

# Health & Medical Scene

## Medications and Behavior

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Many individuals who survive a brain injury suffer from behavioral problems at some time during their recovery. For example, an individual may display signs of agitation, anxiety, low frustration tolerance (resulting in verbal or physical aggression), disinhibition or impulsivity, and mood swings. In some instances, behavioral disturbances result from disorganized thought processes or delusions, or from depression. The condition may be short-term or life-long and the effect on ability to function may be mild to severe. In general, mild problems are addressed through minor environmental adjustments or the implementation of alternative strategies. However, more serious behavioral problems could interfere with the success of rehabilitation and require a more complex intervention plan (Kraus, 2002).

Once the cause of the behavioral problem has been determined, a treatment method can be developed. First, it is important to design appropriate behavioral plans to assist the individual in addressing cognitive and behavioral issues. At times, medications or pharmaceuticals may be required for the person to make the fullest recovery and for the best relief of symptoms.

The field of neuropharmacology is very complicated and it changes daily. It may appear that the best medication has been identified to treat a particular behavior and then a new medicine is developed. In other situations, an individual may experience too many side effects and be unable to tolerate the medication that works for most people.

The process of deciding which medication is best for a particular individual involves the consideration of many

**It takes a team of dedicated health care professionals and caregivers to develop the best medication regimen.**

issues. These include: the main symptom that is being treated or targeted (like anger or anxiety), the underlying injury (neuropathology), the stage of recovery, the medication's chances of affecting recovery, and the medication's side effects. Knowledge about neurotransmitters (brain chemicals) and which ones may be affected in a particular injury or contribute to particular behavioral problems often leads to the choice of a med-

ication that targets that specific neurotransmitter. A medication may be chosen based upon its ability to alleviate more than one symptom. For example, if a specific behavior is being targeted and the patient has additional problems such as seizures, chronic pain, fatigue, or depression, a medication may be chosen that addresses both issues. Sometimes medications are even chosen due to the potential benefit of their side effects (e.g., sedation or lowering blood pressure). In brain injury recovery, we try to avoid medications that might worsen cognitive status and hinder recovery (O'Shanick, n.d.) and use medications that stabilize behaviors and enhance ability to benefit from rehabilitation.

Each person with a brain injury experiences a unique constellation of influences, conditions, and environmental factors that affect behavior. It takes a team of dedicated health care professionals and caregivers to develop the best medication regimen. This article in no way is a substitute for the individual attention needed for making decisions about medications. Rather, it will hopefully serve as an educational tool to help individuals understand and discuss

medications when they are being evaluated for use (Long, 1995-2003).

## MEDICATION BASICS

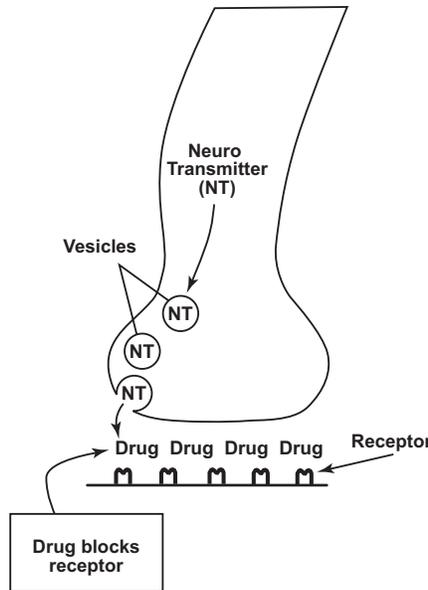
The following information will help you understand how most psychoactive medications work.

### Brain Chemical Information

In the brain, there are tiny nerve cells that don't quite touch one another. A nerve impulse is transmitted from one cell to another across a microscopic space called a synapse. When the impulse reaches the end of the nerve, a chemical called a *neurotransmitter* is released into the synapse from its storage garage, or vesicles. The neurotransmitter then goes to receptor sites on the *dendrite* of the next nerve cell. The receptor sites on the dendrite only fit certain neurotransmitters. When enough neurotransmitter has attached to the receptor sites, the nerve cell fires and the nerve impulse is transmitted to the next nerve sites, the nerve cell fires and the nerve impulse is transmitted to the next nerve cell. The "used" neurotransmitter is released from the receptor sites and goes back across the synapse into its vesicles. This is called *reuptake*. Some of the neurotransmitter doesn't go back but is destroyed in the synapse by enzymes.

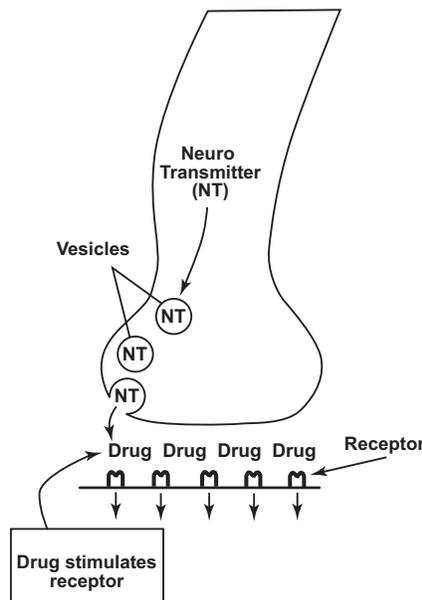
### How Most Psychoactive Medications Work

- The medication attaches to the receptor sites on the nerve cell and "blocks" them so the real neurotransmitter cannot stimulate the nerve (see Figure 1). For example, Haldol or Thorazine block the neurotransmitter dopamine. In this condition the medication serves as an *antagonist*, counteracting or stopping the effects of the neurotransmitter.



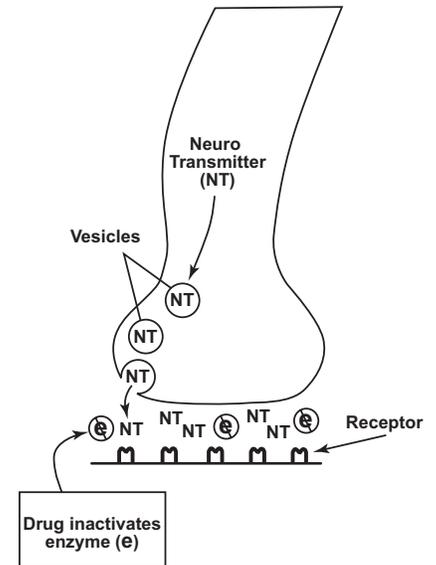
† **Figure 1. Medication blocks the receptor sites, counteracting the effects of the neurotransmitter.**

- The medication attaches to many receptor sites on the nerve cell and makes the nerve fire faster, thus increasing the effects of the nerve's action on the nervous system (see Figure 2). This occurs with Ritalin and Dexedrine (medications known as stimulants). The medication serves as an *agonist*, facilitating the action of the nerve cell.



† **Figure 2. Medication attaches to the receptor sites and facilitates the action of the nerve cell.**

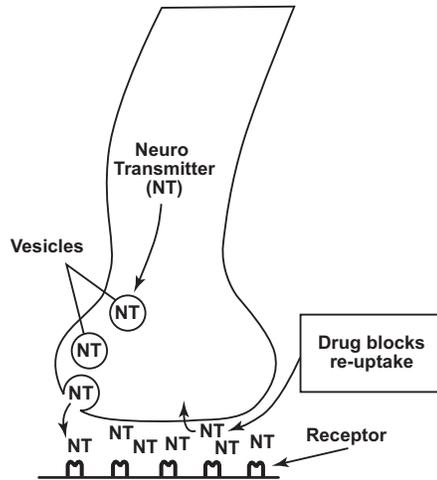
- The medication blocks the enzyme that breaks down the neurotransmitter in the synapse; therefore more neurotransmitter is available in the synapse to stimulate and increase the activity of the nerve cell (see Figure 3). Monoamine Oxidase Inhibitor antidepressants work like this



† **Figure 3. Medication blocks the enzyme that breaks down the neurotransmitter in the synapse, facilitating the action of the neurotransmitter in the synapse.**

- The medication blocks the reuptake of the neurotransmitter by the vesicles after it returns from the nerve cell. Again, this increases the amount of neurotransmitter in the synapse and increases the activity of the nerve (see Figure 4). This is how the newer antidepressants such as Prozac and Lexapro work (Brandis, 2003).

† From Carlson, Neil R. *Physiology of Behavior* 4/e  
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by Pearson Education. Adapted by permission of the publisher.



† **Figure 4. Medication blocks the reuptake of the neurotransmitter, facilitating the action of the neurotransmitter in the synapse.**

While there are numerous neurotransmitters in the brain, four have been associated with the action of medications used in the treatment of behavioral disorders: dopamine, serotonin, norepinephrine and GABA. Their full role and action, in some cases, is still under investigation.

## CLASSES OF MEDICATIONS

There are three major classes of medications used in the treatment of behavioral disorders: *anticonvulsant* (anti-seizure) medications, *antipsychotic* medications,

and *antidepressants*. Other classes of medications used for behavioral intervention include *antianxiety* drugs and *antihypertensives*.

Remember that all medications have *indications* (a sign or circumstance that indicates the proper treatment of a disease), side effects, and precautions. Medications often interact with other drugs. This is true for drugs that are commonly used such as aspirin, as well as less commonly used medications such as Geodon, an antipsychotic medication.

### Anticonvulsant Medications

Injury to the nerve cell or the imbalance of the neurotransmitters around the cell can cause the neurons to work abnormally. Anticonvulsant or anti-seizure medications act to prevent abnormal firing patterns of neurons. There are many anticonvulsant medications on the market that have indications for various forms of seizures.

In addition to their ability to control seizure activity in the brain, anticonvulsant medications can decrease conditions that lead to behavioral problems such as irritability, headache, low frustration tolerance, and mood swings (Edwards & Anderson, 1999). If the individual suffers from seizures as well as a behavioral problem, a medication that will treat both conditions will likely

be chosen. In current practice, there appears to be an increased use of Trileptal, Lamictal, and Keppra for behavioral problems, especially if seizure disorders are present also. It should be noted that the FDA does not list or approve these medications for “behaviors” and only your health care provider can determine if their use is appropriate.

<b>Class</b>
<b>Anticonvulsant</b>

### Behavior That May Be Helped

Mood swings, irritability, headache, frustration tolerance

<b>Class</b>
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### Antipsychotic

### Behavior That May Be Helped

Delusions, hallucinations, aggressive/dangerous behaviors, mood swings

<b>Class</b>
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### Antidepressant

### Behavior That May Be Helped

Explosive episodes, mood disorders, emotional instability, depression, anxiety, impulsivity

<b>Class</b>
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### Antianxiety

### Behavior That May Be Helped

Anxiety, by reducing awareness of stressors or decreasing memory of stressful events

<b>Class</b>
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### Antihypertensive

### Behavior That May Be Helped

Aggressive behavior, impulsivity, headaches

Neurotransmitter	Role Or Action
<b>Dopamine</b>	A neurotransmitter in the brain. Acts on the nervous system to increase heart rate and blood pressure. Controls movements. In the frontal lobe helps with memory, attention and problem solving. A disruption has been linked to psychosis and schizophrenia.
<b>Serotonin</b>	A neurotransmitter in the central nervous system that is thought to be involved with depression, bipolar disorder, and anxiety.
<b>Norepinephrine</b>	A neurotransmitter in the brain that is primarily involved in control of alertness and wakefulness. A disturbance in its metabolism at important brain sites has been implicated in affective disorders.
<b>GABA</b>	A neurotransmitter that works to inhibit the re-firing of a neuron. This may interfere with memory formation. The functional roles are still under investigation, but GABA may be crucial in gating information flow in the nervous system and regulating activity underlying sleep and arousal.

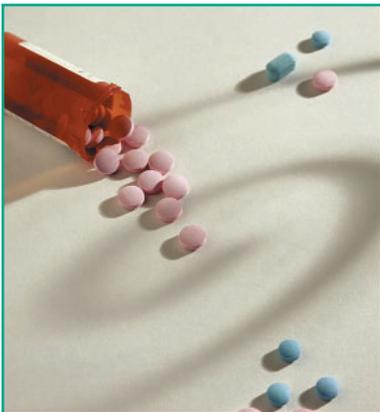
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Anticonvulsant medications may also be chosen for the treatment of psychiatric disorders such as bipolar disorder, a serious, chronic illness marked by mood swings from high or manic states to low or depressed states. Depakote and Tegretol have been used for many years and have been researched extensively in their treatment of psychiatric disorders, primarily bipolar disorder.

## *Depakote*

Depakote, or valproic acid, was approved by the FDA in March of 1983 and is made by Abbott Pharmaceuticals. It is supplied as 125 mg, 250 mg, and 500 mg tablets and as 125 mg sprinkle capsules (these can be opened and sprinkled in food). The Depakote ER-extended release was FDA approved in August of 2000 and is available in 500 mg capsules. It has an advantage over some of the other medications as it has fewer side effects that impair thinking ability and cognition. This is an important issue to consider when recovery from a brain injury is involved. Common side effects are nausea, dizziness, and unsteadiness, but these may be temporary. A fine tremor of the hands is common when using this medication, especially on higher dosages, however, it usually is not disabling. Serious side effects may occur and include thrombocytopenia (decrease in blood platelet count), anemia, and inflammation of the liver. Routine lab work (analysis of blood samples) is usually completed 2-4 times a year to help detect these problems. Medication adjustments can then



## Anticonvulsant or Anti-Seizure Medications

**Dilantin** (phenytoin)  
**Tegretol, Tegretol XR** (carbamazepine)  
**Trileptal** (oxcarbazepine)  
**Luminal** (phenobarbital)  
**Megaril** (mephobarbital)  
**Mysoline** (primidone)  
**Klonopin** (clonazepam)  
**Tranxene** (clorazepate)  
**Depakote** (valproic acid)  
**Neurontin** (gabapentin)  
**Keppra** (levetiracetam)  
**Zarontin** (ethosuximide)  
**Celontin** (methsuximide)  
**Lamictal** (lamotrigine)  
**Gabitril** (tiagabine)  
**Topamax** (topiramate)

be made. The level of this medication in the blood is monitored. The doctor will determine what level is best for the needed treatment. The manufacturer offers precautions regarding potential interactions with Tegretol, Phenobarbital, and Klonopin (clonazepam).

## *Tegretol*

Tegretol, or carbamazepine, was approved by the FDA in 1968 and is produced by Novartis Pharmaceuticals. It is supplied in 100 mg, 200 mg, and 400 mg tablets and 100 mg/5 ml suspension. A long-acting version (Tegretol XR) was FDA approved in March of 1996 and is made in 100 mg, 200 mg, and 400 mg tablets. It has limited influence on thinking, learning, and general mental abilities, which makes it a good medication choice for persons with traumatic brain injury. Side effects include nausea, dizziness, unsteadiness, and occasionally double vision. These symptoms usually clear with time or if the medication is taken with food. A rare potential side effect called aplastic anemia has been reported with Tegretol use. This is a lowering of the white blood cell count, the cells needed to fight infection.

Tegretol use occasionally may lead to a lowering of the blood sodium level, resulting in break-through seizures. Uncommon side effects may include headache, diarrhea, constipation, blurred vision, and difficulty urinating. Lab work is also required when using this medication and should include a complete blood count (CBC), liver function, electrolytes (to check the sodium), and a drug level. This information should be checked three weeks after beginning the drug, then every three months for a year and at least every six months thereafter. Lab work should also be completed after increases in dosages. Drug interactions include: Erythromycin, Tagamet (cimetidine), Darvon, and Calan, as well as several antipsychotics and antidepressants.



## *Lamictal*

Lamictal, or lamotrigine, is an anticonvulsant that is used in adults with complex partial seizures and generalized seizures. It was FDA approved in December of 1994 and is made by GlaxoSmithKline Pharmaceuticals. In June of 2003, Lamictal became the first drug since Lithium to be FDA approved for the treatment of bipolar 1 disorder. Lamictal is available in multiple strengths: 25 mg, 100 mg, 150 mg, 200 mg swallowable tablets and 2 mg, 5 mg, and 25 mg chewable tablets. Common side effects of this medication include dizziness, drowsiness, blurred or double vision, headache, and lack of coordination. A skin rash may occur with this drug (in up to 10%

of patients) especially if the dosage is increased rapidly. If this occurs, the medication is usually stopped and then possibly started again at a lower dosage. Increases would then be introduced slowly. A serious condition called Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis may develop. This condition involves a painful, blistering skin rash, flu symptoms, high fever, and severe ocular (eye) lesions. Needless to say, reporting the development of a rash to your health care practitioner is very important. In studies, Lamictal appears to have more antidepressant activity than either Tegretol or Depakote. Drug precautions include combinations with Tegretol and Phenobarbital, which lower the concentration of Lamictal in the blood, or combination with Depakote, which increases the Lamictal level. For many people, Lamictal can be taken once a day with minimal side effects.

### **Keppra**

Keppra, or levetiracetam, was approved by the FDA in November of 1999 and is made by the UCB Pharma Company. It comes in 250 mg, 500 mg, and 750 mg tablets. Its indications include the treatment of partial seizures in adults and it may be used in conjunction with other medications to help control seizures. It is eliminated in the kidneys rather than the liver like many other seizure medications, which may be a consideration when multiple medications are being used or some liver damage is present. Side effects include sleepiness or feeling tired, weakness, difficulty coordinating muscles, agitation, anxiety and other mood changes, decreased ability to cope with daily life events, feeling depressed, and thoughts of suicide. In a Penn State Medical Center study with 21 patients with mental handicaps (among which TBI was included), 10% became seizure free, 10% had a 75% reduction in seizures, and 19% had a 50% reduction. A Cleveland Clinic Study revealed that Keppra used alone led to a 70% reduction of seizure frequency and improved cognition in the elderly. Unfortunately,

no studies dealing with behavior and brain injury have yet been conducted, but many colleagues have been noting good success with this medication for seizure patients who have behavioral disorders. Keppra has minimal drug interactions with no effect on oral contraceptives, other antiepileptic medications, Digoxin, or Warfarin.



### **Trileptal**

Trileptal, or oxcarbazepine, was approved by the FDA in January of 1999 and is made by the Novartis Pharmaceutical Company. It is supplied in 150 mg, 300 mg, and 600 mg tablets and in a 300 mg/5 ml lemon oral suspension. It has been indicated for the *monotherapy* (used alone) treatment of seizures in adults and *adjunctive* (used along with other seizure medications) therapy for adults and children since its release in 1999. In August of 2003, the FDA approved Trileptal for monotherapy in children also. Trileptal has twice-a-day dosaging and can be taken with or without food. As an advantage over the older seizure medications, no *hepatic* (liver) or *hematologic* (blood cell) monitoring is required. Side effects include dizziness, sleepiness, double vision, fatigue, nausea, vomiting, abnormal gait, abnormal vision, abdominal pain, tremor, and indigestion. Abnormal sodium levels may occur in about 2.5% of at-risk patients; about 30% of patients allergic to Tegretol (carbamazepine) will have an allergic reaction to Trileptal. Trileptal has multiple possible medication interactions including Tegretol, Phenobarbital, Dilantin, Depakote, oral contraceptives,

Verapamil, Tagamet, and Erythromycin.

### **Antipsychotic Medications**

Antipsychotic or neuroleptic, medications act by blocking the transmission of dopamine in the brain. The FDA has approved these medications for the treatment of schizophrenia and mood disorders. Some studies have shown that these medications may slow the recovery rate, so during the initial stages of recovery after brain injury they are only used when absolutely necessary. They are used in severe cases of *delusional thinking* (incorrect beliefs about reality that are continued despite evidence it is not true) or *hallucinations* (false sensory perception; hearing, seeing, smelling, or tasting something that is not actually there) or for very aggressive or dangerous behaviors.

There are two classes of antipsychotics: the *typical* (*traditional or classic*) and the *atypical* (*newer generation*) antipsychotics. The older drugs such as Haldol, Prolixin, and Thorazine belong to the typical class of antipsychotics. These drugs block the D2-dopamine receptors and inhibit dopamine neurotransmission. The atypical or newer generation antipsychotics such as Clozaril, Abilify, and Zyprexa act on both the dopamine and serotonin receptors. They are less likely than the typical or classic agents to cause extrapyramidal effects or motor effects such as tremor (described below). However, recently the newer antipsychotics, especially Zyprexa, have been associated with the development of *hyperlipidemia* (high cholesterol) and *glucose intolerance* (diabetes).

### **Serious Side Effects**

Antipsychotic medication may be effective in treating an extremely serious or uncontrollable behavioral problem but their effects must be monitored very closely. There are two serious side effects of these medications. The first is *Neuroleptic Malignant Syndrome* and the second is *Extrapyramidal Symptoms*.

**Neuroleptic malignant syndrome**  
Neuroleptic Malignant Syndrome or NMS is a rare, yet severe and sometimes fatal disorder. It is associated with drugs that interfere with the neurotransmitter dopamine in the brain. Antipsychotic drugs are the main cause of NMS but it can occur with other medications or the sudden discontinuation of drugs that increase dopamine. The exact incidence of NMS is unknown but some studies suggest 0.2%. While there are no proven risk factors, rapid dose increases and injectable medication seem to increase the risk of NMS occurring. Symptoms of NMS vary, but most commonly include high fever, extreme muscle rigidity, confusion, fluctuations in pulse and blood pressure, and changes in mental status. Laboratory changes may include high white blood cell counts and CPK (or muscle enzyme). Recognizing the early signs of NMS is very important for medical care. Uncomplicated NMS may last 7-10 days but some patients may go on to develop renal failure, abnormal clotting, nerve and muscle damage, and even cardiopulmonary arrest. Remember that this problem occurs very rarely.

## Common Antipsychotic or Neuroleptic Medications

### Typical or Traditional Antipsychotics

**Haldol** (haloperidol)  
**Thorazine** (chlorpromazine)  
**Promazine** (promazine hydrochloride)  
**Serentil** (mesoridazine besylate)  
**Loxitane** (loxapine succinate)  
**Moban** (molindone hydrochloride)  
**Triavil** (amitriptyline hydrochloride, perphenazine)  
**Orap** (pimozide)  
**Prolixin** (fluphenazine decanoate)

### Atypical Antipsychotics

**Clozaril** (clozapine)  
**Zyprexa** (olanzapine)  
**Risperdal** (risperidone)  
**Seroquel** (quetiapine fumarate)  
**Abilify** (aripiprazole)  
**Geodon** (ziprasidone)

Over 23 years, this author has yet to see one incidence of NMS, and of course, hopes not to.

### Extrapyramidal symptoms

Extrapyramidal Symptoms, or movement disorders, are the second serious side effect associated with antipsychotic usage. This disorder is seen more frequently with the typical or traditional antipsychotics than with the newer or atypical antipsychotics. Symptoms include *dystonia* (muscle spasm), *Parkinsonism* (tremor, slow movements), and *akathisia* (restlessness). Practitioners minimize these effects by trying low doses of the antipsychotics or using medicines like Cogentin to decrease the movement symptoms when traditional antipsychotics are prescribed. The traditional antipsychotic medications, like Thorazine and Haldol, are associated with *tardive dyskinesia* (TD), uncontrollable muscle spasms resulting in a twisting of the body or neck. Since there is no known effective treatment, and chronic use of antipsychotics is associated with the development of TD, it is important to closely monitor for the development of any early symptoms and to determine if any alternative therapy is available. The risk of a person developing TD and of the syndrome becoming irreversible appears to increase with the duration of treatment and the total amount of drugs administered. However, in some cases it has occurred at relatively low dosages over a short treatment course. The incidence of TD occurring is reported, overall, in 4% of patients taking typical or traditional antipsychotics. There is a 30% chance of TD occurring after seven years of treatment. Currently there are no studies that break this down per medication.

### Atypical, Newer Generation Antipsychotics

#### Geodon

Geodon, or ziprasidone, was FDA approved on February 5, 2001. Like the other antipsychotics, it is used in the

treatment of schizophrenia. It is made by the Pfizer Pharmaceutical Company and comes in 20 mg, 40 mg, 60 mg, and 80 mg capsules. It is taken twice a day with food. Geodon has a warning that it can increase an abnormal heart rhythm in certain heart conditions such as a recent heart attack, *long QT syndrome* (an abnormality in the heart's electrical system; may lead to a very fast heart rhythm ending in sudden death), severe heart failure, or irregularities of heart rhythm. On initial use and dosage increases, Geodon may cause dizziness and fainting, as well as sleepiness. Geodon may interfere with the ability of the body to adjust to heat and it is recommended that high temperatures and humidity be avoided. Other common side effects are nausea, constipation, restlessness, diarrhea, and rash. Medication interactions include several cardiac medications, Mellaril, and other antipsychotics such as Orap and Thorazine.

#### Seroquel

Seroquel, or quetiapine fumarate, was FDA approved in March of 2001 and is made by the Astra Zeneca Pharmaceutical Company. It is indicated for the short-term treatment of acute manic episodes associated with bipolar disorder as either monotherapy or adjunct therapy. It is also indicated for treatment of schizophrenia. It comes in 25 mg, 100 mg, 200 mg, and 300 mg tablets. Seroquel's package insert states that it has a favorable *weight profile* (does not significantly affect weight) but some studies show a weight increase of 14-23% for those who use it. In studies comparing its use with placebo, it does not cause any significant electrocardiogram changes or extrapyramidal side effects. Adjustments in dosages may be required for patients with kidney or liver problems as it is metabolized or broken down in those areas. Side effects include sleepiness, dizziness, *postural hypotension* (low blood pressure when getting up quickly), and indigestion. One problem with this drug is the similarity of its name to Serzone, an antidepressant in the Selective

Serotonin Reuptake Inhibitor (SSRI) group released in 2002. Many people get these medications confused which results in drug errors. Seroquel is the antipsychotic and Serzone is the antidepressant.

## **Abilify**

Abilify, or aripiprazole, was FDA approved in November of 2002 and is made by the Bristol Myers Pharmaceutical Company. It is indicated for the treatment of schizophrenia. Abilify has effects on both the dopamine and serotonin neurotransmitters. It is available in 10 mg, 15 mg, 20 mg, and 30 mg tablets with an initial starting dose of 15 mg. Dosing is usually once daily and it may be taken with or without food. Overall response in trials was similar to that in patients receiving Haldol or Risperdal. Precautions for heat are like those for Geodon in that you should avoid overheating and dehydration as Abilify may make it harder to lower your body temperature. It may impair judgment, thinking, and motor skills and may cause some trouble in swallowing. More rare side effects include headache, weakness, nausea, vomiting, constipation, anxiety, problems sleeping, lightheadedness, restlessness, sleepiness, and rash. Abilify does not appear to cause the weight increase observed with the use of Zyprexa or the cardiac rhythm disturbances that may occur with the use of Geodon. A higher dosage of Abilify may be needed if Tegretol is being used and lower dosages of Abilify may be needed if Prozac or Paxil are being used. If Erythromycin or Sporanox is being used, the Abilify dose should be cut in half.

## **Zyprexa**

Zyprexa, or olanzapine, was FDA approved in 2000 for treatment of schizophrenia. In January of 2004, Zyprexa received approval for maintenance treatment of bipolar disorder. It is manufactured by the Lilly Pharmaceutical Company and is available in 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg tablets and 5 mg, 10 mg, 15 mg, and

20 mg orally disintegrating tablets for those who cannot swallow a pill. Weight gain can be common and marked with this medication; diabetes can occur. Recently this drug has been in the news due to lawsuits that have been filed because of these side effects. Extrapyramidal symptoms occur rarely and are usually mild, and there are no warnings against their use in persons with certain heart conditions as found with Geodon. Side effects may also include postural hypotension, sleepiness, constipation, hyperlipidemia, and dizziness.

## **Risperdal**

Risperdal, or risperidone, was FDA approved in 1999 and is manufactured by the Janssen Pharmaceutical Company. It is manufactured in tablet form, orally disintegrating pill form (M-tab), and oral solution. The tablet strengths are 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg. The M-tab is 0.5 mg, 1 mg, and 2 mg and the liquid is 1mg/ml. The most common side effects include postural hypotension, insomnia, constipation, dizziness, prolactin elevation, and moderate weight gain. Diabetes occurs less often than with Clozaril or Zyprexa but extrapyramidal symptoms are more likely at dosages over 6 mgs per day. Of all the atypical antipsychotics, Risperdal causes the most hyperprolactinemia problems (galactorrhea, menstrual disturbances, gynecomastia, and sexual dysfunction) which may lead to osteoporosis (Volavka & Citrome, 2003).

## **Clozaril**

Clozaril, or clozapine, is manufactured by the Novartis Pharmaceutical Company and was approved for the treatment of schizophrenia by the FDA in 1989. It is available in 25 mg and 100 mg tablets. Clozaril is usually reserved for those patients who do not do well on the other antipsychotics because its use requires frequent blood count monitoring. This drug has been known to cause *agranulocytosis* (a white blood cell count problem) in 1%-2% of

patients on low doses (under 300 milligrams per day) and 3-4% of patients at higher doses (300-600 milligrams per day). Initially, weekly blood tests are required, and then over time this schedule may be lowered to every other week. Dose-related seizures, sedation, diabetes, weight gain, and high cholesterol are common. Bedwetting and increased salivation occur at higher doses.

## **Outcome Studies**

Of the atypical medications, Clozaril has been rated by Davis and colleagues (2003) as most efficacious, followed by Risperdal and Zyprexa. These three were considered to be superior to the typical or traditional antipsychotics. The other atypical agents were considered to be equally as effective as the typical antipsychotics. In general, the outcomes for the atypical and typical agents are very similar, but due to side effects and the possibility of tardive dyskinesia associated with the traditional antipsychotics, the atypical neuroleptics are often chosen for long-term use. There are very few studies that compare the individual antipsychotic medications on efficacy, but the atypicals do appear to be better tolerated. It should be noted that the atypical antipsychotics are more expensive. All of these medications must be closely monitored. Open discussions with the health care provider are encouraged to decide on the appropriate course of treatment (The Medical Letter, 2003, December 22).

## **Antidepressant Medications**

There are three basic groups of antidepressants: *The monoamine oxidase inhibitors (MAOI's)*, the *Tri-Cyclic antidepressants*, and the *Selective Serotonin Reuptake Inhibitors (SSRI's)*.

## **MAOI's**

Monoamine oxidase inhibitors (MAOI's) stop the breakdown of the monoamines (the neurotransmitters such as serotonin, norepinephrine, and dopamine) in the brain. This then increases the levels of

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these neurotransmitters, which, in turn, is thought to help decrease depressive symptoms. MAOI's are rarely used today because they interfere with the body's ability to defend itself from chemicals that stimulate the sympathetic nervous system. For example, foods such as chocolate, cheeses, nuts, bananas and others which contain phenylalanine (a stimulant) can increase heart rate and other symptoms. When on MAOI's the body's usual ability to counteract these symptoms is inhibited, resulting in severe increases in heart rate, headache, dizziness, or sweating. Therefore such foods must be avoided. Many people are unwilling to make the dietary adjustments needed to take this medication safely. The MAOI's also have several drug interactions and must be monitored very closely by a health care professional who is familiar with the medication. The MAOI's, however, may be the drug of choice for severe depression that doesn't respond to other medications as long as the diet and drug interaction recommendations are followed.

## Tri-Cyclic Antidepressants

Tri-Cyclic antidepressants (TCA's) block the reuptake of the neurotransmitter norepineprine, increasing the amount of neurotransmitter in the synapse, which, in turn, is thought to help decrease depressive symptoms. These medications also may be used for explosive episodes, emotional instability, headache relief, chronic pain, and insomnia. They are closely related to antihistamines and the onset of action takes two to four weeks.

Side effects are sedation, dry mouth, delayed urination, sexual dysfunction, constipation, and lightheadedness. They may also increase heart rate and rarely may cause skipped heartbeats. TCA's may lower the seizure threshold after brain injury. The TCA's continue to be used especially in severe depression. However, due to the side effect profile and potential for toxicity in overdosage compared to the SSRI's, TCA's are no longer the first line drug of treatment.

## Selective Serotonin Reuptake Inhibitors (SSRI's)

SSRI's work by blocking the reuptake of serotonin and other neurotransmitters, increasing the amount of neurotransmitter in the synapse, which, in turn, is thought to help decrease depressive symptoms. Some of the commonly used SSRI's are described below.

### Prozac

Prozac, or fluoxetine, was the first SSRI to enter the market in 1987 and is produced by the Eli Lilly Company. It is available in many dosage forms. A 10 mg, 20 mg, and 40 mg pulvule (a capsule form) and a 10 mg tablet, a 20 mg/5 ml solution, and a 90 mg delayed release weekly capsule. Over the years, Prozac has been used to treat conditions in addition to depression, including obsessive-compulsive disorder and bulimia. Prozac has a *half-life* (half of the time it lasts in the body) of 2-4 days, so is not cleared from the body quickly and can be very dangerous. Half-life has important implications when there are

medication changes, missed pills, or overdoses. It is a once-a-day pill. Side effects include: anxiety, restlessness, trembling, weakness, skin rash, itching, and decreased sexual drive. Prozac should not be taken with an MAOI and should be used with caution in patients that have seizures. Its use should be monitored closely when administered with other drugs such as Lithium, Warfarin, Digoxin, or Valium. Some foods or antacids can affect its absorption. The usual initial dosage is 10-20 mg per day. Prozac is now available in a weekly pill, making dosaging easier for some situations.

### Zoloft

Zoloft, or sertraline, was approved in 1999 for depression, obsessive-compulsive disorder, and panic disorder and in 2002 was FDA indicated for premenstrual dysphoric disorder. It is manufactured by Pfizer and is available in 25 mg, 50 mg, and 100 mg tablets and a 20 mg/5 ml oral concentrate. Zoloft should not be taken with an MAOI and should be used with caution in patients who have seizures. Side effects include gastrointestinal complaints such as nausea, diarrhea, and indigestion and male sexual dysfunction, insomnia, tremor, sweating, dry mouth, and dizziness. The usual initial dosage is 50 mg per day. Zoloft has possible interactions with Warfarin, Tagamet, Valium, and MAOI's.

## Common Antidepressant Medications

Monoamine Oxidase Inhibitors (MAOI's)	Tri-Cyclic Antidepressants	Selective Serotonin Reuptake Inhibitors (SSRI's)
<b>Parnate</b> (tranlycypromine sulfate) <b>Nardil</b> (phenelzine sulfate) <b>Marplan</b> (isocarboxazid)	<b>Elavil</b> (amitriptyline) <b>Tofranil</b> (imipramine) <b>Norpramin</b> (desipramine) <b>Pamelor</b> (nortriptyline) <b>Vivactil</b> (protriptyline) <b>Anafranil</b> (doxepin)	<b>Prozac</b> (fluoxetine) <b>Zoloft</b> (sertraline) <b>Paxil</b> (paroxetine) <b>Celexa</b> (citalopram hydrobromide) <b>Lexapro</b> (escitalopram oxalate)

## *Paxil*

Paxil, or paroxetine, was approved in 1998 and is made by the Glaxo-SmithKline Company. Tablets are available in 12.5 mg, 25 mg, and 37.5 mg dosages, and an oral liquid of 10 mg/5 ml is also made. It is indicated for depression, obsessive-compulsive disorder, and panic disorder. It has a short half-life, which makes it much safer in case the medication needs to be stopped quickly. Food or antacids do not affect its absorption. Paxil should not be used with MAOI's and precautions are made regarding use with patients who have seizures, patients who are elderly, and patients who are at high-risk for suicide. The most common side effects are nausea, sleepiness, sweating, tremor, dizziness, dry mouth, insomnia, and male sexual dysfunction. This drug tends to be more sedating than some of the others in its class. Usual dosage is 20 mg per day initially. Paxil may have drug interactions with Dilantin, Pheno-barbital, MAOI's, Thorazine, and Tagamet.

## *Celexa*

Celexa, or citalopram hydrobromide, is manufactured by Forest Laboratories. It was FDA approved in July of 1998 and is indicated for the treatment of depression. Celexa is made in 10 mg, 20 mg, and 40 mg tablets and a 2 mg/5 ml solution. Two studies found it as effective as Prozac and Zoloft for treating depression. One study showed that there was some increase in sexual side effects as compared to Zoloft. *Hyponatremia* (low sodium) has occurred but reverses when the medication is stopped. Other side effects include nausea, dry mouth, somnolence, and urogenital problems. Celexa should not be used with a MAOI. Gastric bleeding has been noted with aspirin or nonsteroidal anti-inflammatory drugs (NSAID's) like ibuprofen. Other drug interactions were found with antifungals, Prilosec, Tagamet and Erythromycin, Lopressor, and Tofranil. The usual initial and treatment dosage is 20-40 mg per day.

## *Lexapro*

Lexapro, or escitalopram oxalate, is also made by Forest Laboratories. FDA approval was received in August 2002 and it is indicated for the treatment of major depressive disorder and generalized anxiety disorder. It is available in 10 mg and 20 mg tablets. Basically, Lexapro is Celexa with the inactive ingredients removed to leave a safer, more potent, form of the medication. The same bleeding problem with aspirin and NSAID's is present, as well as the contraindication with MAOI use. Caution with the co-administration of Tri-Cyclic antidepressants is recommended. Nausea, insomnia, ejaculation disorder, sleepwalking, and fatigue are reported side effects. The usual initial and treatment dosage is 10 mg per day.

## *Outcome Studies*

Lexapro, Celexa, and Zoloft have a lower potential for drug interactions due to their metabolism sites. Many articles state that there is no good evidence that any SSRI is superior to another for treatment of depression or any other disorder such as obsessive compulsive disorder (OCD), posttraumatic stress disorder (PTSD), panic disorder, or bulimia for which the FDA has approved their use. A patient who does not respond well to one SSRI may do well on another, possibly

due to differences in side effects or tolerability (Fava et al., 2002; Kroenke et al., 2001). The decision of which SSRI to use is based on evaluation of costs (Prozac and Paxil are available in generic), adverse effects, and drug interactions (The Medical Letter, 2003, November 24).

## **Anxiolytics**

Anxiolytics, or anti-anxiety medications, work by inhibiting the neurotransmitter GABA, which slows down the neurons that use GABA. Benzodiazepines and barbiturates are drugs in this class (e.g., Valium, Ativan). Alcohol also causes similar affects in the brain. The person becomes less aware of the environment and its stressors, as well as the memories of stressors that may be causing problems. Side effects include sedation, short-term memory problems, muscle relaxation, and tolerance to the medication (needing more for the same effect). In brain injury, these medications are used for emergency or short-term situations due to their affect on cognitive function, as well as the potential for tolerance or dependence.

## **Antihypertensives**

Antihypertensives are medications used to lower blood pressure. They, however, may also be used to help control headaches and aggressive or impulsive behaviors. Beta blockers such as Inderal



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(propranolol) or Tenormin (atenolol) are often used to improve behavioral control. These drugs slow down the body. They lower the heart rate and blood pressure, but may also lead to exercise fatigue, hypoglycemia, or even depression. Alpha blockers and calcium channel blockers like verapamil may also be used, but they are more commonly prescribed to help control headaches.

## CONCLUSION

Medications can be an important and powerful part of the treatment regime for behavioral disturbances following brain injury. The National Institute of Health's Consensus Statement on Rehabilitation of Persons with Brain Injury reinforces this concept but offers a cautionary statement:

Pharmaceutical agents may be useful in a variety of affective (mood) and behavioral disturbances associated with TBI. Although specific studies with the TBI population are few, these agents are used in TBI for their direct and indirect pharmacological properties. People with TBI may be more likely to experience detrimental side effects from these drugs than people without TBI, therefore, additional caution should be used in prescribing and monitoring psychopharmacologic treatment (National Institute of Health [NIH], 1998, ¶ 4).

This statement underscores the importance of working closely with a health care provider to determine the best treatment regime. It is hoped that the information

provided here has helped to clear up some of the mystery engendered by this complex topic and that it enhances your ability to assist your health care provider.

There are many good additional sources of information including the pharmaceutical websites that now offer their patient information online. Additional sources of information are as follows:

- National Institute of Mental Health – 800-421-4211 or [www.nimh.nih.gov](http://www.nimh.nih.gov)
- National Mental Health Association – 800-969-NMHA or [www.nmha.org](http://www.nmha.org)
- National Alliance for the Mentally Ill – 800-950-NAMI or [www.nami.org](http://www.nami.org)

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