeman R, et al. 2009.)

**Alcohol**: The heritability of alcoholism is 45-50% for both males and females, but there may be gender specific genes. Genetic effects determine how early in life drinking will begin. There is no evidence that delaying age of drinking has any effect in the development of alcohol problems. Interestingly, shared environment (home life) does not play a substantial role in the development of alcohol use problems.

**Tobacco**: Initiation for smoking in girls is highly heritable (62.6%), but not so much in boys (21.7%). Boys were more likely than girls to be influenced by smoking in the home – girls 10.5%, boys 41.5%. In contrast, persistence in smoking is largely governed by factors outside of the home environment – girls 47.4%, boys 49.2%.

**Illicit drugs**: All illicit drugs show heritable effects for initiation (except stimulants) and misuse. The effect of home environment is more important than with alcohol and tobacco. Abuse in any category of drug markedly increases the probability of abusing any other category of drug. There is a common genetic and shared environmental liability underlying all forms of substance abuse.

**Environmental effects**: The following environmental effects seem to modify genetic influence:
- High cohesion and low conflict at home reduces alcohol abuse
- Religiosity (except Catholic) reduces alcohol abuse
- Being married reduces alcohol abuse
- Genetic factors are more important in urban settings, but home environment is more important in a rural environment

**Smoking**

Cigarette smoking, which causes 400,000 deaths annually and 30% of all cancer deaths, is the leading cause of preventable morbidity and mortality worldwide. About 23% of American adults smoke. Most people who smoke regularly are nicotine dependent.

**Teens**: As with other drug addictions, nicotine dependence begins in adolescence. ~25% of high school seniors smoke nationally. Teens smoke 1.1 billion packs of cigarettes yearly and will account for $200 billion in future health care costs. Although teens smoke relatively few cigarettes based on the belief that they will not become addicted, the great majority of young people continues to smoke past high school and
gradually escalates the quantity of cigarettes they consume. Smoking is increasing faster among girls than boys. There is some evidence that girls may also develop nicotine addiction more rapidly than boys. Adolescents endorse symptoms of nicotine dependence within days or weeks of beginning occasional use of cigarettes. 66% regret ever starting to smoke. 70% of these teen smokers report that they have tried to quit, but only 10% will be able to. Tobacco use in teens is associated with a wide range of risk taking behavior, including violence, high risk sexual activity, and drug use. There is a significant risk of developing depression within one year of starting to smoke. Children with psychiatric disorders (depression, anxiety, PTSD) are also more likely to smoke (Krishnan-Sarin S et al. 2003.) Participating in team sports prevents smoking progression in teens, even if they have a genetic predisposition to nicotine addiction (Aubrain-McGovern J et al. 2006.)

**Comorbidity:** Habitual smoking is common among individuals with psychiatric disorders, who consume 45% of all cigarettes in the US. Rates of smoking in different disorders:

- Alcohol/opiate addicts: 90%
- Schizophrenia: 83%
- Bipolar disorder: 69%
- Generalized anxiety: 46%
- Major depression: 46%

In every age and gender group, adults with depression are more likely to be smokers and less likely to have ever quit smoking, than people without depression. Depression is a stronger predictor of smoking than gender (CDC: Nat’l Center for Health Statistics, April 2010.)

There is strong evidence that people with schizophrenia who smoke experience improvement in cognitive function due to improved working memory and screening of extraneous stimuli. These cognitive problems recur when schizophrenics stop smoking and may make it harder for them to resist relapse. Smoking effects blood levels of some medications. Clozapine may help with smoking cessation (McEvoy J 2005.)

**Health Effects:** In humans, nicotine reduces stress, increases relaxation, modulates mood, enhances vigilance, improves cognitive functions, and lowers weight. Nicotine’s rewarding/addicting effects are mediated through nicotinic acetylcholine receptors, causing release of endorphins in the nucleus accumbens and medial prefrontal cortex. The health effects of cigarette smoking are not limited to the tar and other toxic byproducts of smoke. Besides being addicting, nicotine itself may cause sleep disturbance, worsen coronary artery disease, exacerbate arrhythmias and peripheral vascular disease, play a role in airways disease, peptic ulcer disease, reduce birth weight, delay skin wound healing, and exacerbate diabetes (Van Gilder T et al. 1997.)

**Treatment:** Most nicotine dependent people report annual attempts to quit smoking, but less than 15% are successful over the long-term. Nicotine replacement therapies (transdermal patches, nicotine gum, and nicotine nasal sprays) are effective short-term treatments for tobacco addiction. Inhalers and nasal sprays may be more effective than tablets, patches, or gum. Clients do not tend to use gum appropriately. Since nasal spray is aversive to many smokers, the “patch” is the preferred first line treatment. Unfortunately, up to 95% of smokers will relapse (Berrettini W, Lerman C 2005.)
The antidepressant bupropion yields somewhat better results, especially in women, but only for a minority of smokers. Bupropion is a nicotine receptor agonist and may reduce the reinforcing effects of nicotine. It also reduces abstinence induced weight gain and negative mood symptoms. The beneficial effects last only while the medication is taken (Berrettini W, Lerman C 2005.)

Research is focusing on the possibility of longer-term therapy, the development of new anti-smoking medications, and the use of genetic markers to determine which medications may be most effective. A recent 2009 study found that financial incentives (up to $750/person) might be the best treatment to get people to stop smoking (Harvard Mental Health Letter May 2009.)

**Physical Effects of Alcohol**

People who are abstinent from alcohol have higher rates of heart disease. Moderate consumption reduces the risk of coronary artery disease and increases HDL. However, alcoholism is still the 3rd leading cause of preventable death in the US, after smoking (#1) and obesity (#2) with 100,000 deaths per year. Almost every organ system is impacted by chronic alcohol use. Physical diseases include: hepatitis, cirrhosis, gastritis, pancreatitis, high blood pressure, cardiomyopathy, congestive heart failure, stroke, hypoglycemia, diabetes, erectile dysfunction, fetal alcohol syndrome, esophageal cancer, liver cancer, colorectal cancer, Wernicke’s encephalopathy, and Korsakoff’s syndrome. Unfortunately, fewer than 50% of people who go to a doctor with an alcohol related problem are asked about alcohol use (Pagano J et al. 2005.)

Acute administration of alcohol increases the major inhibitory transmitter GABA, and decreases the excitatory neurotransmitter glutamate (NMDA.) This results in sedation and a reduction in anxiety. Chronic use of alcohol has the opposite effect as the central nervous system compensates by increasing activity in the NMDA system. When the person stops drinking, the hyperactive NMDA system causes withdrawal symptoms.

**Marijuana**

There has been a great deal of media attention lately to marijuana due to various state initiatives to legalize its use for medical purposes. Unfortunately most research is based on people who smoke marijuana for recreational purposes rather than medical purposes. In any case, research remains sparse.

Marijuana may be modestly effective for nerve pain, appetites stimulation for people with AIDS wasting syndrome, and control of chemotherapy related nausea and vomiting. Most people can be treated with currently available, FDA-approved medications for these conditions.

Much better established are the risks from marijuana use. These include addiction (10%), anxiety (20%-30%), and psychoses (increasing the risk of developing schizophrenia and worsening prognosis.) Drug delivery is also a major challenge. Only 10%-20% of active ingredient is absorbed through the digestive tract and the drug has a slow onset of action. Smoking marijuana is the fastest way to deliver the active ingredients to the bloodstream, but exposes the lungs to multiple chemicals and poses
respiratory risks. Most experts agree there is not enough evidence to recommend marijuana as a medical treatment for any psychiatric disorder (Harvard Mental Health Letter April 2010.)

**Epidemiology of Substance Abuse**

**Adolescents:** Addiction is a pediatric disease – virtually all addictions begin in adolescence. Substance use generally increases from adolescence to young adulthood then gradually declines. The 2009 Monitoring the Future Survey (Inst. for Social Research, Univ. Michigan) showed the following in the 8th, 9th and 12th grades in US schools:

- Past year methamphetamine use has continued to decline since 2004
- Cigarette smoking remained at its lowest level ever
- Alcohol use continued to decrease in 2009
- Cocaine and ecstasy use decreased in 2009
- Heroin, narcotics, inhalants, tranquilizer use were unchanged
- Hallucinogen use declined in 12th graders
- Most frequent use is of alcohol, followed by marijuana then tobacco
- Rates of disapproval for marijuana use have been falling in 8th graders, probably due to recent medical-marijuana legislation. Marijuana use will likely increase in the next few years.

  Prescription drug abuse remained stable
  62% of teens report that prescription pain relievers are easy to get (half get them free from relatives or friends) and 51% believe that they are not illegal to use. They believe they are safer than “illegal” drugs, and not addictive (Bukstein O 2008.) 51% report that marijuana is easy to get and more teens are starting out smoking marijuana, then moving to tobacco (Gray K 2007.)

**Adults:** National Epidemiological Survey on Alcohol and Related Conditions (NESARC) 2001-2, n=43,093 (Grant B et al. 2004)

- 12 month prevalence:
  - Alcohol abuse: 4.65%
  - Alcohol dependence: 3.81%
  - Drug abuse: 1.37%
  - Drug dependence: 0.63%

- Lifetime prevalence:
  - 7.7% drug abuse
  - 2.6% drug dependence

**Gender Issues**

Men are twice as likely to meet criteria for any drug use disorder over a lifetime (13.8% vs. 7.1%.) the 12-month prevalence rates of alcohol abuse are 3 times higher in men (6.9% vs. 2.6%.) By contrast, prescription drug abuse occurs at the same rate among men and women. Women are more likely to have comorbid anxiety, depression, eating disorders, and borderline personality disorder. Men are more likely to have antisocial personality disorder. Women are less likely to enter substance abuse treatment than men (Back S et al. 2007.)
Prevention of Substance Abuse

Smoking: Most prevention efforts are geared to children because the mean onset of smoking is 16 years old. Resistance training skills have been shown to be useful in reducing smoking initiation. The most successful impediment to preventing smoking is raising the cost of cigarettes (Ahrens D et al. 2005.)

Alcohol: Prevention of alcohol abuse is aided by reducing the number of alcohol outlet stores in an area, restricting times of sales, increasing legal age limits, enforcing responsible beverage service, increasing drunk-driving enforcement, and increasing the cost of alcohol. Screening by primary care doctors has been shown to be effective.

Other illicit drugs: Again, most efforts are targeted at children, since most drug abuse and addiction begins in teens. The most effective programs use peers to deliver information. DARE works better than simple education programs, but is not as effective as programs that use peer delivery of information (Powers R 2007.)

Treatment of Substance Use Disorders

Substance use disorders have more in common with chronic medical conditions than acute illnesses, and the focus of treatment needs to be adjusted accordingly. In the recovery management model, emphasis is placed on the resilience and empowerment of the client for participation in a long-term process, the use of engagement and motivational techniques, longer service duration, cultural awareness, and an emphasis on home or neighborhood based services.

Recent reviews have suggested that most people who change their problem drinking do so without treatment of any kind, including self-help groups. A significant percentage maintains their recovery for more than 8 years. Furthermore, many problem drinkers can maintain a pattern of nonproblematic moderate use of alcohol. Those who do seek treatment have more severe alcohol and comorbid problems. These are the clients we see in treatment centers (Arkowitz H, Lilienfeld S. 2008.)

Stages of Readiness for Change and Treatment

Motivation to change has been intensively studied as a crucial determinant of treatment success. The following is a useful conceptualization of the stages of treatment readiness as developed by Prochaska J et al., 1992:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precontemplative</td>
<td>Engagement (motivational interviewing, contingency management, family/couples therapy)</td>
</tr>
<tr>
<td>Contemplative</td>
<td>Persuasion (same as above)</td>
</tr>
<tr>
<td>Preparation/Action</td>
<td>Active Treatment (abstinence initiation, setting, behavioral/pharmacological treatment)</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Relapse Prevention (RPT, lifestyle modification, ongoing monitoring and care, peer group support)</td>
</tr>
</tbody>
</table>

Clients with severe and persistent mental illnesses need on average 6 months to move from one motivational level to another (Ziedonis D et al. 2004.)
**Behavioral Therapies** (Carroll K, Onken L 2005)

**Contingency Management**
Clients receive incentives for specific behavioral goals. There is strong evidence that these programs work across a wide range of addictions. The effects tend to weaken after the contingencies are no longer available. Such programs are also costly, and do not work for everybody.

**Cognitive Behavioral Therapies**
These therapies emphasize education about drug addiction and teach skills in recognizing vulnerable states and dealing with them adaptively. There is evidence that these approaches work for alcohol and other drug addictions. Improvement can continue to occur even after the end of treatment. These therapies are relatively complex, however, and require carefully trained clinicians.

**Relapse Prevention Therapy**
As with other chronic medical conditions, longitudinal studies have shown that treatment duration, continuing care, and ongoing monitoring contribute more to positive outcome than the type of treatment at the acute phase (McGovern M et al. 2005.) Relapse prevention therapy focuses on the following:
- Reducing exposure to substances
- Increasing motivation for abstinence
- Enhancing self-monitoring
- Learning to recognize and cope with craving and negative affect
- Identifying relapse potential behaviors and thoughts
- Using a crisis plan

Relapse prevention therapy has proven useful for clients with substance abuse, but so far there have been no studies looking at the co-occurring disorders population. Pilot studies indicate that older age and placement in therapeutic residential programming are the most important variables associated with successful treatment (Rollins A et al. 2005). Relapse rates are ~50% at one year.

**Motivational Interviewing**
Research has been mixed on the effectiveness of motivational interviewing for the general population of substance abusers, although results are more positive for alcoholics. It appears that motivational interviewing works best when combined with other therapies for substance abusers, rather than as a single session intervention.

**Couples/family Treatment**
Studies show that these interventions are effective for adolescents and adults, but the therapies are so diverse it is difficult to distinguish among them. The therapies also involve multiple components, so studies are hard to replicate.

**Twelve Step Groups**
Alcoholics Anonymous is the prototypical twelve-step group. AA does not engage in or support research, so there is not much research-based data on effectiveness. The MATCH study, a comprehensive ten-year research program, compared cognitive behavioral therapy, motivational enhancement therapy, and a twelve-step group. Participants were permitted to participate in AA if they desired. There was no significance difference among therapy outcomes at ten years. AA was better at years one and three, but at year ten, abstinence rates were CBT: 31%, MET: 35%, AA: 24%. The study also found that many AA participants did not regularly attend meetings and did not
necessarily place their faith in a higher power. Half still considered themselves members of AA, regardless, and stated that reading core literature helped them stay sober (Connery H, et al. 2005.)

Brief Intervention

People with risky alcohol use patterns, as uncovered during medical appointment screenings, may be helped by office-based interventions consisting of 10-15 minutes of counseling to provide feedback, advice, and goal-setting, along with follow-up visits (Brady K et al. 2007.)

Alternative Therapies/ Adjuncts to Treatment

The following have shown some efficacy in helping addicts avoid relapse. The evidence for these treatments is not very robust, but some clients may find them quite helpful (Lake J 2007.)

Exercise
Mindfulness training
Cranio-electrotherapy
Biofeedback
Acupuncture has very mixed findings

Medications for Treatment

Heroin:
Methodone - substitute drug
Buprenorphine (Buprenex, Suboxone) – sublingual substitute drug

Alcohol:
Naltrexone (ReVia, Trexan, Nalorex, Vivitrol) – binds to opiate centers in the brain and may block the alcohol “high”, but it also has anti-craving properties. It reduces the priming effect of the first drink. Available as long-acting injection (Vivitrol).
Acamprosate (Campral) – an anti-craving drug that affects several different neurotransmitter systems, but not the opioid system. Therefore, it may work well in combination with naltrexone. An increase in suicidal behavior has been observed with this medication.
Disulfiram (Antabuse) – creates a toxic reaction with alcohol. Compliance is a problem
Topiramate (Topamax) – an anticonvulsant that is presently under investigation as a treatment for alcoholism

Nicotine:
Bupropion (Wellbutrin, Zyban) – an antidepressant that reduces nicotine craving
Nicotine replacement – patch, gum, or spray
Varenicline (Chantix) – binds to nicotine receptors which block the reward mechanism of smoking. Recent reports of serious psychiatric side effects.

Cocaine:
Disulfiram (Antabuse) – reduces frequency of cocaine use through an unknown mechanism
Topiramate (Topamax) – may reduce relapse in cocaine users
Modafinil (Provigil) – a treatment for narcolepsy, this drug reduces the “high” from cocaine and craving by unknown mechanisms

Propranolol (Inderal) – reduces relapse, perhaps by reducing the strength of cocaine conditioned cues

Baclofen – GABA agonist that may reduce cocaine use

The COMBINE study, the largest, independently funded pharmacotherapy clinical trial for treating alcohol dependence involved 1,383 subjects from 11 sites. All treatment groups benefited. The best results were obtained with the group receiving naltrexone and office counseling, or specialty alcohol counseling with placebo. Specialty alcohol counseling without placebo or medication did the worst! Acamprosate did not have much effect (Kirn T 2006.)

**CO-OCcurring disorders (COD's)**

2001 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC, n=43,093) (Grant et al. 2004)

- 9.21% of Americans presently have a mood disorder
- 11.08% of Americans presently have an anxiety disorder
- 8.46% presently have an alcohol use disorder
- 2% presently have a drug use disorder
- 20% of people with AODA problems have a mood disorder
- 18% of people with AODA problems have an anxiety disorder
- 20% of people with mood disorders have AODA problems
- 15% of people with anxiety disorders have AODA problems

Of those seeking treatment:

- 40.7% of those with alcohol abuse problems had mood disorders
- 60% of those with drug problems had mood problems
- 33% of those with alcohol problems had anxiety disorders
- 43% of those with drug problems had anxiety disorders
- 21% of those with mood disorders had AODA problems
- 17% of those with anxiety disorders had AODA problems

**Lifetime prevalence of alcohol abuse/dependence**

- Bipolar I 46.2%
- Bipolar II 39.2%
- Schizophrenia 33.7%
- Personality Disorder 28.7%
- Obsessive-Compulsive 24%
- Dysthymia 21%
- Major depression 16.5%
- General population 13.8%

Epidemiologic studies show that psychiatric disorders increase the risk of substance abuse, and substance use increases the risk of psychiatric disorder. Comorbidity is greater in individuals who are drug dependent, rather than alcohol dependent, and individuals with multiple dependencies experience the highest rate of psychiatric problems.
Although the reasons for this high degree of comorbidity are not known, certain biochemical commonalities have been observed. Neuroendocrine and neuroimaging studies indicate dysregulation in frontal-limbic systems associated with stress and reward pathways in both depression and substance abuse. Amygdalar activation is seen in PTSD, panic disorder, and social phobia, as well as in cocaine dependent individuals. Dopamine and glutaminergic dysfunction in schizophrenia mimics the motivational changes in long-term substance abusers, making problems with motivation and craving a primary disease symptom in schizophrenia. (Brady K, Sinha R 2005.)

**Characteristics of Co-occurring Disorders**

- Worse treatment outcomes for either disorder
- Higher healthcare utilization and higher medical costs
- Increased risk of violence, trauma, suicide, child abuse and neglect, criminal justice involvement
- Faster progression to heavier use
- Less likely to comply with psychiatric treatment
- More likely to be hospitalized
- Higher risk of suicide
- More likely to relapse: 66% relapse over a 10-year period (Xie H et al. 2005.)

In asking clients what helps them most with prevention of relapse, the following were identified (Davis K, O’Neill S 2005):

- Stable housing
- “Positive” social support
- Relying on a higher power
- Participating in meaningful activity
- Changing how they think about their lives
- Attention to eating well, sleeping well and looking presentable

**Assessing for Co-occurring Disorders** (Geppert C, Minkoff K 2004)
1) Assessment tools: CAGE, MAST (Michigan Alcohol Screening Test)/DAST (Drug Abuse Screening Test), DALI (Dartmouth Assessment of Lifestyle Instrument), MIDAS (Mentally Ill Drug and Alcohol Screening), RAFFT for adolescents.
2) Assess past and present substance use patterns to see if criteria for abuse or dependence were ever met.
3) Examine patterns of psychiatric illness and substance use and relationship to abstinence, social support, participation in treatment programs, use of proper medications.
4) People whose symptoms of mental illness occur during periods of sobriety or after 30 days off drugs can be considered to have a primary mental illness.
5) When the criteria for both are met, assume that both are primary.
6) Female clients need to be assessed for traumatic disorders.

**Treatment of Co-occurring Disorders**

**Principles of Treatment** (Geppert C, Minkoff K 2004)
1) Not all COD's are the same - some have more severe mental illness, some more severe substance abuse
2) Treatment success depends on integrating the mental health and substance abuse treatment - either by program or by practitioner.
3) Patience is required. Research indicates that it takes 4 years for 50% of mentally ill clients to achieve abstinence in some sort of program. Different clients respond to different approaches: "wet, damp or dry."
4) The best treatment for the mental disorder is usually the same as for non-COD clients, but some conditions may need to be modified.
5) Interventions need to be matched to phase (acute stabilization, motivational enhancement/engagement, prolonged stabilization, rehabilitation, recovery) and stage (pre-contemplation, contemplation, preparation, action, maintenance) of recovery.
6) There is neither single correct COD intervention nor a single correct program. A comprehensive listing of treatment algorithms may be found at www.bhrm.org.
7) Clients with mental illnesses benefit from psychiatric treatment even when they continue to abuse substances. Clozapine has reduced substance use in 85% of psychotic clients. SSRI's have reduced substance use in depressed clients. Benzodiazepines should not be used in general, but they can be used safely in some individuals with addictions. Similarly, stimulants may be used for ADHD.
8) Medications work best when they are part of an overall treatment program.
9) Modifications needed in AODA treatment for mental health clients:
   - Smaller caseloads
   - Shorter meetings
   - Educational programs simplified to accommodate cognitive limitations
   - Education about proper use of medication, the difference between useful and harmful drugs
   - Low confrontation, more support
   - Specific social skills training to ask for help, use phone numbers, or resist peer pressure

Specific Medication Issues (Geppert C, Minkoff K 2004)
While abstinence before treatment with psychotropic medication is desirable, it is not necessary in most cases.
As a rule, avoid benzodiazepines because of their abuse potential.
Beware of the potential for overdose in clients who have poor judgment or high suicide risk.
Keep careful track of the amount of medication you are prescribing.
Psychotic disorders: typical antipsychotics may worsen substance abuse, atypical psychotics may improve, especially clozapine
Affective disorders: anticonvulsants are superior to lithium in rapid cycling and mixed, which are more common with substance abuse. SSRI’s are more effective than TCA’s in reducing alcohol consumption
Anxiety disorders: avoid benzodiazepines. Gabapentin, SSRI’s, clonidine, SNRI’s and atypical antipsychotics are safe
ADHD: stimulants are beneficial once sobriety is established; bupropion and clonidine are options, as is atomoxetine
Integrated Treatment Programs

Integrated programs contain the best treatment components from mental health and addiction. They are motivation based, recovery oriented, and provide a continuum of services. Integrated treatment considers the biological, cognitive, affective and interpersonal vulnerabilities in clients and includes a need for medications, addressing low motivation and cognitive deficits. Integrated treatment also considers spiritual health and is gender and culturally competent. Treatment begins with screening and assessment, including assessing motivation to change. Clinicians should be aware of the formal and informal ways of doing these assessments. A positive therapeutic alliance promotes recovery. Research supports that clients are more responsive when the therapist is empathic and non-judgmental (Ziedonis D 2004, Brunette M, Mueser K 2006).

THE ANXIETY DISORDERS

Demographics

According to the National Comorbidity Survey Replication (Kessler R et al. 2005), anxiety disorders are the most common emotional disorders in this country. Lifetime prevalence for anxiety disorders is 28.8%. This is also true for young people. A recent survey shows that up to 32% of young people have experienced symptoms of an anxiety disorder at some point in their lives (Merikangas K, et al. 2010.) A survey done by the American Psychological Association in 2009 identifies worries about doing well in school, family having enough money, and what to do after high school as the three top worries among youth.

Clients who suffer from anxiety disorders make 37 medical visits per year (compared to the average of 5) accounting for 1/3 of nation’s total mental health bill ($46.6 billion). Comorbidity of more than three anxiety disorders is not unusual (14%.) Comorbidity with depression is very common (60-80%).

Biological Basis of Anxiety

Four neurotransmitter systems are implicated in anxiety (Bender K 2003)
1) altered HPA (hypothalamus-pituitary-adrenal axis)
2) dysregulated serotonin response
3) overactive norepinephrine response
4) inhibited GABA functioning

These systems are intricately intertwined with each other and with brain areas involved in the normal human fear response (amygdala, hippocampus, locus coeruleus and the prefrontal cortex.) Excessive levels of cortisol from HPA dysfunction can cause neuronal damage and death, and may be responsible for some long-term consequences of chronic anxiety.

Genetic Issues

Genetic research indicates that the anxiety disorders are more influenced by environmental factors, and less by genetic factors (~30%), than any of the other major mental illnesses. This supports a “learning model” for the development of these disorders, and explains why all the anxiety disorders can be successfully treated with cognitive behavioral therapy. Generalized anxiety disorder separates from the other anxiety
disorders in many analyses, and links more closely to depression, bringing into question whether it should be considered a distinct anxiety disorder (Jang K 2005.)

**Gender Issues**

Anxiety disorders are 1.5-2x more prevalent in women than men (NCS-R). Developmental, societal, and reproductive factors all contribute. Even as children, girls are more likely to suffer separation anxiety, negative affect, and panic attacks than boys. Pregnancy may be associated with a reduction in anxiety and panic symptoms.

**Anxiety and Substance Abuse**

In the NESARC data, 18% of substance abusers suffer from an independent anxiety disorder. Since substance abuse also causes anxiety among users, anxiety as a symptom among AODA clients has been estimated at 70%. 15% of anxiety disorder clients have substance use disorders. Having either an anxiety disorder or substance abuse increases the probability of developing the other later in life. The relationship is bidirectional and complex (Kushner M et al. 2007.) For social phobia and agoraphobia, alcohol problems tend to begin after the onset of the anxiety disorder. Generalized anxiety disorder and panic disorder tend to begin after or at the same time as alcohol problems, making diagnosis difficult (Brady K et al. 2007.)

Alcohol relieves anxiety in the short term, but in the dependent drinker, alcohol makes agoraphobia and social phobia worse. Panic can be precipitated in the withdrawal phase. Since clients with substance abuse problems generally minimize their use, it is difficult to detect substance dependence in the presence of a presenting anxiety disorder.

Anxiety can be precipitated by caffeine, diet pills, androgenic steroids, alcohol, stimulants, marijuana, and hallucinogens. Anxious clients often stop abusing marijuana and hallucinogens, but increase their use of alcohol or benzodiazepines.

In treating substance-abusing clients with medications for anxiety, it is important that the clinicians keep firm control over dosage schedules, amounts dispensed, and refills. In general, because of their abuse potential, benzodiazepines should not be used. Medication should be discontinued if it is not helpful.

**GENERALIZED ANXIETY DISORDER**

GAD is the second most frequent emotional disorder seen in the primary care setting. The lifetime prevalence is 5.7% (NCS-R). It is a clinical syndrome characterized by excessive, uncontrollable worrying, hypervigilance and anxiety. GAD is unique among anxiety disorders in that 66% of clients will present to their primary care physicians asking for help. Their main complaints will be insomnia and somatic problems. Medically, they will regard their physical health as only fair to poor, they will be high utilizers of healthcare resources, and will not do well occupationally or economically (Allgulander C et al. 2003.) Comorbidity is high (60-90%), predominantly with depression. In fact, the overlap between generalized anxiety and depression is bidirectional – 70% of anxiety sufferers have a history of depression, and 50% of people with a history of depression have a history of anxiety. This suggests the disorders are linked in some way (Stein M 2009.)
**DSM-IV Criteria**

DSM requires excessive anxiety and worry about a number of activities most of the time for six months, which the person finds difficult to control. The worry is associated with 3 of the following (one if a child):

1) restlessness, feeling on edge
2) being easily fatigued
3) difficulty concentrating
4) irritability
5) muscle tension
6) sleep disturbance

**DSM-5 Proposed Revisions**

The duration of symptoms is changed to 3 months. There is no statement that the person needs to have difficulty controlling the worry. The symptoms are limited to either restlessness/on edge, or muscle tension or both. The other symptoms are regarded as too nonspecific. Added is a behavioral requirement of one of the following:

- Marked avoidance of situations
- Marked time and effort preparing for the worst
- Marked procrastination due to worries
- Repeatedly seeking reassurance due to worries

(DSM-5 website)

**Gender Issues**

The incidence of GAD in women is 2-3x higher than for men, although this declines as women age. Women are more likely to have comorbid depression, more likely to seek treatment, and more likely to be prescribed benzodiazepines rather than antidepressants. The course of the illness is often more complicated in women (Pigott T 2003.)

**Genetics**

GAD is 6x more likely among first-degree relatives with the same disorder, so it is clearly familial. There is not a genetic relationship to the other anxiety disorders. Given the genetic linkages being uncovered, it has been proposed that GAD represents a vulnerability factor, or final common pathway for a number of other disturbances, rather than a separate illness (Marshall 2005.) Shared symptoms among relatives are anxious expectation, vigilance, motor tension, and autonomic hyperactivity. Other genetic studies closely link GAD to major depression, the major differentiation being environmental exposure to “danger” events (anxiety) versus exposure to loss events (depression) (Jang K 2005.)

**Comorbidity of GAD and Substance Abuse**

16% of clients have substance abuse problems. 12% of alcohol abusers and 22% of drug abusers suffer from generalized anxiety. The odds ratio of having substance abuse issues and generalized anxiety is 2.3. (The odds ratio is the odds of having a specific disorder among substance abusers relative to having the disorder in the general population. >1.0 is significant.) (NESARC data)
**GAD in Young People**

GAD is a relatively new diagnosis in young people, having previously been called overanxious disorder. They are only required to endorse one symptom rather than three from the symptom list. Children tend to worry about the health of significant others, personal performance, family matters, and world issues. They are least likely to complain of restlessness or muscle tension.

The prevalence of the disorder is not clear – perhaps 1-5%. It is often comorbid with depression, and some researchers suggest it is a subsyndrome of major depression in this population (Victor A, Bernstein G. 2009.)

**Natural History and Treatment Course of GAD**

The mean age of onset of GAD appears to be 31 years, the oldest median age of onset of any of the anxiety disorders, and a pattern that is more akin to major depressive disorder than other anxiety disorders (Weisberg R 2009.) The course of the illness is chronic, with waxing and waning symptoms. While most anxiety disorders decrease with age, GAD does not. Older people tend to worry more and for longer periods of time. Fewer than 33% of cases completely remit (Pigott T 2003.)

Patients with generalized anxiety disorder often have multiple medical comorbidities. Medical disorders associated with anxiety include migraines, rheumatoid arthritis, peptic ulcer disease, irritable bowel syndrome, coronary artery disease, hyperthyroidism, diabetes, asthma, and chronic obstructive pulmonary disorder. These patients experience pain more acutely and have increased awareness of symptoms (Culpepper L 2009.)

Clients with GAD have the same degree of disability as experienced by clients with depression, or coronary artery disease. GAD is also associated with frequent suicide attempts (2-fold increase) (Weisberg R 2009.)

In the past, benzodiazepines were the primary treatment for GAD. Given the chronic nature of the disorder and the risks of long-term BZD therapy, a reasonable recommendation is for cognitive-behavioral therapy with or without a serotonin reuptake inhibitor (Marshall R 2005.)

**PANIC DISORDER**

A panic attack is a discrete episode of unexpected terror accompanied by a variety of physical symptoms, including fear, anxiety, catastrophic thinking with a sense of impending doom or the belief that loss of control, death, or insanity is imminent. Physical symptoms can be neurological, GI, cardiac, or pulmonary, mimicking many different types of medical illnesses. A panic attack usually lasts from 5 to 30 minutes, with the symptoms peaking at about 10 minutes, but attacks have been known to last for hours. Attacks may occur during sleep. Many psychiatric disorders have panic attacks associated with them. Panic attacks can be triggered by certain situations for certain individuals - driving or riding in a vehicle, esp. in heavy rain or over bridges, shopping in crowded stores, waiting in line, etc.

Panic disorder is the presence of recurrent unexpected panic attacks followed by at least 1 month of persistent anxiety or concern, or a significant change in behavior related to the attacks. 10% of the population report having a panic attack, but do not develop the disorder.
**DSM-5 Proposed Revisions**

The primary change is related to agoraphobia, suggesting that it should be diagnosed independently, rather than in conjunction with or without panic disorder.

**Demographics of Panic Disorder**

The lifetime prevalence of panic disorder is 4.7% (NCS-R). The disorder is chronic and shows a high degree of comorbidity with other disorders. Agoraphobia, fear of being in places away from home where escape might be difficult, is a complication in about 33% of panic disorder clients. There is some evidence that panic disorder may be linked to cardiovascular disease, and men with panic disorder have an increased rate of cardiac death. The social and health consequences of panic disorder are similar to those of major depression. These clients use more healthcare resources than other anxiety disorder clients, especially emergency rooms, and there is an elevated risk of suicide. 20-42% of panic disorder clients have made a suicide attempt (Pollack M et al. 2003.)

**Gender Issues**

Women are 2.5 - 3 times more likely to have panic disorder than men. They also have more panic attacks. Women are more likely to complain of shortness of breath, nausea, and the perception of being smothered. (Men complain of sweating and stomach pain.) Women are twice as likely to develop agoraphobia. They have greater phobic avoidance, more reliance on family members, and more reports of attacks when trying to leave home. They have an elevated risk of a comorbid disorder with 3x the relapse rate of men. Symptoms may increase during the premenstrual phase and decrease post-menopause (Pigott T 2003.)

**Genetics**

Genetic findings in panic disorder are quite interesting. It has long been observed that panic disorder is familial. Careful analysis reveals that the inheritability of the disorder differs by gender, males 47%, females 30%. Breaking the results down further, it appears that sensitivity to physical discomfort is inherited, but the mental symptom of panic is learned.

It is known that anxiety sensitivity (the belief that physical symptoms of anxiety have harmful consequences) is a precursor for panic disorder. Anxiety sensitivity is inherited in females (48%) but not in males, for whom social learning factors are more important. More data is needed, but it appears that the gender difference seen in incidence of panic disorder reflects some significant differences in biologic predisposition and etiology of the illness (Jang K 2005.)

**Comorbidity of Panic Disorder and Substance Abuse**

NESARC data show that 22% of panic disorder clients with agoraphobia who seek treatment suffer from concurrent substance abuse problems. The odds ratio of having panic disorder with agoraphobia in a substance abuser is 3.1. This is the highest odds ratio for any anxiety disorder.

Addiction can cause panic disorder in vulnerable people. Withdrawal can precipitate panic attacks. Panic attacks can also complicate addiction if the client finds that alcohol
temporarily relieves the symptoms. However, the “self-medication” hypothesis is rarely justified, since most clients do not find alcohol helpful, and treating the panic disorder does not lessen alcohol abuse in addicted clients.

**The Natural History and Treatment of Panic Disorder**

Panic disorder usually begins in late adolescence or early adulthood. Onset is rare after 40. Only 20% of clients with panic disorder will present to a psychiatrist. Most will seek help from other medical specialists because of cardiovascular, respiratory, or gastrointestinal complaints. Panic disorder clients may have the worst outcome of any of the anxiety disorders, including social and occupational dysfunction, marital and financial problems, and poor health (Pigott T 2003.)

Relapse rates have not been as exhaustively studied as in depression, but apparently can be very high once treatment has stopped. 60-75% remain symptomatic after treatment. Long duration of illness and the presence of agoraphobia predict poor outcome (Pollack M et al. 2003.)

All of the newer antidepressants have efficacy in treating panic disorder. Two medications used for other anxiety disorders, buspirone and gabapentin, do not. Clients with panic disorder are extremely sensitive to side effects and need to start on lower doses with longer titrations than normal.

A careful review by the Cochrane Collaboration concludes that combination therapy of CBT and antidepressant medication, or CBT alone should be the first options. They do not recommend medication alone (Harvard Mental Health Letter June 2008.) Benzodiazepine use during CBT may increase the risk of relapse (Tynes L et al. 2005.) Using benzodiazepines only as needed may increase body scanning and induce panic if they are left at home.

**OBSESSIVE-COMPULSIVE DISORDER**

Obsessive-compulsive disorder is a syndrome characterized by obsessions, compulsions and doubting. All of us have some intrusive thoughts. (In fact, OCD seems to merge closely with normal human behavior.) When they are disruptive, and the client recognizes them as irrational and actively resists them, they may reflect the disorder. Obsessional ideas are different from depressive ruminations in that they are not about guilt or self-criticism, and they are more specific than the worries seen in GAD. Common obsessions include:

- contamination
- pathological doubt (Did I unplug the iron? I see it is off but I don’t get the feeling of certainty that it is.)
- somatic fears
- need for symmetry
- aggressive impulses
- sexual impulses

Compulsions are repetitive behaviors or purposeful mental acts that can be observed by others, which clients feel driven to perform to provide relief from the anxiety caused by the obsessions. Performing them does not provide pleasure, as an addictive behavior...
does. Compulsions often have no relationship to the obsessions and anxiety they relieve. Common compulsions include:

- checking
- cleaning/washing
- counting
- need to ask or confess
- ordering/arranging
- hoarding/collecting

Component analysis identifies five factors that explain 65.5% of the variance in most cultures, and seem to be transmitted together genetically. They are (Pallanti S 2008):

- Symmetry/ ordering
- Hoarding
- Contamination/ cleaning
- Aggressive/ checking
- Sexual/ religious obsessions

**DSM-IV Criteria**

*DSM-IV* defines obsessions as

1) recurrent, persistent thoughts, impulses, or images that are experiences as intrusive and cause anxiety  
2) the worries are not simply about real-life problems  
3) the person tried to get rid of the worries  
4) the person recognizes the thoughts are a product of his/her own mind  
5) Compulsions are defined as

1) repetitive behaviors or mental acts that the person feels driven to perform in response to an obsession  
2) the behaviors are aimed at preventing or reducing distress, but are not connected in a realistic way

The obsessions and compulsions are recognized as unreasonable and cause marked distress or interfere with functioning

**DSM-5 Proposed Revisions**

The major revision proposed is that obsessive-compulsive disorder be included in a new group – Anxiety and Obsessive-Compulsive Spectrum Disorders. This group would include trichotillomania and possibly other conditions. Obsessions would be described as urges, rather than impulses, to distinguish them from impulse control problems. Finally, a diagnosis of Hoarding Disorder is proposed. (*DSM-5* web site)
Demographics

The lifetime prevalence of obsessive-compulsive disorder is 1.6% (NCS-R). As with the other anxiety disorders, it is a chronic condition. Many clients with OCD are deeply embarrassed by their symptoms, and often come to the clinician seeking help for a different comorbid anxiety disorder (Marshall R 2005.) Tic disorders and body dysmorphic disorder may be related to OCD. There is also clear evidence linking OCD and rheumatic fever (Hounie A et al. 2006.) Untreated OCD has a significant impact on the quality of life of the client, as well as the client’s family, friends, and potential for employment.

Gender Issues

Women have only a slightly higher risk (1.5x) of developing OCD than men, unlike the other anxiety disorders. While boys may have an early onset of the illness, girls do not usually develop OCD until they are adults. The course may be more episodic and less severe in women. In general, women have increased comorbid depression, anxiety and eating disorders. Cleaning compulsions and checking behaviors are more common in women. Men are more concerned with symmetry. Gender does not affect outcome.

13-39% of women may first become symptomatic during pregnancy or postpartum. They may have aggressive impulses toward the baby. The risk of postpartum depression is high in women with OCD during pregnancy (Pigott T 2003.)

Genetics

Research indicates that OCD runs in families, but more recent data indicates that obsessions and compulsions are inherited from different genetic sources. Inheritability is 33% and 26% respectively. Tourette’s Syndrome, body dysmorphic disorder, hypochondriasis, and grooming conditions (trichotillomania, etc.) are genetically related. Obsessive-compulsive personality disorder is not. Curiously, juvenile onset OCD does not appear to be inherited (Jang K 2005.)

Natural History of OCD

OCD usually develops at an early age - males 17.5 yrs., females 20.8 years. It can often be diagnosed in young children. Different obsessions and compulsions may appear at different times. The illness can be quite incapacitating. As many as 13% of patients may attempt suicide. Sustained total remission is rare, although up to 50% of clients show some improvement over time without treatment. A comorbid depression predicts poorer outcome (Pigott T 2003.)

OCD in Young People

The prevalence of OCD in children ranges from 1-4%, and starts out with a slight male preponderance, which tends to equalize as young people get older. Common comorbid conditions are tic disorders, other anxiety problems, ADHD, pervasive developmental disorders, and depression. The most common obsessions tend to be about germs, danger to self or family, and symmetry. The most common compulsions are excessive washing, repeating rituals, and checking behaviors (Victor A, Bernstein G 2009.)
Some children suffer OCD symptoms as a result of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS.) These children have dramatic, overnight onset of symptoms preceded by a Strep. throat infection. They will generally show a slow gradual improvement in symptoms, which will worsen again if they develop another Strep. infection. Treatment of the OCD is the same as in other pediatric OCD cases (NIMH web site.)

Hoarding
Hoarding is described in DSM-IV under obsessive-compulsive personality disorder, but it appears most frequently with the anxiety disorder. Around 2 years old, most children develop a variety of rituals, some of which look like OCD. By 3, 80% of parents report a bedtime ritual, and most children show a need to arrange things, becoming concerned about dirt and germs, and finally a need to collect objects. Lower IQ children show persistence in many of these behaviors. These behaviors also reappear at developmental transitions – falling in love, having a child, etc. (Leckman J, Bloch M 2008.)

Hoarding behavior consists of either acquiring, or being unable to discard large quantities of worthless items, to the extent that there is impairment in the person’s life. The most commonly saved items are newspapers, old clothing, bags, mail, and lists. There are no published epidemiological studies. The disorder seems to be heritable (Iervolino A, et al. 2009.)

About 25% of people with OCD will show clinically significant hoarding. 22.6% of people with dementia engage in hoarding. Hoarding symptoms also develop in patients with autism, schizophrenia, and mental retardation, as well as healthy people. Usually, the problem first comes to light in an elderly person when health problems lead to an inspection of the home (Harvard Mental Health Letter Dec 2009.)

Some hoarders are unable to discard things because they are indecisive, others because of emotional attachment, and others because they are cognitively unable to organize. Hoarding does not respond well to SSRI treatment or typical psychotherapies. A special cognitive-behavioral therapy has shown some results (Brown W, Meszaros Z 2007.)

Hoarding Disorder has been proposed as a new diagnosis for DSM-5.

Diagnosis of Obsessive-Compulsive Disorder
Many people are ashamed of their inability to control their recognizably irrational behaviors, and are hesitant to seek help for their symptoms. Dr. Michael Jenike of Harvard has said that three questions can help identify the vast majority of cases:

1) Do you have any repetitive thoughts that interfere seriously with your life?
2) Do you wash excessively?
3) Do you constantly check to see that things are right?

Treatment of OCD
A cognitive-behavioral therapy called exposure and ritual prevention is the most effective treatment for OCD. For clients unwilling or unable to participate in this therapy, serotonin antidepressants have proven effective. Venlafaxine, phenelzine, and norepinephrine antidepressants apparently do not work. Augmenters that do not work include lithium, clonazepam, desipramine, and buspirone (Marazziti D et al. 2006.)
PHOBIC DISORDERS
Phobias are persistent and unreasonable or excessive fears about certain objects or situations. The lifetime prevalence of phobia is 12.5% (NCS-R), making it the most common type of anxiety disorder. Phobias may range in severity from causing a minor nuisance to creating a significant disability. There are two types: specific and social phobia or social anxiety disorder.

DSM-IV Criteria for Specific Phobia
The diagnostic criteria are:
1) a marked and persistent fear that is excessive or unreasonable, cued by the presence or anticipation of the object or situation
2) the exposure invariably invokes an anxiety response
3) the person recognized the fear as unreasonable
4) the situations are avoided or experienced with great distress
5) the avoidance or distress creates problems in the persons life
   Certain types are specified: animal, natural environment, blood-injection-injury, situational, or other.

Social Phobia (Social Anxiety Disorder)
Social phobia is an intense, irrational fear of social or performance situations in which the person is exposed to unfamiliar people or possible scrutiny by others, and fears humiliation and embarrassment. Sufferers experience the triad of worry, avoidance, and physical complaints. Few will seek psychiatric help. 70-80% will suffer from another diagnosis, usually alcohol dependence, depression, or another anxiety disorder. These clients have significant functional impairment with more than 70% making a below average income (Stein M 2006.) 66% are single, divorced, or widowed. 20% are unable to work and collect welfare or disability. Risk of suicide is increased.

There are two subtypes of social anxiety disorder:
Circumscribed (discrete) - fear a specific situation and performance anxiety. The most common fears are:
   speaking in front of people
   speaking to strangers or meeting new people
   eating in public
   writing or working in front of others

General - high interpersonal sensitivity and feelings of rejection in lots of situations.
Clients hate being the center of attention, dating, speaking in class, etc. Most clients who seek help have the generalized variety.

DSM-IV Criteria for Social Phobia
These criteria include:
1) marked and persistent fear of social or performance situations
2) the fear provokes anxiety
3) the person recognizes the fear as unreasonable or excessive
4) the situations are avoided or endured with extreme distress

23
**DSM-5 Proposed Revisions**
The main proposal for phobias is to change the diagnosis from Social Phobia to Social Anxiety Disorder (DSM-5 website.)

**Gender Issue**
Specific phobias occur twice as often in women than men. Social anxiety disorder occurs only slightly more frequently in women. The only anxiety related fears that are more common in men than women are urinating in public and returning goods to a store. (Pigott T 2003.)

**Genetics**
Genetic analysis indicates that all of the phobias are related, and that avoidant personality disorder is an extreme form of social anxiety disorder, rather than a distinct entity. The individual phobias do show variation in their degree of inheritability. Blood and injury phobias demonstrate the most inheritability and situational phobias the least (Jang K 2005.)

**Comorbidity of Phobias and Substance Abuse**
16% of clients with specific phobia and 21.3% of clients with social anxiety disorder have substance abuse problems. Among alcoholics, 8.5% will have social anxiety disorder and 17.2% will have specific phobias. The odds ratio of social anxiety disorder in substance abusers is 1.9 (NESARC).

**Natural History of Phobias in Children and Adults**
Specific phobias usually begin in childhood, although many new cases of height phobia begin in early adulthood. Phobias caused by traumatic events (car accidents, etc.) may start at any age.

Social anxiety disorder has an early onset (11-16 years old) and a chronic, unremitting course with significant lifelong disability. Symptoms experienced by young people are essentially the same as those in adults. Social anxiety disorder becomes most disabling at a critical period in life and distorts normal social development (Stein M 2006.)

**Treatment of Social Phobia**
The primary treatment for specific phobia is exposure and ritual prevention. Cognitive therapy is an effective treatment for social anxiety disorder, as are a range of newer antidepressants and the MAOI’s (Van Ameringen M et al 2003.).

**POSTTRAUMATIC STRESS DISORDER**
PTSD is an illness that occurs in vulnerable people exposed to severe trauma. PTSD is usually accompanied by persistent biologic abnormalities and significant social and occupational impairment. The lifetime prevalence of PTSD is 6.8% (NSC-R).
**DSM-IV Criteria for Acute Stress Disorder**

The criteria are that the person be exposed to a traumatic event that involved actual or threatened death injury, or a threat to the physical integrity of self or others. The person’s response involved intense fear. While the person was experiencing the event, the individual had 3 of the following dissociative symptoms:

1) numbing, detachment
2) reduction of awareness of surroundings
3) derealization
4) depersonalization
5) dissociative amnesia

The person re-experiences the trauma, avoids reminders of the trauma, and shows autonomic arousal. The disturbance causes distress and lasts from 2 days to 4 weeks.

**DSM-IV Criteria for Posttraumatic Stress Disorder**

The person is exposed to a traumatic event as described above under Acute Stress Disorder (criterion A). The response evoked fear or horror in the individual. The following are present:

1) (criterion B) the events are persistently re-experienced by the person
2) (criterion C) the person persistently avoids reminders of the event and/or experiences emotional numbing
3) (criterion D) the person experiences autonomic arousal

The duration of the disturbance is longer than 4 weeks, and causes distress.

**DSM-5 Proposed Revisions**

The trauma described in Acute Stress Disorder is now specified to exclude witnessing events on TV or other electronic media, and dropping the requirement that the person experience intense fear. The symptoms required no longer necessarily involve dissociation. The requirement is now 8 of the following:

1) Intrusion symptoms
   a. Recurrent involuntary memories
   b. Recurrent dreams
   c. Flashbacks
   d. Distress at exposure to cues
2) Dissociative symptoms
   a. Sense of numbing, detachment
   b. Altered sense of reality, being in a daze
   c. Dissociative amnesia
3) Avoidance symptoms
   a. Avoidance of thoughts
   b. Avoidance of activities
4) Arousal symptoms
   a. Sleep disturbance
b. Hypervigilance
c. Irritability, aggression
d. Exaggerated startle
e. Agitation or restlessness

Revisions in the diagnosis of PTSD are similar to revisions for Acute Stress Disorder in that they exclude exposure to TV or other media as the source of the trauma and drop the requirement that the person experience intense fear. Flashbacks are now clarified as dissociative events, not just memories. Avoidance of cues as a symptom is now separated from emotional numbing in criteria C. A new criterion is established – negative alternations in cognitions and mood that are associated with the traumatic event as evidenced by 3 of the following:

1) dissociative amnesia
2) negative expectations of the self, others, or the world
3) persistent distorted blame of the self
4) pervasive negative emotional state
5) diminished interest in significant activities
6) feeling detachment from others
7) inability to experience positive emotions

The criteria under arousal now include reckless or self-destructive behavior. (DSM-5 website)

**Acute Stress vs. Posttraumatic Stress Disorder**

After a traumatic event, most people will experience elements of both stress and traumatic stress. Perceived threat triggers intense bodily reactions that influence memory storage and retrieval, as well as cognitive factors and symptoms of autonomic arousal. Acute Stress symptoms appear shortly after the event, subside in many survivors, but persist in others in the form of chronic PTSD. Since at least 60% of people with early PTSD symptoms recover over the next 6 years, almost all within the first year, chronic PTSD might be seen as a “disorder of recovery” (Shalev A 2009.)

For people who recover from trauma, four indicators of successful coping are:

1) sustained task performance after the event
2) controllability of emotions
3) capacity to enjoy rewarding human contacts
4) sustained sense of personal worth

Successful stress management focuses on helping people develop coping mechanisms around these four indicators. Survivors are helped to identify concerns and goals, set strategies, and set up a plan. They are coached on how to reduce distress, increase social connectedness, and correct cognitive distortions (Watson P, Shalev A 2005.)

The symptoms of re-experiencing and hyperarousal are common and reflect normal responses to trauma. Avoidance and Numbing are stronger markers of psychopathology and more predictive of developing chronic PTSD. Emotional numbing is often a manifestation of dissociative processes – presumably as a defensive dissociation between cognitive awareness and affect. A dissociative type of PTSD is probably more prominent among those who have experienced chronic trauma such as prolonged childhood abuse or
combat exposure. Those who are experiencing emotional numbness and detachment may not be able to fully engage in exposure treatment (Chu J 2010.)

**Demographics**

In the US general population, 61% of men and 51% of women will experience trauma. Of them, 5% of men and 10.4% of women will develop PTSD. Men and women differ in the kind of trauma encountered – sexual abuse is more common in women, physical conflicts and accidents are more common in men. Despite this, even when subjected to the same type of trauma, women still have twice the risk of developing PTSD and their symptoms are likely to persist longer. Interestingly, this may not be the case for combat-related PTSD, where rates of PTSD in the Gulf War, Iraq, and Afghanistan seem to be comparable (Nemeroff C et al. 2009.)

**Subtypes of PTSD – Proposed and Established**

- **Acute Stress Disorder** - symptoms less than a month
- **Acute PTSD** - symptoms of 3 months or less
- **Chronic PTSD** - symptoms for more than 3 months
- **Delayed Onset** - symptoms don't appear until more than 6 months later
- **Complex PTSD** (Disorders of Extreme Stress - DES) - the result of protracted trauma, usually including sexual abuse. The primary spokesman for including a special category of Complex Trauma in the next *DSM* is Bessel van der Kolk. Severely traumatized children who have experienced their trauma in the context of an intimate relationship experience neurologic changes leading to depression, attention disorders, somatic illness, interpersonal problems, impulsive and self-destructive behaviors. These children are frequently treated as though they have bipolar disorder. Instead, treatment needs to focus on establishing the child’s capacity to regulate arousal, learning to negotiate safe interpersonal attachments, and integration and mastery of body and mind (Cook A et al. 2005.)

**Secondary Traumatic Stress** (Vicarious Traumatization, Compassion Fatigue) - Two kinds of patterns are described:

1) Emergency workers who encounter those injured in accidents, fire, or battle develop symptoms that closely resemble PTSD, including intrusive memories, avoidance, withdrawal, poor sleep, and hypervigilance. Risk factors include the extent of exposure and identification with the victim.

2) Psychotherapists/attorneys working with traumatized clients whom they feel powerless to help. Symptoms develop over slowly over time.

There is no good evidence that that “secondary traumatic stress exists as a special syndrome, and it is probably best described as a normal stress reaction or “burnout” (Kadambi M, Ennis L 2004.)

There is an ongoing concern about “bracket creep” in PTSD as more and more stressors are viewed as causing PTSD (sexual harassment, hearing horrific news but not being present, etc.) It is important to delineate between distress reactions and PTSD (McNally R, 2003.) PTSD has also generated sociological attention because it is being attached to experiences that until recently have been seen as an expected part of life (Flouri E, 2005.) In one recent study, 78% of those screened met the criteria for PTSD without have undergone trauma (Bodkin J et al 2007.)
Gender Issues

Women have a significantly increased risk (2x) of developing PTSD, especially if the trauma occurs before the age of 15. The most common cause in women is sexual assault or abuse. 62% of all forcible rapes occur in women under 18. 29% occur in children under 11. By adolescence, the prevalence of PTSD among girls is the same as among adult women. Adolescent girls may be particularly vulnerable. (Girls' self-esteem, confidence, and school performance all decline significantly in adolescence.) Women are more likely to exhibit the symptoms of avoidance and numbing than men, and they are more likely to develop comorbid problems (anxiety, mood disorders, substance abuse.) (Pigott T 2003.) Currently, 10% of returning Iraq vets, men and women, screen positive for PTSD.

Genetics

Genetic studies show the heritability of PTSD to be from 32-45%. Nevertheless, the most important factor in the development of the illness is exposure to trauma. Researchers have investigated the inheritability of undergoing trauma itself. It seems that some people are born for trouble! The heritability of marital difficulties is 14% being robbed or assaulted is 33%, interpersonal difficulties 39%, financial problems 18%, illness or injury 21% and problems at work 18% (Jang K 2005.)

Comorbidity of PTSD and Substance Abuse

30-50% men and 25-30% women with PTSD have a substance abuse disorder. Substance abusing individuals who seek treatment have a lifetime 36-50% PTSD risk (NCS).

Risk Factors for Development of PTSD (Watson P, Shalev A 2005)

Pre-event
female gender
40-60 years of age
ethnic minority
low socio-economic status, poor resources
prior psychiatric diagnosis or neuroticism or family history
prior trauma
below average cognitive ability (higher intelligence is protective both for avoiding trauma and for subsequent PTSD (Breslau N et al. 2006.)

Within event
trauma type: severity, intensity, duration, injury, death of loved one
intense experience: sense of confusion, panic, horror, disorientation
dissociation: may be the strongest predictor of PTSD (Flouri E 2005)

Post-event
loss of social support, presence of social criticism
continued lack of control
marital distress
loss of home or resources
derealization and time distortion 1-week post trauma
emotional numbing, restlessness, sense of reliving trauma within 1-month post trauma
exaggeration of future possibility of trauma
avoidance

Protective Factors:
low degree of distress (but not numbing)
intrusive recollections that lead survivor to recruit sympathy
upon repetition of the event, trauma narrative becomes richer and takes on a reflective tone (“All in all, I could have done worse.”)
nightmares that change from mere repetition to more remote renditions
neuropeptide Y, released with norepinephrine under stressful conditions, seems to dampen arousal, and may prove to be a marker for resilience.

Biological Correlates of PTSD
PTSD symptoms are hypothesized to reflect either pathological changes in stress-response systems or failure of neurobiological systems to recover from extreme stress. Although acute stress increases the release of cortisol in normal individuals, cortisol levels have been found to be low in people with PTSD. Studies also indicate reduced volume of the hippocampus, a region responsible for inhibiting cortisol release. Low levels of cortisol, caused by negative feedback loops to chronic stress (consistent with risk factors of previous abuse, mental illness, etc) may predict the development of PTSD. Neuropeptide Y, a chemical that reduce the release of norepinephrine, has been found to be relatively low in subjects who develop PTSD, compared to those who do not. A number of other neurochemicals and pathways are being investigated (Benedeck D, Ursano R (2009.)

PTSD in Youth
Prevalence rates vary, but about 10% of physically abused adolescents may meet the criteria for PTSD. Youth exposed to urban violence may have rates as high as 24-34%. After a single motor vehicle accident, the prevalence of PTSD in children is about 12%. Pediatric patients with PTSD frequently have comorbid depression, substance abuse, social deficits, and behavioral problems. In preschool children, dysfunctional attachment, aggression, and impulsivity are often seen (Strawn J, et al. 2010.)

Clinical presentation of PTSD in older children and adolescents is similar to that in adults. The most frequent symptoms seen in youth age 7-14 are avoidance of thoughts, feelings, and conversations about the trauma, inability to recall important aspects of the trauma, and problems concentrating. Children rate irritability, distressing dreams, and detachment as the symptoms that bother them the most. Younger children are less likely to demonstrate emotional numbing and avoidance. They tend to exhibit overt aggression, destructive behavior, and repetitive play about the traumatic event (Victor A, Bernstein G 2009.) There is also evidence that many children will show signs of PTSD after experiencing only a low-magnitude stressor (death of a loved one, parental separation, breaking up with a romantic partner) rather than the extreme stressors described in DSM (Copeland W et al. 2010.)
Proposed revisions for DSM-5 include Posttraumatic Stress Disorder in Preschool Children that will reflect these differences between younger and older children by including an item about negative alternations in cognitions and mood.

Finally, while selective serotonin reuptake inhibitors are often used to treat PTSD symptoms in adults, the data do not support SSRI’s as a first line treatment for PTSD in children and adolescents. There is limited evidence for the use of any pharmacologic agent (Strawn J, et al. 2010.)

Natural History of PTSD
It is important to remember that people are often highly labile, intensely reactive and distressed after a trauma, and that this does not indicate psychopathology. There are no particular symptoms that predict long-term adjustment to trauma, so it is difficult to know who needs specific intervention. However, the severity of post-trauma symptoms from 1-2 weeks after the trauma does correlate with subsequent symptom severity (Watson P, Shalev A 2005.)

Once PTSD develops, it is often chronic. The typical person with chronic PTSD has over 20 years of active symptoms. There is a high degree of academic failure (40%), teenage pregnancy (30%), marital instability (60%), and unemployment. There is a significant risk of comorbidity with other disorders, including depression (7x risk for men, 4x risk for women), generalized anxiety (6x risk for men, 3x risk for women), and panic (4x risk for men, 3x risk for women.) Suicide occurs in 19% of clients, comparable to major depression (Stein D et al. 2003.)

Prevention of PTSD Immediately Post-Trauma
Since most people gradually adapt after a traumatic exposure, recovery is the expected outcome of a time-limited exposure to a stressor. Feeling better following trauma and having a sense of support make a positive outcome more likely. Mental health professionals can assist by providing practical, pragmatic support in a sympathetic manner.

Psychological debriefing is reported by many people to be beneficial, but there is no solid empirical evidence that it helps prevent the development of PTSD, and there is some evidence that it may have toxic effects by impairing the natural recovery that occurs following trauma (Bisson J et al. 2007.) Regardless of the mechanism, it is not helpful to provide psychotherapy to everyone exposed to trauma (Harvard Mental Health Letter, Oct 2009.)

Cognitive behavioral therapy directed at those at high risk for developing PTSD, targeting anxiety management and providing exposure therapy over a series of sessions, might be helpful. However, a significant proportion of clients drop out of therapy. And some people are not able to tolerate CBT (Shalev A 2009.)

The use of D-cycloserine (a partial agonist of NMDA) to enhance memory extinction at receptors in the amygdala during exposure therapy is promising (Hofmann S et al. 2006.)

In some studies, blocking the memory enhancing effects of epinephrine with propanolol for 2-3 weeks after the event has been shown to reduce subsequent PTSD.
Also, cortisol given to medical-surgical patients during hospital stays can reduce the development of PTSD (Bennet W et al. 2007.)

Benzodiazepines do not help, and may increase the incidence of PTSD (Davidson J 2004.)

**Treatment of Established PTSD**

A recent review of early interventions for PTSD concluded that those patients who do not meet full criteria for PTSD tend to recover without intervention. The conclusion is that early treatment for PTSD should start within the first 5 months of exposure, include only survivors with full PTSD, and consist of trauma-focused cognitive behavior therapy (Shalev A 2009.)

Longer term PTSD is often comorbid with other disorders and more difficult to treat. The average duration of a PTSD episode is 7 years.

**Pharmacotherapy:** Many, if not most, patients with PTSD receive antidepressants. A majority also receives anxiolytics/tranquilizers. The evidence about efficacy for pharmacological treatment is fairly poor. The British National Institute for Clinical Excellence no longer recommends antidepressants as first line treatment, instead recommending CBT. In the US, two SSRI’s are approved for PTSD, but their efficacy is modest, and they do not appear to work for combat-related PTSD (Benedeck D, Urasano R 2009.) Benzodiazepines may be useful, but should be avoided if substance abuse or dependence is also a problem. Off-label uses of medication with some clinical support include clonidine for hyperarousal, prazosin for insomnia, topiramate for flashbacks and nightmares, trazodone for insomnia and nightmares (Carlat D 2007.)

**Psychotherapies**

Cognitive behavioral therapy typically includes two components:

1) **Cognitive restructuring:** helps clients identify and challenge inaccurate cognitions and replace them with more realistic ones. The most common erroneous cognitions are that the world is entirely dangerous, and that they are incompetent.

2) **Exposure therapy,** both in vivo and imaginal: works for many PTSD victims, but not all. It is less effective for those with symptoms of numbing and avoidance. Research is being done to try to find biological markers that will indicate who will and won't respond. There is preliminary evidence that cognitive therapy without exposure maybe very effective, perhaps more effective than exposure-based therapy (Benedeck D, Ursano R 2009.)

Eye movement desensitization and reprocessing (EMDR) has clients generate a mental image that represents the targeted traumatic event and to think about a trauma-related cognition they would like to change. The therapist induces a series of rapid left-to-right eye movements followed by instructions to “blank out” the image, then a query about “What do you get now?” This is repeated until distress declines (desensitization.) Alternative positive cognitions are “installed,” again using the eye movements (reprocessing.) Sometimes eye movements are replaced by listening to tones, or hand tapping. Recent research has established EMDR as efficacious for PTSD. Studies do not find that the eye movements are any better than a range of other control conditions (close
your eyes, look into the distance, etc.) The “installation” stage does not appear to be essential (Cahill S et al. 2005.)

Also of recent interest, based on animal studies of memory reconsolidation, are therapies that combine pharmacologic intervention that are administered during sessions when traumatic memories are being recalled, with the hope of erasing the negative affect associated with them (Shalev A 2009.) The observation is that when memories are recalled, they become unstable. There is a period of time before they are reconsolidated when they may be modified. While older exposure therapies may work by creating “competing” memories to the trauma-based memories, reconsolidation therapies work toward “replacing” the original memory with one less overwhelming.

Coping and Resilience

Resilience is a dynamic process of healthy adaptation by people faced with significant adversity. Resilience and recovery are the norm for most peoples after experiencing trauma. For instance, New Yorkers living in proximity to the terrorist attacks of Sept 11 experienced probable PTSD at 7.5% at one month, but 1.6% at 4 months and 0.6% at 6 months (Bisson J et al. 2007.) Resilience is distinct from recovery in that resilient people are able to cope quickly and effectively and function with little or no disruption in their lives. For people who have been able to integrate their experience into a new view of the world, there is a sense of appreciation and newfound sensitivity in their lives. Reports of growth experiences far outnumber reports of psychiatric disorder following trauma. A commonly reported change is a sense of vulnerability balanced by newfound strength. People report that they value the smaller things in life more, and have changed in the religious/philosophical aspects of their lives (Tedeschi R et al. 2004.) Resilience can be measured by several tests, notably the Connor-Davidson Resilience Scale (CD-RISC).

Several studies have looked at resilience and its relationship to mental illness. One study looking at the outcome of emotional neglect and wellbeing found that individuals with high resilience have fewer psychiatric symptoms no matter how much emotional neglect they experience (Campbell-Sills L, et al. 2006.) In another study, resilience was found to protect against the development of PTSD following severe trauma. Spirituality and forgiveness also had a less robust, but still protective effect. Feelings of revenge and anger had a strong predictive influence on developing subsequent PTSD (Connor K et al. 2003.)

While researchers have been able to describe individual character traits of resilience – commitment, dynamism, humor in the face of adversity, patience, optimism, and environmental aspects of resilience – social support, connectedness, altruistic action - it has proven much harder to uncover how these qualities are attained. The concept of hardiness has been suggested as a pathway to resilience. Hardiness is described as being committed to find meaning in life, self-efficacy, and believing that one can grow from both positive and negative experiences (Kelinman S, Tuchapsky S 2009.)

Studies of children raised in a variety of settings, including war, family violence, and poverty have shown a pattern of individual characteristics related to successful adaptation (Charney D 2004):

1) good intellectual functioning
2) good emotional self-regulation and warmth
3) positive self concept
optimism

altruism

capacity to turn helplessness into self-efficacy

active coping style (problem solving)

the ability to attract and utilize social support

With adults, much of the work has been done with men in combat or other dangerous situations. Characteristics include:

1) ability to bond with a group with a common mission
2) altruism
3) capacity to tolerate fear and continue to function
4) ability to form supportive social attachments and maintain bonding following loss

Inborn temperament is clearly a factor, as well as early environmental support and attachment.

The final question is, can we teach people to become more resilient. The answer is uncertain. A number of neurochemicals have been identified as important for psychobiological resilience. Some are listed below (Charney D 2004):

1) Cortisol mobilizes and replenishes energy stores, contributes to increased vigilance and memory formation, and contains the immune response. Cortisol must be constrained through negative feedback because sustained and excessive cortisol secretion can have serious adverse effects, including hypertension, osteoporosis, insulin resistance and cardiovascular disease.

2) Dehydroepiandrosterone (DHEA) has antiglucocorticoid and antiglutamatergic effects and may be protective during prolonged stress.

3) Corticotropin releasing hormone (CRH) increases the release of cortisol and DHEA. It inhibits neurovegetative functions such as food intake and sexual activity. Increased CRH levels have been linked to PTSD and major depression. CRH in conjunction with cortisol and norepinephrine consolidates traumatic memories.

4) The Locus Coeruleus-norepinephrine system activates the sympathetic nervous system and inhibits the function of the prefrontal cortex, favoring instinctual responses rather than cognitive ones.

5) Neuropeptide Y has regulatory effects on cortisol and the LC-norepinephrine system. Patients with PTSD have reduced neuropeptide Y levels.

6) Serotonin receptors (5-HT1A) serve to relieve anxiety. Reduction of these receptors in early life can produce long-term abnormalities in anxiety.

7) Estrogen in low doses can suppress cortisol secretion, but a higher, more prolonged dose increases cortisol response, primarily by decreasing 5-HT1A receptors.

Understanding these neurochemical interactions and how to modify them will provide some important insights in how to reduce the effects of trauma and promote resilience.

In the meantime, researchers suggests ten characteristics that people can work towards to increase resilience (Haglund M et al. 2007):

1) be optimistic and hold onto your sense of humor
2) develop cognitive flexibility – look for the good in adverse situations
3) develop a personal moral compass – live by meaningful principles, cultivate a spiritual dimension to your life
4) be altruistic
5) practice facing your fears
6) develop active coping skills
7) establish and nurture a supportive social network
8) keep fit

**SCHIZOPHRENIA**

The most current view is that schizophrenia is a syndrome rather than a disease, i.e. individuals diagnosed with schizophrenia may have substantial differences in psychopathology, in the same way that individuals with congestive heart failure will have different causes for their condition.

Schizophrenia is associated with marked social and occupational dysfunction and a course of chronic remissions and exacerbations. The three major dimensions of schizophrenia are psychotic symptoms, deficit symptoms, and cognitive symptoms.

**DSM-IV Criteria**

Schizophrenia is defined by the presence of 2 or more of the following for a one-month period, over at least 6 months, with significant social or occupational dysfunction:

1) Delusions
2) Hallucinations
3) Disorganized speech (derailment, incoherence)
4) Grossly disorganized or catatonic behavior
5) Negative symptoms (affective flattening, alogia, avolition)

There are five subtypes of schizophrenia: paranoid, disorganized, catatonic, undifferentiated, and residual. Schizoaffective disorder is described as schizophrenia with periods of major depressive, manic or mixed mood episodes.

**DSM-5 Proposed Revisions**

One recommendation is for the addition of a Psychosis Risk Syndrome:

a) delusions, hallucinations, disorganized speech – but not as intense as in a psychotic episode
b) symptoms occur at least once per week
c) symptoms are progressively worsening
d) symptoms cause distress or disability

It is also recommended that the subtype categories be eliminated (DSM-5 website)
Demographics

Schizophrenia occurs in ~1% of the population at any given time. There are 20 million cases world-wide, 2-4 million in the U.S. There are 50,000 new cases each year with some pockets worldwide of greater and lower risk. The course of remissions and relapse may differ across cultures. Age of onset is almost always before 35 years old. Intelligence follows a normal bell curve. Slightly more men than women develop schizophrenia (3:2.) No racial differences are seen (MacDonald A, Schulz S 2009.)

The Three Aspects of Schizophrenia

1) Deficit Symptoms (restricted emotional expression, reduced drive, poor rapport) Deficit symptoms may be the most distinctive feature of schizophrenia. They appear earlier, show more heritability, and are harder to treat. Psychotic symptoms remain relatively stable over time, but negative symptoms worsen. Recent studies suggest that deficit/disorganizational pathology is most strongly associated with early age of onset and male gender, implicating a developmental/genetic cause (Dominguez M et al. 2010.) Antipsychotics can cause negative symptoms in healthy volunteers (Artaloytia J et al. 2006.) Clozapine is the only antipsychotic drug that has any efficacy for deficit symptoms (Ongur D 2009.)

2) Psychotic Symptoms (hallucinations, delusions) Auditory hallucinations are experiences of hearing voices or sounds that are generated in the brain, rather than by sound waves. (It is estimated that most adults will have experiences of hearing their name called, etc. which are labeled pseudo-hallucinations. Up to 5% may experience occasional actual hallucinations not due to schizophrenia (Thraenhardt B 2007.)) Delusions are fixed, false ideas caused by a mental illness. Most frequent are delusions of persecution, as well as being controlled by a force, atomic power, or X-rays from space. Sometimes private language, neologisms, mutism, echolalia, and word salad are seen, as well as excessive concreteness, thought blocking, and thought withdrawal. Psychotic symptoms occur later in development and are associated with environmental risk factors (urbanicity, cannabis exposure, trauma.) It is possible that genetic/in utero risks which lead to deficit syndromes, may in turn create a vulnerability for developing psychotic symptoms after environmental stresses (Carpenter W 2010.)

3) Cognitive Symptoms A normal score on the Wisconsin Card Sorting Test among 10 year olds is 5 out of 6 categories correct. People with schizophrenia who are employed can get 3 categories correct. Unemployed people with schizophrenia typically get 1 correct. The level of psychosocial incapacity primarily relates to cognitive symptoms (Evins A et al. 2004, MacDonald A, Schulz S 2009.) As mentioned above, these symptoms may be linked to deficit symptoms through some sort of common genetic/in utero risk. There are 7 different areas of disruption:

1) Verbal learning and memory
2) Speed of processing (verbal fluency)
3) Working memory
4) Reasoning and problem solving
5) Attention and vigilance
6) Visual learning and memory
7) Social learning

None of the drugs currently used to treat schizophrenia restores cognition (Ongur D 2009.)

**Gender Issues**

There is a higher incidence of schizophrenia among men, with a correspondingly earlier age of diagnosis. Deficit symptoms are more prevalent in men. Men smoke and abuse substances more. They have worse premorbid histories, more negative symptoms, and a poorer course (MacDonald A, Schulz S 2009.)

Therapeutic alliance is stronger in women. Women have more comorbid problems with mood, sleep, pain, allergies, endocrine, eating disorders, personality disorders, and psychophysiological disorders. Women have more affective symptoms, auditory hallucinations, and persecutory delusions, but experience less severe symptoms, fewer hospitalizations, shorter admissions, more employment, less trouble with the law, and have better intimate relationships. They respond to lower doses of medication. Women tend to have more side effects and tardive dyskinesia (Seeman M 2004.) Mortality is lower in women. Risk of unplanned pregnancy is high due to rape or ineffective birth control.

**Genetics**

Genetic Risk for Schizophrenia

<table>
<thead>
<tr>
<th>Relative Type</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>1%</td>
</tr>
<tr>
<td>Second degree relative</td>
<td>5%</td>
</tr>
<tr>
<td>Parent</td>
<td>13%</td>
</tr>
<tr>
<td>Twin ( dizygotic)</td>
<td>17%</td>
</tr>
<tr>
<td>2 parents</td>
<td>46%</td>
</tr>
<tr>
<td>Twin ( monozygotic)</td>
<td>48%</td>
</tr>
</tbody>
</table>

The most significant risk factor for developing schizophrenia is having a first-degree relative. However, most people with schizophrenia do not have an affected relative. Furthermore, studies have shown that while the overall genetic contribution to schizophrenia may be large, the contribution of individual genes is small. At most, individual genes increase risk from 1 to 1.5 per 100. Pre and peri-natal complications and exposures have a stronger effect than individual genes (Gilmore J 2010.)

A number of environmental risk factors have been demonstrated:
1) Winter birth (Saran M et al. 2007)
2) Urban density may account for up to 30% of the risk (Krabbe et al., Os J 2005)
3) Maternal infection with Toxoplasma gondii (parasite), herpes simplex.
   Cytomegalovirus. The risk of having a child with schizophrenia increases 3x if the mother has flu in the first trimester (Brown A, Derkits E 2010.)
4) Malnutrition during fetal life
5) Extreme prematurity
6) Hypoxia and ischemia that may affect brain volume
7) Level of family functioning (i.e. a healthy environment is protective. There is no evidence that families cause schizophrenia in genetically protected children)
8) A small, but significant association with cannabis use (Foti D et al. 2010, Henquet C et al. 2005)
9) A puzzling association with a range of autoimmune diseases (Eaton W et al. 2006)
10) Maternal depression combined with genetic vulnerability to psychosis (Gilmore J 2010.)

In essence, schizophrenia is likely the result of an abnormal developmental trajectory contributed to by the interaction of thousands of genes and multiple environmental risk factors (Gilmore J 2010.)

**Brain Studies and Neurochemistry**

Brain imaging shows enlargement in the ventricular system and decreases in volume in most of the cortical gray matter regions. There are significantly reduced anterior cingulate volumes and white matter abnormalities (Pies R 2008.) Most current hypotheses focus on disturbances of broad systems of interconnected regions, like the frontolimbic or frontostriatal systems. Interestingly, treatment with antipsychotic medication can increase overall volume of brain structures. Functional MRI scans show reduced activity in the frontal lobe of clients with schizophrenia that can also be reversed by antipsychotics. At a molecular level, there is evidence of excessive dopamine transmission in the subcortex (D₂ receptors), and decreased transmission in the cortex (D₁ receptors), which may be accounted for by an abnormality in N-Methyl-D-aspartate (NMDA) transmission (Sabb F, Bilder R 2006.) Specifically, too little glutamate in the cortex leads to low stimulation of mesolimbic GABA neurons, allowing too much dopamine to be released in the mesolimbic area, leading to the positive symptoms. In the cortex, too little glutamate leads to low excitation of mesocortical dopamine neurons and too little dopamine in the cortex, accounting for cognitive and negative symptoms. There is also great research interest in glial cells, cells in the brain between neurons, and their function in clearing out glutamate and GABA in the synapses between neurons (Ongur D 2009.)

**Comorbidities**

**Uncontrolled Hostility/Excitement:** People with schizophrenia frequently become excited/agitated and sometimes hostile when under stress. Most do not become violent. A recent longitudinal study of 13,800 people with at least two hospitalizations for schizophrenia found a violence conviction rate of 17.1% for men and 5.6% for women. The hazard ratio for risk factors was 3.54 for previous violence, 3.22 for drug abuse, 2.35 for alcohol abuse, and 2.33 for parental violent crime. This highlights the importance of genetic and early environmental influences on violence (Fazel S, et al. 2009.) Command hallucinations increase risk in some people but not others (McNiel D et al. 2000.)

**Anxiety/Depression:** 40% of people with schizophrenia report suicidal ideation, 25-50% attempt suicide, 10-15% die of suicide. This is 50x higher than the general population. At high risk are young white males who are depressed, unmarried, unemployed, socially isolated, functionally impaired, and lack external support. Those who have been to college may be a higher risk (Palmer B et al. 2005.) Most depressive episodes coincide with psychotic episodes and antipsychotics are the treatment of choice. Often, an antidepressant is not needed, but clients should be regularly evaluated for symptoms of
depression, and antidepressants can be used with antipsychotics. 45% of schizophrenic clients have an anxiety disorder. Panic disorder is the most frequent comorbidity, followed by social anxiety, PTSD, and obsessive-compulsive disorder (Evins A et al. 2004.)

Substance abuse: Substance abuse and psychosis commonly appear together, and many people with schizophrenia engage in polysubstance abuse. Substance abuse exacerbates the illness, increases the risk of suicide, victimization and number of hospitalizations. There is a worse prognosis, and worsening of economic status (Buckley P 2006.) On the positive side, clients report using substances helps them cope with symptoms of schizophrenia, alleviates boredom, anxiety, sadness, distress, and gives them an activity to share with friends. The CATIE study showed that compared with abstinence, substance use and substance use disorder (except for cocaine) was associated with higher psychosocial functioning in people with schizophrenia (Swartz M, et al. 2006.)

People with schizophrenia have rates of smoking between 74-92%. Smoking induces P450 liver enzymes, and lowers the blood levels of haloperidol, fluphenazine, thiothixene, clozapine and olanzapine. Smoking may be so prevalent because:

1) nicotinic cholinergic receptors may normalize auditory sensory gating in schizophrenic clients
2) concentration is improved
3) nicotinic receptors on dopamine neurons may increase dopamine and decrease EPSE’s.
5) smoking may have antidepressant effects (Anthenelli R 2005.)

Treatment of Substance Abuse in a Schizophrenic Population

Treatments designed for individuals with substance use disorders cannot simply be applied to people with schizophrenia. Treaters must face the additional problems of the effect of the thought disorder and other symptoms, problems with motivation, poor self-efficacy, and maladaptive personal skills.


1) Integration of substance abuse and mental health treatment. These individuals are often excluded from traditional substance abuse treatment settings. The complications of navigating different settings, different providers, different insurance benefits are particularly daunting for the client with schizophrenia. Unfortunately, while there’s strong evidence that integration of treatment services work well for dually diagnosed clients, the typical financing and organization of health care systems do not allow this to occur.

2) Harm reduction approaches should be used. Harm reduction approaches place a priority on reducing the risks of substance abuse, rather than insisting on abstinence as the only goal. Any reduction in the frequency or intensity of substance abuse is a positive change. Research shows that a requirement of abstinence for admittance to a program, or for housing is often too difficult a threshold to achieve. Such requirements exclude too many clients from treatment.
Accommodation of cognitive and motivational deficits. Cognitive and social deficits in schizophrenia affect memory, consequential thinking, and problem solving. Social impairments include asking for appropriate help and support. Treatment must take into account how these clients differ from the usual participants in substance abuse treatment groups.

Clients need a nonjudgmental, nurturing ally. Clinicians need to recognize:
1) possible stigma against clients with mental illness and on medication in 12-step programs
2) the need to be more active in therapy because of problems with attention, memory and reality awareness
3) the need for patience and persistence
4) the problem of denial of both illnesses and subsequent poor adherence to treatment

One of the keys to success is to ensure that patients have access to residential services and vocational support. Some second-generation antipsychotics may be helpful in reducing substance abuse, but first-generation antipsychotics are not (Green A. et al. 2007.)

**Natural History of Schizophrenia**

Schizophrenia begins with genetic vulnerability. The illness lies dormant until the *premorbid phase*, which may be entirely asymptomatic or may cause impaired attention, some social deficits, and soft neurologic signs. Next the illness enters the *prodromal phase*. Nearly 80% of clients with schizophrenia experience a prodrome beginning in puberty that lasts a few months to several years. Common features include anxiety, blunted affect, depression, irritability, loss of initiative, sleep disturbance, social withdrawal, worsening referential and paranoid thinking, cognitive deficits and declining academic functioning. An estimated 30-50% will progress to schizophrenia within a year. (This may be as high as 74-81% if there is also a family history and other specific variables (Harvard Mental Health Letter Dec 2009.) With the onset of illness, the disease enters the *progressive phase*. 86% of first episode clients recover after their first episode with treatment (75% to full remission and 11% to partial remission) and 14% remain treatment refractory. The vast majority of clients will relapse in three years. Most of the deterioration in the illness occurs during the first 5 years. The illness then moves into the *chronic/residual phase* with repeated episodes and relapses. Sufferers often become resistant to medication (Lieberman J et al. 2006.)

The model that best describes the above progression is one that combines a developmental and degenerative focus. Genes probably create a neurodevelopmental and neurodegenerative risk, which in a certain environment, results in the progression seen above (Lieberman J et al. 2006.) However, there is preliminary evidence that cognitive behavior therapy and medication may decrease the risk of progression. Furthermore, one study of 274 clients suggests that a large number of clients with schizophrenia will show periods of recovery and will not experience the severe social isolation that was once described as part of the illness (Harrow M et al. 2005, Cohen C et al. 2008.) Recovery was also found in a ten-year study of schizophrenic clients with substance use disorders (Drake R et al. 2006.)
Childhood onset schizophrenia does exist, although it is quite rare. Less than 1% of people with schizophrenia have this diagnosis in childhood. Symptoms overlap with autism spectrum and speech and language disorders. The earlier the onset, the poorer the prognosis (Khurana A et al. 2007.)

**Prevention of Schizophrenia**

Researchers have devoted considerable effort evaluating ways to prevent the progression to schizophrenia from the premorbid or prodromal phase. Early use of antipsychotics has proven to be disappointing. There is some preliminary evidence that cognitive behavior therapy geared toward improving memory, attention, and social skills may be helpful. The early use of antidepressants is inconclusive. Finally, there is evidence that omega-3 dietary supplements may have some preventative effect (Harvard Mental Health Letter Dec 2009.)

**Treatment**

Treatment needs to be initiated as quickly as possible after the beginning of symptoms, since the duration of untreated psychosis is related to poor outcome (MacDonald A, Schulz S 2009.)

The goals of treatment are defined by the model of treatment that is assumed by the treater. In the maintenance model, relapse prevention is the focus and the emphasis is on higher doses of antipsychotics with a strong emphasis on compliance and risk reduction. Success is measured by the number of psychotic relapses. In the remission model, the goal is to treat to the point where there are no longer any psychotic symptoms. Medications are the primary modality and success is measured by symptom scales. In the recovery model, the goal is to help people live and participate fully in their communities. Specific goals are set by the client. Success is measured by client satisfaction and community measures. Evidence is accumulating that the recovery model is a realistic approach (Harrow M et al. 2005, Cohen C et al. 2008, Drake R et al. 2006.)

In surveys, clients with schizophrenia identify depression/anxiety, Parkinsonian side effects from medication, and not wanting to take medication as the factors that most interfere with the quality of their lives. Employment enhances quality of life. These should be important targets for intervention (Hofer A et al. 2004.)

A large, non-industry sponsored medication research trial is the Clinical Antipsychotic Trials for Interventions Effectiveness (CATIE). This study, sponsored by NIMH, has had 2 published phases. Altogether, 1,493 patients began the study. The results confirm that a significant number of clients discontinue their antipsychotic treatment because of side effects and lack of efficacy (74%). There may be some small, but clinically significant differences in efficacy and tolerability among the second-generation antipsychotics. Clozapine is the most effective drug for those who fail to respond adequately to initial treatment, but has serious side effects. Among the other drugs, the fact that there is little difference in efficacy (confirmed by more recent studies) suggests that if a patient is doing “well enough,” don’t switch drugs to find a better one. If the patient is having trouble with side effects, do consider another drug, since side effects do vary (Lieberman J et al. 2005, McEvoy J et al. 2006, Stroup T et al. 2006.)
Antipsychotic drugs are effective for psychosis, but are not "anti-schizophrenic." Efficacy for negative symptoms and cognitive impairments is modest at best (Green M 2007.) The benefit of maintenance drug treatment is primarily relapse prevention, not comprehensive treatment.

Some data that suggest antipsychotic medications may have a neuroprotective effect in schizophrenia if they are given early enough in the illness. Research is ongoing (Lieberman J et al. 2006.)

Psychosocial Treatments

There is 40% relapse rate even in medication compliant clients, so medication should not be the sole treatment for this condition. Research shows the following interventions are effective:

Assertive Community Treatment: reduces the frequency of hospitalization, increases housing stability, and shows high satisfaction on ratings from clients and families. It has not been shown to be superior to standard care on measures of mental state and social functioning. It does not result in cost savings except for populations that are already high users of inpatient care (Clark R, Samnaliev M 2005.) (Case management alone is not the same as ACT and does not have clinically significant results.)

Integrated Dual Disorders Treatment

Supported Employment: the individual placement and support (IPS) model is effective in maintaining competitive employment (Clark R, Samnaliev M et al. 2005.)

Family Intervention: reduces relapse, improves symptomatic recovery, and enhances family outcomes. Programs must last longer than 6 months (Kuipers E 2007.)

Social Skills Training: improves social skills.

Personal Therapy: improves psychosocial functioning (Dickerson F et al. 2006)

Akathisia is one of the most important variables that determines whether clients choose to stay in psychosocial treatment.

Cognitive-Behavioral Therapy

Two randomized controlled trials have demonstrated that patients with schizophrenia who receive cognitive-behavioral therapy along with medication show improvement in depressive and positive and negative symptoms, although the studies were contradictory as to whether these were short or long-term gains. Results are also contradictory concerning relapse, rehospitalization, and social functioning (Dickerson F et al. 2006, Turkington D et al. 2006.)

Key techniques of cognitive therapy include:

1) developing a therapeutic alliance
2) developing an explanation of the client’s symptoms that is satisfactory to both the client and the clinician
3) reducing the stress and severity of positive symptoms by normalization, exploration, and building strategies of adaptation

Vocational Needs

Among clients treated with first-generation antipsychotics, only 10% ever work fulltime, 33% work at supported employment. Working at a paid job is one of the most
important determinants of quality of life. Cognitive dysfunction is the most important variable in being able to work.

The CATIE Project collected data on employment and functioning of 1,400 clients. 14.5% of clients reported participating in competitive employment, 12.6% reported other employment, and 72.6% reported no employment. Employment was associated with:

- Less severe negative and positive symptoms
- Better cognitive function
- Psychological characteristics of motivation, empathy
- Higher education
- Availability of psychosocial rehabilitation

African-Americans and those receiving disability payments were less likely to be competitively employed, i.e. the differences between being competitively employed and having supported employment seem to be primarily social (Rosenheck R et al. 2006).

The cognitive mechanisms that cause the actual functional disability in schizophrenia appear to be those that affect making social inferences (Sergi M et al. 2006). Patients with schizophrenia have difficulty in correctly identifying emotions in others (Schneider F et al. 2006). Consequently, clients will have problems with:

- interpreting the behaviors of co-workers (playful or threatening)
- understanding how personal work relationships should be recognizing how their behavior affects others
- job-related living supports such as transportation and clothing
- performance of job tasks

**Health Problems**

Mortality of clients with schizophrenia is 1.6-2.6x greater than in people without schizophrenia. Medical and surgical hospitalizations for people with schizophrenia have twice the odds of adverse events than those without (Daumit G et al. 2006). Life expectancy is 20% shorter (61 versus 76). This differential mortality gap has worsened in recent decades (Saha S et al. 2007.)

The major cause of premature death is cardiovascular. In human beings, cardiovascular risk is additive with the following:

- Body Mass Index (BMI) >27
- Total cholesterol >220
- Hypertension
- Diabetes
- Smoking

People with schizophrenia are at higher risk for all of these.

The “metabolic syndrome” increases the risk for cardiovascular events above and beyond the risks of these individual factors. Metabolic syndrome consists of 3 or more of the following:

- Abdominal obesity (waistline men >40, women >35
- Triglycerides >=150
- HDL men <40, women <50
- Blood pressure >=130/85
- Fasting glucose >=110
Clients who have schizophrenia and bipolar disorder, as well as people who take certain second-generation antipsychotics are at increased risk for metabolic syndrome (Meyer J et al. 2007.)

**Specific Issues With Health** (Marder S 2004)

**Weight gain and obesity:** Patients with schizophrenia are more likely to be overweight than the general population (42% vs. 27%). Clients on antipsychotics frequently experience a weight gain of 7-10%. Clozapine and olanzapine cause the most significant increase. Weight gain caused by medications is not dose related. Health recommendations are:
1) Monitor body mass index (BMI) for all patients.
2) Weigh for each visit for 6 months when starting new medication
3) Weight gain of 1 BMI (~6 pounds) indicates medication change

**Diabetes:** Clients with schizophrenia have twice the incidence of diabetes. Some antipsychotics are associated with the onset of diabetes. Health recommendations include:
1) Baseline glucose for all patients starting on a new antipsychotic.
2) Clients with significant risk for diabetes (family history, BMI>24, waist >34 for women, >39 for men) should have fasting glucose or HbA1c every 4 months then yearly.
3) Clients should know symptoms of new onset diabetes (weight change, polyuria, polydipsia).

**Hyperlipidemia:** Clients with chronic psychiatric disorders have a higher incidence of hyperlipidemia. Clozapine and olanzapine worsen lipid profiles. Health recommendations:
1) Monitor lipids.
2) Clients with metabolic syndrome should be monitored by a primary health care provider.

**QT prolongation:** Certain antipsychotics can be associated with ECG abnormalities that may indicate a risk of potential fatal arrhythmias.
1) Clients with known heart disease, history of syncope, family history of sudden death at an early age, or congenital long QT syndrome should not be prescribed thioridazine, mesoridazine, or pimozide.
2) If ziprasidone is prescribed, these clients should have a baseline ECG and follow-up ECG if symptoms occur.

**Cardiac arrhythmia and risk of death in older adults:** A “black box warning” from the FDA notes a doubling risk of death in patients with dementia who are treated with atypical antipsychotics. More recent reviews have found that both typical and atypical antipsychotics cause an increased risk of cardiac death at any age (Ray W et al 2009.) Getting baseline and follow-up ECG’s may be prudent for at risk patients who are taking any antipsychotic.
Elevated prolactin: Certain antipsychotics are associated with increases in prolactin. The health effects of this increase are variable.
1) Ask female clients about changes in menstruation, libido, and lactation
2) Ask men about libido erectile and ejaculatory dysfunction.
3) Prolactin levels should be taken if indicated.

EPS, akathisia, tardive dyskinesia: Second-generation antipsychotics reduce the risk of tardive dyskinesia.
1) Clients should be examined for movement disorders before starting antipsychotic medication and should be monitored for 2 weeks after starting.
2) Clients should be examined every 6 months if they are on a first-generation antipsychotic and yearly if they are on a second-generation.

MAJOR DEPRESSION

Depression is a mood (experienced by everyone) and a medical syndrome (a cluster of symptoms, only one of which is mood). In clinical practice, the diagnosis of “depression” is used in a wide variety of different disorders, including major depressive disorder, bipolar disorder, dysthymia, bereavement, and bipolar disorder. People with a major depressive episode tend to withdraw and are able to express a limited range of emotions. They are often obsessively focused on themselves and how they feel. In the primary care setting, the following often indicate depression: sleep disturbance, fatigue, and multiple somatic complaints.

DSM-IV Criteria

The criteria for major depressive disorder are the presence of a major depressive episode, or recurrent depressive episodes, without a history of mania. A major depressive episode is defined as having 5 of the following for a 2-week period, including at least item 1 or 2:
1) depressed mood (in children may be irritable)
2) markedly diminished interest or pleasure in activities
3) weight loss or weight gain, change in appetite
4) insomnia or hypersomnia
5) psychomotor agitation or retardation
6) fatigue or loss of energy
7) feelings of worthlessness or inappropriate guilt
8) diminished ability to think or concentrate
9) recurrent thoughts of death, suicidal ideation or behavior

Dysthymia is described as a depressed mood (milder than a major depression) with symptoms persistent over a two-year period.

DSM-5 Proposed Revisions

A new diagnosis has been proposed – Mixed Anxiety Depression – in which the patients has 3 or 4 symptoms of major depression (including 1 or 2 above), and two of the following:
1) irrational worry
2) preoccupation with unpleasant worries, feeling uneasy
3) having trouble relaxing, feeling nervous
4) motor tension
5) fear that something awful may happen

Also being considered are Seasonal Affective Disorder and Complicated Grief Syndrome. It is recommended to remove the qualifier that a major depressive disorder should not be considered if bereavement is present, due to lack of evidence that major depression caused by bereavement is any different than major depression caused by any other stressor.

Another recommendation is that each mood disorder diagnosis be accompanied by an anxiety dimension and a suicide assessment dimension. The anxiety dimension uses the above symptoms of anxiety and rates the patient from 0 (no anxiety) to 4 (severely anxious with 5 symptoms and motor agitation.)

The suicide assessment dimension looks at 7 risk factor groups, adds them together and comes up with a score of 1 (no concern) to 4 (5-7 items, high concern.) The seven risk factor groups are:
1) history of suicide attempt
2) tendency to temper or aggression with little provocation
3) living alone, chronic severe pain, recent significant loss
4) recent psychiatric hospital admission/discharge, first diagnosis of major depression, bipolar disorder, schizophrenia
5) recent increase in alcohol abuse or worsening of depression
6) current (within last week) preoccupation with or plans for suicide
7) current psychomotor agitation, anxiety, hopelessness

(DSM-5 website)

Symptoms of Depression
Affective
depressed mood
Vegetative
weight loss, weight gain, or change in appetite
insomnia or hypersomnia
diminished sex drive
Behavioral
psychomotor retardation or agitation nearly every day
fatigue
diminished interest or pleasure in almost all activities
Cognitive
feelings of worthlessness or guilt
diminished ability to think and concentrate
poor frustration tolerance
negative distortions
Impulse Control
recurrent thoughts of death or suicide, homicide
Somatic
headaches, stomachaches, muscle tension, pain
The overlap of depression and pain is particularly apparent in syndromes such as fibromyalgia, irritable bowel syndrome, low back pain, headaches, and nerve pain. About 65% of people seeking help for depression report at least one type of pain syndrome. Researchers have found that pain, depression and anxiety share both neuroanatomy (somatosensory cortex, amygdala, hypothalamus, and anterior cingulated gyrus) and two neurotransmitters (serotonin and norepinephrine) (Harvard Mental Health Letter May 2010.)

Clients with depression have difficulties in interpersonal relationships, largely related to problems with emotional perception and executive function (memory, attention.) People suffering from acute episodes of depression have a diminished ability to distinguish facial emotional expression. They have problems misidentifying happy facial expressions as sad (Fu C et al. 2007.) There is impaired ability to perceive black and white contrast (Harvard Mental Health Letter Nov 2010.) In addition, there is evidence of mood state-dependent learning. Clients don't remember ever feeling good, possibly increasing the risk of suicide. These memories can be retrieved with proper prompting and cueing.

**Depression in Borderline Personality Disorder**

The dysphoria or depression that is usually seen in borderline personality is experienced in the context of interpersonal relationships. The mood shifts, hour by hour, and includes feelings of emptiness, loneliness, fears of abandonment, and self-condemnation. There are frequent low injury suicide attempts.

Antidepressants do not ameliorate these feelings and behaviors. If vegetative symptoms are present, indicating a major depressive episode, antidepressants can be useful in relieving them (Paris J 2010, Silk K 2010.)

**Demographics**

Depression is one of the most common psychiatric disorders. According to NESARC, the 12-month prevalence of depression is 5.28% and lifetime prevalence is 13.23%. Those at high risk for depression include Native Americans (19.17%) and whites (14.58%). African Americans (8.93%), Hispanics (9.64%), and Asians (8.77%) are at lower risk. There is high comorbidity for anxiety disorders (36%), especially generalized anxiety disorder and a personality disorder (37%) (Hasin D et al. 2005.)

Mortality from depression is high. 45.5% of depressed clients report they want to die, 36.4% have considered suicide, and 8.8% report a suicide attempt (Hasin D et al. 2005.) Risk of completed suicide is 20x that of the general population, a 14.6% lifetime risk. 30-70% of suicides have a depressive disorder (Baldessarini R 2003.) 20% of clients experience depression after a myocardial infarction, and have a 2.5 greater risk of mortality. Responding to treatment with antidepressants lowers this risk, and non-responders to antidepressants have the highest risk for new cardiac events in the next 2.5 years, regardless of their cardiac impairment (de Jonge P et al. 2007, Carney R, Freedland K 2009.) This risk seems to be specifically related to depression that first appears a month after the initial heart attack (Parker G et al. 2008.)
Depression in Children and Adolescents

Until the 1980’s, it was not thought that young people could become depressed. It is now known that depression affects up to 2.5% of children and 8.3% of adolescents (Singh M et al. 2007.) Among preschoolers, anhedonia is the most specific symptom of depression, accompanied frequently by sadness, social withdrawal, excessive guilt, extreme fatigue, diminished cognitive abilities, and irritability (Luby J 2004.) Irritability, in fact, is the most common presentation of many mental health problems in children, including depression, but is not a good proxy for feelings of sadness in preschool children, as has previously been thought. Caregivers may fail to report symptoms, or may unwittingly accommodate to them, complicating the diagnosis. There is little empirical basis for treatment, but antidepressants should not be used as first or even second-line treatments in preschool children. Family therapy is the recommended approach, with an emphasis on emotion development. In older school-age children, fluoxetine is the only approved antidepressant (Luby J 2009.)

By adolescence, depression rates have started to climb, and young people are more able to describe themselves as depressed. The three strongest risk factors for adolescent depression are 1) parental depression, 2) symptoms of depression but not yet a full-blown episode, 3) prior depression. Risk may be reduced by participating in sports and going to bed by 10 p.m. (Harvard Mental Health letter May 2010.) Substance abuse has a bidirectional relationship with depression in adolescents, both leading to depression and resulting from depression (Hallfors D et al. 2005.)

Suicidality first arises as a public health problem in adolescence. The use of certain antidepressants seems to increase the risk of suicidal thinking and behavior, but not increase mortality among teens, so they should not be withheld from young people who need them (Singh M et al. 2007.) The unfortunate result of these warnings has been a decrease in prescriptions of antidepressants for those who need them (Emslie G 2008.)

Three non-industry funded studies have looked at depression treatment in adolescents (Treatment Resistant Depression in Adolescents TORDIA, Treatment for Adolescents with Depression Study TADS, Adolescent Depression Antidepressant and Psychotherapy Trial ADAPT.) The results suggest that teens are a very responsive treatment group, with 60-70% getting better with medication alone or medication plus CBT. Of those who fail the first antidepressant, 40% will respond to a second. Finally, there is no evidence that CBT alone or as an adjunct is useful in severe depression (Walkup J 2010.)

Psychosocial interventions are also an effective treatment approach for depression in teens. Effective interventions include increasing teen competence in at least one self-identified area, psychoeducation about depression and treatment, teaching self-monitoring skills, cognitive restructuring, and behavioral activation (Parry P 2010.)

Depression in the Older Adults

There is no increase in depression for those elderly people living in the community. However, all medical illnesses increase the rate of depression. Rates of depression among older people are as follows (Harvard Mental Health Letter, Feb 2008):

- Community: 1-5%
- Hospitalized: 12%
- Requiring assistance at home: 15%
- Nursing home: 29-52%
Being treated for a serious illness: 39-47%

Older clients do not complain of depression to their doctors because that is not why they come to the doctor. They complain of low energy, poor appetite, poor sleep, and various somatic complaints like heart palpitations, tremor, and shortness of breath. Certain illnesses and drugs may mimic symptoms of depression, including hypothyroidism, B vitamin deficiencies, blood pressure medicine, etc. (Harvard Mental Health Letter, Feb 2008.)

Mild cognitive impairment in depression ranges from 25-50% and may persist for up to a year after an episode. Deficits include slowed information processing, poor attention and concentration, difficulty with memory and executive functions. Later onset depression (60 years or older) is more frequently characterized by greater apathy, greater cardiovascular morbidity, and a stronger association with dementia. It seems that depression is a risk factor for dementia in some individuals, while it is an early sign of dementia for others (Potter G, Steffens D 2007.) Older people with symptoms of depression should always have a good cardiovascular assessment, as well as an assessment of their cognitive status.

Distinguishing the cognitive impairments of depression from dementia is an important clinical skill. Decline in mental functioning is more rapid with depression than dementia. People with depression are less often disoriented. Concentration is more a problem with depression and short-term memory more a problem with dementia. Writing, speaking, and motor skills are not usually impaired in depression (Harvard Mental Health Letter Feb 2008.)

In addition to increasing morbidity and mortality from various medical conditions, depression is a strong risk factor for suicide. Older white and Native-American men have the highest suicide rate in the US general population.

Bereavement

Bereavement is a universal experience related to the loss of a loved one. It can be thought of as an attachment trauma. The psychological reaction to bereavement is grief. Grief is not a single emotion, but a combination of different emotions, including the negative feelings of sadness, anxiety, guilt, anger and shame; and the positive emotions of happy reminiscence, pride in the deceased, warmth, and relief.

Acute grief lasts most of the day, every day for up to six months, and then recurs transiently. It is characterized by a sense of disbelief, dominant painful emotions, preoccupation with thoughts of the deceased, and attenuation of interest and engagement with ongoing life. This painful state normally transitions into “integrated grief,” which can be thought of as a permanent background state, where positive emotions, such as acceptance, forgiveness, and compassion predominate. Rarely, grief may be complicated – great difficulty accepting death, excessively painful memories which may be very difficult to access or very intrusive, overwhelming feelings of guilt or yearning. Complicated grief is not limited to those people who had ambivalent relationships with the deceased. It is seen just as frequently in those with very positive and close relationships. Complicated grief is usually not diagnosed until more than six months after the death (Shear K 2006.) Complicated grief is associated with bad health outcomes, including cancer diagnosis, high blood pressure, cardiac problems, and suicide (Hensley P 2006.)
Although grief may look like depression, there are some important differences. The symptoms of depression tend to be pervasive, as opposed to grief where the symptoms are more episodic. Depression is more likely to show the following: apathy, suicidality, pervasive guilty ruminations, and poor self-esteem. Grief is more likely to show yearning, preoccupation with the loved one, crying, disbelief, and the retained ability to experience positive emotions. Symptoms of PTSD are more likely to have symptoms of hyperarousal, scanning for threat, avoidance, be associated with a traumatic death (Gray M et al. 2006.).

In children the course of grief is determined by who else is important in the child’s life. This is not an important feature in grief progression in adults. Children don’t usually develop complicated grief unless they are afraid of their own death.

There is some controversy about treating the symptoms associated with grief. Approximately 40% of the bereaved meet criteria for a major depressive episode a month after the loss, 15% at one year post-loss. This appears to have a 1:1 gender distribution, unlike major depressive disorder. Studies indicate that symptoms of depression are helped by antidepressant treatment, but symptoms of grief are not (Hensly P 2006.) Since in almost every case, bereavement resolves on its own in about 6 months, the overwhelming consensus is to let grief take its course as part of the range of normal human experience, as long as the symptoms are manageable and the individual is not suffering from a major depressive episode. This is supported by the observation that virtually all people suffering from bereavement regard their reactions as normal. It must be kept in mind, however, that severe symptoms in the first six months, or the presence of depression, predict a poor outcome, and should be treated (Shear K 2009.)

Complicated grief does not seem to respond to medication, and probably requires specialized therapy. Such therapy involves both grieving the loss and restoring life functioning (Shear K 2005.)

**Gender Issues**

Women are twice as likely to suffer from depression as men. The separation emerges during a short time span (5 years) that is coincident with the onset of puberty. Social and hormonal influences contribute to making adolescence a difficult transition for girls (Seeman M 2006.) Additionally, menopause is strongly associated with new onset depression (Cohen L et al. 2006.)

Women are more likely than men to describe themselves as depressed. They have more depressive symptoms and a higher degree of distress, and more seasonal affective disorder. They more commonly present with the “atypical” symptoms of depression: hypersomnia, psychomotor retardation, worthlessness, guilt, anxiety, and somatization. Women attempt suicide 3x as often as men. They are more likely to have comorbid anxiety and eating disorders (Sloan D, Kornstein S 2003.)

College education and being in a first marriage confers a lower risk of depression for women. If a woman hasn't been to college, she does better if she works outside the home. Single mothers have twice the risk of depression as married mothers (Sloan D, Kornstein S 2003.)

Emotionally supportive relationships are substantially more protective against major depression for women than men (Kendler K et al. 2005.) Women’s friendship networks are larger, and this theoretically serves as both a buffer and risk for exposure to stress.
Family ties are perceived differently between men and women, with marriage protecting men from mental illness, but creating more of a risk to mental health for women. Presumable this is due to the burden of the caretaking role women usually assume (Seeman M 2006.) For men, the most likely reason to seek help is a feeling of failing to meet expectations. The precipitant is likely to be work problems or divorce/separation. Men also complain of difficulty adjusting to major life changes, increasing self-doubts, and feeling overwhelmed by the needs of others. Their symptoms are likely to be social isolation, substance abuse, irritability, and risk taking. Men are more likely to have substance abuse problems (Sloan D, Kornstein S 2003.)

Pregnancy: Recent studies indicate 10% of women have depressive symptoms during pregnancy. Women with a previous major depression are most at risk. Discontinuation of antidepressants is associated with high rates of relapse, although the risk of suicide is low during pregnancy. Maternal depression is linked to poor neonatal outcome including preterm birth, lower birth weight, smaller head, and lower APGAR scores. (Nonacs R, Coen L 2003.) Antidepressant medications diffuse readily across the placenta. No psychotropic drug has been approved by the FDA for use during pregnancy. Antidepressants carry a small risk for birth defects. More likely is the 30% chance that a neonate will experience an abstinence syndrome of lack of crying, increased muscle tone, irritability, abnormal breathing, and disrupted sleep within 48 hours after birth if exposed to antidepressants in the third trimester. These symptoms are mild and self-limiting (Pies R 2006.) There is also evidence that antidepressants during pregnancy may increase the risk of pre-term birth (Suri R et al. 2007.)

Postpartum Depression: Postpartum depression is the most common complication of childbirth in the US. In the first 48 hours after birth, the mother’s levels of estrogen and progesterone drop suddenly by a factor of 50 (Gaschler K 2008.) Postpartum “baby blues” are fairly common and effect up to 75% of women. These typically resolve within a week or two. 13% of women will develop post-partum depression. (The prevalence of depression in childbearing age women is 12%). Risk factors for PPD are a history of depression in the woman or her family, poor intimate relationships, inadequate social support, stressful life events, and child-care related stressors. The most significant impact of the depression are the effects on the baby, which include behavioral problems, delayed cognitive and linguistic development, and higher risk for future psychiatric problems (Flynn H 2005, Johnson P, Flake E 2007.)

0.1% of women will develop a post-partum psychosis, which is a medical emergency and can lead to the mother hurting her child. Onset is usually within 2 weeks of delivery. The risk seems to be highest in women with a history of bipolar disorder (Flynn H 2005.) See www.womensmentalhealth.org for current information about women and mood disorders (website run by Massachusetts General Hospital). See also www.toxnet.nlm.nih.gov and www.postpartum.net.

Seasonal Affective Disorder
Seasonal affective disorder (SAD) is one of the few psychiatric conditions with a predictable time of onset and remission. As originally defined, it is a syndrome in which depression develops during autumn or winter and remits in the spring or summer. This
tendency to experience seasonal mood changes is quite common and ranges from the mild to the subsyndromal, to the extreme.

Many patients develop so-called atypical depressive symptoms, including increased duration of sleep, increased appetite, weight gain and carbohydrate craving. Patients tend to have less suicidal ideation and less morning worsening of symptoms. Children will often present with fatigue, irritability, sleep inertia, and school problems.

The most interesting facet of the disorder is the response to light. 94% of patients report that travel nearer to the equator during the winter months markedly decreases their symptoms. Exposure to bright light is the treatment of choice. The illness occurs more frequently in women than men, and in younger individuals. Some patients remit as they get older, others retain their seasonal pattern throughout their life (Magnusson A, Partonen T 2005.)

Evidence is strong that bright light therapy works for those patients with a seasonal pattern. It is not so strong as an adjunctive therapy for depression without a seasonal component. Most recommendations are for an exposure of 10,000 lux for 20-30 minutes a day. The less bright the light, and the smaller the light box, the more exposure that’s needed. The light must shine in the patient’s eyes. Morning exposure is best, especially for “morning people” (Carlat D 2006). Side effects are uncommon. Hypomania is a rare, but possible side effect (Terman M, Terman J. 2005).

Genetics

Family history increases the risk of depression by 1.5 to 3x. Like most things in mental health, though, the picture is complicated. It appears that the role of genes in this parent to child transmission of depression is relatively small – less than 40%. Genes that influence the development of childhood depression appear to be different than genes that cause depression later on. There are apparently genes that affect the risk of depression differently in men and women. These genes may be hormone specific. The inheritability of major depression is higher in women (42%) than men (29%) (Kendler K et al. 2006, Reiss D 2008.)

The fact that identical twins show significant differences in incidence of depression, the slow progress in identifying candidate genes, and female predominance have all suggested that “epigenetic” factors may play an important role in depression. In rats, low levels of maternal nurturance lead to increased methylation (repression) of genes in certain areas of the brain (Krishnan V, Nestler E 2010.) Various epigenetic changes have been linked to vulnerability to stress and depressive behaviors.

In humans, parental depression decreases warmth of interaction and increases negativity in the parent-child bond and thereby increases child pathology. But it is also observed that temperament (genes) in children influences parental warmth and negativity. So we are looking at a multifactorial influence of depression genetics, epigenetics, parenting styles, and temperament genes in the child. Fetal exposure to toxins and stress in the mother almost certainly also plays a role (Reiss D 2008.)

In a recent, large adoption study, it was found that maternal, but not paternal, depression was a risk for the development of depression in both biological and adopted adolescents living in the home, continuing the line of evidence that familial transmission of depression results from the environment, not simply the genes (Tully E et al. 2008.)
Environmental Contributors to Depression

The primary environmental predictors for the onset of depression are:
- Stressful life events in the past year
- Genetic factors
- Previous history of major depression
- Neuroticism
  (Jang 2005.)

There is compelling evidence that early life stress such as childhood neglect, physical or sexual abuse, and early parental loss constitutes a major risk factor for depression. In one large prospective longitudinal study, child abuse and neglect were clearly correlated with risk of major depressive disorder in adulthood (Widom C et al. 2007.)

Biological Basis of Depression

The combination of genetics, early life stress, and ongoing life stress may determine individual vulnerability. Stress and glucocorticoids directly lead to cell death and reduce cell resilience by making them more vulnerable to other toxicities, like hypoxia, and hypoglycemia. These changes also decrease the brain’s ability to create new neurons. (Gillespie C, Nemeroff C 2005.) Is this the cause of depression?

The observation that 50% of depressed patients improve when treated by agents that increase norepinephrine and serotonin neurotransmission has lead to a hypothesis that deficits in monoamine function are the fundamental “lesion” in depressive illness. There is little primary evidence that this is true (Krishnan V, Nestler E 2010.)

With improvements in neuroimaging techniques, several “network models” of major depression have been described. Defined by dysfunctional interactions among different brain regions (cingulate, paralimbic, subcortical, frontal) when stressed, these models may lead to new treatments, including deep brain stimulation (Mayberg S 2006, Krishnan V, Nestler E 2010.)

Other lines of investigation include neurogenesis and cell death, the dopamine reward pathways, and the effect of sex hormones, cortisol, and metabolic peptides (Krishnan V, Nestler E 2010.)

Medical Causes of Depression

Medications - antihypertensives, sedatives, hormones, cimetidine, L-dopa
Neurological disorders - stroke, subdural hematoma, multiple sclerosis, brain tumors,
  Parkinson’s, Huntington’s, seizure disorders, syphilis, dementia
Metabolic - hypothyroidism, hyperthyroidism, Cushing’s disease, pellagra,
  hypercalcemia, hyponatremia, diabetes, B12 deficiency
Other - pancreatic cancer, viral infections (especially mononucleosis)

Comorbidity With Substance Abuse

Among those with a history of depression, 40.3% have an alcohol use disorder, 17.2% have a drug use disorder, and 30% have nicotine dependence (Hasin D et al. 2005.)
Among those with alcohol abuse disorders, 32.75% have a major depression. Among drug abusers, 44.26% have depression (NCS-R.)

Individuals with substance abuse often present in a primary care setting with complaints of anxiety, sleep disturbance, and depression. Withdrawal from stimulants,
especially cocaine causes anhedonia, apathy, depressed mood and possibly suicidal ideation. Chronic use of CNS depressants like alcohol, benzodiazepines, barbiturates, and opiates is associated with depressed mood, poor concentration, anhedonia, and insomnia. People with late stage alcoholism feel worthless and helpless, have decreased sense of pleasure, sleep disruption, decreased libido, and feel depressed. If the depression is treated, abstinence is more successful with less risk of relapse (Geppert C et al. 2004.)

Natural History and Treatment of Depression

The onset of depression usually occurs from 20-40 years old. Most people do not seek help for their depression, even if it is severe (CDC, Sept 2008.) Depression is a lifelong illness, with people likely to relapse within several months of the first episode, especially if antidepressants are discontinued. It is clear from relapse and symptom data that sub-syndromal symptoms represent a continuation of the illness and mean that more treatment is necessary (similar to treating an infection.) It is important to treat residual symptoms of depression because they represent a continuation of the disease (Van Rhoads R, Gelenberg A 2005.)

Untreated, an episode of depression will last 6 to 24 months or longer (5-10% have episodes continue for more than two years). The risk of recurrence is 50% after one episode, 70% after two episodes, and 90% after three episodes. People with frequently recurring depression and early age of onset (teens) may suffer from bipolar disorder (DSM-IV-TR.) Antidepressant treatment without a mood stabilizer will make them worse.

Psychotherapy

Many kinds of psychotherapy have proven as efficacious for the treatment of depression as medication, and may be better at preventing relapse. Recent review suggests that even the severity of depression does not predict a better response to medication than to psychotherapy (Simon G, Perlis R 2010), although standard practice would be to treat the most severe depressions with medications. The kind of therapy seems to be less important than other variables, such as treatment alliance, skill of the therapist, belief in the therapy, etc. Cognitive behavioral therapy plus medication may have a synergistic effect, i.e. they work better together than each alone (Hollon et al. 2002.) A recent large meta-analysis confirms a small, but statistically significant advantage to using therapy with medication, including better treatment adherence (Cuijpers P et al. 2009.)

Treatment Response to Medication

A seven-year NIMH funded study of 4,041 depressed subjects, Sequences Alternatives to Relieve Depression (STAR*D), found that 33% of patients with depression achieve remission on their first antidepressant (Trivedi M et al. 2006.) Switching to a different antidepressant can improve remission to 50-66% (Quitkin F 2005, Carlat D 2007.) Achieving remission in symptoms is important because patients who fail to achieve remission:

- Relapse 3x faster
- Continue to have social and work impairments
- Are at increased risk for substance abuse and suicide
- May develop treatment resistance
Reviews in the *New England Journal of Medicine* (Kirsch et al. 2008) and the *Journal of the American Medical Association* (Fournier et al. 2010) have seriously questioned the efficacy of antidepressants compared to alternative treatments. The conclusion seems to be that antidepressants are as effective, but no more effective than psychotherapy, exercise, stress relief/meditation, and often, placebo. However, standard clinical practice would be to use antidepressants as first line treatment for the most severe depressions.

In terms of how to begin treatment, research to date does not identify any biologic or genetic predictors (e.g. previous response or family response in the past) of sufficient usefulness to guide the choice of medication or psychotherapy, which medication, or which psychotherapy (Simon G, Perlis R 2010.) Discussing potential side effects of the different drug choices with the patient is a good way to begin the selection process.

**Treatment Resistant Depression**

Approximately 33% of people with depression fail to respond to multiple treatments. Making sure the patient has been tried long enough (12 weeks) on an effective dose of an antidepressant with *no active substance abuse* is a necessary first step. There are no guidelines for which antidepressant to try after the first one has failed, but a second should be tried (Carlat D 2007.) After this, several different augmentation and treatment strategies have been explored (Holzheimer P, Mayberg H 2010, *Harvard Mental Health Letter* Dec 2010):

- Augmentation with second-generation antipsychotics – modestly effective but problematic side effects cause adherence problems
- Augmentation with T3 hormone or lithium – 25% response rate with either but significant side effects and ongoing blood monitoring for lithium
- Augmentation with omega-3 fatty acids - weak, but positive evidence
- Augmentation with SAMe – weak but positive evidence, expensive
- Augmentation with folic acid – weak evidence, females more responsive
- Electroconvulsive therapy (ECT) – remission rates of 50-60% but high relapse rate
- Repetitive transmagnetic stimulation (rTMS) – very low response rates, maintenance data unknown, expensive
- Vagus nerve stimulation (VNS) – does not separate well from placebo and has a high relapse rate, expensive
- Deep brain stimulation – promising but little data, requires neurosurgery

**Other Treatments**

- Aerobic exercise - 30 minutes/day
- Light therapy – generally useful only for seasonal affective disorder
- Sleep deprivation - works temporarily. Second half of the night deprivation is as effective as whole night
- Psychosurgery - no controlled studies, a very last resort

Free depression outcome scale:

Patient Health Questionnaire-9 (PHQ-9)

[www.depression-primarycare.org/forms/phq_9/](http://www.depression-primarycare.org/forms/phq_9/)
**BIPOLAR DISORDER**

Bipolar disorder has received an enormous amount of attention over the last ten years. Whereas the illness used to be considered primarily a disorder of mood swings, it is now thought of as a lifelong illness that creates a vulnerability to depressive and manic episodes and related problems. The nature of this illness is not well understood, but it includes not just episodic mania and depression, but also problems with arousal and catecholaminergic physiology, motivation, impulsivity, and behavioral sensitization in which stressors and substance abuse lead to increased frequency and severity of episodes over time (Swann A 2007.)

**DSM-IV Criteria**

DSM defines Bipolar I Disorder as a disorder in which there has been at least one manic or mixed (mania and depression) episode. There may or may not have been an episode of depression. Bipolar II Disorder is defined by the presence of recurrent depressive episodes and one or more hypomanic episodes.

Mania is defined as:

A) a distinct period of abnormally and persistently elevated, expansive, or irritable mood lasting at least a week

B) 3 of the following (4 if mood is only irritable)
   a. inflated self-esteem
   b. decreased need for sleep
   c. more talkative than usual
   d. flight of ideas
   e. distractibility
   f. increase in goal-directed activity, agitation
   g. excessive involvement in pleasurable activities with a high potential for painful consequences

Hypomania is described with the same criteria as mania, but without significant impairment (DSM-IV.)

**DSM-5 Proposed Revisions**

Major proposed changes in the criteria for mania include the addition of “increased energy/activity” as a core symptom. It is recommended that the word “pleasurable” be removed from g) above. Also, it is suggested that instead of using “mixed episode” as a criteria, that a term “mixed features” be used as a specifier for each mood episode type, manic or depressed, as appropriate. It is recommended that an anxiety dimension and a suicide assessment dimension be used for all mood disorders, as discussed under depression above. Finally, a category is added for youth – Temper Dysregulation Disorder with Dyshoria, as an alternative to bipolar disorder, discussed below (DSM-5 website.)

**Demographics**

Approximately 2.3 million Americans suffer from bipolar disorder. According to NCS-R, the lifetime prevalence of bipolar disorder is 5.1%. The NESARC survey
indicates a lifetime prevalence of bipolar I disorder of 3.3%. Native Americans have the highest incidence. Asians and Hispanics have the lowest.

There is ongoing disagreement as to whether bipolar disorder is overdiagnosed or underdiagnosed.

According to the World Health Organization (1990), bipolar disorder is the sixth leading cause of disability worldwide among people 15-44 years old. There is an enormous economic and social impact from this illness (Kessler et al. 2006.) Suicide is a significant risk in bipolar disorder, the highest of any psychiatric disorder at 20% (NIMH 2000.) As many as 25-50% of clients will make a suicide attempt (Jamison 2000.) Most suicidal ideation occurs during depressed or mixed episodes. Suicidal ideation is also highly associated with comorbid substance abuse.

**Features/Subtypes**

Bipolar disorder is classified according to the severity of the manic state, with bipolar I having full blown mania, bipolar II and cyclothymia having hypomania. Cyclothymia also has milder depressions. Bipolar II does not represent a “milder” illness than bipolar I. Bipolar II is often accompanied by more severe depressions, more chronicity, and more suicidal behavior than bipolar I (Swann A 2007.)

<table>
<thead>
<tr>
<th></th>
<th>Bipolar I</th>
<th>Bipolar II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychomotor</td>
<td>retarded</td>
<td>agitated or retarded</td>
</tr>
<tr>
<td>Sleep</td>
<td>hypersomnia</td>
<td>insomnia/hypersomnia</td>
</tr>
<tr>
<td>Suicide</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>Switching to</td>
<td>mania</td>
<td>hypomania</td>
</tr>
<tr>
<td>Gender</td>
<td>m = f</td>
<td>f &gt; m</td>
</tr>
<tr>
<td>Prevalence</td>
<td>1%</td>
<td>1-2.5%</td>
</tr>
</tbody>
</table>

There is often confusion between bipolar disorder and borderline personality disorder because of the frequent mood shifts seen in the latter. Clinicians rarely have difficulty distinguishing a bipolar I manic episode from borderline mood instability but there is a problem with the differential diagnosis between borderline and bipolar II. It is worth noting that the mood “swings” of borderline clients are usually from depression to anger, almost always precipitated by interpersonal stressors. Mood shifts in bipolar II are usually internally driven and the swing is from depression to euphoria or happiness (Paris J 2010.)

**Mixed States:** In mixed states, there are symptoms of both depression and mania at the same time, either one of which can be more severe than the other. Sometimes mixed state periods can come and go during a single episode of illness. There is also considerable overlap with agitated depression. The mix of depression and impulsivity can be quite lethal in terms of suicide and violence.

Some people with bipolar disorder seem to be more prone to mixed states. Their illness is characterized by early onset, frequent episodes, substance abuse, often head trauma, and early severe stressors (Swann A 2007.)
**Rapid Cycling:** This type exhibits frequently recurring (4+ episodes/yr) treatment resistant depression alternating with hypomaniac/ manic episodes. Rapid cycling is most commonly seen in female clients and with bipolar II disorder. It occurs in 15-25% of clients. Early onset is common. It is believed that antidepressants can initiate rapid cycling. Variations include ultra-rapid (1 day to 1 week), ultradian (<24 hours), and continuous (Altman L et al. 2004.)

**The Manic Phase**
Three stages of mania:
1) hypomania - energetic, extroverted, assertive, hypersexual, self-confident, rapid speech
2) mania - loss of judgment, euphoria, grandiose, paranoid, irritable, hyperactive, ideas of reference, pressured, manipulative, demanding, hyper-religious
3) psychotic - paranoid, hyperactive, assaultive, delusional, labile, depressed, circumstantial, distractible, confused. Delusions are the most frequent psychotic symptoms in mania. Hallucinations are less common. No symptom or cluster of symptoms reliably distinguishes bipolar mania from schizophrenia.

Diagnosing a history of mania is complicated by the fact that many patients do not remember their hypomania episodes as illnesses. A good social history, as well as talking with family members, is crucial.

**Sleep Disruption**
Decreased need for sleep is one of the criteria for mania and the ability to maintain energy without sufficient sleep is not seen in other disorders. Sleep disturbance usually escalates just before an episode, and it is the most common prodrome to mania. An increase in sleep is often associated with the onset of depression. Moderating sleep and social rhythms is often key to preventing relapse (Frank E et al. 2006, 2008.)

**Medical Causes of Mania**
**Drugs:** amphetamines, alprazolam, antidepressants, baclofen, bromide, bronchodilators, calcium, cocaine, corticosteroids, cyclobenzaprine, cyclosporine, decongestants, digitalis, flutamide, isoniazid, levodopa, methylphenidate, metoclopramide, niridazole, phenocyclidine, procarbazine, procyclidine, reserpine withdrawal, thyroid, tolmetin, antidepressants.
**CNS disorders:** brain tumors, cerebrovascular disorder, trauma, epilepsy, Huntington’s, multiple sclerosis, Pick’s, postencephalitic, Parkinson’s, spinocerebellar atrophy, Wilson’s Disease.
**Toxic/Metabolic:** AIDS, calcium, Cushing’s, hemodialysis, hyperthyroidism, influenza, neurosyphilis, postoperative, post St. Louis type A encephalitis, Q fever, lupus, vitamin B12 deficiency.

**Bipolar Depression**
Depression is usually the first, and most frequent episode in bipolar illness, and most of the psychosocial impairment of bipolar disorder is due to depression. Compared with those whose first episode was mania, patients with a depressive onset have a more unstable course, more mixed states, and more suicidal behavior. This may be due in part
to early treatment with antidepressants, which make bipolar disorder worse. Or it may reflect a more severe form of the illness.

The earlier the onset of depression in young people, the more likely the illness is bipolar disorder. In individuals with recurrent depression, “conversion” to bipolar disorder can happen at any time and is more likely with each depressive episode (Swann A 2007.)

**Gender Issues**

There is no gender difference in the incidence of bipolar I disorder. Both genders have onset in puberty, although men may have a slightly earlier onset. There is some evidence that women may have a more depressive course than men, who in turn may have more manic symptoms. Women have more comorbidities (anxiety, obesity, migraine, thyroid), greater relative increase in AODA and suicide, more rapid cycling and mixed states (Suppes T 2006.) Women are more likely to be treated than men and receive treatment earlier in the illness (NESARC).

Polycystic ovary syndrome (PCOS) is a metabolic condition that occurs in 7-15% of reproductive-aged women. These women have elevated androgens, chronic anovulation, insulin resistance, elevated LDL's with low HDL's, and a 3x risk of endometrial cancer. (They do not necessarily have polycystic ovaries.) Women with epilepsy and women with bipolar disorder have a high risk of anovulatory disorders and PCOS. The mood stabilizer valproate is also associated with PCOS (Rasgon N 2006.)

**Pregnancy:** Although 50% of women with bipolar disorder have the onset of symptoms within 1 year of menarche, many are not accurately diagnosed until they have had a child and developed postpartum depression (Swann 2004.) The postpartum period is a high-risk period for women with bipolar disorder for depression, manic, mixed, and psychotic episodes. Postpartum psychosis is a medical emergency (Ketter T 2006.) Stopping a mood stabilizer, particularly abruptly, during pregnancy carries a high risk for recurrence of the illness (Viguera A et al. 2007.)

No psychotropic drugs are known to be safe for pregnancy or breastfeeding, but bipolar disorder itself is also dangerous for pregnancy due to substance abuse, poor self-care and suicide. When prescribing medication for bipolar reproductive-age females, it is important to remember that 50% of pregnancies in the U.S. are unplanned. Different drugs are associated with different risks, including birth defects. Valproate should not be considered a drug of first choice for women of reproductive age, especially if they are not on birth control, due to the high rate of birth defects (Morrell M 2006.)

**Bipolar Disorder in Young People**

Children and adolescents are being diagnosed with bipolar disorder in increasing numbers. From 1996 to 2004, the number of children diagnosed with bipolar disorder has increased by a factor of 6 from 1.3 to 7.3 per 100,000 (Blader J, Carlson G 2007.) The burning question is whether this represents an over-diagnosis of the condition. Currently, there is little agreement on the validity of symptoms such as elated mood and grandiosity in children, the role of irritability, whether symptoms must be episodic, or how to consider subthreshold presentations (Horst R 2009.)

Classically, bipolar symptoms in children follow a cyclic pattern and are as follows:
Mania: hyperactivity, irritability, psychosis/grandiosity, elated/expansive mood, rapid speech/racing thoughts, lack of need for sleep
Depression: personality change, drop in grades, morbid/suicidal, pessimistic, somatic

A young person meeting these criteria would be said to fit the “narrow phenotype.” They would be highly likely to be genetically related to another person with bipolar disorder. They will be likely to continue to have bipolar disorder symptoms as an adult. There is little controversy about this group among clinicians.

DSM-IV does not have a “hallmark” symptom for mania – a symptom that must be present for the diagnosis to be made. A person can be extremely irritable, without grandiosity, and still meet the criteria. Some child psychiatrists believe that chronic severe irritability accompanied by aggression and volatility is the predominant mood state in children with bipolar disorder. Grandiosity and expansive mood need not be present. This is called the “broad phenotype.” There is little evidence that this group will continue to be bipolar as adults.

The difficulty is that irritability is a very non-specific finding. In children, it is seen in oppositional defiant and conduct disorders, depression, anxiety, ADHD, autism, and PTSD. Most researchers consider irritability alone, no matter how extreme, to be inadequate in making a diagnosis of mania in youth (Horst R 2009.)

A second issue concerns how episodic the mood shifts should be. In adults, it is expected that there be clear inter-episode periods of recovery. Child psychiatrists, however, have described children with bipolar disorder who present with chronic, continuous rapid cycling, with low rates of inter-episode remission. Children have also been described with ultrarapid cycling, sometimes with multiple episodes in a day. At this point, however, an episodic course continues to be a reasonable requirement for increasing the probability of an accurate diagnosis (Horst R 2009.) This is confirmed by the Course and Outcome of Bipolar Youth (COBY) study of 413 youths with bipolar spectrum disorder. These young people had episodic illness with depressive and mixed symptoms with rapid mood changes (Brimaher B et al. 2009.)

Who are the children with explosive, aggressive behavior without other classic symptoms of mania? They are children who are described by parents as having “mood swings,” who have explosive outbursts of extreme intensity and duration. They are not particularly at risk for developing becoming bipolar adults. They are more likely to have problems with depression and anxiety as adults. Their parents are less likely to have psychopathology than parents with bipolar children.

Some researchers suggest a new category – severe mood dysregulation – to categorize children with chronic presentation, no discernable episodes, sometimes overlapping ADHD symptoms, and severe rage attacks. These children look very much like a combination of ADHD and oppositional defiant disorder (Brotman M et al. 2007.) The DSM-5 workgroup has proposed a similar disorder – Temper Dysregulation Disorder with Dysphoria – to try to capture the distinction of children who have rages but not mania (DSM-5 website.)

A further complication of diagnosis is that up to 80% of children with bipolar disorder will also have ADHD. Distinguishing between the two is difficult. Grandiosity, elated mood, hypersexuality in the absence of sexual abuse, flight of ideas, decreased need for
sleep, and episodic presentation seem to distinguish between bipolar disorder and ADHD (Horst R 2009.)

**Treatment**

Treatment should involve both psychotherapeutic and psychopharmacologic interventions. Family therapy with an emphasis on education and managing symptoms and treatment adherence is crucial. Studies regarding efficacy of medication in young people are very limited.

For ADHD, stimulants remain the treatment of choice. There is also evidence that stimulants may benefit some children with disruptive behavior disorders (oppositional defiant and conduct disorder) and bipolar disorder (Carlson G 2009.) The only medications approved for bipolar disorder in young people at this point are lithium (12 and up), and several second-generation antipsychotics for manic states (10-17.) Probably all of the atypical antipsychotics are effective for mania, but all cause significant weight gain. None of the anticonvulsants are useful (McVoy M, Findling R 2009, Harvard Mental Health Letter 2009.)

In summary, if the young person has classic symptoms of bipolar disorder, treat with a second generation antipsychotic. If they have severe ADHD with aggression (severe mood dysregulation, ADHD + a disruptive behavior disorder), treat with a stimulant, possibly adding risperidone (approved for treatment of irritability associated with pervasive developmental disorders.)

**Genetics**

Bipolar disorder is genetically linked. If one parent has bipolar illness, chances are 1:7 that their child will. Despite this clear genetic relationship, there are relatively few studies of the heritability of bipolar disorder. Part of the problem lies in the numerous subtypes of the disorder, and part of the problem is the categorical distinction between major depression and bipolar disorder (the presence of one manic episode) that confounds all genetic studies of depression since the disorders seem to be clearly related at some level. One study estimates heritability at 73%. Because the same study came up with a similar estimate for unipolar depression, the question arose as to whether the genetic vulnerability represented the same disease, with bipolar disorder being a more severe variant of major depression. If this is the case, what determines the development of bipolar vs. unipolar illness? There is no current research that answers this question, although it is fairly well established that non-shared environmental effects are more important than family environment (Jang K 2005.)

**Comorbidity with Substance Abuse**

Bipolar disorder is the affective disorder most commonly associated with substance abuse. 23.6% of bipolar clients have an alcohol use disorder, 12.9% have a drug abuse disorder, and 37% have nicotine dependence (NESARC).

**Odds ratio of substance abuse in bipolar disorder (NESARC):**

<table>
<thead>
<tr>
<th>Substance</th>
<th>BPI</th>
<th>BPII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol abuse</td>
<td>3</td>
<td>3.9</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>5.5</td>
<td>3.1</td>
</tr>
</tbody>
</table>
Bipolar clients are unreliable reporters of substance use. They also underreport psychiatric symptoms. Substance abuse complicates bipolar disorder and its diagnosis (Vornik L, Brown S 2006.)

1) Stimulants may precipitate a manic episode. Chronic use of CNS stimulants like amphetamine and cocaine cause euphoria, decreased appetite, increased energy, grandiosity, and sometimes paranoia that mimics mania.

2) Treatment adherence declines with more frequent hospitalizations and lower rates of recovery

3) Patients report a lower quality of life than those who do not abuse substances

4) Substance abuse is related to higher mortality by suicide (15-19%) and other causes.

Treatment of one does not resolve the other, but controlled bipolar disease usually leads to the diminishing of substance abuse symptoms.

**Natural History of Bipolar Disorder**

Onset can occur at any time, from childhood to old age, but most commonly in adolescence. Early onset of depression, anxiety disorder, substance abuse, and behavioral disorders are all linked to eventual diagnosis of bipolar disorder in those with a family history of bipolar disorder. (Swann A 2007.)

30% of bipolar clients have both manic and depressive episodes, 32% have mixed manic and depression, 22% have only manic episodes, and 10% have only mixed episodes. Depression is the most frequent episode. Depressive episodes last longer (25.4 weeks) than manic episodes (5.5 weeks). 48.5% of bipolar clients will have an anxiety disorder and 70.8% will have a personality disorder (NESARC).

Severe psychosocial stressors appear more important in the first episode than latter episodes - each episode requires less stress to occur. 90% of clients who have one manic episode will have another. Two years after remission, even with excellent treatment 49% will have relapsed. The interval between episodes will usually diminish and episodes will become more treatment resistant (Perlis R 2006.)

Since 1990, there is evidence that clinicians are seeing more cycling, mixed states, and lithium resistance. Age of onset seems to be declining and there is increased prevalence in younger people. This corresponds with a 10x increase in prescriptions for antidepressants (Ghaemi S 2008.)

Bipolar disorder is associated with high morbidity and mortality. Medical problems associated with bipolar disorder include cardiovascular disease, diabetes, obesity, and thyroid disease. In addition, risk factors associated with nicotine use, alcohol and drug abuse, anxiety and eating disorders lead to early onset of medical diseases (Roshanaei-Moghaddam B, Katon W 2009.)

**Diagnosis**

A recent review of 85 sequential admissions to a dual diagnosis unit who were diagnosed with bipolar disorder and substance abuse found that 67% were misdiagnosed as bipolar. The misdiagnosis occurred because clinicians were confused by the mood
instability caused by substance abuse, and failed to carefully evaluate for the presence of clear manic episodes when the patients were abstinent (Goldberg J et al. 2008.)

Because of the importance of identifying bipolar disorder correctly and therefore, not exposing the patient to ineffective or dangerous therapy (e.g. antidepressants), it is important to do a careful evaluation looking for the presence of manic episodes, and a cyclic pattern in the illness. A life chart is a good way to do this. Life chart templates are available on the web at NIMH. Also, consider non-manic markers of the illness. These include (Phelps J 2007):

- Family history of mood and substance abuse problems
- Early age of onset
- Illness course over time
- Poor response to antidepressants in the past

**Treatment**

The prevention of episodes improves long-term prognosis. The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) is a 7-year NIMH study with 4,361 participants at 20 sites to provide optimum treatment (Perlis 2006). The early findings from STEP-BD indicate that with state-of-the-art care, 58.4% of clients will achieve recovery, but 5% of clients will relapse each month, 48.5% within 2 years, and that 80% of the relapses will be to depression. One of the strongest predictors of relapse is residual symptoms. There is no evidence that antidepressants improve recovery, either with or without mood stabilizers.

Trying to determine the best treatment for bipolar disorder is one of the most complex clinical challenges in psychiatry. Every month brings new information, often of questionable usefulness. The difficulty so far has been that the three aspects of bipolar disorder – mania, depression, and relapse – all seem to respond differently to different treatments. The following is a general summary based on a synthesis of many trials (Carey T et al. 2008, Schneck C et al. 2008, Goldberg J et al. 2007):

**Mania and relapse of mania (first 3 months after treatment for mania):** Lithium remains the gold standard for the treatment of mania. It has a large research base and also has suicide prevention effects. It is less effective in mixed mania and rapid cycling. It may work better early in the illness and may lose effectiveness if it is stopped and restarted several times. It does not work as well when there is comorbid substance abuse.

The first and second-generation antipsychotics all treat manic episodes. First generation antipsychotics may cause depression.

The anticonvulsants divalproex and carbamazepine are effective, as is electroconvulsive therapy. There is no good evidence of manic response to topiramate, gabapentin, lamotrigine, or oxcarbazepine, although lamotrigine may be helpful for mixed episodes.

**Bipolar depression and relapse of depression (first 3 months after treatment):** The newer antidepressants cause switching into mania from a depressive episode about 20-30% of the time. This is half the rate of switching caused by older antidepressants (TCA’s, MAOI’s.) If there is also treatment by a mood stabilizer, switching rates are reduced further. Bipolar II patients switch to hypomania half as frequently as bipolar I patients.
switch to mania. STEP-BD does not recommend using antidepressants at all. Some other studies do, if there is concomitant use of a mood stabilizer.

Lithium, lamotrigine, quetiapine, and olanzapine (and olanzapine+fluoxetine) have been shown to have some efficacy in treating bipolar depression. All other medications are either unproven or ineffective.

**Maintenance (1 year after episode):** The most robust evidence is for lithium, olanzapine for the prevention of mania, and aripiprazole for the prevention of mania.

Carbamazepine, valproate, and lamotrigine each have a few studies showing efficacy in maintenance, but the quality of the evidence is low. There seems to be little reason to choose one over any of the others. Efficacy for bipolar II disorder is uncertain. There is some suggestion that the calcium channel blocker verapamil and omega-3 fatty acids may be alternative treatments for prophylaxis during pregnancy.

There is fairly strong evidence that long-term treatment with antidepressants not only does not protect from further depressive episodes, but also destabilize the illness, even in the presence of a mood stabilizer. Antidepressants, if used at all, should only be used short term.

Most people with bipolar disorder end up taking at least two medications for their illness, and we know very little about using combinations of drugs.

**Non-Pharmaceutical Interventions**

Cognitive behavioral therapy and psychoeducation have been shown to prevent relapse. Certain common principles can be described (Roman B, Gillig P 2006, Frank E et al. 2006):

1) Identify signs of relapse and make plans for an early response
2) Use education to increase the likelihood of adherence
3) Practice stress management and problem solving
4) Maintain regular rhythms for exercise, sleep, and eating
5) Keep negative expressed emotion in the family at a minimum
6) Don’t make important decisions while symptomatic

A review of these various strategies indicates that early recognition of mood symptoms and treatment adherence have the strongest effect in preventing manic relapse. Cognitive and interpersonal coping strategies have the strongest effect on preventing depressive relapse (Miklowitz D 2008.)

**Treatment Adherence**

Rates of non-adherence to treatment for bipolar disorder range from non-adherent (21.4%) to partially adherent (24.5%) in one large VA study (Sajatovic M et al. 2007.) People with bipolar disorder often have limited insight. This isn’t denial or wish to distort the facts. There is something in the illness that distorts the way they see themselves and the world. Regardless of the reason, the best predictor of a poor outcome is poor treatment adherence.
BIBLIOGRAPHY


Benedeck D, Ursano R. Posttraumatic Stress Disorder: From Phenomenology to Clinical Practice. Focus (Spring 2009) 7:2;160-175.


Breslau N, et al. Intelligence and Other Predisposing Factors in Exposure to Trauma and Posttraumatic Stress Disorder. *Arch Gen Psych* (Nov 2006) 63;1238-1245.


Davis K et al. A Focus Group Analysis of Relapse Prevention Strategies for Persons With Substance Use and Mental Disorders. *Psych Serv* (Oct 2005) 56:10;1288-1291.


Morrell M. Effects of In Utero Exposure to AED’s on Morphology and Neurodevelopment. *CNS Spect* (May 2006) 11:5; (Suppl 5) 9-10.


Suppes T. Gender Differences in Bipolar Disorder. CNS Spect (May 2006) 11:5; (Suppl 5) 2-4.


Xie H et al. Substance Abuse Relapse in a Ten-Year Prospective Follow-up of Clients With Mental and Substance Use Disorder. *Psych Serv* (Oct 2005) 56:10; 1282-1287.