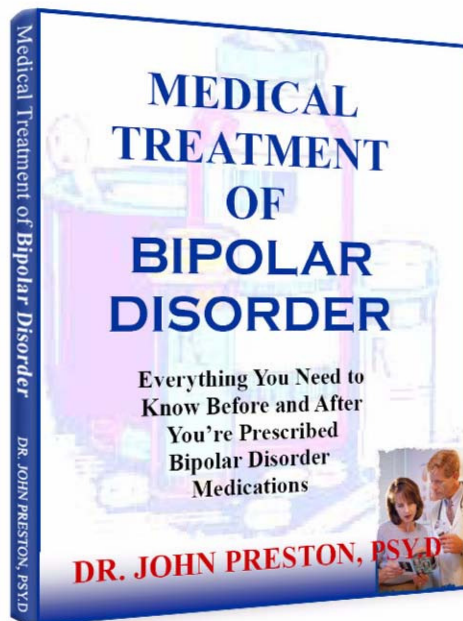


The Medical Treatment of Bipolar Disorder

**Everything You Need to Know Before and
After You're Prescribed Bipolar Disorder
Medications**



By John Preston, Psy.D., ABPP

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Medical Treatment of Bipolar Disorder
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This e-book discusses the medical treatment of bipolar disorder in a detailed fashion presenting current treatment guidelines. It is followed by an appendix that lists medications commonly used to treat bipolar disorder addressing dosing, side effects, special precautions, required laboratory tests, abuse potential and safety during pregnancy and breast feeding. To the best of my knowledge recommended doses and side effects listed in this book are accurate. However, this is meant to be a general reference only, and should not serve as a guideline for prescribing medications. For prescribers, please check with the manufacturer product information sheet or the PDR for any changes in dosage schedules or contraindications. All brand names mentioned are registered trademarks. This publication is sold with the understanding that the publisher/author is not engaged in rendering psychological, financial, legal, medical, or other professional services. If expert assistance or counseling is needed, the services of a competent professional should be sought.



About the Author

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Bipolar Spectrum Disorders Introduction and Diagnostic Issues

Bipolar disorder is a common type of mood disorder affecting between 3.5-6% of the population (lifetime prevalence: Akiskal, et al. 2000). Previously it was thought that the lifetime prevalence was 1-1.5% of the population, however, more recent epidemiological studies and new, refined diagnostic criteria have revealed the higher prevalence rate. It is now appreciated that there are a number of different types of bipolar disorder and together these are often referred to as bipolar spectrum disorders. Bipolar disorders are a group of genetically transmitted illnesses that result in recurring episodes of depression and mania or hypomania (see below). This is a life-long disorder, which requires on-going medical treatment. Mood-stabilizing medications can effectively reduce episode severity and frequency; however there is currently no cure. Sixty percent of manic episodes are classic manias, 40% are referred to as dysphoric or mixed mania.

Symptoms of Classic Mania

- Euphoria or an inflated sense of self-worth
- Restlessness, agitation, hyperactivity
- High level of energy
- Decreased need for sleep (e.g. sleeping 3-4 hours per night, yet without daytime fatigue)
- Racing thoughts and rapid, pressured speech
- Poor judgment and impulsive behavior, e.g. spending enormous amounts of money, driving fast/recklessly, marked alcohol or drug abuse, promiscuity and engaging in unsafe sex
- Psychotic symptoms can occur such as hallucinations and delusions

Symptoms of Dysphoric or Mixed Mania

- Symptoms in common with classic mania
- Agitation, restlessness, hyperactivity
- Decreased need for sleep
- Racing thoughts and rapid, pressured speech
- Psychotic symptoms can occur
- Marked irritability
- Negative, pessimistic thinking
- Feelings of worthlessness
- Suicidal ideas

Hypomania is a milder version of mania that typically involves much less intense mood symptoms. The duration of hypomania is often only 1-4 days and is frequently not noticed as being a sign of illness by the person experiencing hypomania (although most times family members are more clearly aware of the mood changes and increased energy). During some hypomanias the person can feel highly motivated and productive, is witty, gregarious and “up beat” (although there is often underlying irritability). One very common sign of hypomania is a decreased need for sleep with no daytime fatigue. DSM IV required a minimum of 4 days of hypomania to diagnose bipolar II disorder, however the most common presentation of hypomanias is 2-3 days; thus the higher prevalence rates of this disorder (revised diagnostic standards reflecting these new findings are slated to appear in DSM V).

There are six subtypes of bipolar disorder:

1. **Bipolar I:** severe manic (classic or dysphoric) and depressive episodes (often with periods of normal/euthymic mood between episodes).
2. **Bipolar II:** characterized by frequent, severe and prolonged depressions with periodic, brief episodes of hypomania, a normal/euthymic mood can occur between episodes, but often during these in-between times there is a low-grade/mildly depressed mood. Judd, et al. (2003) studied the course of bipolar II disorder for a period of thirteen years and found that 15% of days were spent in major depressions, 40% in minor depressions and only 1.4% in hypomanias.
3. **Bipolar III:** severe, highly recurrent unipolar depressions with no manias or hypomanias. However if the patient is treated with certain drugs (e.g. stimulants, antidepressants or steroids) there is a likelihood that the medication will provoke a switch into mania or hypomania, and from that point on, manic episodes may begin to occur. A more common outcome is simply that standard antidepressant medications may be ineffective unless combined with a mood stabilizer. This subtype of bipolar is fairly rare, and is also characterized by early onset depressions (in childhood or early adolescence) and a positive family history of bipolar disorder.
4. **Pre-pubertal or early adolescent bipolar disorder:** likely to be a more severe variant of bipolar disorder. Manias tend to be non-episodic (i.e. more chronic) and 95% are of the dysphoric variety.
5. **Cyclothymia:** mild depressions and hypomania (note: this less severe version of bipolar can become worse with time and most people with cyclothymia eventually convert to Bipolar I or Bipolar II).
6. **Schizoaffective disorder:** with characteristics of both bipolar disorder and schizophrenia.

Rapid Cycling

A complication of bipolar disorder affecting about 20% of sufferers is called rapid cycling. This represents a time limited worsening of the illness in which episodes occur with greater frequency (i.e. 4 or more episodes of depression, mania or hypomania per year). Most cases of rapid cycling last a few months to a year and a half and then subside. The most common cause for rapid cycling is substance use/abuse. If more frequent episodes are evident it is referred to as ultra-rapid cycling or ultradian cycling bipolar.

Untreated or poorly treated bipolar illness leads to disaster. Careers and marriages are ruined, physical health problems abound, and there is a high rate of suicide (15% lifetime risk). If not treated, most cases of bipolar disorder become progressively worse, likely owing to kindling effects. The sooner this illness can be diagnosed and properly treated, the better.

Treatments for Bipolar Disorder

Although the focus of this e-book is on psychopharmacology, we will also briefly address adjunctive treatments. Medication treatment alone is never adequate to fully control bipolar disorders. Treatment must have a two-pronged focus: bringing to an end the current manic or depressive episode and relapse prevention. With proper medical treatment most people can experience a marked decrease in episode frequency and severity.

Life-Style Management

People with bipolar illness have a very unstable and fragile neurobiologic mechanisms for affect regulation and extreme emotional lability and mood episodes can be triggered by a number of environmental, psychological and physiological stressors. It is especially important to regulate ones lifestyle closely: without this, medical treatments often are only partially effective (Malkoff-Schwartz, et al. 1998).

Most important are:

- Maintain regular bed times and awakening times. Such regularities in sleep patterns are crucial.
- Avoid substance abuse and alcohol use/abuse like the plague (substance abuse is very common in bipolar disorder and often significantly aggravates the illness.)

- Avoid sleep deprivation, shift work and crossing time zones.
- Avoid or greatly minimize caffeine use since it can significantly disrupt the quality of sleep.
- Keep the amount of bright light exposure (e.g. sunlight) and the amount of physical exercise stable year round.

Medication Treatments: General Considerations General references:

- Goodwin, F.K. and Jamison, K.R. (2007) Manic-Depressive Illness. Second edition. Oxford: Oxford University Press
- Ketter, T.A. (2005) Advances in the Treatment of Bipolar Disorder. American Psychiatric Publishing, Washington, D.C.
- Preston, O'Neal and Talaga (2008) Handbook of Clinical Psychopharmacology for Therapists. New Harbinger Publishers, Oakland
- World Health Organization: International Psychopharmacology Algorithm Project: www.IPAP.org

The choice of medications used to treat bipolar disorder depends on the mood state the patient is currently experiencing (i.e. whether it is mania or depression). In addition, the medication choice always must take into consideration the ultimate goal of preventing recurrences (i.e. maintenance treatment). Currently there are eleven medications that are approved by the Food and Drug Administration (FDA) for the treatment of bipolar disorder: Lithium, Thorazine, Depakote, Lamictal, Symbyax, Risperdal, Seroquel, Abilify, Geodon, Equetro, and Zyprexa. However, a number of other highly effective drugs are in common use. The use of medications not approved by FDA for the treatment of certain conditions is referred to as “off label use”... and it must be emphasized that off label use of medications is very common practice in every branch of medicine.

Recent surveys reveal that in the United States only 30% of people being treated for bipolar disorder are taking just a single drug (i.e. mono-therapy); thus, this is the exception and not the rule. On average, most people being treated are taking 3 or 4 medications simultaneously. The reason for this is simple: medication combinations are often clearly superior to mono-therapy for most people suffering from bipolar disorder.

All medications have side effects and unfortunately the drugs used to treat bipolar disorder are known to produce significant side effects for the majority of people being treated. Poor compliance is seen in at least 50% of those treated and the primary reason for such poor compliance is a difficulty with long-term tolerability. Side effects, at times are mild and easy to

tolerate. But often they are more noticeable and in rare instances they can be dangerous. In every single case, once the current mood episode has subsided, people with bipolar disorder must continue to take certain medications to help prevent or reduce the likelihood of recurrence. This is absolutely essential! However, some estimates suggest that as many as 90% of people who start medical treatment for bipolar disorder will recover from their first episode, but within weeks or several months, will stop taking the medications (against medical advice). The most common reasons for doing so are understandable:

1. Patients are plagued by unpleasant side effects and/or

2. They conclude that the episode they experienced is not really bipolar disorder, but was just a single episode and that there will not be recurrences.

This conclusion is borne of hopefulness that this is not really going to be a recurring illness (Pope and Scott, 2003). These reasons for discontinuing the medication are entirely understandable, but they almost invariably lead to the emergence of another episode (this may occur within a few months following the initial episode, but more commonly occurs several years later). Somewhat better compliance rates (i.e. 50% noted above) are seen after two or more episodes when it becomes increasingly clear that mood swings are, in fact, recurrent.

For many patients, taking medications when you feel well is counter-intuitive. However, the picture is clear that bipolar disorder is almost always recurring, and over a period of time there is a tendency for episodes to become increasingly severe and harder to treat. There is also research that reveals that untreated or poorly treated bipolar illness can ultimately result in lasting damage to the nervous system.

During mood episodes there are often toxic levels of certain neurotransmitters (e.g. glutamate) and stress hormones (e.g. cortisol) that are released that can damage nerve cells. Fortunately, studies also reveal that on-going treatment with some bipolar medications may prevent this from happening (Dreven, et al. 2002). In a very real sense, some of these drugs (e.g. lithium and Depakote) appear to be “neuro-protective.”

Many side effects can be managed by dosage adjustments or by switching to other medications. This is one reason that most times people will need to go through systematic trials on a variety of medications to determine which ones are the most effective and also which drugs are best tolerated for any given individual. Every effort should be made to find the right medication or

medication combinations in an attempt to minimize side effects. And this is often something that can be accomplished. However, it is often the case that it takes a year of trials on various medications to finally discover the specific medication or medication combinations that will be effective and that will be best tolerated.

This is the rule and not the exception. It is very important for patients to not feel too discouraged if the first medications used are less than optimally effective or that they have problematic side effects.. A sign of a competent and compassionate psychiatrist is their willingness to be persistent in carrying out systematic medication trials until the best treatment is finally identified. Sometimes side effects can be minimized, however, many people end up having to find ways to tolerate some side effects. Obviously, this is not pleasant, but is ultimately necessary to reduce or eliminate severe mood swings. And unfortunately, a very small number of people are simply unable to tolerate any bipolar medications.

Medication Treatments: What are Realistic Outcomes?

Bipolar disorder is like a number of other chronic medical conditions (such as diabetes, asthma, arthritis, etc.). It is not a condition that can be cured by currently available medications. However, the medications discussed below are effective in relieving many of the more serious symptoms of bipolar illness and often can reduce the frequency of mood episodes for most people, if patients receive appropriate treatment and stick with it. Good news and not so good news: with aggressive, appropriate, and on-going medication treatment, and if the treatment is started during the first or second mood episode, about 30% of people will not experience major recurrences (Bowden and Singh, 2005). That is, in about one out of five people the medications are successful in preventing relapses (please note: if the first appropriate medical treatments begin after the second episode, typically treatment becomes somewhat more challenging and the outcomes are not quite as robust). However, for the majority of other people receiving treatment, the recurrence rates for severe episodes can be reduced by about 75% and hospitalizations can often be avoided. Subsequent episodes that do occur tend to be mild depressions and hypomanias (Gitlin, 2002). This all assumes adequate compliance with medication treatment.

Medication treatments are far from perfect, but it is the kind of effectiveness that can substantially reduce suffering, keep families together, avoid catastrophes, and save lives.

Bipolar Medications

There are six major classes of psychiatric medications that have been found to be effective in treating various symptoms of bipolar disorder. Generic and brand names (registered trademarks) and typical adult daily doses are listed below. (note: this information is for general reference and should not be used as a guide for prescribing. Prescribers must see the PDR or drug package insert for specific information on dosing and contraindications).

Lithium: Eskalith, Lithonate 600-2400 mg

Therapeutic blood levels:

Acute mania: 0.8-1.2

Maintenance and Relapse prevention: 0.6-0.8

Anticonvulsants:

Divalproex	Depakote	750-1500 mg
Carbamazepine	Tegretol	600-1600 mg
	Equetro	
Oxcarbazepine	Trileptal	1200-2400 mg
Lamotrigine	Lamictal	50-500 mg
Topiramate	Topamax	50-300 mg

Anticonvulsant: Therapeutic blood levels

Depakote blood levels: 50-125 mcg/ml

Tegretol blood levels: 4-12 mcg/ml

Trileptal blood levels: not yet established

Lamictal blood levels: not necessary to monitor

Topamax blood levels: not yet established

Atypical Antipsychotics: the name commonly used for a class of newly developed antipsychotic medications that treat psychotic symptoms and as well as anti-manic effects as well.

Olanzapine	Zyprexa	5-20 mg
Risperidone	Risperdal	4-10 mg
Ziprasidone	Geodon	60-160 mg

Antipsychotics contd..

Aripiprazole	Abilify	15-30 mg.
Quetiapine	Seroquel	150-400 mg (sometimes used in doses up to 750 mg)
iloperidone	Fanapt	12-24 mg

Seroquel has antidepressant effects in bipolar depression.

Antidepressants:

Fluoxetine	Prozac, Sarafem	10-80 mg
Bupropion	Wellbutrin	50-400 mg
Sertraline	Zoloft	50-200 mg
Paroxetine	Paxil	20-50 mg
Venlafaxine	Effexor	75-350 mg
Nefazodone	Serzone	100-500 mg
Mirtazapine	Remeron	15-45 mg
Citalopram	Celexa	10-60 mg
Escitalopram	Lexapro	5-20 mg
Duloxetine	Cymbalta	20-80 mg
Atomoxetine	Strattera	60-180 mg
Olanzapine-fluoxetine combination	Symbyax	

Symbyax not a class in itself, but rather a combination drug (antipsychotic and antidepressant) FDA approved for the treatment of bipolar depression.

Calcium Channel Blockers

Verapamil Calan, Isoptin 360-480 mg

Benzodiazepines: also referred to as minor tranquilizers or anti-anxiety drugs.

Diazepam	Valium	4-30 mg
Clonazepam	Klonopin	0.5-2 mg
Lorazepam	Ativan	2-6 mg
Alprazolam	Xanax	1-4 mg

Benzodiazepine Sleeping Pills:

Temazepam	Restoril	15-30 mg
Triazolam	Halcion	0.25-0.5 mg
Zolpidem	Ambien	5-10 mg
Zaleplon	Sonata	5-10 mg

The following two sleeping medications are non-benzodiazepines and appear to not be habit forming.

Eszopiclone	Lunesta	1-3 mg
Ramelteon	Rozerem	4-16 mg

In addition there are a number of other medications that are occasionally used, including some experimental drugs (e.g. Omega-3 fatty acids) and over-the-counter products (St. John's Wort and SAMe). This monograph will provide a brief overview of standard treatment guidelines that have been developed primarily by the American Psychiatric Association (Hirschfeld, et al., 2002) and also includes more updated material from the American Psychiatric Publishing company (Ketter, 2005).

Targets for Medication Treatment

The following provides a brief overview of standard treatment guidelines that have been developed primarily by the American Psychiatric Association (Hirschfeld, et al., 2002) and also includes more updated material from the American Psychiatric Publishing company (Ketter, 2005) and Goodwin and Jamison (2007).

There are three primary goals in medication treatment of bipolar disorder: 1) dealing with potentially dangerous emergency issues (e.g. extremely severe agitation or suicidal impulses), 2) resolving the current episode (whether mania or depression), and 3) relapse prevention. The choice of medications used will always be influenced by these goals. In addition, the medication choice will also be dictated by the need to minimize side effects.

Getting Started with Medication Treatment

Emergency Medication Treatments and Laboratory Tests: Sometimes there is a need for emergency treatment; for example if a person is experiencing a sudden onset of severe manic agitation (which may include extreme restlessness, impulsivity, severely impaired judgment and/or aggression) or serious suicidal impulses during a depression. At such times acute medical treatment may be necessary.

When there is such a crisis hospitalization almost always is necessary. Emergency medical treatments for agitation include the use of either benzodiazepines (anti-anxiety tranquilizers, such as Ativan, Klonopin, and Valium) or antipsychotic medications (such as Zyprexa, Risperdal, Seroquel, or Haldol). These two classes of drugs are often very effective in rapidly

reducing agitation. On occasion there is a need for emergency medical treatment for very severe depression (where there is either a grave suicide risk or refusal to eat accompanied by severe weight loss).

In such cases ECT (electro-convulsive therapy; “shock” treatments) can be successfully used. ECT is also very effective for the emergency treatment of severe mania.

If the situation is not extremely urgent, then it is commonplace to order some pre-treatment laboratory tests. This is done for two purposes. The first is to rule out the possibility that the mood symptoms may be caused by a primary medical illness (such as thyroid disease). The other reason has to do with the tendency for many of the bipolar medications to cause significant changes in a variety of bodily functions. Some bipolar medications are known to affect a broad range of organs and glands especially when they are taken for prolonged periods of time.

Thus typically, pre-treatment labs include measures of cardiac, kidney, liver and thyroid functioning as well as a complete blood count. Laboratory monitoring of blood levels of certain medications may also be required. This is routinely done for the following mood stabilizing medications: lithium, Tegretol, Equetro (a long-acting version of carbamazepine), Trileptal, and Depakote.

Treatment Guidelines: Mania

Several classes of psychiatric medications have been found to be effective in treating acute manic episodes:

- Lithium

- Anticonvulsants:

Depakote, Tegretol, Equetro, Trileptal, Topamax

- Antipsychotic medications:

Zyprexa, Risperdal, Abilify, Geodon, Seroquel, Invega, Fanapt, Haldol (the last of these is an older generation antipsychotic that is still sometimes used)

- Calcium Channel Blockers:

Verapamil (generally only used for treating mania in pregnant women because it is the safest mood stabilizer for use during pregnancy)

- Benzodiazepines (minor tranquilizers):

Benzodiazepines and antipsychotic medications are given initially to reduce agitation, which

can often be achieved within a few hours (note: for reasons that are not well understood, the tranquilizer, Xanax can sometimes aggravate mania, and thus is generally not used to treat acute mania).

The anti-manic medications (e.g. lithium and anticonvulsants) typically require 7-10 days of treatment before you see an onset of action and symptom reduction. Once symptoms begin to be reduced, continued treatment for several weeks will often be necessary to eliminate acute manic symptoms. As noted earlier, most people will ultimately be treated with 3 or 4 medications simultaneously to achieve the best outcomes.

There are three stages in the medical treatment of mania

1. Reduce extreme agitation (the goal is to get agitation under control within a few hours). Severe agitation can be dangerous to the patient as well as to others around them and this must be addressed as soon as possible.
2. Reduce core manic symptoms such as restlessness, sleeplessness, rapid speech, flight of ideas, paranoid ideas, impaired judgment, etc.
3. Begin treatment for relapse prevention.

Stage One: As mentioned above, antipsychotic medications and benzodiazepines are the best medications for treating acute agitation; they quickly produce substantial sedation, calming, or sleep. It is important to note that although antipsychotic medications do successfully treat psychotic symptoms (such as hallucinations) the more recently developed drugs (i.e., atypical antipsychotics) have been found to be effective medications used to treat mania. Most anti-manic medications require the 7-10 day period of time before symptom reduction, but with one notable exception: the anticonvulsant, Depakote, when given in large doses, can begin to show anti-manic effects in about 4 days.

Once severe agitation has subsided, often benzodiazepines are gradually reduced and then within a few days are discontinued. This may also be true for antipsychotic medications. However, there are times when antipsychotic drugs may continue to be used for a more prolonged period of time. During stage one of treatment, as mentioned above, a number of lab tests are often done to monitor the early effects of the drugs.

Stage Two: The choice of medications used to treat core symptoms of mania is important and often complex. As noted above, there are several different types of mania and a considerable amount of research has been done to discover which medications are best suited for treating particular subtypes of mania. Dozens of large-scale research studies have been conducted in recent years and specific treatment guidelines have been developed that are very useful in helping physicians to decide on initial medication choices (see below). However, the fact is that each person will have a number of factors unique to them that will influence the choice of medications, such as age, gender, body weight, history of allergies to medications, liver metabolism rate, the presence or absence of other medical conditions and other medicines being used to treat such conditions. Patients must anticipate that it is extremely common for psychiatrists to make initial medication choices, begin treatment and then during the following weeks or months make what are often frequent changes in the doses or medications prescribed. There is an important reason for emphasizing this. Many times people being treated for bipolar illness or their family members become worried as they begin to encounter side effects, or they must go through what seems like an endless number of lab tests or changes in medications or medication doses. Many people become concerned that these medication changes suggest that their doctor may not be competent or that their case of bipolar is especially treatment-resistant. This then can lead to discouragement and feelings of pessimism. Here is the truth: the pathway to recovery and good outcomes, more often than not, is complicated.

The rule, not the exception is that people will be tried on several if not many medications in the search for the right drug or medication combinations. It is so important to help patients understand this and not conclude that the frequent changes in medications are necessarily a reason for concern.

The fact is that bipolar disorder is challenging to treat and often requires a considerable amount of time systematically trying various medications before the right medications combinations are found.

“Classic Mania” (with euphoria, expansiveness, up-beat mood, irritability, etc.) has been found to respond best to treatment with lithium or Depakote (other anticonvulsants or atypical antipsychotic medications often can treat classic mania, but in head-to-head comparisons, lithium and Depakote appear to be the best first-line medications for this type of mania). Generally during stage two of treatment, especially if this is a person’s first episode of mania, just one of these medications will be prescribed. Assuming that the medication is tolerated (i.e. that side effects are mild or manageable) treatment will continue for a period of several weeks. As mentioned earlier, 70% of people being treated for bipolar disorder ultimately must take two

or more medications at the same time to adequately treat mania. Thus it is possible that the one medicine initially prescribed may be tolerated and may eventually be effective. Decisions to increase the dose or to change or add another medication in the ensuing weeks will depend on tolerability, effectiveness, and co-morbidity. Since there are always possible drug-drug interactions, then generally the recommended approach is to first optimize treatment with one medication (which means to progressively increase the dose while always being watchful for the emergence of side effects). What is hoped for is that the first signs of symptomatic change will occur during the first 7-10 days and that symptomatic improvement will continue to unfold over the next few weeks. Just how long it takes to fully resolve a manic episode varies from one individual to another.

Should side effects be significant, typically there will be either a dosage adjustment or possibly a change to another medication. If side effects are mild to moderate and tolerable, but there is only partial improvement in symptoms after several weeks of treatment, then a decision will be made to either change to a different medication or to add another medication (the addition of medications is commonly referred to as augmentation). Medications typically used for augmentation include anticonvulsants and/or antipsychotic medications.

Dysphoric or Mixed Mania: (agitation, decreased need for sleep, rapid speech, feelings of despair, hopelessness, etc.). There is some controversy regarding the treatment of dysphoric mania. However, most experts agree that the best first-line medication is Depakote. Many people experiencing dysphoric mania do have positive responses to lithium as a mono-therapy. The use of just one medication again, initially is the typical strategy and again, before adding or changing medications, the drug used will be optimized. As in the treatment of classic mania, we are looking for the first signs of improvement within the first 7-10 days.

If after several weeks of treatment and if increased doses of the medication yield only partial symptomatic improvement then augmentation can be used. Often the first augmentation strategy is to combine Depakote and lithium. If other medications are required then the addition of the following are commonly prescribed: anticonvulsants: Tegretol, Topamax, or Trileptal. The anticonvulsant, Neurontin has been found to be relatively ineffective as a mono-therapy, but it is often used as an augmenting agent, especially helpful in reducing anxiety (60-90% of bipolar patients have comorbid anxiety disorders). Other choices include atypical antipsychotics.

Childhood Onset Bipolar Disorder

The treatment of childhood-onset bipolar disorder is beyond the scope of this monograph, however a few brief comments will be made. When mania occurs in pre-pubertal children, it almost always presents as a form of dysphoric mania with rapid cycling and marked irritability. With adults the general strategy is to begin treatment with one mood stabilizer and only later add additional medicines if they are needed. This is done with the intention of avoiding unnecessary side effects that occur when multiple drugs are prescribed. Obviously there are compelling reasons for wanting to minimize side effects in children, as well.

However, preliminary research has rather strongly indicated that most children suffering from mania ultimately end up requiring two or more anti-manic agents (this is often necessary to effectively eliminate manic symptoms). Thus there currently is a trend to begin treatment with children using two mood stabilizers (often this combination is Depakote and lithium). It is generally felt that the much higher success rate with two mood stabilizers outweighs the added side effects of using two drugs. Also, it is felt that the earlier you can put a lid on mania and arrest its development, the better...to do so matters not only regarding the current episode but may also have a positive effect on reducing the severity of future episodes.

Rapid Cycling

As mentioned above, rapid cycling generally is a period of time lasting anywhere from a few weeks to a year or year and a half where there is a significant increase in the frequency (and often) severity of mood episodes. In only about 2% of people is rapid cycling continuous for very prolonged periods of time. Three factors account for the majority of cases of rapid cycling: substance abuse (including alcohol), the use of certain prescription medications (e.g. antidepressants, steroids, stimulants), or disorders of the thyroid gland. Thus it is very important to determine whether or not any of these factors are present and take appropriate action to ameliorate them. Note that in 1960 20% of bipolar patients had co-morbid substance abuse, while currently the rate is 60-70%. In addition, rates of rapid cycling have doubled during the past 15 years. Thus a careful evaluation of possible unreported substance abuse is critical in the assessment of patients with rapid cycling bipolar disorder.

Beyond this, special attention must be taken to stabilize the patient's lifestyle, especially making sure that there is regularity to one's sleep patterns and making every attempt to reduce or avoid sleep deprivation (e.g. establishing regular bed and awakening times, completely avoiding sleep destroying substances such as caffeine, alcohol and decongestants, no pulling all-nighters cramming for exams or late night partying).

Beyond these strategies, the following medication strategies have been found to be helpful. Preferred mood stabilizers include: Depakote, Tegretol, and Lamictal (of these medications Lamictal has the best research support for the treatment of rapid cycling). Atypical antipsychotic medications are frequently also prescribed. An experimental treatment that has been found to be helpful for some people is the use of omega-3 fatty acids as an add-on treatment (this is an over-the-counter dietary supplement that has some research support in the treatment of bipolar disorder. Discussed below). Finally, the most common mood symptoms seen in rapid cycling are depression or a combination of depression and irritability. However, antidepressants can, unfortunately, contribute to cycle acceleration and rapid switches in mood. Thus the use of antidepressants in rapid cycling is risky and generally not indicated.

Treatment-Resistant Mania

For people that experience very severe mania that does not respond to more traditional treatments there are a number of options. The antipsychotic medication clozapine (brand name Clozaril) has been found to be effective in some cases of treatment resistant mania. This drug has antipsychotic effects (e.g. for treating hallucinations, delusions, etc.). It also is proving to be effective for treating not only mania but also for relapse prevention. Unfortunately Clozaril is plagued by numerous, significant side effects, some of which are potentially dangerous. ECT (electro-convulsive therapy) is a safe and highly effective treatment for severe mania.

Stage Three: Relapse prevention Once the current manic episode is completely controlled it is common practice to continue medications, even though there are no obvious symptoms. This is necessary because it is clear that once symptoms subside, if one discontinues then, the acute relapse rate can be as high as 85%.

Typically episodes reoccur on average every 18-24 months (with no treatment or inadequate treatment), although there is a good deal of variability in the frequency of episodes. Thus once a person is stabilized, for a period of several months, typically, medication treatment is continued and often at the same doses used during treatment of the acute phase of the episode. This phase of treatment appropriately is called continuation treatment. After several months, assuming there have been no “breakthrough” symptoms, then the next stage of treatment, maintenance treatment begins. Here the focus of treatment is on the prevention of recurrent episodes. Often if a person has been receiving lithium, the dose is gradually reduced (which often results in fewer side effects).

The doses of other medications may also be reduced, however such a decision is highly individual and is influenced by a number of factors including a person's clinical history and the presence of particular side effects.

In general, the medications used to treat mania are considered to be very effective for most people experiencing a manic episode (Note: this is true for bipolar mania seen in patients who have a late adolescent or adult-onset illness. Mania in pre-pubertal children is significantly more difficult to treat). However the more long-term goal of preventing recurrences is more challenging. Despite the fact that there have been decades of experience in treating bipolar illness, there are no good long-term studies on relapse prevention (the longest studies available only extent to about a year).

Yet this is a life-long illness and all experts agree that life-long treatment is required. It is important to know that most medications used to treat bipolar disorder do have side effects that may emerge with very long-term use. Thus necessitating periodic lab tests to monitor blood levels of the medication and various glands and organ system functioning. What is clear is that failure to treat (or to adequately treat) bipolar disorder almost always leads to disasters.

The medications for which the best data exist for long-term maintenance treatment are the following: lithium (the best data), Lamictal (for recurring episodes of depression), and Zyprexa (for recurring episodes of mania). Most people on maintenance treatment will continue to take several medications. However, longer-term treatments generally do not include treatment with benzodiazepines or antidepressants.

Treatment Guidelines: Bipolar Depression

Several classes of psychiatric medications are often used to treat bipolar depression:

Lithium (must have blood levels of at least 0.8)

Symbyax (a combination of Zyprexa and Prozac...FDA approved to treat bipolar depression)

Lamictal: the only anticonvulsant used to treat bipolar depression

Two atypical antipsychotic medications have antidepressant properties:

Seroquel (best supported in the research)

Abilify

The biggest issue is that many treatments that ordinarily are effective in reducing depression carry a risk of provoking manic episodes (a phenomenon referred to as switching) or causing cycle acceleration (this refers to a gradual, over-all worsening of bipolar disorder in which, over

time, there is an increased frequency of episodes and episodes tend to become more severe and more difficult to treat).

Switching and cycle acceleration have been clearly documented with the use of antidepressants and thus these drugs are almost never used in the treatment of bipolar depression (Ghoemi, et al. 2001; Post, et al. 2001; STEP-BD, 2008). Excessive bright light exposure (which can treat some types of seasonal depression) has also been associated provoking manias. Additionally, two popular over-the-counter products that have antidepressant properties may, likewise, cause switching or cycle acceleration: St. John's Wort and SAM-e . While omega-3 fatty acids may be useful as an add-on medication along with other standard bipolar drugs, the over the counter medications St. John's Wort and SAME should never be taken by those diagnosed with bipolar disorder without medical supervision.

There are also three stages in the treatment of bipolar depression

Stage One: In the event of life threatening symptoms such as strong suicidal impulses or refusal to eat, ECT is a highly effective treatment. The treatment approach is much the same as used to treat acute mania. The other emergency treatment is hospitalization. Unfortunately aside from ECT most approaches to treating depression require several weeks before one is likely to see symptomatic improvement.

Stage Two: The choice of medication is dictated primarily by whether or not there has been a history of rapid cycling or any evidence of switching when being treated with antidepressants. If there has ever been rapid cycling or switching, then the risks of cycle acceleration and/or another incident of switching are much higher, and thus antidepressant medications are generally avoided. Thus the following are recommended guidelines:

With No History of Rapid Cycling or Switching (bipolar I) or with bipolar II: Start with a medication that has been found to have antidepressant actions, but low risk of causing switching. The drugs that have the best track record of effectiveness are Symbyax, Seroquel and Lamictal (however, there is an important consideration when using Lamictal: as treatment is begun, it is required that Lamictal be given in small doses and that dosage changes are done very gradually during the first 4-6 weeks of treatment. This is done to avoid inducing a potentially dangerous rash [Stevens-Johnson Syndrome] that is more common if there is rapid dose escalation. Since this more gradual titration approach has been initiated the incidence of severe rashes is extremely low and equals that seen in those treated with Depakote). Lithium has also been shown to have antidepressant effects when administered as a monotherapy in

bipolar depression (although not in unipolar depression); however, the blood level of lithium that is effective in combating depression appears to require at least a 0.8 level.

If treatment with one of these medications is not successful or there is only a partial response then there are several options:

1. *Combine two of these medications (e.g. Lamictal and Seroquel)*
2. *Add lithium*

With a History of Rapid Cycling or Switching

1. Start with Seroquel or Symbyax (these drugs have both antidepressant and antimanic properties, and thus may reduce the risk of provoking mania)
2. Lamictal (note: Lamictal has on occasion, been associated with inducing mania in bipolar I patients, thus is not a first line treatment).
3. If necessary add medications in the following order:
 - Combine two of the above
 - Combine three of the above
4. Add lithium

If still no response then consider ECT (electro-convulsive/shock therapy)

Stage Three: This is much the same as stage three treatments for mania. Among the medications that have the best record of effectiveness in the prevention of depressive episodes, Lamictal appears to be the front-runner.

Adjunctive Therapies

Bright light therapy (using a commercially available light box which generates 10,000 lux of light intensity for 10-30 minutes a day) has been used for treating bipolar depression, especially for those who routinely have winter depressions or who work the night shift. This treatment is typically combined with medication treatments and like all treatments for depression; it too carries a risk of provoking mania in people with bipolar disorder.

Omega-3 Fatty Acids: Approximately 60% of the human brain is composed of lipids (fats) and between 30-35% of brain mass is made up of omega-3 fatty acids. These molecules are important in forming cell membranes, synapses and in facilitating nerve cell actions. The most abundant dietary sources of omega-3 fatty acids are fish and shellfish. In cross-cultural studies

it has been found that in countries where people eat a lot of fish and other seafoods, the severity of mood disorders is less.

This interesting finding led researchers to carefully evaluate the impact of diet on mood. During the past five years a number of studies have been conducted with people suffering from bipolar disorder and also major depression. Preliminary findings strongly suggest that adding omega-3 fatty acids to the diet can have a positive effect on reducing the severity of mood episodes in some individuals. In all studies to date, omega-3 fatty acids have been added to traditional medications (i.e. mood stabilizers).

Uses and General Considerations: Omega-3 fatty acids are not effective in treating severe episodes of mania or depression. However their role appears to be in reducing the severity of episodes and possibly having a positive impact on preventing recurrences. Studies have found that people treated with omega-3 fatty acids must take these dietary supplements on a daily basis and over a prolonged period of time (i.e. building this in to ones ongoing diet). As noted above, the main sources of omega-3 fatty acids are fish and shellfish, and presumably adding more fish to your diet may be a way to enrich levels of these molecules in the brain.

However, all of the studies that have had positive results have used dietary supplement capsules (available from health food stores). There are three types of omega-3 fatty acids: LNA (derived from seed and nut oils, principle from flax seed oil), EPA, and DHA (both from fish oil). Most studies have demonstrated that DHA is the most effective type of omega-3 fatty acids used to treat bipolar. The early studies used mega-doses of DHA (9 grams per day). However, it appears that much lower doses may be effective (for example, 1000 mg. taken twice a day). It has recently been discovered that omega-3, derived from fish oil, is superior to that found in nut and seed oil; it has greater bio-availability (more readily enters the brain).

There are also indications that what may also be involved is achieving a balance between omega-3 and omega-6 fatty acids (the main omega-6 is arachidonic acid). Unfortunately dietary habits in the United States are notoriously poor, and lots of snack and junk foods contain significant amounts of omega-6 fatty acids (this may throw things out of balance). Thus a recommended strategy is to reduce junk foods and add omega-3 fatty acids. Omega-3 fatty acids (especially at lower doses) have few if any side effects and are well tolerated; high doses can cause gastrointestinal discomfort (Stoll, et al., 1999).

Exercise therapy has been shown to be effective in treating major depression, however, to date there are no studies of this approach in treating bipolar depression.

Psychotherapy

Although medication treatment is the backbone of successful therapy for bipolar, a number of studies have clearly shown that psychotherapy (especially interpersonal and social rhythm therapy, cognitive behavioral therapy, or family-based psychoeducational therapy) can significantly contribute to better treated outcomes.

Appendix Medications for Bipolar Disorder: A Quick Reference Guide to medications, side effects, required lab tests and special precautions.

Note: To the best of our knowledge doses and side effects listed below are accurate. However, this is meant as a general reference only and should not serve as a guideline for prescribing medications. Brand names are registered trademarks.

Anti-Manic Medications: Lithium

Lithium Facts:

- The drug with the best track record in preventing recurrences of episodes.
- Lithium is a naturally occurring element.
- Lithium is the only psychiatric drug proven to substantially reduce the incidence of suicide.

Brand Names: Lithium carbonate: Lithotabs, Eskalith, Lithonate, Lithane, Carbolith, Lithobid, Duralith Lithium citrate: Cibalith

Uses: treats mania, bipolar depression and is used to reduce recurrences of mania and depression.

Typical Adult Daily Doses: (Eskalith or Lithonate: most commonly prescribed): 600-2400 mg. per day. Note: what matters with lithium treatment is not the dose, per se, but the blood level (which is carefully monitored). A lithium level between 0.8 and 1.2 mEq/l (mEq/l is the technical designation for what is commonly called the lithium level) is generally felt to be in the therapeutic range for treating mania.

Lithium contd..

Once the manic episode is resolved, then it is common practice to lower the dose to establish a blood level somewhere between 0.6 and 0.8 mEq/l. Blood levels above 1.2 are associated with significant side effects, and levels above 2.0 can be dangerous.

Onset of effects (how long it takes to start working): generally 7-10 days

Laboratory Tests: Prior to starting treatment with some medications, laboratory tests are required to establish baseline measures of the functioning of certain bodily systems. The following are typically required prior to starting treatment (and those with an * will need to be monitored periodically during treatment). ECG (EKG)*, electrolytes, complete blood count, kidney function tests (BUN, creatinine, urinalysis), thyroid tests*, calcium*, pregnancy test (optional).

Laboratory Tests routinely done in an on-going basis: Those tests above flagged with an asterisk are repeated periodically. In addition it is necessary to periodically check lithium blood levels. This is done frequently during the first weeks of treatment and when there are significant changes in dosage. Once a person is stabilized on lithium for several months, lithium levels will then be checked less often (e.g. 3-4 times a year).

Common Side Effects: Nausea or heartburn, muscle tremor or weakness, decreased sex drive lethargy, drowsiness (may impair the ability to safely drive an automobile), difficulty concentrating, weight gain, increased thirst and frequency of urination, rash or acne

Less Common Side Effects (these should be reported to the treating doctor immediately) Loss of balance, double vision, vomiting, diarrhea, slurred speech, trembling

Rare or Potentially Dangerous Side Effects (if these occur, immediately contact the treating doctor) Soreness of mouth, throat or gums, severe rash or itchiness, swelling of the neck or face, severe: nausea, vomiting, weakness, fever, flu-like symptoms, marked increase in thirst and very frequent urination

Habit –Forming / Addiction Potential: none

Interactions with other medications: Here are listed only the most common medications with which the drug may cause adverse interactions: diuretics (water pills), calcium channel

Lithium contd...

blockers, ACE inhibitors, non-steroidal anti-inflammatory pain medications such as ibuprofen, theophylline.

Safety during pregnancy: Lithium is generally considered to be safe for use during pregnancy, however there is a slight risk for a rare birth defect (Ebstein's anomaly, a heart defect) if taken during the first trimester. This occurs 0.1-0.2% of fetuses exposed to lithium. If a female patient is planning to get pregnant or thinks that she may be pregnant, she should contact a doctor who specializes in the field.

Breast feeding: not recommended when taking lithium

Special Concerns:

Lithium is a very dangerous drug if taken in an accidental or intentional over-dose. In the event of an over-dose seek immediate medical attention. Also lithium levels can become dangerously high if there is dehydration; e.g. seen when people experience excessive vomiting or diarrhea or in people suffering from bulimia, who may become dehydrated due to frequent purging.

Anti-Manic Medications: Anticonvulsants

Anticonvulsant Facts

Anticonvulsants are medications originally developed to treat epilepsy. It was only by accident that it was discovered that some anticonvulsants also have the ability to treat mania. In addition one of the anticonvulsants (Lamictal) has antidepressant actions and can be used to treat bipolar depressive episodes.

Anticonvulsants: Generic and Brand Names and typical adult daily doses:

Divalproex	Depakote	750- 150 mg.
Carbamazepine	Tegretol	600-1600 mg.
Oxcarbazepine	Trileptal	1200-2400 mg.
Gabapentin	Neurontin	300-2400 mg.
Lamotrigine	Lamictal	50-200 mg.
Topiramate	Topamax	50-1300 mg.

An additional anticonvulsant, Tiagabine (brand name Gabitril) is considered to be an experimental treatment, but to date there are no well-controlled research studies.

Anticonvulsants contd..

Uses: Treating mania

Lamictal is used to treat bipolar depression. Research evaluating the ability for anticonvulsants to help prevent recurrences of mania and bipolar depression is not yet conclusive. Depakote and Tegretol likely help to prevent recurrences of mania and Lamictal likely reduces the recurrence of bipolar depression.

Therapeutic blood levels: two of the anticonvulsant mood stabilizers must be periodically monitored to check the levels of medication present in blood.

Depakote	blood levels: 50-125 mcg/ml
Tegretol (Equetro)	blood levels: 4-12 mcg/ml
Trileptal	blood levels: not yet established
Neurontin	blood levels: not necessary to monitor
Lamictal	blood levels: not necessary to monitor
Topamax	blood levels: not yet established

Onset of effects: generally 7-10 days (one exception: if high doses of Depakote are administered, effects can be seen in four or five days)

Laboratory Tests: Required for: Depakote, Tegretol, Equetro and Trileptal. Specific tests depend on which drug is used, but often include the following: Complete blood count, platelets, electrolytes, cholesterol, triglycerides, sonogram of ovaries (optional: for females under the age of 20 treated with Depakote), liver function tests, ECG (EKG), pregnancy test. For Topamax: kidney function tests (BUN and creatinine). Pre-treatment labs are generally not required for Neurontin or Lamictal

Laboratory Tests routinely done in an ongoing basis:

Tegretol, Equetro, Depakote and Trileptal blood levels must be monitored (especially during the initial weeks of treatment). Generally once a person is stabilized on Depakote or Trileptal, blood level monitoring is not necessary. However, those treated with Tegretol must have periodic and on-going monitoring of Tegretol levels. On-going lab test are generally not required for Topamax or Lamictal

Common Side Effects: each medication has specific side effects, however listed here are side effects that can be seen in most of the anticonvulsants:

- Drowsiness, lethargy
- Mild dizziness
- Unsteadiness when standing or walking
- Difficulty concentrating

Anticonvulsants contd..

Anticonvulsants contd..

- Blurred vision
- Dry mouth
- Muscle tremor
- Nausea or heartburn
- Weight gain (can occur in all except Topamax; also less likely with Lamictal)
- Weight loss: Topamax
- Changes in menstrual cycle
- Decreased sex drive

Less Common Side Effects: (should be reported to the treating doctor)

- Infertility problems (seen with some women under the age of 20 treated with Depakote), also accompanied by menstrual irregularities.
- Changes in hair: hair loss (usually transient) or changes in hair texture.
- Rash or itching.

Habit-Forming / Addiction Potential: none

Interactions with other medicines: (varies depending on the specific drug)

- Birth control pills (especially with Tegretol; may occur with Topamax)
- Anticoagulants (blood thinners)
- Aspirin (moderate to high doses)
- Cimetidine (Tagamet)
- Antibiotics (especially with Tegretol)
- Calcium channel blockers
- Lamictal and Depakote prescribed together can cause drug-drug interactions Propoxyphene (Darvon) (especially with Tegretol)
- Antidepressants (anticonvulsant mood stabilizers are often prescribed for patients who are also taking antidepressants...generally there are no problems unless the antidepressant doses are high)
- Antacids: may affect the absorption of some anticonvulsants

Safety during pregnancy: there is a risk of birth defects when taking some anticonvulsants during pregnancy (especially the first trimester). Most psychiatrists do not prescribe these medications during pregnancy.

Breast feeding: not recommended when taking anticonvulsants.

Antipsychotic Medications

Antipsychotic Medication Facts

Antipsychotic medications were first developed to treat psychotic symptoms such as hallucinations. The first such drugs were found to be effective in reducing psychotic symptoms, but they were notoriously “dirty” drugs, causing significant side effects. Since the mid-1990s new antipsychotics have been developed and marketed. These newer generation medications are not side effect-free, but they are somewhat safer and better tolerated. The newer drugs are commonly referred to as atypical antipsychotics.

Although atypical antipsychotic medications are highly effective in treating psychotic symptoms it has been found that they are also good treatments for mania and possibly for mood stabilization. Thus these medications are currently being widely used to treat bipolar disorder even in individuals who have no psychotic symptoms.

Atypical Antipsychotic Medications: Generic and Brand Names and typical adult daily doses

Olanzapine	Zyprexa	5-20 mg. (mania; possibly depression)
Risperidone	Risperdal	4-10 mg. (mania)
Quetiapine	Seroquel	150-400 mg. Possibly up to does of 750 mg (mania and depression)
Ziprasidone	Geodon	60-160 mg.
Aripiprazole	Abilify	15-30 mg. (mania)
iloperidone	Fanapt	12-24 mg

Clorazil: Another antipsychotic medication that is used occasionally is clozapine (generic), Clozaril (brand name). This older-generation antipsychotic medication has significant side effects (e.g. dry mouth, constipation, sedation, seizures, excessive salivation, blurred vision, nausea, heartburn and weight gain) and has been associated with a serious blood disorder (agranulocytosis: which causes soreness of the mouth, throat and gums and a high fever). Thus it is never considered to be a first line medication choice. However, despite the problematic side effects, Clozaril is an important medication that can often successfully treat those rare people who have not responded to more traditional anti-manic. The typical adult daily doses for Clozaril are: 300-900 mg.

Please note that all of the following information regarding antipsychotics pertains to the atypical antipsychotics (but not Clozaril).

Uses: To treat mania and agitation and the psychotic symptoms associated with both manic and depressive episodes. The effectiveness of antipsychotic medications in the long-term prevention of recurrences is as yet inconclusive.

Antipsychotics contd...

Onset of effects: Antipsychotic medications used to treat mania and can begin to reduce severe agitation within a few hours to a few days, however, the reduction of more pronounced, core manic symptoms, is similar to that seen with other anti-manic agents such as lithium and anticonvulsants (7-10 days or longer).

Laboratory Tests: generally not required. However, some antipsychotics may cause an increase in cholesterol and triglycerides and may cause or aggravate type II diabetes, monitoring blood lipids and glucose may be required.

Common Side Effects for Atypical Antipsychotics:

- Drowsiness and lethargy (can occur with all, except Abilify)
- Weight Gain (can occur with all, however minimal with Geodon and unlikely with Abilify)
- Nausea, vomiting, heartburn
- Stuffy nose
- Mild dizziness

Less Common Side Effects Atypical Antipsychotics (these should be reported to the treating doctor)

- Constipation
- Decreased Sex Drive
- Breast tenderness, liquid discharge from breasts (can occur with high doses of Risperdal)
- Rash
- May elevate levels of cholesterol and triglycerides (especially clozapine, Symbyax, and Zyprexa).
- May increase risks of type II diabetes (especially: clozapine, Symbyax, and Zyprexa).
- Severe sunburn when exposed to even moderate amounts of sunlight.
- Muscle rigidity
- Tremor
- Rash
- Blurred vision

Rare or Potentially Dangerous Side Effects of Atypical Antipsychotics: (if these occur, patient should immediately contact the treating doctor)

- Soreness in mouth, throat and gums
- Moderate to severe nausea, vomiting and flu-like symptoms
- Yellow tint to skin or eyes
- Seizures
- High fever (especially if accompanied by muscle stiffness)
- Confusion
- Abnormal, involuntary movements of the mouth, tongue and sometimes head, neck and hands
- Extreme restlessness
- Unusual bruising or bleeding
- Severe rash
- Frequent urination or loss of bladder control

Antipsychotics contd...

Habit-Forming / Addiction Potential: none

Interactions with other medications (varies depending on the specific drug)

- levodopa: decreases effectiveness of levodopa
- amphetamines
- anticonvulsants: can decrease antipsychotic blood levels
- Digoxin: may increase blood levels of digoxin and the antipsychotic
- Warfarin: may increase Warfarin blood levels
- Antacids: may interfere with the absorption of the drug

Safety during pregnancy: atypical antipsychotics are generally considered to be safe during pregnancy.

Breast-feeding: antipsychotic medications are secreted in breast milk. Since these are recently developed medications, there is inadequate information regarding safety to infants.

Special Concerns:

- Avoid exposure to extreme heat (e.g. saunas)
- Grapefruit juice may interfere with the effects of the drug
- Excessive cigarette smoking may interfere with the effects of the drug
- Avoid direct exposure to sunlight: antipsychotic medications can increase the likelihood of severe sunburns.

Antidepressant Medications

New Generation Antidepressants: Generic, brand name and typical adult daily doses.

Trazodone	Desyrel	50-400 mg.
Fluoxetine	Prozac, Sarafem	20-80 mg.
Bupropion	Wellbutrin1	50-400 mg.
Sertraline	Zoloft	50-200 mg.
Paroxetine	Paxil	20-50 mg.
Venlafaxine	Effexor	75-350 mg.
Nefazadone	Serzone	100-500 mg.
Fluvoxamine	Luvox	50-300 mg.
Mirtazapine	Remeron	15-45 mg.
Citalopram	Celexa	10-60 mg.
Escitalopram	Lexapro	5-20 mg.
Duloxetine	Cymbalta	20-80 mg.

Antidepressants (all except Wellbutrin) are effective in treating severe anxiety, panic attacks, generalized anxiety, social anxiety, and obsessive-compulsive disorder (OCD). These medications are sometimes used to treat bulimia.

Uses: treat unipolar depression, anxiety, and obsessive-compulsive disorder (OCD), however, can be associated with switching into mania and cycle acceleration

Onset of Effects: generally 2-6 weeks

Laboratory Tests: not required

Common Side Effects:

- Nausea, heartburn
- Energized or anxious feelings; i.e. “activation”; (typically subsides within 1-2 weeks)
- Headaches
- Sedation (primarily with Remeron and Desyrel)
- Difficulty falling asleep (often subsides in a few weeks)
- Sexual dysfunction: primarily inorgasmia (difficulty achieving an orgasm despite adequate arousal) (can occur in 14-30% of people treated with antidepressants. One exception: very rare with Wellbutrin)
- Weight gain (primarily with Remeron; with other antidepressants, weight gain can occur in up to 10% of people, however the weight gain typically does not occur until the person has been taking the drug for a period of time longer than six months)
- Muscle tremor
- Rash

Rare Side Effects (if these occur, patient should immediately contact the treating doctor)

- Soreness of mouth, throat, or gums
- Severe rash
- Seizures
- Unusual bruising or bleeding
- Severe nausea, vomiting and flu-like symptoms
- Severe agitation or restlessness
- Yellow tinge to skin or eyes
- Dark colored urine
- Rapid shift into mania or hypomania; racing thoughts

Habit-Forming / Addiction Potential: none

Interactions with other medications: (varies depending on the drug) Do not take with St. John’s Wort, 5-HTP (dietary supplement), MAOIs, cimetidine (Tagamet)

Antidepressants contd...

Safety during pregnancy: most experts agree that some new generation antidepressants are safe for use during pregnancy (e.g. Prozac, Zoloft, Effexor, Wellbutrin and Luvox); however, recently concerns have been raised regarding the drug Paxil during pregnancy. (note: the following antidepressants have been only recently come to market and there is inadequate data to evaluate safety during pregnancy: Cymbalta, Lexapro, Celexa, Serzone, and Remeron). High doses of Desyrel should not be used during pregnancy.

Breast-feeding: antidepressants are secreted in breast milk, but the amounts are extremely low. Most experts agree that it is safe to breast feed while taking new generation antidepressants. Lowest amounts of antidepressants found in breast milk with Zoloft.

Special Concerns: If you have been taking antidepressants for a period of six weeks or more, if you abruptly stop taking the medications, there can be withdrawal symptoms (this can occur with any of the antidepressants with the exception of Prozac). Withdrawal symptoms include: nausea, stomach upset, nervousness, flu-like symptoms, and occasionally a peculiar electrical shock sensation in the body (head or limbs). Withdrawal symptoms are very unlikely if a person has been taking the medication for less than six weeks. Withdrawal symptoms range from very mild to severe. And withdrawal symptoms can be avoided almost 100% of the time by reducing the dose gradually over a period of several weeks to a couple of months.

Benzodiazapines: Anti-Anxiety Medications

Benzodiazepine Facts: Benzodiazepines are also commonly referred to as minor tranquilizers or anti-anxiety medications.

Benzodiazepines: Generic and Brand Names and Typical Adult Daily Doses:

Diazepam	Valium	4-30 mg.
Chlordiazepoxide	Librium	15-75 mg.
Clorazepate	Tranxene	15- 67.5 mg
Clonazepam	Klonopin	0.5-2.0 mg.
Lorazepam	Ativan	2-6 mg.
Oxazepam	Serax	30-60 mg.
Alprazolam	Xanax	1-4 mg

Benzodiazapines used for sleep: Typical Adult Night-time Doses:

• Temazepam	Restoril	15-30 mg.
• Triazolam	Halcion	0.25-0.5 mg.
• Estazolam	Prosom	1-2 mg.
• Zolpidem	Ambien	5-10 mg.
• Zaleplon	Sonata	5-10 mg.

Anti-Anxiety medications contd...

Non-benzodiazepine prescription sleeping medication: non-habit forming:

- Eszopiclone Lunesta 1-3 mg
- Ramelteon Rozerem 4-16 mg

Benzodiazapine Uses: treats acute anxiety, agitation and insomnia during episodes of mania. Also used to treat anxiety disorders (such as panic disorder, post-traumatic stress disorder and generalized anxiety disorder) and insomnia. In the treatment of mania, benzodiazepines are generally used only for the first few days of treatment to reduce agitation; only rarely are these drugs used beyond a couple of weeks.

Onset of Effects: 30-60 minutes

Laboratory Tests: none required

Common Side Effects:

- Drowsiness
- Dizziness
- Forgetfulness
- Slurred speech

Less Common Side Effects:

- Confusion
- Nervousness
- Rash
- Loss of balance and falls

Habit-Forming / Addiction Potential: Significant risk for people with a prior personal or family history of alcoholism or other forms of serious drug abuse.

Interactions with Other Medications: When taking benzodiazepines any other type of medication that causes drowsiness or impaired alertness and reaction time can be potentially dangerous, especially if one has to drive and automobile. In addition, alcohol should not be consumed when taking benzodiazepines.

Safety During Pregnancy: Benzodiazepines typically are not to be used during pregnancy.

Breast Feeding: Benzodiazepines are secreted in breast milk and should not be used when breast-feeding.

Anti-anxiety medications contd...

Special Concerns: If benzodiazepines are being taken on a regular basis the body develops a tolerance for the medication. When this happens, typically the drugs continue to work to reduce anxiety, but the problem is that when there is tolerance, the drug is discontinued abruptly the result can be withdrawal symptoms. Withdrawal symptoms usually include nervousness, agitation, difficulty falling to sleep, and on occasion can produce seizures. This needs to be taken very seriously. If patients have been taking a benzodiazepine on a daily basis for more than 6 weeks and especially if the dose is moderate to high, withdrawal reactions are a very real risk. One should never abruptly stop taking the medication without first consulting with their treating physician. It is also a good idea to be especially careful for patients to monitor their supply of the medications so that refills can be requested in a timely fashion. Many people find it helpful to keep at least a two-day supply on hand in the event that it takes longer than usual for a prescription to be refilled.

Calcium Channel Blockers

Calcium channel blockers are medications that are often used to treat certain cardio-vascular diseases. One of these drugs has been found to be effective in the treatment of mania, and possibly as a treatment to prevent the recurrence of mood episodes.

Generic name Brand Names Typical Adult Daily Doses

Verapamil	Calan, Isoptin	120 mg. given 3 or 4 times a day Thus total daily: 360-480 mg.
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Uses and General Considerations: for people who cannot tolerate lithium, for rapid cycling bipolar, or for use during pregnancy (verapamil is considered to be the safest mood stabilizing medication for the treatment of bipolar disorder during pregnancy). Verapamil, like most other anti-manic agents, generally takes 7-10 days to begin reducing symptoms.

One additional calcium channel blocker is used occasionally to treat mania: nimodipine (brand name: Nimotop). This medication looks promising in terms of efficacy however it is very expensive and to date although there are positive case reports, there are no well-controlled studies.

Miscellaneous Medications

The following medications are used less often in the treatment of bipolar disorder and thus will be discussed briefly.

Omega-3 Fatty Acids

Approximately 60% of the human brain is composed of lipids (fats) and between 30-35% of brain mass is made up of omega-3 fatty acids. These molecules are important in forming cell membranes, synapses and in facilitating nerve cell actions. The most abundant dietary source of

omega-3 fatty acids is fish and shellfish. In cross-cultural studies it has been found that in countries where people eat a lot of fish and other seafoods, the severity of mood disorders is less. This interesting finding lead researchers to carefully evaluate the impact of diet on mood. During the past five years a number of studies have been conducted with people suffering from bipolar disorder and also major depression. Preliminary findings strongly suggest that adding omega-3 fatty acids to the diet can have a positive effect on reducing the severity of mood episodes in some individuals. In all studies to date, omega-3 fatty acids have been added to traditional medications (i.e. mood stabilizers).

Uses and General Considerations: Omega-3 fatty acids are not effective in treating severe episodes of mania or depression. However their role appears to be in reducing the severity of episodes and possibly having a positive impact on preventing recurrences when co-administered with mood stabilizers or anti-manic agents. Studies have found that people treated with omega-3 fatty acids must take these dietary supplements on a daily basis and over a prolonged period of time (i.e. building this in to ones ongoing diet). As noted above, the main sources of omega-3 fatty acids are fish and shellfish, and presumably adding more fish to one's diet may be a way to enrich levels of these molecules in the brain.

However, all of the studies that have had positive results have used dietary supplement capsules (available from health food stores). There are three types of omega-3 fatty acids: LNA (derived from seed and nut oils, mainly from flax seed oil), EPA, and DHA (both from fish oil). Most studies have demonstrated that DHA is the most effective type of omega-3 fatty acids used to treat bipolar.

The early studies used mega-doses of DHA (9 grams per day). However, it appears that much lower doses may be effective (for example, 500 mg. taken twice a day). There are also indications that what may also be involved is achieving a balance between omgea-3 and omega-6 fatty acids (the main omega-6 is arachidonic acid). Unfortunately dietary habits in the United States are notoriously poor, and lots of snack and junk foods contain significant amounts of omega-6 fatty acids (this may throw things out of balance).

Thus a recommended strategy is to reduce junk foods and add omega-3 fatty acids. Omega-3 fatty acids (especially at lower doses) have few if any side effects and are well tolerated (high doses can cause gastrointestinal discomfort) (Stoll, et al., 1999).

Older Generation Antipsychotics

First generation antipsychotic drugs (brand names): Thorazine, Mellaril, Serentil, Moban, Trilafon, Loxitane, Stelazine, Prolixin, Navane, Orap, and Haldol. Of these the most common drug that is still used these days is Haldol (often useful to initially treat very severe agitation seen in some types of mania).

Anticholinergic Medications

This class of medications is used occasionally to combat side effects of some antipsychotic drugs (side effects such as: muscle rigidity or spasms, restlessness, tremor). Again, we will only list these medications (brand names): Cogentin, Akineton, Artane. Anticholinergic drugs have their own set of side effects including: constipation, blurred vision, dry mouth, difficulty beginning urination, and occasionally memory loss, confusion and delirium.

SAM-e

SAM-e (S-adenosylmethionine) is a naturally occurring bio-molecule found in most living cells. It is felt to be necessary for carrying out a number of important intra-cellular chemical reactions. SAM-e has been used in Europe for more than 20 years as a treatment for depression. A number of studies have shown it to be equally effective when compared to prescription antidepressants. Most notable is the virtual lack of side effects. It has not been subjected to systematic research studies in the treatment of bipolar disorder, even though it has been found to be effective in treating some cases of unipolar depression. SAM-e is not useful for treating mania and has, in fact, been found to switch people with bipolar depression into states of mania. Doses for the treatment of depression range from 400-1600 mg per day, although recent investigations indicate that often the higher doses (1200-1600 mg per day) may be necessary for effectively reducing depressive symptoms. This is available over-the-counter (i.e. not requiring a prescription). It is recommended that if your patient is considering using SAM-e, it should only be taken with close observation by their treating psychiatrist.

St. John's Wort

St. John's Wort is an over-the-counter dietary supplement that has been found to have antidepressant properties. Two recent meta-analyses have shown that St. John's Wort is equally effective to prescription antidepressants in the treatment of mild-to-moderate depression, if given in high enough doses. This herbal remedy is generally well tolerated with few if any side effects.

There are reported cases of possible infertility problems associated with its use, although it is as yet unclear whether this is a common side effect. St. John's Wort requires daily dosing of 900-1800 mg. per day (taken in three divided doses), and typically the first signs of symptom improvement take about six weeks to emerge. Thus the onset of action is longer than that seen with prescription antidepressants. Research on the treatment of bipolar depression is sorely lacking. And as with any other treatment that has antidepressant properties, St. John's Wort can potentially provoke mania. Caution: St. John's Wort, when it is the only medication being taken, appears to be quite safe, but it has been found to cause very significant drug-drug interactions. It is strongly advised that patients never take St. John's Wort without first consulting with their doctor. Given its tendency to cause multiple and complex interactions with a host of medications and its propensity to provoke mania, it is recommended that it not be used by people being treated for bipolar disorder.

Resources for Families and for Patients with Bipolar Disorder

Taking Charge of Bipolar Disorder: By Julie Fast and John Preston, 2006

Loving Someone with Bipolar Disorder: Understanding and Helping Your Partner. By: Julie A. Fast and John Preston. New Harbinger Publications, 2004

The Bipolar Disorder Survival Guide: By: D.J. Miklowitz. Guilford Press, 2002

Depression and Bipolar Support Alliance: www.ndmda.org...800-826-3632

National Alliance on Mental Illness: www.nami.org

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