13th Annual
Science Symposium
Volume II
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Paradise Valley College
Foreword

The 13th Annual Science Symposium was held on May 10, 2007 in the Center for the Performing Arts. Students enrolled in General Organic Chemistry II, CHM 236, and General Physics II, PHY 112, from Paradise Valley Community College (PVCC) participated in the event. I want to acknowledge Dr. Casey Durandet for her participation.

Each contributor was responsible for selecting and researching their topic and preparing a paper. A few orally presented their project to their peers. This booklet contains each of those papers.

As an instructor and faculty advisor for this symposium, I want to thank and congratulate each participant for their effort, courage and dedication. By participating, these individuals perpetuate this event annually. I am both proud and honored to present the work of these individuals.

William L. "Hank" Mancini, PhD
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Bipolar Disorder: Symptoms, Diagnosis, Causes, Treatment, and Risks

By:
Seth Lowy

April 20, 2007
Abstract

Bipolar disorder is a mental illness that affects millions of Americans every year. It is important to look for the many symptoms that characterize the illness because more often than not, the person suffering from bipolar disorder is not even aware of it; thus making the earliest possible diagnosis and treatment of the disorder even more important. The causes of bipolar disorder are not yet known or fully understood and there is no cure. People suffering from the disorder are susceptible to several risks that must be monitored and even though bipolar disorder can be an emotionally debilitating disorder, it can be maintained with the proper treatment.

Introduction

Approximately 5.7 million people, or roughly 2.6 percent, of the American population age 18 and older suffer from a brain disorder known as bipolar disorder. 1 Also known as manic-depressive illness or manic-depression, bipolar disorder elicits abnormal and often extreme shifts in a person’s mood, more severe than the typical “ups and downs” that most people experience. 1, 2, 3, 4 Unfortunately, bipolar disorder is commonly undiagnosed, meaning people suffer from the disorder for years before it is correctly diagnosed and treated. 1 While the disorder can develop at any time in a person’s life, it generally appears in late adolescence or early adulthood. The causes of bipolar disorder are yet to be discovered, and there is no cure, but with proper treatment, people with the disorder can enjoy normal lives. 1, 4

Symptoms

Bipolar disorder is characterized by an alternation between emotional highs (mania) and lows (depression) with periods of normal mood separating them. 1 According to the National Institute of Mental Health, signs and symptoms are as follows:

“Signs and symptoms of mania (or a manic episode) include:

- Increased energy, activity, and restlessness
- Excessively “high,” overly good, euphoric mood
- Extreme irritability
- Racing thoughts and talking very fast, jumping from one idea to another
- Distractibility, can't concentrate well
- Little sleep needed
- Unrealistic beliefs in one's abilities and powers
- Poor judgment
- Spending sprees
- A lasting period of behavior that is different from usual
- Increased sexual drive
- Abuse of drugs, particularly cocaine, alcohol, and sleeping medications
- Provocative, intrusive, or aggressive behavior
- Denial that anything is wrong

"Signs and symptoms of depression (or a depressive episode) include:

- Lasting sad, anxious, or empty mood
- Feelings of hopelessness or pessimism
- Feelings of guilt, worthlessness, or helplessness
- Loss of interest or pleasure in activities once enjoyed, including sex
- Decreased energy, a feeling of fatigue or of being "slowed down"
- Difficulty concentrating, remembering, making decisions
- Restlessness or irritability
- Sleeping too much, or can't sleep
- Change in appetite and/or unintended weight loss or gain
- Chronic pain or other persistent bodily symptoms that are not caused by physical illness or injury
- Thoughts of death or suicide, or suicide attempts

It is important to note that most people with bipolar disorder don’t just shift from a normal state or mood to full-blown mania or depression; there are different degrees of both through which they may, or may not, pass. Hypomania is the state of mild to moderate mania. It seems to be the most difficult aspect of bipolar disorder because it is difficult to tell that anything is wrong, especially for the person experiencing it. Hypomania generally feels good and can even be linked with "good functioning and enhanced productivity." While in a state of hypomania, the person may deny something is wrong. This is exceptionally precarious because without suitable treatment, hypomania can progress into full-blown mania, or even flip into depression.

Bipolar disorder can be viewed as a spectrum of the moods ranging from severe depression to severe mania, with a normal/balanced mood right in the middle dividing the two. A normal person’s mood would fall somewhere within the first 3 bars above/below the median, normal mood. In comparison,
someone with bipolar disorder can measure anywhere in the spectrum, showing the much more extreme range of moods experienced when suffering from the disorder.

In some people, symptoms of mania and depression occur simultaneously in what is called a mixed bipolar state. Symptoms of psychosis, such as “hallucinations (hearing, seeing, or otherwise sensing the presence of things not actually there) and delusions (false, strongly held beliefs not influenced by logical reasoning or explained by a person’s usual cultural concepts)” may be present in extreme episodes of both mania or depression.¹ Regrettably, these severe symptoms can lead to the misdiagnosis of bipolar disorder as schizophrenia, unipolar depression or other severe mental illnesses. Also, bipolar disorder may appear to be a problem not related with any mental disorder such as alcohol or drug abuse, deficient performance at work or school, or “strained interpersonal relationships.”³

**Diagnosis**

The diagnosis of bipolar disorder is not an exact science. Like most mental disorders, there is no known way to identify it physiologically — “for example, through a blood test or brain scan.” Instead, bipolar disorder is diagnosed depending on the results of a psychological test known as the behavioral assessment test and factors such as symptoms, course of illness, and family history when available.¹⁵ The diagnosis of bipolar disorder can be difficult as most people do not exhibit symptoms of extreme mania or depression. This makes bipolar disorder difficult to distinguish from the normal “ups and downs” of human life. It is possible that the person is just more temperamental or moody, making a clear-cut yes/no answer impossible in most cases. Sometimes, people who may not actually be suffering from the disorder but exhibit some of the symptoms are misdiagnosed and medicated with mood-stabilizing drugs when they are not necessary.

There are two classes of bipolar disorder.¹⁵ “The classic form of the illness, which involves recurrent episodes of mania and depression, is called bipolar I disorder. Some people, however, never develop severe mania but instead experience milder episodes of hypomania that alternate with depression; this form of the illness is called bipolar II disorder.”¹ Rapid-cycling, found to be more common in women than in men, is the term used to describe a person with bipolar disorder that experiences more than three episodes in a one year period. However, it is possible for people to have multiple episodes in the same week or even in a single day.

**Causes**

Experts don’t know exactly what causes bipolar disorder.¹⁶ Most scientists now agree that bipolar disorder cannot be attributed to a single cause, but that many factors contribute to produce the illness. One theory suggests that it is related to certain chemicals in the brain which can cause neurotransmitters, and their levels of neutrons, to become unbalanced deteriorating the ability of the brain to properly send messages to the body.
Bipolar disorder tends to run in families so the possibility of the disorder being genetic is a co-existing theory. Studies have been conducted using identical twins (identical genealogy) which lead to some important discoveries about bipolar disorder. The theory basis for the study was that if bipolar disorder was in fact caused entirely by genes, the identical twin of someone with the illness would always develop the illness. The research has shown that this theory was not correct. However, the study did show that if one twin has bipolar disorder, the other twin is more likely to develop the illness than another sibling.\(^1\)

In addition, further genetic research has shown that bipolar disorder is not caused by a single gene, but a combination of many different genes acting in conjunction with other factors of the person or their environment. Pin-pointing these genes has been extremely difficult, but scientists anticipate that the use of advancing technology, especially in brain imaging, will lead the way to important discoveries and new treatments.\(^1\)

**Treatment**

While there is no cure for bipolar disorder, proper treatment can stabilize mood swings and symptoms. Long-term preventative treatment, combining medication and psychotherapeutic treatment, is a cornerstone in the treatment of bipolar disorder. Usually, bipolar disorder is better controlled if treatment is continuous than if it is intermittent. But, even with continuous treatment and medication, mood changes can occur and must be reported to the doctor so adjustments can be made to compensate and hopefully prevent an episode.\(^1\)

"Medications for bipolar disorder are prescribed by psychiatrists -- medical doctors (M.D.) with expertise in the diagnosis and treatment of mental disorders. While primary care physicians who do not specialize in psychiatry also may prescribe these medications, it is recommended that people with bipolar disorder see a psychiatrist for treatment."\(^1\)

Most often, medications known as "mood stabilizers" are prescribed to help control the illness. Mood-stabilizers are generally a preventative treatment in which patients take the medication continuously for a long period of time, if not the rest of their life. Other medications are added, only when necessary, to treat episodes that emerge despite the mood stabilizer, only for short periods of time.

There are many mood stabilizers on the market today. Lithium was the first medication approved by the FDA (Food and Drug Administration) for treatment of mania. Anticonvulsant medications such as valproate (Depakote\(^{®}\)), carbamazepine (Tegretol\(^{®}\)), lamotrigine (Lamictal\(^{®}\)), gabapentin (Neurontin\(^{®}\)), and topiramate (Topamax\(^{®}\)) have mood-stabilizing effects. Also, atypical antipsychotic medications like clozapine (Clozaril\(^{®}\)), olanzapine (Zyprexa\(^{®}\)), risperidone (Risperdal\(^{®}\)), quetiapine (Seroquel\(^{®}\)), ziprasidone (Geodon\(^{®}\)), and Aripiprazole (Abilify) are being studied as possible treatments for bipolar disorder.\(^1\)

Sometimes other medications are prescribed to treat issues that arise indirectly from bipolar disorder. For example, clonazepam (Klonopin\(^{®}\)), lorazepam (Ativan\(^{®}\)), or
zolpidem (Ambien®) are prescribed if insomnia is a problem for the patient. However, these medications may be habit-forming, so they are usually prescribed for shorter periods of time. Also, it is common for people with bipolar disorder to have abnormal thyroid gland function. In these cases, medication is often prescribed for thyroid levels because too much or too little thyroid hormone can lead to mood and energy changes.¹

Psychosocial treatments are an important part of bipolar disorder treatment as they are helpful in providing support, education, and guidance to the people with the disorder, and their families. Studies have shown that psychosocial treatments, or "talk" therapy, can lead to increased mood stability. A licensed psychologist or counselor usually provides the therapies, working closely with the psychiatrist to monitor the patient’s progress.

There are four different psychosocial treatment techniques that are used for bipolar disorder, cognitive behavioral therapy, psycho-education, family therapy, and the newest technique, interpersonal and social rhythm therapy. Research is currently being done to compare these techniques to one another. “Cognitive behavioral therapy helps people with bipolar disorder learn to change inappropriate or negative thought patterns and behaviors associated with the illness. Psycho-education involves teaching people with bipolar disorder about the illness and its treatment, and how to recognize signs of relapse so that early intervention can be sought before a full-blown illness episode occurs. Psycho-education also may be helpful for family members. Family therapy uses strategies to reduce the level of distress within the family that may either contribute to or result from the ill person’s symptoms. Interpersonal and social rhythm therapy helps people with bipolar disorder both to improve interpersonal relationships and to regularize their daily routines. Regular daily routines and sleep schedules may help protect against manic episodes."¹

If medication and/or psychosocial treatments aren’t working, or aren’t working fast enough, to relieve severe symptoms, alternative treatments are available and are being researched further along with new alternatives. Electroconvulsive therapy (ECT) has been used to treat severe symptoms such as psychosis and is sometimes used when medication is too risky, such as during a pregnancy. Risks of ECT treatments, such as the possibility of long-lasting memory problems, have been significantly reduced with modern ECT techniques.

Herbal or natural supplements, like St. John’s wort (Hypericum perforatum) have not been studied because the FDA does not regulate their production, and little is known about their effects on bipolar disorder. Before trying herbal supplements, it is important to discuss it with a doctor as there is evidence that St. John’s wort can reduce the effectiveness of certain medications. Omega-3 fatty acids found in fish oil are being studied to determine their usefulness in the long-term treatment of bipolar disorder.¹
Risks

A common and serious risk associated with bipolar disorder is suicide. With all the mood changes, especially with depressive episodes, people with bipolar disorder may become suicidal. "While some suicide attempts are carefully planned over time, others are impulsive acts that have not been well thought out."  

The risk for suicide has been found to be more prevalent in the earlier course of the illness when the person may be struggling with strong mood swings and emotions unaware that anything is wrong with them. This makes the need to recognize the disorder early and getting the proper treatment to manage it even more important.

“Signs and symptoms that may accompany suicidal feelings include:

- Talking about feeling suicidal or wanting to die
- Feeling hopeless, that nothing will ever change or get better
- Feeling helpless, that nothing one does will make any difference
- Feeling like a burden to family and friends
- Abusing alcohol or drugs
- Putting affairs in order (e.g. organizing finances or giving away possessions to prepare for one’s death)
- Writing a suicide note
- Putting oneself in harm’s way, or in situations where there is a danger of being killed

Other risks include alcohol and drug abuse, which are common in people with bipolar disorder. Research suggests that these substance abuse problems may arise from self-medication of symptoms, or mood symptoms resulting from the disorder. Anxiety disorders, including post-traumatic stress disorder and obsessive-compulsive disorder are also fairly common. Co-occurring anxiety disorders may respond to the treatments for bipolar disorder, or they may require separate treatment.

Conclusion

Unfortunately, there is no known cure for bipolar disorder. But, with the help of trained professionals and preventative therapies like medications and psychosocial treatments, it is possible to manage the illness so the person can lead a normal life. It is important to note that the successful treatment and management of bipolar disorder is directly dependent on recognizing and treating the disorder as early as possible.
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Cigarettes and Their Addictive Components

Prepared for
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CHM236

April 16, 2007
Abstract

Tar and nicotine are commonly known as two separate entities in cigarettes, when in actuality nicotine is a component of cigarette tar. When burning a cigarette a chemical decomposition through heat occurs producing over 4,000 different chemical particles, collectively known as tar.\(^1\) Most of these chemicals are additives mixed in with the tobacco during the manufacturing process, resulting in a more addictive cigarette. This paper will provide information about cigarette tar, nicotine and its addictive properties, and how some of the additives physically and chemically work with nicotine to make cigarettes more addictive.

Cigarette Tar

Description

Tar is the term used to describe the toxic chemicals found in cigarettes. It contains polycyclic aromatic hydrocarbons which are chemical compounds that consist of fused aromatic rings without heteroatoms or substituents.\(^1\) They are formed by the combustion of carbon-containing fuels with size ranging from three to over six fused rings. Being one of the most prevalent organic pollutants, their toxicity is very structurally dependant having isomers varying from nontoxic to extremely toxic.\(^1\) The polycyclic aromatic hydrocarbon benzo[a]pyrene was the first chemical carcinogen to be discovered and is one of the many carcinogens found in cigarette smoke.\(^1,2\) Benzo[a]pyrene is a five-ring polycyclic aromatic hydrocarbon with a molecular weight of 252.31 g/mol and a chemical structure as follows:\(^1\)

![Chemical Structure of Benzo[a]pyrene](image)

Chemical Formula: \(C_{20}H_{12}\)

Mechanism of Action/Synthesis

In 1996, a study was published that provided clear molecular evidence conclusively showing benzo[a]pyrene to cause genetic damage in lung cells that was identical to the damage observed in the DNA of most malignant lung tumors.\(^1\) First, benzo[a]pyrene is activated by cytochrome P4501A1, the product (+)-benzo[a]pyrene-7,8-oxide is metabolized by epoxide hydrolase to yield (-)-benzo[a]pyrene-7,8-dihydrodiol, which forms the ultimate carcinogen benzopyrenediol epoxide ((+)-7R,8S-dihydroxy-9S,10R-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene).\(^1,3\) The two carbons of the epoxide are electrophilic resulting in a covalent bond to the nucleophilic guanine nucleobases at the N2 position.\(^3\)
Health

In the 1950's, doctors and researchers reported possible links between lung disease and cigarette tar which ultimately led to the popularity of the cigarette filter. The purpose of the filter was to trap the tar, making a "safer" cigarette. Unfortunately, the tar and its 4000 plus chemicals make their way into a smoker's lungs. Tar is deposited in the mouth all the way to the lungs, where it can find its way into the blood. Therefore, every part of the body is susceptible to the ill effects of the harmful toxins in tar. The majority resides in the lungs and contributes to numerous lung diseases.
Nicotine

Description

Nicotine is an alkaloid, it is chemically designated as (S)-3-(1-methyl-2-pyrrolidinyl)pyridine, and is a heterocyclic compound containing a pyridine ring.\(^1\) This hygroscopic, oily liquid is miscible with water in its base form and forms salts with acids that are usually solid and water soluble.\(^1\) Nicotine will burn at a temperature below its boiling point of 247 °C, and its vapors will combust at 95 °C in air despite a low vapor pressure of 0.006 kPa at 25 °C.\(^1,2\) It easily penetrates the skin but because of its combustion, most of the nicotine is burned when a cigarette is smoked; however, enough is inhaled to provide the desired effects.\(^1,5\) It has a molecular weight of 162.23 g/mol and a chemical structure as follows:\(^1\)

![Chemical Formula: C\(_{10}\)H\(_{14}\)N\(_2\)](image)

History

Nicotine is found in the Solanaceae family of plants, but is predominantly in the tobacco plant Nicotiana tabacum. It constitutes about five percent of the plant by weight, with biosynthesis taking place in the roots, and accumulating in the leaves.\(^1\) It was first isolated from the plant in 1828 by German chemists, Posselt and Reimann.\(^1\) Eventually, tobacco extract of pure nicotine was found to be highly toxic with particular specificity to insects. It is commonly diluted with water to be used as an insecticide on a wide range of fruit and vegetable crops and it degrades quickly so it can be used near harvesting.

Pharmacokinetics/Metabolism/Elimination

A cigarette contains eight to twenty milligrams of nicotine, but approximately one milligram is actually absorbed in the body when smoking.\(^5\) Ingesting forty milligrams is a lethal limit for adults, but at lower concentrations it acts as a stimulant and is one of the main factors responsible for the dependence forming properties of tobacco smoking.\(^1,5\) As nicotine is inhaled, it moves to the small blood vessels that line the lungs, into the bloodstream, and crosses the blood-brain barrier in about seven seconds.\(^1,2,5\) The half-life of nicotine is around two hours but depends on the rate at which the individual metabolizes it.\(^1,2,5,7\) About eighty percent is broken down in the liver by cytochrome P450, P2A6, and P2B6 enzymes to the metabolite cotinine.\(^1,5\) Cotinine is excreted in the urine and because of its twenty-four hour half-life, urine tests can reveal if someone has been smoking within a day or two.\(^5\) Also, some nicotine is metabolized in the lungs to cotinine and nicotine oxide, while the remaining is filtered from the blood by the kidneys and excreted in the urine.\(^5\)
Pharmacodynamics

Nicotine acts on cholinergic neurons which are neurons that synthesize and release the chemical neurotransmitter acetylcholine.\textsuperscript{1,5,8} Released acetylcholine causes cell depolarization and an influx of calcium through voltage-gated calcium channels, triggering the exocytosis of chromaffin granules.\textsuperscript{1,8} This causes a series of reactions in the catecholamine-secreting neurons where tyrosine is converted to dopamine, to norepinephrine, and then to epinephrine (also known as adrenaline).\textsuperscript{1,5,8}

Acetylcholine leads to a burst of receptor activity, but is typically released from the cholinergic neurons in small amounts and in a regulated manner.\textsuperscript{5} Nicotine is not regulated by the body and activates the cholinergic neurons in many different areas of the brain simultaneously, increasing the release of acetylcholine.\textsuperscript{5,8} The increased release of acetylcholine increases the amount of dopamine and epinephrine produced in the body. Nicotine also increases the level of other neurotransmitters and chemicals such as glutamate and \( \beta \)-endorphins.\textsuperscript{5,8} In high doses, nicotine will cause a blocking of the cholinergic neuron receptors, which is the reason for its toxicity and its effectiveness as an insecticide.\textsuperscript{1}

Side Effects/Addiction

The increased levels of dopamine, epinephrine, glutamate, and \( \beta \)-endorphins are responsible for the addictive properties of nicotine:

**Dopamine** is chemically designated as 4-(2-aminoethyl)benzene-1,2-diol with a chemical structure as follows:\textsuperscript{1}
Dopamine activates the reward pathways in the brain providing feelings of enjoyment and reinforcement, motivating a person proactively to perform certain activities such as eating and sex.\(^1,5\) Nicotine slows the body's natural ability to produce dopamine, making the brain attempt to compensate for artificial stimulation.\(^1\) Therefore, a smoker lacks natural dopamine release and desires the cigarette for the rewarded feeling of pleasure.

**Epinephrine** is chemically designated as 4-(1-hydroxy-2-(methylamino)ethyl)benzene-1,2-diol with a chemical structure as follows:\(^1\)

\[
\begin{align*}
\text{Chemical Formula: } & C_9H_{13}NO_3 \\
\end{align*}
\]

Epinephrine increases heart rate, blood pressure, respiration, and blood glucose levels.\(^1\) Through these pathways, nicotine improves reaction time, the ability to pay attention, and may be the "wake-up call" many smokers use to re-energize themselves throughout the day.\(^1,5\) Also, the brain may see the excess glucose levels and down-regulate the hormones and signals that are perceived as hunger.\(^5\) Many smokers feel that this curbs their appetite and fear that quitting will make them put on weight.

**Glutamate** is chemically designated as (2S)-2-aminopentanedioic acid with a chemical structure as follows:\(^1\)

\[
\begin{align*}
\text{Chemical Formula: } & C_5H_{9}NO_4 \\
\end{align*}
\]

Glutamate is a neurotransmitter involved in learning and memory by enhancing the connections between sets of neurons.\(^5,8\) With nicotine use, glutamate may create a memory loop of the "good feelings" felt from smoking and further drive the desire to use nicotine.\(^5\)

**β-endorphins** are endogenous opioid peptide neurotransmitters that are thirty-one amino acids long and can give rise to other peptide hormones.\(^1\) The brain can make more β-endorphins in response to nicotine which can promote the felling of well-being, relaxation, decreased pain, and euphoria.\(^1,5\)
According to the American Heart Association, "Nicotine addiction has historically been one of the hardest addictions to break."\textsuperscript{1,6} Modern research shows that nicotine is addictive because it activates reward pathways and meets both physiological and psychological measures of addiction.\textsuperscript{1,5} A smoker becomes more and more tolerant to nicotine’s effects, having to use more and more to reach the same degree of stimulation.\textsuperscript{1,5,6} Lacking nicotine, the physiological adaptations remain and withdrawals occur such as irritability, anxiety, depression, and cravings for nicotine.\textsuperscript{1,5} Nicotine withdrawal is short-lived and should pass in time but for many smokers, the withdrawals are too uncomfortable to overcome. The Food and Drug Administration has approved several treatment options to relieve withdrawal symptoms, such as nicotine supplementations and antidepressants, for people who are serious about quitting.\textsuperscript{9}

**Additives in Cigarettes**

In April of 1994, a list of 599 additives used in the manufacturing of cigarettes was submitted by the five major American cigarette companies to the Department of Health and Human Services.\textsuperscript{7,10} These chemicals were approved by the U.S. Government as additives for food, but were not tested by burning them, where the burning changes the properties of many of these chemicals.\textsuperscript{1,10} Over 4000 chemical compounds are created by burning a cigarette, many of which are toxic and/or carcinogenic.\textsuperscript{1,16} The major reasons for using these additives are to control the burn rate, create an attractive ash, enhance the flavor, make the smoke easier to inhale, keep the tobacco moist, and to increase the addictive effects of nicotine.\textsuperscript{1,10} Nicotine by itself is extremely addictive, where the additives used to increase its effects may contribute to the overwhelming success of tobacco companies and the overwhelming failure rate of people trying to quit. Many researchers believe that the tobacco companies have expertly developed ways to manipulate the delivery of nicotine with extreme precision.\textsuperscript{13}

**Additives Increasing the Effects of Nicotine**

**Ammonia Technology**

Ammonia technology is the primary chemical tool used to enhance the effects of nicotine.\textsuperscript{13,15,16} Diammonium phosphate, having the chemical formula of (NH₄)₂HPO₄, is the additive in cigarettes that decomposes to ammonia when heated.\textsuperscript{1,13,15,16}
Ammonia scavenges nicotine from tobacco and extracts "free nicotine" through an acid-base interaction.\textsuperscript{13,15,16} Ammonia in the cigarette increases the pH of the smoke and turns some of the solid nicotine into a gaseous free-based nicotine.\textsuperscript{13,15,16} Once the nicotine gas is in the lungs, it moves quickly into the bloodstream and to waiting nicotine receptors.\textsuperscript{13,15,16} Without ammonia, nicotine in burned tobacco smoke is a solid, tiny particle that must travel in the smoke stream to the smoker's lungs, where it is absorbed more slowly.\textsuperscript{13,15,16} The use of ammonia can boost the availability of nicotine up to 100 times, having a stronger physiological effect on the smoker.\textsuperscript{13,15,16} By harnessing ammonia-producing additives, a manufacturer can enhance nicotine delivery without actually adding nicotine and may explain how tobacco companies have been able to reduce tar levels over the past twenty years while still furnishing smokers with sufficient nicotine levels.\textsuperscript{13,15,16} There is argument that ammonia technology deceives smokers for two-thirds of smokers now buy cigarettes with reduced tar and nicotine.\textsuperscript{13,15,16} The tobacco companies state that the primary purpose for using diammonium phosphate is to increase flavor, reduce irritation, improve body, and the fact that it increases nicotine delivery is an "incidental" effect.\textsuperscript{13,15,16}

A Few Sweeteners and Flavorings

Sugar is the largest additive used, which masks the unpalatable taste of nicotine.\textsuperscript{13} The addition of sweeteners and flavoring is to make the cigarettes smoother and taste better, which is being branded as a cynical attempt to lure young smokers and turn them into addicts.\textsuperscript{11,13,14} Eighty percent of new smokers start below the age of eighteen which is recognized by the industry and targeted in production and marketing strategies.\textsuperscript{1} These additives have addictive properties by themselves, but also increase the absorption of nicotine.\textsuperscript{11,13,14}

Menthol is the flavoring additive in menthol cigarettes. Menthol is chemically designated as 2-(2-Propyl)-5-methylcyclohexanol and is a waxy crystalline substance that melts slightly above room temperature.\textsuperscript{1}

\begin{center}
\includegraphics[width=0.3\textwidth]{chemical_formula.png}

Chemical Formula: C\textsubscript{10}H\textsubscript{20}O
\end{center}

It has local anesthetic and counterirritant qualities, and is widely used to relieve minor throat irritation without any harmful side effects.\textsuperscript{1} It does not change chemical properties when burned in a cigarette, but does enable a smoker to inhale more easily by numbing the throat.\textsuperscript{1,13,14} This allows smokers to inhale increased volumes of smoke, which increases the absorption of nicotine into the lungs.\textsuperscript{11,13}
Cocoa is another ingredient commonly added to cigarettes for taste and smoothness.\textsuperscript{1,13,14} When burned, it releases theobromine.\textsuperscript{1} Theobromine is chemically designated as 3,7-dihydro-3,7-dimethyl-1H-purine-2,6-dione with a chemical structure as follows:\textsuperscript{1}

\begin{center}
\includegraphics[width=0.2\textwidth]{theobromine_structure.png}
\end{center}

Chemical Formula: $C_7H_8N_4O_2$

Theobromine is a potent cyclic adenosine monophosphate phosphodiesterase inhibitor. Cyclic adenosine monophosphate phosphodiesterase is commonly referred to as cAMP and is chemically designated as 3'-5'-cyclic adenosine monophosphate with a chemical structure as follows:\textsuperscript{1}

\begin{center}
\includegraphics[width=0.2\textwidth]{cAMP_structure.png}
\end{center}

Chemical Formula: $C_{10}H_{12}N_5O_6P$

Theobromine acts as a bronchodilator, increasing nicotine absorption, but also prevents the enzyme phosphodiesterase from converting active cAMP to an inactive form.\textsuperscript{1} The active form of cAMP works as a second messenger, transferring the effects of hormones, like adrenaline, through cell membranes.\textsuperscript{1} When theobromine is inhaled, the effects of the hormone are longer lived and the net result is generally a stimulatory effect.\textsuperscript{1}

\textbf{Glycyrrhizin} is the chemical ingredient of liquorice.\textsuperscript{1,13} It is a powerful sweetener that maintains its sweetness under heating.\textsuperscript{1,13} It acts as a bronchodilator, making it easier to inhale harsh cigarette smoke and increases nicotine absorption.\textsuperscript{1,13} Glycyrrhizin is the common name for (3-beta,20-beta)-20-carboxy-11-oxo-30-norolean-12-en-3-yl 2-O-beta-D-glucopyranuronosyl-alpha-D-glucopyranosiduronic acid, with the chemical structure as follows:\textsuperscript{1}

\begin{center}
\includegraphics[width=0.4\textwidth]{glycyrrhizin_structure.png}
\end{center}

Chemical Formula: $C_{42}H_{62}O_{16}$
Humectants

The humectants glycerol and/or propylene glycol are added for moisture control, but when burnt, they decompose forming acrolein and/or formaldehyde.\textsuperscript{1,11,12}

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Systematic Name</th>
<th>Chemical Formula</th>
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</thead>
<tbody>
<tr>
<td>Glycerol</td>
<td>Propane-1,2,3-triol</td>
<td>C\textsubscript{3}H\textsubscript{8}(OH)\textsubscript{3}</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Propane-1,2-diol</td>
<td>C\textsubscript{3}H\textsubscript{6}O\textsubscript{2}</td>
</tr>
<tr>
<td>Acrolein</td>
<td>2-propenal</td>
<td>C\textsubscript{3}H\textsubscript{4}O</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>Formaldehyde</td>
<td>CH\textsubscript{2}O</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
\text{HO-} & \text{--OH} \quad \text{and/or} \quad \text{HO-} & \text{--OH} \\
\text{Glycerol} & \quad \text{and/or} \quad \text{Propylene glycol} \quad \text{280}^\circ \text{C} \quad \text{Acrolein} \quad \text{and/or} \quad \text{Formaldehyde}
\end{align*}
\]

Formaldehyde and acrolein are carcinogens by inhalation, where formaldehyde causes cancers of the nose and throat and acrolein causes lung cancer.\textsuperscript{1} Along with being carcinogenic, they also increase the absorption of nicotine by opening air passages in the lungs.\textsuperscript{1,11,12}

Conclusion

This report only contains a small fraction of the additives used in cigarettes, where 599 of the additives used have adverse effects on smokers. Tobacco smoking has been around for centuries and used to be considered a harmless and attractive habit. The growth in the scientific and medical communities has provided overwhelming evidence on the detrimental effects of cigarette smoking, yet it remains a multibillion dollar industry. It seems that the monetary benefits have taken precedence over the public’s health. With nicotine ranking as one of the most powerful and addictive substances, smokers often ignore the facts due to their physical and psychological dependence. The tobacco companies not only prey on these weaknesses but are using science in an unethical way. It is no surprise that the failure rate for quitters is extremely high, even with drug treatment and various means of support. Hopefully, one day the government will put an end to the use of these harmful additives in cigarettes by implementing more stringent regulations. In a perfect world, the government will work beside the scientific and medical communities in achieving a way to combat nicotine addiction and bankrupt the tobacco companies.
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Suboxone: A Possible Cure for Opioid Dependence

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Abstract

Suboxone (buprenorphine HCL and naloxone HCL dehydrate) is a sublingual tablet approved by the FDA in October 2002 under priority to treat opioid dependence. Suboxone is a combination of two drugs that work together to antagonize the mu-opioid receptor and the kappa-opioid receptor. This paper will discuss the history of opioid dependence, how this specific class III narcotic opioid-dependence drug works and the future of Suboxone for opioid treatment.

History of Opioid Dependence

Opioids have been used for pleasure and to treat pain for almost 6,000 years. In 460 BC, Hippocrates, the great Greek physician, used opium to treat everything from headaches and coughing to asthma and melancholy. Opioids were reaching popularity at this time but disappeared during the Holy Inquisition in Europe. For around 200 years the history record has no documentation of this type of drug being used at all.

Opioid abuse became prevalent during the second half of the 19th century, after the invention of the hypodermic syringe. Injecting opium allowed for a more rapid, potent effect. During the American Civil War, morphine was used to treat injuries, and opioid dependence became so common among the armed forces that it was referred to as the "soldiers' disease."

In 1898 a new drug called "heroin" was invented by Bayer Laboratories to offset the addictive effects of morphine. Heroin was believed to be so non-addictive that free doses were available for addicts to try and "step down" from more addictive opioids. Fortunately the negative effects of heroin were recognized and medical use of the drug was stopped in 1924; later in 1970 a total ban of heroin was issued by the US government.

Currently, opioids are still used and recognized as highly effective analgesic medications. The increasing demand for more effective, longer acting pain relievers has been met and with the more potent drugs comes the higher chance of addiction. In 2001, opioid dependence accounted for 18% of all substance abuse treatment admissions, exceeding cocaine admissions for the 5th consecutive year. At present, the number of untreated opioid-dependent patients in the United States is believed to be at least 1.2 million.

The growing problem of opioid addicted people warranted a cure. In cooperation with the National Institute of Drug Abuse, Suboxone was developed to help these patients. In 2000, Congress approved the Drug Addiction Treatment Act (DATA 2000), giving physicians the right to use approved opioids to treat opioid dependence in their offices. In October of 2002, Suboxone was approved by the FDA to treat opioid dependence. Since its acceptance in the US, Suboxone has been approved in over 30 countries and is currently helping opioid addicted patients worldwide.
Description

Suboxone sublingual tablets contain a 4:1 ratio of buprenorphine HCl and naloxone HCl. The lowest strength of the drug contains 2mg of buprenorphine and 0.5mg of naloxone while the highest strength consists of 8mg of buprenorphine and 2mg naloxone. Suboxone is chemically designated as an antagonist at the mu-opioid and kappa-opioid receptors located in the central nervous system.

Buprenorphine appears as a white powder that is weakly acidic in water. Its molecular formula is $\text{C}_{29} \text{H}_{41} \text{NO}_4 \text{HCl}$ and molecular weight is 504.10. The chemical structure is as follows:

![Buprenorphine HCl](image)

Naloxone is also a white powder and soluble in water. The molecular weight is 399.87 and it has a formula of $\text{C}_{19} \text{H}_{21} \text{NO}_4 \text{HCl} \cdot 2\text{H}_2\text{O}$. The chemical structure appears as follows:

![Naloxone HCl](image)

Mechanism of Action

Drugs that treat opioid dependence work by blocking the receptor sites of opioids, located in the Central Nervous System. The two drugs in Suboxone work very differently but the outcome is similar. Naloxone is a pure opioid antagonist that competes and displaces narcotics at the opioid receptor site. Buprenorphine has an analgesic effect that binds to $\mu$-opiate receptors in the CNS. It shows both agonist and antagonist characteristics.
Pharmacokinetics/Metabolism/Elimination

Suboxone is administered orally in a sublingual tablet form. Plasma levels of buprenorphine and naloxone increased with each sublingual dose of Suboxone. Both peak plasma level (C_max) and area under the curve (AUC) of buprenorphine increased in a linear fashion with the increase in dose (in the range of 4 to 16 mg), although the increase was not directly dose-proportional. Naloxone does not affect the pharmacokinetics of buprenorphine however the levels of naloxone are too low to assess dose-proportionality. In Table 1 the C_max and AUC are shown for each available dose of Suboxone.4

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Suboxone® 4 mg</th>
<th>Suboxone® 8 mg</th>
<th>Suboxone® 16 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_max, ng/mL</td>
<td>1.84 (39)</td>
<td>3.0 (51)</td>
<td>5.95 (38)</td>
</tr>
<tr>
<td>AUC 0-48, hour*ng/mL</td>
<td>12.52 (35)</td>
<td>20.22 (43)</td>
<td>34.89 (33)</td>
</tr>
</tbody>
</table>

The two ingredients in Suboxone are metabolized quite differently. Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated by cytochrome P-450 3A4 isozyme. Norbuprenorphine, an active metabolite, can further undergo glucuronidation.4 Buprenorphine is metabolized primarily in the liver and undergoes extensive first-pass effect.3 Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.4 Much like buprenorphine, naloxone is metabolized in the liver.3

Suboxone is eliminated primarily by hepatic metabolism with complete recovery of radiolabel. 11 days after dosing, urine and feces contained 30% and 69% of the isolated drug respectively.4

Clinical Studies

In a double blind placebo- and active controlled study, 326 heroin-addicted subjects were randomly assigned to either Suboxone 16 mg per day, 16 mg per day of Subutex (a similar opioid-dependence drug) or placebo tablets. Subjects were told to take one tablet (8mg) of either Suboxone, Subutex or placebo tablet on day one, then increase to two tablets on day two and hold that dose for four weeks.4 Subjects were told to place the tablet under the tongue and hold for 5-10 minutes until completely dissolved. The test subjects were seen Monday through Friday in a clinic for dosing and efficacy assessments. The purpose of the study was to compare the efficacy of Subutex and Suboxone against a placebo. The results demonstrated that the percentage of urine samples taken three times per week that were negative for opioids was statistically higher for Subutex and Suboxone than for placebo.4
In a dose-controlled, double-blind, parallel-group, 16-week study, 731 subjects were randomized to receive one of four doses of buprenorphine ethanolic solution. Buprenorphine was titrated to maintenance doses over 1-4 days (Table 2) and continued for 16 weeks. Subjects received at least one session of AIDS education and additional counseling ranging from one hour per month to one hour per week, depending on site.\textsuperscript{4}

Table 2. Doses of Sublingual Buprenorphine Solution used for Induction in a Double-Blind Dose Ranging Study

<table>
<thead>
<tr>
<th>Target Dose of Buprenorphine *</th>
<th>Induction Dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
</tr>
<tr>
<td>1 mg</td>
<td>1 mg</td>
<td>1 mg</td>
</tr>
<tr>
<td>4 mg</td>
<td>2 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>8 mg</td>
<td>2 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>16 mg</td>
<td>2 mg</td>
<td>4 mg</td>
</tr>
</tbody>
</table>

*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes:
- 2 mg solution would be roughly equivalent to 3 mg tablet
- 4 mg solution would be roughly equivalent to 6 mg tablet
- 8 mg solution would be roughly equivalent to 12 mg tablet
- 16 mg solution would be roughly equivalent to 24 mg tablet

Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opioids, the three highest tested doses were superior to the 1mg dose. Therefore, this study showed that a range of buprenorphine doses may be effective. The 1mg dose of buprenorphine sublingual solution can be considered to be somewhat lower than a 2 mg tablet dose. The other doses used in the study encompass a range of tablet doses from approximately 6 mg to approximately 24 mg.\textsuperscript{4}

**Drug Interactions**

Buprenorphine is metabolized by cytochrome CYP 3A4 in the liver to norbuprenorphine. Since CYP 3A4 inhibitors may increase buprenorphine concentrations, patients already on CYP 3A4 inhibitors should have their drug doses closely monitored. There also has been anecdotal evidence that buprenorphine and benzodiazepines also may interact negatively. Reports have detailed events such as coma and death because of the simultaneous use of these two drugs.\textsuperscript{5} Enzyme inducers may reduce serum concentrations of buprenorphine, resulting in loss of efficacy.\textsuperscript{3}
Side Effects

Since Suboxone is similar to more powerful opioids the side effects are similar. The most commonly reported adverse events with Suboxone include: headache (36%, placebo 22%), withdrawal syndrome (25%, placebo 37%), pain (22%, placebo 19%), nausea (15%, placebo 11%), insomnia (14%, placebo 16%), and sweating (14%, placebo 10%). Determining whether the symptoms are from the opioids or Suboxone is for the physician to decide. Suboxone can also cause blood pressure to drop. This can cause the patient to feel dizzy if he or she gets up too fast from sitting or lying down.

The safety of Suboxone was evaluated in 497 opioid-dependent subjects. The prospective evaluation of Suboxone was supported by clinical trials using Subutex (buprenorphine tablets without naloxone) and other trials using buprenorphine sublingual solutions. In total, safety data are available from 3214 opioid-dependent subjects exposed to buprenorphine at doses in the range used in treatment of opioid addiction. Few differences in adverse event profile were noted between Suboxone and Subutex or buprenorphine administered as a sublingual solution. In a comparative study, adverse event profiles were similar for subjects treated with 16 mg Suboxone or 16mg Subutex. The following adverse events were reported to occur by at least 5% of patients in a 4-week study (Table 3).

<table>
<thead>
<tr>
<th>Body System/Adverse Event (COSTART Terminology)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body As A Whole</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>7 (6.5%)</td>
<td>5 (4.9%)</td>
<td>7 (6.5%)</td>
</tr>
<tr>
<td>Chills</td>
<td>8 (7.5%)</td>
<td>8 (7.8%)</td>
<td>8 (7.5%)</td>
</tr>
<tr>
<td>Headache</td>
<td>39 (36.4%)</td>
<td>30 (29.1%)</td>
<td>24 (22.4%)</td>
</tr>
<tr>
<td>Infection</td>
<td>6 (5.6%)</td>
<td>12 (11.7%)</td>
<td>7 (6.5%)</td>
</tr>
<tr>
<td>Pain</td>
<td>24 (22.4%)</td>
<td>19 (18.4%)</td>
<td>20 (18.7%)</td>
</tr>
<tr>
<td>Pain Abdomen</td>
<td>12 (11.2%)</td>
<td>12 (11.7%)</td>
<td>7 (6.5%)</td>
</tr>
<tr>
<td>Pain Back</td>
<td>4 (3.7%)</td>
<td>8 (7.8%)</td>
<td>12 (11.2%)</td>
</tr>
<tr>
<td>Withdrawal Syndrome</td>
<td>27 (25.2%)</td>
<td>19 (18.4%)</td>
<td>40 (37.4%)</td>
</tr>
<tr>
<td><strong>Cardiovascular System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasodilation</td>
<td>10 (9.3%)</td>
<td>4 (3.9%)</td>
<td>7 (6.5%)</td>
</tr>
<tr>
<td><strong>Digestive System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>13 (12.1%)</td>
<td>8 (7.8%)</td>
<td>3 (2.8%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (3.7%)</td>
<td>5 (4.9%)</td>
<td>16 (15.0%)</td>
</tr>
</tbody>
</table>

Table 3. Adverse Events (≥5%) by Body System and Treatment Group in a 4-week Study
Table 3. Adverse Events (≥5%) by Body System and Treatment Group in a 4-week Study

<table>
<thead>
<tr>
<th>Body System/Adverse Event (COSTART Terminology)</th>
<th>SUBOXONE 16 mg/day N = 107</th>
<th>SUBUTEX 16 mg/day N = 103</th>
<th>Placebo N = 107</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>16 (15.0%)</td>
<td>14 (13.6%)</td>
<td>12 (11.2%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (7.5%)</td>
<td>8 (7.8%)</td>
<td>5 (4.7%)</td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>15 (14.0%)</td>
<td>22 (21.4%)</td>
<td>17 (15.9%)</td>
</tr>
<tr>
<td><strong>Respiratory System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5 (4.7%)</td>
<td>10 (9.7%)</td>
<td>14 (13.1%)</td>
</tr>
<tr>
<td><strong>Skin And Appendages</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>15 (14.0%)</td>
<td>13 (12.6%)</td>
<td>11 (10.3%)</td>
</tr>
</tbody>
</table>

From the above study one can see that side effects are relatively rare compared to other drugs. The effects associated with this drug are much less severe than those of similar more powerful opioids. The symptom seen most was headache which is hard to fully contribute to a single drug. Opioid users may have other medications or drug in their system, which contribute to the headache feeling.

**Future of Suboxone**

The destiny of Suboxone looks promising. Never before has a drug like this been able to help with such a terrible, unfortunate addiction. By simply using Suboxone patients have the opportunity to be cured of a debilitating illness and return to a sober life. Since this drug has very little serious complications or side effects a variety of patients can use it without fear. Unless a better medication comes along that can provide the same relief with less side effects Suboxone will be the go-to drug for opioid dependence. This drug truly has the power to transform lives, from one of addiction and poor health to a life of vibrant, wonderful sobriety.

**Conclusion**

In the never ending cycle of dependence and treatment, Suboxone holds the key to a new and improved life. Opioids are excellent pain relievers but with that power comes the potential of addiction, either physical or psychological. Since the potency keeps increasing to meet demand of stronger drugs, dependence also keeps rising. Drugs like Suboxone are available to meet the addict when normal use turns into abuse. Since approved by the FDA in 2002, patients have the ability to treat and manage addiction in a manner like never before.
References


Levaquin®

Prepared for:
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CHM 236
April 20, 2007
Abstract

Levaquin® (levofloxacin), marketed by Ortho-McNeil, is a fluoroquinolone antibiotic, which was approved by the FDA on December 20, 1996 for the treatments of lung, skin, sinus, and urinary tract infections. Levofloxacin, like many other fluoroquinolones, can be administered orally, intravenously, and ophthalmically. It is highly effective against specific bacteria that is resistant to penicillin, thus making it the preferred antibiotic. This paper will discuss the history of quinolones and levofloxacin, the mechanism of the action, possible side effects and the future of Levaquin®.

Brief History of Quinolones and Levofloxacin

Antibiotics fight against infections that are caused by bacteria. A transformation in medical care occurred when antibiotics emerged in the 1930s and 1940s, drastically reducing illnesses and deaths caused by infectious diseases. Quinolone antibiotics were originated from nalidixic acid in 1962 to fight against a broad spectrum of bacterial infections.¹ They have progressed from first-generation to the more advanced third-generation agents. Originally developed to fight against Gram-negative bacteria and against a limited amount of indications, quinolones have diverged into a class of widely used oral and intravenous antibiotics with “extensive indications for infections caused by many bacterial pathogens in most body tissues and fluids.”

Fluoroquinolones, a quinolone subgroup, are fluorinated at the 6-position and have a carbon atom substituted for nitrogen at the 8-position of the naphthyridine nucleus.¹ Levofloxacin, a more advanced fluoroquinolone, is an antibacterial agent consisting of a wide range of activity against Gram-positive and Gram-negative bacteria and atypical respiratory pathogens.²

Although the FDA approved the levofloxacin tablets and injection to treat community-acquired pneumonia, sinusitis, chronic bronchitis, skin infections, urinary tract infection and acute pyelonephritis in December 1996, an additional approval was later granted in November 2002 for the treatment of nosocomial pneumonia.³ In addition, the FDA approved two levofloxacin ophthalmic solutions, Quixin™ and Iquix™, in order to treat bacterial conjunctivitis and bacterial corneal ulcers. Recently, in November 2004, the FDA approved the levofloxacin oral solution as well.

Description

Levaquin® tablets are available in 250 mg, 500 mg, and 750 mg dosages. The oral solution contains 25 mg/ml of levofloxacin aqueous solution. Levaquin injection is available in single-use vials where “each vial contains a concentrated solution with the equivalent of 500 mg of levofloxacin in 20 ml vials and 750 mg of levofloxacin in 30 ml vials”.⁴ Quixin™ contains 0.5% levofloxacin and Iquix™ is comprised of 1.5% levofloxacin.³

Levaquin® is a chiral fluorinated carboxyquinolone known as (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-
carboxylic acid hemihydrate. Levofloxacin is the S-enantiomer of ofloxacin, as well as the optically active L-isomer of ofloxacin. The empirical formula is C<sub>18</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>4</sub> • ½ H<sub>2</sub>O, the molecular weight is 370.38 g/mol, and this molecule exists as a zwitterion at the pH conditions of the small intestine (approximately pH 0.6-5.8). Levofloxacin is considered soluble to freely soluble under these pH conditions. It has an in vitro chelation potential to form stable coordination compounds with metals in the following order: Al<sup>3+</sup>&gt;Cu<sup>2+</sup>&gt;Zn<sup>2+</sup>&gt;Mg<sup>2+</sup>&gt;Ca<sup>2+</sup>.

![Chemical Structure of Levofloxacin](image)

**Figure 1: Chemical Structure of Levofloxacin**

**Mechanism of Action**

Levofloxacin inhibits two, type II topoisomerases- bacterial topoisomerase IV and DNA gyrase. Topoisomerases change “DNA by introducing superhelical twists into double-stranded DNA” and by initiating and assisting with the unraveling of the DNA strands. The two subunits on the DNA gyrase are encoded by the gyrA gene. This gene causes the strand to break on a bacterial chromosome and then reunites the chromosome together after supercoiling. Fluoroquinolones, including levofloxacin, inhibit the A subunits of DNA gyrase, thus, resulting in the inhibition of bacterial DNA replication and transcription. Although human cells do not contain DNA gyrase, humans do however contain a topoisomerase enzyme that functions in a similar manner.

**Dosage and Indications**

Levaquin® is usually administered orally; however, it is available as an injection and ophthalmically. It is based on a once-daily dosage regimen. On average, levofloxacin 500 mg once daily tablets are given over a 7-14 day span, a 750 mg once daily dosage is dispensed for 5 days, and a 250 mg once daily dosage is recommended for 10 days or 3 days respectively, depending on the severity and type of infection. Furthermore, it is formulated for slow intravenous infusion for a period of 60 minutes for 250 mg or 500 mg dosages and 90 minutes for 750 mg. Patients may also be sequentially transferred from intravenous to oral therapy without altering the dosage. It does not need to be taken with food; however, it should be administered at least two hours before or after taking preparations such as metal cations, multivitamins and antacids. The oral solution should be taken one hour before or two hours after eating. Ophthalmically, the solution is applied topically to the eye, taking care to avoid contamination.
<table>
<thead>
<tr>
<th>Infection</th>
<th>Unit Dose</th>
<th>Freq.</th>
<th>Duration</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comm. Acquired Pneumonia</td>
<td>500 mg</td>
<td>q24h</td>
<td>7-14 days</td>
<td>500 mg</td>
</tr>
<tr>
<td>Comm. Acquired Pneumonia</td>
<td>750 mg</td>
<td>q24h</td>
<td>5 days</td>
<td>750 mg</td>
</tr>
<tr>
<td>Nosocomial Pneumonia</td>
<td>750 mg</td>
<td>q24h</td>
<td>7-14 days</td>
<td>750 mg</td>
</tr>
<tr>
<td>Acute Bacterial Sinusitis</td>
<td>500 mg</td>
<td>q24h</td>
<td>10-14 days</td>
<td>500 mg</td>
</tr>
<tr>
<td>Acute Bacterial Sinusitis</td>
<td>750 mg</td>
<td>q24h</td>
<td>5 days</td>
<td>750 mg</td>
</tr>
<tr>
<td>Complicated SSSI</td>
<td>750 mg</td>
<td>q24h</td>
<td>7-14 days</td>
<td>750 mg</td>
</tr>
<tr>
<td>Acute Bacterial Exacerbation of Chronic Bronchitis</td>
<td>500 mg</td>
<td>q24h</td>
<td>7 days</td>
<td>500 mg</td>
</tr>
<tr>
<td>Uncomplicated SSSI</td>
<td>500 mg</td>
<td>q24h</td>
<td>7-10 days</td>
<td>500 mg</td>
</tr>
<tr>
<td>Chronic Bacterial Prostatitis</td>
<td>500 mg</td>
<td>q24h</td>
<td>28 days</td>
<td>500 mg</td>
</tr>
<tr>
<td>Complicated UTI</td>
<td>250 mg</td>
<td>q24h</td>
<td>10 days</td>
<td>250 mg</td>
</tr>
<tr>
<td>Acute pyelonephritis</td>
<td>250 mg</td>
<td>q24h</td>
<td>10 days</td>
<td>250 mg</td>
</tr>
<tr>
<td>Uncomplicated UTI</td>
<td>250 mg</td>
<td>q24h</td>
<td>2 days</td>
<td>250 mg</td>
</tr>
<tr>
<td>Inhalational anthrax (post-exposure)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>500 mg</td>
<td>q24h</td>
<td>60 days</td>
<td>500 mg</td>
</tr>
</tbody>
</table>

**Figure 2**: Dosage and Administration for Patients with Normal Renal Function

To maintain the effectiveness of levofloxacin and to minimize the development of drug-resistant bacteria, Levaquin® should only be used to cure or prevent infections strongly believed to be caused by susceptible bacteria. The tablets, injection, and oral solution are "indicated for the treatment of adults (18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms." For example, Levaquin® has been proven to be active in vitro against the following bacteria: *Streptococcus pneumoniae* (including penicillin-resistant strains), *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Proteus mirabilis*, *Streptococcus pyogenes*, *Moraxella catarrhalis*, *Legionella pneumophila*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*. Levofloxacin is only somewhat active against *Enterococcus faecalis* and *Pseudomonas aeruginosa* and is only used to treat urinary tract infection resulting from these organisms.

Levaquin® is excellent in treating the following infections caused by the bacteria listed above. Pneumonia is an infection of the small air sacs of the lungs and the surrounding tissues. Nosocomial pneumonia and community-acquired pneumonia (CAP) are contracted during hospital stays or outside the hospital, respectively. Sinusitis is an inflammation of the hollow air spaces surrounding the nose. Chronic bronchitis is the inflammation of the bronchial tubes in which the patient has an increased production of mucus and a difficult time breathing. Levaquin® is also indicated for the treatment of genitourinary infections, such as urinary tract infections (UTI) in both men and women, acute pyelonephritis, and chronic prostatitis. UTI's are complicated and uncomplicated and involve the kidneys, ureters, and the bladder. Acute pyelonephritis results from an inflammation of one or both kidneys. Chronic prostatitis only occurs in men due to an inflamed or infected prostate, a small gland which is part of the reproductive system. Skin infections also range from uncomplicated to complicated, depending on the severity and size of the affected area. Levaquin® is used for the treatment of skin infections including cellulitis, impetigo, abscesses and wound infections.
Figure 3: Pneumonia

Figure 4: Sinusitis

Figure 5: Bronchitis

Figure 6: UTI in Female

Figure 7: Uncomplicated Skin Infections

Figure 8: Complicated Skin Infections
Pharmacokinetics

Levofloxacin is rapidly absorbed into the blood stream after oral administration. It has an absolute bioavailability of about 99%. Consumption of food does not affect the bioavailability of this antibiotic; however, food delays the time of the peak concentration by approximately one hour. Peak plasma concentrations are achieved approximately 1-2 hours after an oral dose. In addition, “the plasma concentration profile of levofloxacin after intravenous administration is similar and comparable in extent of exposure (AUC) to that observed for levofloxacin tablets when equal doses (mg/mg) are administered.” Thus, oral and intravenous formulations are believed to be interchangeable. Furthermore, a small amount of levofloxacin is absorbed after ophthalmic administration. In vitro, levofloxacin is approximately 24% to 38% bound to serum proteins, mainly albumin, and it is widely distributed into all bodily tissues.

Metabolically, levofloxacin does not invert to its enantiomer, D-ofloxacin. It undergoes limited metabolism and approximately 87% of the prescribed dose is excreted as an unchanged drug in the urine. The only metabolites recovered in the urine that are identified in humans are desmethyl and N-oxide metabolites, which account for less than 5% of the entire dose. Renal elimination of levofloxacin is “greater than glomerular filtration, suggesting active tubular secretion.” The average elimination half-life of levofloxacin ranges from six to eight hours and is prolonged in patients with impaired renal function.

Drug Interactions

The safety and effectiveness of levofloxacin has not been determined in pediatric patients, adolescents under 18 years of age, or in pregnant and nursing women.

Levaquin® should not be concurrently administered with antacids containing magnesium or aluminum, sucralfate, or metal cations such as iron, nor with multivitamins containing zinc or didanosine, due to possible interference with the gastrointestinal absorption of levofloxacin, thus resulting in lower than desired systematic levels.

Although no significant interactions between levofloxacin and theophylline have been detected, simultaneous administration of other quinolones with theophylline has caused prolonged elimination half-life, increased serum theophylline levels, and a higher risk for theophylline-related adverse reactions. Theophylline levels are to be closely monitored and appropriate dosage adjustments should be made when co-administering with levofloxacin.

Various post-marketing reports have shown that patients taking levofloxacin have experienced enhanced effects of warfarin, an anticoagulant (blood thinner). Elevations of the prothrombin time and episodes of bleeding have occurred when using levofloxacin and warfarin concurrently.

Levofloxacin decreases the clearance of caffeine, which causes the caffeine to persist longer in the blood. Those who consume greater amounts of caffeine-containing beverages are to receive extra attention while concurring with quinolones.
The concurrent use of a non-steroidal anti-inflammatory drug (NSAID) with a quinolone, such as levofloxacin, may further promote the risk of central nervous system (CNS) stimulation and convulsive seizures. Because of possible disturbances of blood glucose levels, including hyperglycemia and hypoglycemia, careful monitoring of blood glucose is suggested when antidiabetic agents and quinolones are co-administered.  

Side Effects and Warnings

Levofloxacin is generally well tolerated. The most frequently reported adverse reactions are nausea and diarrhea. Other side effects include insomnia, abdominal pains, dizziness, rash, vaginitis, constipation, headache, dry mouth, agitation and vomiting. Reports have shown that convulsion and toxic psychosis have occurred in patients receiving quinolones. In addition, quinolones may cause “increased intracranial pressure and central nervous system stimulation which may lead to tremor, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and rarely, seizures (<0.3%).” In rare cases, levofloxacin has also been reported to affect small and/or large axons causing paresthesias, hypoesthesias, dysesthesias and weakness.

Additionally, tendon ruptures, such as in the shoulder, hand, and Achilles tendon have been reported in twenty-five cases in patients receiving levofloxacin. In post-marketing reports state that patients receiving concomitant corticosteroids have a higher risk for tendon ruptures. Levaquin® should be immediately discontinued at the first appearance of an allergic reaction, symptoms of neuropathy, or if patients experience pain, inflammation or a ruptured tendon. Usage of levofloxacin should be avoided in patients known to have “prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents.”

Nonetheless, liver toxicity, tendon disorders, hypoglycemia and hyperglycemia are rare with levofloxacin. In comparison to other quinolones, levofloxacin has a low phototoxicity potential. Even though levofloxacin is more soluble than other quinolones, patients should maintain adequate hydration to prevent high concentrated urine from forming.

Clinical Studies

As discussed in many clinical studies, levofloxacin has been proven to be more effective than other comparator drugs. In the treatment of respiratory tract infections, such as community-acquired pneumonia, several comparative trials indicated that the bacteriological response rates were similar in patients with intravenous and/or oral administration of levofloxacin 500 mg once daily for 7-14 days compared to the comparators, including antibiotics such as clarithromycin, azithromycin, and amoxicillin/clavulanic acid. The response rate was 86%-96% and 85%-98% for levofloxacin in relationship to the comparator, 83%-96% and 75%-98%.

In genitourinary tract infections, such as urinary tract infections, the bacteriological response rates for levofloxacin administered orally ranged from 93%-98% and 94%-96%. The
comparator had response rates of 89%-97% and 92%-94%. It was determined that a 3-day levofloxacin treatment of 250 mg dosed once a day was as effective as ofloxacin 200 mg twice daily in patients with uncomplicated UTI. In patients with complicated UTI, levofloxacin 250 mg once daily for 7-10 days had similar efficacy as ciprofloxacin 500 mg twice daily for 10 days. In male patients with chronic bacterial prostatitis, a 28-day regimen of oral levofloxacin 500 mg once daily had similar efficacy results compared to a 28-day oral administration of ciprofloxacin 500 mg twice daily.

In patients with complicated skin infections, the bacteriological response rate was higher with oral levofloxacin 750 mg once daily than with oral amoxicillin/clavulanic acid 875 mg twice daily, both administered for 7-14 days. The response rate was 84% levofloxacin versus 71% comparator. In patients with uncomplicated skin infections, oral levofloxacin 500 mg once daily for 7-10 days was as effective as ciprofloxacin 500 mg twice daily for the same period of time.

**Future of Levaquin®**

Penicillin-resistant strains of *Streptococcus pneumoniae* are rapidly increasing, thus, a need for an antibiotic that can fight against this is increasing as well. Although Levaquin® is a costly antibiotic, in the year 2000, it was approved to be the first anti-infective to treat more than 25% of penicillin-resistant cases. Penicillin-like antibiotics, regardless of resistance, also cause many allergic reactions. This gives Levaquin® more opportunities to fight against the infection. In addition, “levofloxacin is approximately twice as potent *in vitro* as ofloxacin against a variety of aerobic gram-positive and gram-negative bacteria.” Unlike other quinolones, it does not significantly interact with theophylline and very rare cases have reported harmful interactions and side effects. Furthermore, levofloxacin is administered only once daily, whereas other quinolones are administered twice daily. This means that patients do not have to worry about taking this medication more frequently, which reduces the hassle of remembering the exact time the medication should be taken. Because Levaquin® is a well-tolerated antibiotic that treats a wide spectrum of infections, patients with community-acquired pneumonia, urinary tract infection, sinusitis, and certain skin infections will continue to utilize this antibiotic, regardless of the $10+ per pill cost.

**Conclusion**

Levaquin® is an excellent fluorquinolone antibiotic that works only against specific bacteria; it does not combat viruses such as the common cold. This antibacterial drug should only be used in adults over the age of 18. It is available orally, ophthalmically and intravenously in once daily dosages. Due to its high bioavailability and greater effectiveness against infections, Levaquin® is considered to be the preferred treatment for respiratory tract infections, skin infections, and genitourinary tract infections.
Bibliography


Heterotopic Ossification:
The Transformation of Muscle Into Bone

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Abstract

Heterotopic Ossification is the abnormal formation of true bone in connective soft tissues and other areas of the body where it does not belong. Most types of heterotopic ossification, including Myositis ossificans traumatic, are acquired and occur as a result of trauma. There are also types of heterotopic ossification that are hereditary, although they are extremely rare. These include Fibrodysplasia Ossificans Progressiva, Progressive Osseous Heteroplasia and Albright’s Hereditary Osteodystrophy.

Introduction

Heterotopic ossification (HO) is the abnormal formation of true bone in areas of the body where bone does not normally grow such as muscles, tendons, ligaments and other soft tissues. Although ossification can happen anywhere, it occurs most commonly near the long bones and joints. It is frequently found near the hips in the flexor and adductor areas and in the knees along the “medial-collateral ligament.” HO of the shoulders is also common, but does not generally cause problems with functionality because it is less severe. Heterotopic ossification is usually seen after musculoskeletal trauma, injury to the spinal cord or injury to the central nervous system. Although it is much less common, there are also hereditary causes of heterotopic ossification.

Pathophysiology

Heterotopic ossification “originates from osteoprogenitor stem cells lying dormant within the affected soft tissues.” Osteoprogenitor cells “express the transcription factor Cbfa1/Runx2. Once osteoprogenitor cells start to differentiate, they begin to express a range of other bone markers including Osterix, Coll, ALP, Osteocalcin, Osteopontin and Osteonectin.” Influenced by growth factors, usually bone morphogenetic proteins, the osteoprogenitor cells differentiate into osteoblasts. Osteoblasts are specialized “cells that secrete osteoid,” which is a protein mixture that mineralizes and forms bone. Two distinct types of stem cells are needed to form a heterotopic skeleton. One type will form the bone marrow and the other will form the “skeletal scaffold.”

Figure 1. Osteoblast Formation
**Histology**

Within the first week of the trauma that causes ossification, the population of spindle cells in the damaged tissue increases dramatically.\(^3\) Seven to ten days later, osteoblast formation and osteoid can be noted at the outside edge of the lesion. In the second week, primitive cartilage and woven bone are formed. Within five weeks, trabecular bone is formed.\(^3\) Trabecular bone is lower in density and strength, and it is the kind of bone that fills the long bones of the body. Six weeks after the trauma occurs, lamellar bone, which is stronger mature bone, can be found on the outside of the lesion, with immature and undifferentiated tissues in the center.\(^3\)

![Figure 2. Sodium Etidronate](image.png)

**Treatment**

There is no cure for heterotopic ossification, which makes prophylaxis and early treatment important. After being diagnosed with heterotopic ossification, range-of-motion exercises are used to conserve joint mobility. Nonsteroidal anti-inflammatory drugs and bisphosphonates are also used to treat HO. Bisphosphonates, such as sodium etidronate, function by inhibiting “calcium phosphate precipitation, slowing of hydroxyapatite crystal aggregation, and finally inhibition of the transformation of calcium phosphate to hydroxyapatite.”\(^5\) Bisphosphonates can only prevent the crystallization of the osteoid, not the formation of the bone matrix.\(^5\) After stopping treatment with bisphosphonates “the matrix undergoes uninhibited mineralization known as the ‘rebound-effect.”\(^5\) Therefore, it is important to treat HO as soon as it is diagnosed and continue treatment for an adequate period of time, usually at least six months.\(^5\) After treatment with etidronate, rebound ossification does not usually occur, and “the new HO foci show a milder course without severe functional impairment, and total joint ankylosis does not occur.”\(^5\) In cases using bisphosphonates, the results seem to be effective as long as treatment is continuing.\(^5\)

**Acquired Disorders**

Most cases of heterotopic ossification are acquired. Myositis ossificans traumatica is a form of HO that occurs after trauma including burns, surgery or blunt injury.\(^3\) When located in the subcutaneous fat, the lesion is called panniculitis ossificans. Lesions that are in the adductor muscles are called rider’s bones, and lesions in the deltoid are called shooter’s bones.\(^4\)

Neurogenic Heterotopic Ossification is the most common type of acquired HO.\(^5\) It generally occurs after spinal cord injury or other neurologic disorders such as closed head injury and strokes.\(^7\) HO occurs in forty to fifty percent of individuals after spinal cord injury.\(^15\) Neurogenic
heterotopic ossification is characterized by "the growth of a knot-like piece of bone in the soft tissues of your body below the level of your spinal cord injury." The ossification occurs between muscles that are usually located close to a joint. It may affect all joint areas below the level of your spinal cord injury. In neurogenic HO, ossification stops on its own, usually between 18 and 30 months.

According to Banovac, trauma is the main requirement to start ossification. Other requirements include "traumatic ischemic degeneration of involved muscle" and "tissue expression of bone morphogenetic proteins." Muscle trauma including tears, ruptures bleeding and edema have also been suggested to cause HO after spinal cord injury. Other researchers have "suggested that factors such as intensive rehabilitation, transfer activities, or repeated minor trauma during activities of daily living can cause superimposed mechanical stress and initiate HO." Symptoms of neurogenic HO include decreased joint mobility, swelling, redness and high skin temperature.

There are several methods used to test for neurogenic heterotopic ossification. Alkaline phosphatase, x-rays, and bone scans are the most frequently used. Alkaline phosphatase is used to test the alkaline phosphatase levels in the blood. High levels indicate bone formation. When bone formation stops, the alkaline phosphatase decreases to a normal level. X-rays are used to find the exact location of the new bone formation and to assess the maturity of the bone. However it is not possible to tell the length of time the bone has been there. Bone scans are the most efficient test for heterotopic ossification because they can identify HO about a month before x-ray. When alkaline phosphatase levels are normal and bone scans show no new ossification, the bone may be surgically removed to increase joint mobility.

**Hereditary Disorders**

Fibrodysplasia Ossificans Progressiva (FOP), also known as Munchenmeyer Disease, is an extremely rare genetic disorder. It is caused by a mutation in which the amino acid histidine is substituted for arginine at position 206 of the ACVR1 protein, also known as Activin Receptor Type 1A. This is a rare mutation because it affects the same exact nucleotide in every person with FOP. ACVR1 is a bone morphogenetic protein receptor and is extremely important in developing the heart, spine, joints and limbs. ACVR1 is also stated in skeletal muscle as well as connective tissue. An uninfected person has two normal ACVR1 genes. A person with FOP has one normal ACVR1 gene and a gene with the mutation. This mutation causes enchondral bone formation in the muscles, tendons, ligaments, and other connective tissues, "forming bridges of extra bone across the joints." This restricts movement greatly. Fibrodysplasia ossificans
progressiva is characterized by physical disability, resulting from heterotopic ossification, and monophasanlgic deformed big toes.\textsuperscript{10} “Occasional features include short thumbs, fifth finger clinodactyly, malformed cervical vertebrae, short broad femoral necks, deafness, scalp baldness and mild retardation.”\textsuperscript{10} FOP progresses in “characteristic anatomical patterns.”\textsuperscript{13} “Heterotopic ossification [proceeds] in a direction that [is] axial to appendicular, cranial to caudal, and proximal to distal.”\textsuperscript{10} The exact pathogenesis of Fibrodysplasia ossificans progressiva remains unknown. A study by de la Penta et al. suggested that FOP pathogenesis may be related to “altered BMP receptor trafficking.”\textsuperscript{10}

The rate of FOP is inconsistent, but patients are usually immured to wheelchairs before their twenties and will require assisted living for the remainder of their lives\textsuperscript{11} Most cases of FOP are caused by a spontaneous mutation and are not passed down from the patient’s parents; however, several cases of affected twins and triplets indicate a genetic origin.\textsuperscript{10} Examples of several successive generations of FOP shows dominant inheritance.\textsuperscript{10} There is a fifty percent chance that a person with FOP will pass it on to their child.\textsuperscript{9} Approximately 2500 people worldwide have FOP. That is nearly one in every two million people. Experts believe that FOP is often misdiagnosed because it is such a rare disease, which means that its occurrence could be much higher than known.\textsuperscript{9}

“Any trauma to the muscles of an individual with fibrodysplasia ossificans progressiva, such as a fall or invasive medical procedure, may trigger episodes of muscle swelling and inflammation (myositis) followed by more rapid ossification in the injured area.”\textsuperscript{15} Consequently, attempting to surgically remove bone irrevocably induces more heterotopic bone formation. Injury is usually the cause of HO in Fibrodysplasia ossificans progressiva, but it can also occur with no known trauma. For example, influenza or a common cold could initiate ossification.

In a study done by Cohen et al. it was found that the “average age of onset of ossification was five years (range, birth to 25 years).”\textsuperscript{10} The neck, spine and shoulder girdle were the most frequent location of early heterotopic ossification.\textsuperscript{10} By the age of seven, eighty percent of the patients had some restraining heterotopic ossification. More than ninety-five percent of the patients had “severely restricted mobility of the arms.”\textsuperscript{10} Death from the
disease usually occurs from severe chest complications as a result of the extra bone that forms around the rib cage.\textsuperscript{12}

Progressive Osseous Heteroplasia (POH), also known as Osteoma Cutis and Familial Ectopic Ossification, is another rare genetic disorder of heterotopic ossification. It is caused by a mutation that inactivates the GNAS1 gene.\textsuperscript{13} The mutation is usually hereditary, but may also be sporadic.\textsuperscript{13} The disease is characterized by ossification of the skin during infancy\textsuperscript{12,13} and by "progressive heterotopic ossification of subcutaneous and deep connective tissue during childhood."\textsuperscript{13} Although they are similar, POH is different from FOP and Albright’s hereditary osteodystrophy. Individuals with POH do not show malformed big toes,\textsuperscript{13} inherited skeletal malformations, predictable progression of HO as in FOP.\textsuperscript{11} In addition, the ossification of POH is intermembranous, unlike the enchondral ossification of Fibrodysplasia ossificans progressiva.\textsuperscript{13} The first sign of the disease is the “appearance of cutaneous plaques of intermembranous ossification during infancy.”\textsuperscript{13} The plaques join together and attack the deeper connective tissues.\textsuperscript{13} Individuals with progressive osseous heteroplasia have “normal intelligence, normal developmental milestones, and lack sustained biochemical or endocrine abnormalities.”\textsuperscript{13} POH can be differentiated from Albright’s Hereditary Osteodystrophy by the location of the lesions. In Albright’s hereditary osteodystrophy, the lesions are only found on the skin. The lesions of progressive osseous Heteroplasia are also located in the deep tissues of the skin.\textsuperscript{13}

Albright’s Hereditary Osteodystrophy (AHO) is also commonly known as pseudohypoparathyroidism and pseudopseudohypoparathyroidism.\textsuperscript{14} Pseudohypoparathyroidism type 1A is most common.\textsuperscript{11} AHO is an autosomal dominant disorder\textsuperscript{11} caused by mutations, along with imprinting effects, in the GNAS1 gene.\textsuperscript{14} The majority of these mutations are single-base inherited mutations.\textsuperscript{14} Albright’s hereditary osteodystrophy “involves dermatologic, skeletal, and endocrine systems, with variable features including cutaneous and subcutaneous ossification, pseudoparathyroidism, hypoparathyroidism, gonadotropin resistance, obesity, brachydactyly.”\textsuperscript{11} They have unusual skeletal and skin formations and “resistance to multiple

\textbf{Figure 6. Progressive Osseous Heteroplasia}\textsuperscript{18}

\textbf{Figure 7. Brachydactyly that is characteristic of Albright’s Hereditary Osteodystrophy}\textsuperscript{19}
hormones that activate adenylate cyclase."^{11} Brachydactyly is the shortening of metacarpals III, IV, and V and is the most distinct sign of AHO.^{13} Seventy percent of individuals with AHO suffer from brachydactyly.^{14} In individuals with AHO, the activity of the stimulatory G protein of adenylate cyclase is reduced by fifty percent.^{11} Multiple organ resistance is caused by the inactivation of the G protein.^{14} Some individuals with AHO also exhibit retardation.^{14}

Heterotopic ossification is a very serious disorder that affects the lives of many individuals all over the world. Not much is known about the pathogenesis of the disease which makes it extremely difficult to understand and treat. Researchers are currently working on developing a better understanding of this disease in order to better the lives of the people that are affected by it. This research will also help in the prevention of osteoporosis and other disease that involve bone formation.
References


Gemzar (Gemcitabine HCl) and the Treatment of Pancreatic Cancer

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Abstract

Gemcitabine (pronounced gem-sight-a-been) is a chemotherapy drug that is given as a treatment for some types of cancer. It is most commonly used to treat non-small cell lung cancer, pancreatic, bladder and breast cancer. This paper will focus on how it is used to treat pancreatic cancer, the history of the drug and the cancer, as well as precautions and the future of the drug.

Introduction

The empirical formula for gemcitabine HCl is C_{9}H_{11}F_{2}N_{3}O_{6} HCl. It has a molecular weight of 299.66. Gemcitabine is a nucleoside analog used as chemotherapy. It is marketed as Gemzar® by Eli Lilly and Company.

Approval and Availability

Gemzar is one of the most widely studied treatments in the history of chemotherapy agents, and has been approved for use in more than 90 countries worldwide. It is the worldwide standard for care of pancreatic cancer and in many parts of the world for non-small cell lung, bladder and breast cancers. Gemzar is approved in more than 75 countries as a single agent for the treatment of locally advanced or metastatic pancreatic cancer. It’s also approved, in combination with Taxol(R)(paclitaxel), in more than 60 countries for the treatment of metastatic breast cancer. In most European countries, Gemzar is approved as a single agent or in combination with cisplatin for the treatment of advanced non-small cell lung cancer. Gemzar, in combination with carboplatin, is approved in several European markets for the treatment of recurrent epithelial ovarian
cancer. Most recently, Gemzar was approved in Mexico for cervical cancer, making it the first approval for this disease. Gemzar is a nucleoside analogue that interferes with the process of DNA production, thereby preventing cancer cells from replicating and thus slows or stops tumor growth.  

| Alkylating agents | Nitrogen mustard: (Cisplatin, Chlorambucil, Cyclophosphamide, Hexamethylmelamine, Mitomycin), Alkylating agents: (Carmustine, Carmustine, Lomustine, Streptozotocin), platinum: (Carboplatin, Cisplatin, Oxaplatin, BBP245), Busulfan, Cephalo, Mesna, Mitomycin, Platin, Thiotepa, Urethane, Ukrainian 
| Antineoplastics | Fullerene: (Amsacrine, Methotrexate, Pentostatin, Vincristine), Folinic acid, Folinic acid, Mitomycin, Platin, Thiotepa, Thioptene, Pyrimidine (Captopril, Cytosine, Fluorouracil, Fluorouracil, Gemcitabine) 
| Stimulant or plant alkaloids | Taxol: (Docetaxel, Paclitaxel), Vinca: (Vinblastin, Vincristin, Vindeine, Vincristine) 
| Cytoxic and tumor-inhibitors | Anthracycline family: (Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Miloxanthine, Vincristine), Bleomycin, Hydroxyurea, Mitomycin, Actinomycin 
| Topoisomerase inhibitors | Camptothecin: (Camptothecin, Topotecan, Irinotecan), Podophyllotox (Epothilone, Topotecan) 
| Cytoskeletal/kinase inhibitors | Alsensan, Brevacin, Cefotaxim, Gemcitabine, Pantothenic, Perhexil, Tecnilacton, Tacrubizing 
| Photodynamic agents | Amiclovir, Acid, Methyl aminoquinol, Pimel, Prednisone, Verapamil 
| Protein inhibitors | Dasatinib, Erlotinib, Gefitinib, Lapatinib, Nilotinib, Sorafenib, Supinib, Vandetanib (ZD6474) 
| Other | Aliskiren, Aliskiren, Amnacine, Atorvastatin, Arterios, Bexarotene, Bortezomib, Domox, Diltiaz, Estramustine, Hydroxyurea, Masopurcol, Lifetin, Pegaptanib, Tetrathin 

The pancreas is a gland located deep in the abdomen between the stomach and the spine (backbone). The liver, intestine, and other organs surround the pancreas. The pancreas is about 6 inches long and is shaped like a flat pear. The widest part of the pancreas is the head, the middle section is the body, and the thinnest part is the tail. 

![Diagram of the pancreas and nearby organs](image)

This picture shows the pancreas and nearby organs.
The pancreas makes insulin and other hormones. These hormones enter the bloodstream and travel throughout the body. They help the body use or store the energy that comes from food. For example, insulin helps control the amount of sugar in the blood. The pancreas also makes pancreatic juices. These juices contain enzymes that help digest food. The pancreas releases the juices into a system of ducts leading to the common bile duct. The common bile duct empties into the duodenum, the first section of the small intestine.5

Most pancreatic cancers begin in the ducts that carry pancreatic juices. Cancer of the pancreas may be called pancreatic cancer or carcinoma of the pancreas. A rare type of pancreatic cancer begins in the cells that make insulin and other hormones. Cancer that begins in these cells is called islet cell cancer. When cancer of the pancreas spreads (metastasizes) outside the pancreas, cancer cells are often found in nearby lymph nodes. If the cancer has reached these nodes, it means that cancer cells may have spread to other lymph nodes or other tissues, such as the liver or lungs. Sometimes cancer of the pancreas spreads to the peritoneum, the tissue that lines the abdomen. When cancer spreads from its original place to another part of the body, the new tumor has the same kind of abnormal cells and the same name as the primary tumor. For example, if cancer of the pancreas spreads to the liver, the cancer cells in the liver are pancreatic cancer cells. The disease is metastatic pancreatic cancer, not liver cancer. It is treated as pancreatic cancer, not liver cancer.5

**Mode of Action**

Gemzar works by interfering with the process by which cells divide and repair themselves, thus preventing the further growth of cancer cells and leading to cell death. Clinical studies showed that Gemzar helped improve survival for some patients with cancer of the pancreas. In a study of Gemzar versus the drug 5-FU in previously untreated patients:

- Nearly 1 in 5 patients was alive at 1 year after starting therapy with Gemzar, compared with 1 in 50 who were given 5-FU.
- The typical patient lived about 6 months after starting therapy with Gemzar, which was 6 weeks longer than those given 5-FU.

In a study of GEMZAR in patients previously treated with the drug 5-FU:

- After starting on Gemzar, about 1 in 25 patients was alive at 1 year.
- After starting on Gemzar, the typical patient lived for 4 months

Nearly 1 in 4 patients had improvement in 1 or more of the following for at least 1 month, without any sustained worsening in any of the other symptoms:

- Amount of pain medication taken
- Level of pain experienced
- Ability to perform usual activities6
**Dosage and Administration**

Gemzar should be administered by intravenous infusion at a dose of 1000 mg/m² over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks. Gemcitabine undergoes intracellular metabolism to the active moieties and is rapidly deaminated in the blood, liver, kidneys and other tissues. In the plasma, it is metabolized to its inactive metabolite.

Dosage adjustment is based upon the degree of hematologic toxicity experienced by the patient. Clearance in women and the elderly is reduced and women were somewhat less able to progress to subsequent cycles.

Patients receiving Gemzar should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 13. 7

<table>
<thead>
<tr>
<th>Absolute granulocyte count (x 10⁹/L)</th>
<th>Platelet count (x 10⁹/L)</th>
<th>% of full dose</th>
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<td>100</td>
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<tr>
<td>500-999 or</td>
<td>50,000-99,999</td>
<td>75</td>
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<tr>
<td>&lt;500 or</td>
<td>&lt;50,000</td>
<td>Hold</td>
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</tbody>
</table>

Laboratory evaluation of renal and hepatic function, including transaminases and serum creatinine, should be performed prior to initiation of therapy and periodically thereafter. Gemzar should be administered with caution in patients with evidence of significant renal or hepatic impairment as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations.

Patients treated with Gemzar who complete an entire cycle of therapy may have the dose for subsequent cycles increased by 25%, provided that the absolute granulocyte count (AGC) and platelet nadirs exceed 1500 x 10⁹/L and 100,000 x 10⁹/L, respectively, and if non-hematologic toxicity has not been greater than WHO Grade 1. If patients tolerate the subsequent course of Gemzar at the increased dose, the dose for the next cycle can be further increased by 20%, provided again that the AGC and platelet nadirs exceed 1500 x 10⁹/L and 100,000 x 10⁹/L, respectively, and that non-hematologic toxicity has not been greater than WHO Grade 1.

**Use and Handling**

The recommended diluent for reconstitution of Gemzar is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for Gemzar upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided.
To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200-mg vial or 25 mL of 0.9% Sodium Chloride Injection to the 1-g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200-mg vial or 1.3 mL for the 1-g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL.

Reconstituted Gemzar is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution or container permits. If particulate matter or discoloration is found, do not administer. When prepared as directed, Gemzar solutions are stable for 24 hours at controlled room temperature 20°C to 25°C (68°F to 77°F) [See USP]. Discard unused portion. Solutions of reconstituted Gemzar should not be refrigerated, as crystallization may occur.  

**Over Dosage**

There is no known antidote for overdoses of Gemzar. Myelosuppression, paresthesias, and severe rash were the principal toxicities seen when a single dose as high as 5700 mg/m2 was administered by I.V. infusion over 30 minutes every 2 weeks to several patients in a Phase 1 study. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.  

**Clinical Pharmacology**

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.
Gemcitabine demonstrated dose-dependent synergistic activity with cisplatin in vitro. No
effect of cisplatin on gemcitabine triphosphate accumulation or DNA double-strand breaks was
observed. In vivo, gemcitabine showed activity in combination with cisplatin against the LX-1
and CALU-6 human lung xenografts, but minimal activity was seen with the NCI-H460 or NCI-
H520 xenografts. Gemcitabine was synergistic with cisplatin in the Lewis lung murine xenograft.
Sequential exposure to gemcitabine 4 hours before cisplatin produced the greatest interaction.  

Precautions

While you are being treated with gemcitabine, and after you stop treatment, do not have
any immunizations (vaccinations) without your doctor’s okay. Try to avoid contact with people
who have recently taken the oral polio vaccine. Check with your doctor about this. Gemcitabine
can lower your blood counts (white blood cells, red blood cells, platelets). Your doctor will
check your blood counts before and after each treatment to see how it affects your blood counts.
Your doctor or nurse will give you specific instructions if your blood counts are low.  

Gemcitabine can decrease your white blood cell count, especially 10 to 14 days after the
drug is given. This can increase your risk of getting an infection. Report fever of 100.5°F or
higher, or signs of infection such as pain in passing your urine, coughing, and bringing up
sputum. Gemcitabine can decrease the platelet count. This can increase your risk of bleeding.
DO NOT take any aspirin or aspirin-containing medicines. Report unusual bruising, or bleeding
such as nosebleeds, bleeding gums when you brush your teeth, or black, tarry stools.  

Tell your doctor your medical history, especially of: recent illness, radiation therapy,
kidney problems, liver problems, bone marrow problems (e.g., leukopenia, thrombocytopenia,
anemia), heart disease, allergies (especially drug allergies). This drug may make you dizzy or
drowsy; use caution engaging in activities requiring alertness such as driving or using machinery.
Limit alcoholic beverages as they may aggravate certain side effects (e.g., tiredness). Caution is
advised when using this drug in women because they may be more sensitive to the effects of the
drug. Caution is advised when using this drug in the elderly because they may be more sensitive
to the effects of the drug. This medication is not recommended for use during pregnancy.
Consult your doctor for more details. It is not known whether this medication passes into breast
milk. Because of the potential risk to the infant, breast-feeding while using this drug is not
recommended. Consult your doctor before breast-feeding.  

Side Effects

Get emergency medical help if you have any of these signs of an allergic reaction: hives;
difficulty breathing; swelling of your face, lips, tongue, or throat. Call your doctor at once if you
have any of these serious side effects:

- pale skin, easy bruising or bleeding, unusual weakness;
- urinating less than usual or not at all;
- nausea, stomach pain, low fever, loss of appetite, dark urine, clay-colored stools, jaundice
  (yellowing of the skin or eyes);
- chest pain or heavy feeling, pain spreading to the arm or shoulder, nausea, sweating,
general ill feeling;
• sudden numbness or weakness, especially on one side of the body;
• sudden headache, confusion, problems with vision, speech, or balance;
• fever, chills, body aches, flu symptoms;
• white patches or sores inside your mouth or on your lips;
• pain, swelling, or skin changes where the needle was placed;
• hearing problems;
• blood in your urine; or
• breathing problems.

Less serious side effects may be more likely to occur, such as:

• mild nausea, vomiting, upset stomach;
• diarrhea or constipation;
• swelling in your hands, ankles, or feet;
• skin rash;
• numbness or tingly feeling;
• drowsiness; or
• hair loss.  

**Drug Interactions**

One should tell his doctor or pharmacist of all prescription and nonprescription drugs one may use, especially of: other anti-cancer drugs, recent/upcoming vaccinations (e.g., oral polio, measles). One also should report his use of drugs that cause drowsiness such as: sleeping pills, sedatives, tranquilizers, anti-anxiety drug (e.g., diazepam), narcotic pain relievers (e.g., codeine), psychiatric medicines (e.g., phenothiazines or tricyclics), anti-seizure drugs (e.g., carbamazepine), muscle relaxants, drowsiness-causing antihistamines (e.g., diphenhydramine). Check the labels carefully on all medicines (e.g., cough-and-cold products) because they may contain drowsiness-causing ingredients. Asking a pharmacist about the safe use of those products is a good idea. Do not start or stop any medicine without doctor or pharmacist approval.

**Summary and Conclusion**

Gemzar (Gemcitabine hydrochloride; 2’-deoxy-2’,2’-difluorocytidine) has been used in various carcinomas: non-small cell lung cancer, pancreatic cancer, and breast cancer. It is being investigated for use in oesophageal cancer, and is used experimentally in lymphomas and various other tumor types. Gemcitabine represents an advance in pancreatic cancer care. It is also not as debilitating as other forms of chemotherapy. 

It is one of the most widely studied treatments in the history of chemotherapy treatments and is recognized and used all over the world. The reason why I researched this therapy is because pancreatic cancer has struck close to home for me. Earlier this year, I lost my grandfather to the disease and hope that from writing this paper, I have informed others about this terrible disease but have also given hope to those families who are suffering because there are therapies out there.
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Synthetic Blood: Oxycyte

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Abstract

This paper examines the complex functions of human blood and chronicles the historical development of transfusions as well as their shortcomings. The criteria for synthetic oxygen carriers are explored as well as the two fundamental types of blood substitutes. HBOC's and PFC's pros and cons are discussed, and specific examples are given. Oxycyte is evaluated and analyzed. Difficulties regarding FDA approval are mentioned and viability of synthetic blood is scrutinized.

Blood is classified as a connective tissue because it contains several types of cells in a liquid matrix of plasma.[1] Blood in mammals consists of three components: red blood cells, also known as erythrocytes, comprise approximately 96% of the total number of cells, white blood cells, leukocytes, make up 3% of cells and are a key element of the immune system attacking pathogens and removing old, dead, or dying cells, and platelets, thrombocytes, that make up the remaining 1% of cells, are responsible for blood's ability to coagulate.[1] Blood is the elixir of life in the human body. It has a multifaceted purpose and performs a myriad of functions. Blood is much more than just a nutrient giver and waste remover for every cell in the body. It also functions as the last line of defense to invasion by foreign substances as diverse as microbes; like bacteria, viruses, PLO's (Pneumonia-like-organisms) and prions (Mad Cow's Disease), pollen, parasites, and even transplanted organs. The immune system, an efficient and complex conglomeration of specialized blood cells and other cells, that are moved to the front lines by the blood, identifies these interlopers (antigens), reacts to them immediately from its memory banks of antibodies, or forms a new defense mechanism (new antibodies) to deactivate, cope with (allergies), or destroy (by Killer Cells) the invader: thus shutting down the threat. Hormones, the secretions of the body's endocrine glands, course through the blood to appropriate cells and activate and deactivate a multitude of physiological functions using a system of feedback mechanisms. Blood also plays an important role in keeping the body to exacting standards that allow for optimum performance and maximum efficiency. This is called homeostasis and it regulates such bodily functions as temperature, sugar levels, and chemical concentrations by increasing or decreasing blood flow through constriction and dilation of blood vessels. This heats up or cools down the body as needed, maintains proper concentrations of water, minerals, and salts for optimum cell performance, and concentrates or eliminates sugar for maximum cell nutrition. Blood platelets have a coagulation mechanism that stops minor blood loss. Blood's last major function is to carry oxygen, a vital component for cellular reactions, from the lungs to every cell in the body.

Just as blood is the elixir of life, so it becomes the harbinger of death when the body loses it through traumatic accidental injury or surgery, and it cannot perform its vital and life sustaining functions. William Harvey, in 1628, was the first scientist to understand and describe the circulatory system.[2] This led others to initiate the idea of transfusions as a stop gap method
for preserving life. Physicians Richard Lower and Jean Baptiste began experiments in the 1660’s, with animal to animal and later animal to human transfusions.\textsuperscript{[3]} James Blundell performed the first transfusion from human to human in 1818 with a reported success rate of 50%.\textsuperscript{[2,3]} Necessity breeds invention, and in the 19\textsuperscript{th} century, increased military activity was accompanied by a greater need for blood transfusions. This triggered the idea of artificial blood alternatives like milk.\textsuperscript{[4]} Milk from cows and goats was used as a substitute for human blood with severe reactions.\textsuperscript{[2]} New discoveries in 1901, like that of blood types A, B, and O, by Karl Landsteiner made blood transfusions more successful and therefore safer, and with the advent of typing and cross-matching in 1907, and the creation of donor services in England and the U.S. shortly after, transfusions became more readily available.\textsuperscript{[2]}

As knowledge of the blood’s makeup increased, so did our ability to formulate new techniques for transfusions. Science discovered that red blood cells do not possess a nucleus or organelles but instead contain hemoglobin. Hemoglobin’s structure was discovered in 1959, by Max Perutz, who later received the Nobel Prize for Chemistry in 1962.\textsuperscript{[5]} "Hemoglobin is a 64kDa tetrameric protein comprised of two subunits that fold into a compact quaternary structure. Each α and β subunit contains an iron-heme group that binds to an oxygen molecule allowing for transport."\textsuperscript{[6]} Hemoglobin is capable of carrying four oxygen molecules when fully saturated.

![Heme group](image)

Without hemoglobin in blood, mammals would not be able to supply enough oxygen to any vital organs and death would occur. Each gram of hemoglobin is capable of binding to 1.39mL of oxygen.\textsuperscript{[3]} Hemoglobin is also responsible for blood’s red pigment when saturated with oxygen and blue tint, when deoxygenated. Although hemoglobin is capable of carrying four oxygen molecules, its affinity can be affected by blood pH, temperature, and concentration of red blood cells in the anion.\textsuperscript{[3]}

Transfusions were successful in treating blood loss up until the 1980’s because they incorporated screening techniques to combat transmission of STD’s and other diseases like
hepatitis. The tainted blood problems at this time, caused by the HIV virus, precipitated a need and desire for an artificial blood substitute.\[4] To date, for this and other reasons, pressures from many areas have created a real need for ‘artificial blood’. I.M. Sarteschi, in his article “Rationale for the development of red-cell substitutes and status of the research,” discusses many of these needs: fear of new viruses or prion based diseases that could accidentally be spread into the population via transfusions, better pre-testing that has eliminated more possible donors, a decline in altruism that has resulted in low blood supplies which cause cancellation of surgeries, the fact that improper testing for HIV of 13 million units of blood per year in other countries of the world spreads this deadly disease, and also that blood transfusions have a negative effect on the immune system and cause increased post-operative infection.\[8] More cause for artificial blood use is given by Blumberg who estimates that “the death rate from allogenic transfusion related post-operative infection and cancer recurrence combined may exceed the death rate due to all other transfusion risks combined.”\[8] In some surgical procedures, the risk of death increased by 62% for every one unit per hour increase of transfusion rates, and immunosuppression from transfusions is suspected to lead to the development of non-Hodgkin’s lymphoma as well as transmission of oncogenic viruses or viral activation. Truly the need for a replacement for conventional transfusions exists.

Each year, about 12.6 million units of blood are collected from 8 million donors, which accounts for approximately 11.5 million red blood cell transfusions annually.\[9] Blood transfusions can be life saving procedures if performed directly after surgery where massive blood loss has occurred, after traumatic injury, or to help treat blood borne diseases such as severe anemia.\[10] Only 3% of the population donates blood on average 1.6 times per year.\[9] The demand for a clean, healthy source of blood is growing while the supply is shrinking. Blood shortages are now common, especially during summer and winter months.\[9] The quality of the blood donated is extremely high due to the thorough screening procedures used to protect recipients from Hepatitis, AIDS, and Creutz-Jakob disease that was predominant in the 1990’s, but new sources for transfusable material are needed.\[11] Donated blood, even when properly frozen, expires 42 days after the donation date.\[11] Donations are increasing at a rate of approximately 2% to 3% annually while demand is climbing 6% to 8% per year.\[11] One key factor for the rate at which demand is rising is the increase in the elderly population’s need for blood transfusions after complex surgeries.\[11]

Unfortunately, the cost of obtaining, screening, and storing blood is continually increasing and this also makes an ‘artificial blood’ more desirable. The term ‘artificial blood’ is a misnomer. The new blood substitutes or synthetic blood are actually ‘oxygen carriers’ because they perform only this one function of blood and do not coagulate, have cells, or contain enzymes and antibodies. “Their main function is to replace lost blood volume and oxygen carrying capacity.”\[6]
The ideal blood substitute could be defined by the following terms:

- increased availability that would rival that of donated blood, even surpass it
- oxygen carrying capacity equaling or surpassing that of biological blood
- volume expansion
- universal compatibility: elimination of cross matching
- pathogen free: elimination of blood contained infections
- minimal side effects
- survivability over a wider range of storage temperatures
- long shelf life
- cost efficient

Cultural and religious objections to transfusions such as those raised by the Jehovah’s Witnesses, could be met by artificial blood, and those clinically unable to receive a transfusion, like patients with autoimmune hemolytic disease, could also benefit from a synthetic transfusion.\(^3\)

Blood substitutes are found in two basic types: those that are based on hemoglobin and those that are based on perfluorochemicals. The first successful use of extracted hemoglobin in solution as a transfusible was in 1916, by Wilson Sellards and George Minot.\(^3\) Their limited success may have been due to toleration of a small sample size rather than any noticeable effects. Further studies had extreme problems with renal toxicity and low oxygen off-loading. Toxicity was due to fragments of the red cell membrane, the stroma, found in the sample as well as by the fact that the hemoglobin tetramere quickly dissociated into two dimers once extracted from the red blood cell and were quickly excreted through the kidneys within hours.\(^3\) Oxygen remained bound to the hemoglobin molecule because of the absence of the enzyme 2,3-Diphosphoglycerate (2,3-DPG) found in the red blood cells that causes decreased oxygen binding affinity and allows oxygen to leave the molecule and oxygenate tissues\(^3\) These two problems were solved by improved purification and stabilizing processes. The functional analogous coenzyme pyridoxal-5-phosphate, was bound to hemoglobin to reduce oxygen affinity, and three methods of stabilization were used: conjugation or coding with a polyethylene glycol-like molecule, intramolecular cross-linking with diaspirin to create larger and tetramere stable molecules, and polymerization with glutaraldehyde or o-raffinose to produce inter-molecularly cross-linked hemoglobin.\(^3\) Future developments for this technique include encapsulation of pyridoxylated hemoglobin with a lipid producing a synthetic cell that could be impregnated with enzymes and other cellular components to make it more like a functioning red blood cell. Research projects are also being done to form recombinant human hemoglobin molecules from genetically modified micro-organisms, plants, and invertebrates. This would produce specialized molecules on a large scale in a process called “molecular farming.”\(^3\) Three forms of hemoglobin-based oxygen carriers (HBOC’s) that are in the Phase III form of Clinical Trials and may soon be submitted to the FDA for approval are found in the following table:
### Comparison of HBOC's:

<table>
<thead>
<tr>
<th></th>
<th>Biopure</th>
<th>Northfield</th>
<th>Hemosol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Source:</strong></td>
<td>Bovine Hgb</td>
<td>Expired Human</td>
<td>Expired Human</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Human RBC's</td>
<td>RBC's</td>
</tr>
<tr>
<td><strong>Shelf – Life:</strong></td>
<td>3 years</td>
<td>1 year</td>
<td>1 year</td>
</tr>
<tr>
<td><strong>Storage:</strong></td>
<td>Room Temperature</td>
<td>Refrigerated</td>
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<td></td>
<td></td>
<td></td>
<td>Room Temperature</td>
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<tr>
<td><strong>Half-life:</strong></td>
<td>18-22 hours</td>
<td>24 hours</td>
<td>14 hours</td>
</tr>
<tr>
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<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>oxygen</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>therapeutics:</strong></td>
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<tr>
<td><strong>Product Name:</strong></td>
<td>Hemopure &amp;</td>
<td>PolyHeme</td>
<td>Hemolink</td>
</tr>
<tr>
<td></td>
<td>Oxyglobin</td>
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</tbody>
</table>

Perfluorocarbon Emulsions (PFC's) represent the second major class of oxygen therapeutics. They are linear, cyclic, or polycyclic hydrocarbons that have hydrogen atoms substituted with fluorine. Two that are most used in biology are perfluorodecalin (C₁₀F₁₈), a bicyclic perfluorinated alkane and bromoperfluoro-𝑛-octane (C₈F₁₂Br).[3]

![Perfluorodecalin](image)

![Perfluoron](image)
These compounds were first produced during World War II as part of the Manhattan Project as an inert coating material that would prevent rust caused by reactive uranium isotopes. Because of their ability to bind with oxygen and carry it throughout the body they are good blood substitutes. They do not mix directly with blood so an emulsion must be made. One of the benefits of perfluorocarbons is that they are 40 times smaller than the diameter of a normal red blood cell allowing them to be able to access capillaries that would normally be blocked to red blood cells.\textsuperscript{11} They have the highest gas dissolving capacity of any liquid, and when used with oxygen, they produce a situation of extreme oxygenation in blood that is many times more than that of normal blood or hemoglobin-based substitutes.\textsuperscript{14} PFC’s make an excellent universal oxygen carrying solution that can be used in various specific medical applications where a great deal of oxygen is needed by tissues. In general, PFC’s have a short tissue life (about one week), can be stored at room temperature, have a shelf-life of three years or more, release oxygen by diffusion and may be better at off-loading than that from hemoglobin, can be used for solid tumor treatment with chemotherapy and or radiotherapy for enhanced tumor kills, can be effective in cardio-pulmonary bi-pass surgery, trauma surgery, and can be used to preserve tissues and prolong storage time of transplant organs.\textsuperscript{16} PFC’s are released by the reticuloendothelial system into the plasma and are released as a gas by the lungs. They do have limitations. They can be given only in small single doses, last a short period of time in the body, and are dependent upon Henry’s Law of Partial Pressures for delivery which limits their use to patients with a certain amount of pulmonary pressure.\textsuperscript{8} Some PFC’s developed to date: Fluosol (1989) used in angioplasty for five years, Perfloran (1996) approved in Russia for use in severe anemia, hemorrhagic traumatic shock, cerebral ischemia, and cardiac surgery, Oxygent (2001) has reached Phase III level trials for non-cardiac surgery with large blood loss by using it in normovolaemic haemodilution where it replaces several units of blood before surgery and the patient’s blood is replaced after surgery,\textsuperscript{2} and the most advanced PFC to date, Oxycyte, has undergone Phase II trials in 2005 and is being tested for its effectiveness in traumatic brain injury. There is not very much information available about Oxycyte because it is so new. It is a second generation PFC with a particulate diameter of 0.19 microns. Doctor Bruce Spiess, who is running the study, believes that specializing in a treatment for a trauma that has no specific drug may enable it to get to Phase III clinical trials soon, and with luck, because of a military need for such a treatment, Oxycyte may even make it to the FDA for approval. Doctor Jason Highsmith has also done research with this PFC on created spinal cord injuries in rats with great success, and has found that Oxycyte’s small size allows oxygen to get to injured tissues that would normally be deprived because of swelling. With an oxygen level six times that of normal blood, Oxycyte prevents the death of blood vessels (veins) and allows for a higher recovery rate.\textsuperscript{14} Oxycyte has some drawbacks. It requires inhalation of pure oxygen which can cause tissue and membrane damage by free radicals. It causes liver swelling from absorption of its oily molecules, causes some decrease in platelet count, and some short-term flu-like symptoms. The viability of Oxycyte as a synthetic blood oxygen carrier rests in two areas: first, PFC’s must
become the preferred synthetic blood when compared to HBOC’s. Many believe that hemoglobin based synthetics which are further along in test trials, a few have reached Phase III, have a larger scope of usability because they resemble normal blood more closely and can be used in much larger doses. Second, Oxycyte must achieve FDA approved status before it can be widely used. This presents a great problem. Producing enough clinical trials to reach this status and to meet the criteria of the FDA to be accepted is an arduous task that few synthetic blood oxygen carriers have reached. In this respect, Oxycyte may have an advantage over HBOC’s. In order for a drug to be approved for use by the FDA, it has to demonstrate that it is superior to current treatments available. Since HBOC’s are created using hemoglobin, their capabilities do not surpass those of normal blood. It is for this reason that the FDA has not approved them for general use. Oxycyte, a PFC, is totally synthetic and has limited specific uses. If these can be deemed effective and unique then they will be green-lighted by the FDA for approval. Another hurdle that Oxycyte must overcome is to be able to set up enough clinical trials to achieve status. This is very difficult in the U.S. and trials may have to be done in other countries such as Mexico and China, places where other companies have gone to be successful in this respect. Traumatic injuries that would cause permanent damage to the brain, spinal cord or heart muscle may be a thing of the past, providing that Oxycyte is approved for use by the FDA and used widely.
References


The Symptoms, Diagnosis, and Treatment Options of Hyperthyroidism

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Prepared by
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CHM 236
March 26, 2007
Abstract

Hyperthyroidism is a type of thyroid disorder where the thyroid over produces hormones. There are two main types of thyroid disorders: Hyperthyroidism and Hypothyroidism. However, this paper will only include topics covered for Hyperthyroidism. The topics will discuss “what is a thyroid hormone”, symptoms, diagnosis, and treatments for Hyperthyroidism. An overview of treatments administered for Hyperthyroidism will be briefly discussed, but the most common forms of treatment—the administration of antithyroid drugs—will be covered in great detail.

What is a Thyroid Hormone?

The thyroid gland is what controls the production of thyroid hormones. The thyroid gland takes iodine found in many foods and converts it into thyroid hormones T₄ and T₃. T₃ may also be derived from the T₄ hormone. The gland itself is located along the trachea just below the larynx. It is held together by bands of thyroid tissue called isthmus. The thyroid gland is controlled by the pituitary gland, which is a small peanut shaped gland at the base of the forehead. The pituitary gland is controlled by the hypothalamus. The hypothalamus produces TSH Releasing Hormones, TRH, which tells the pituitary gland to stimulate the thyroid gland to make a hormone called Thyroid Stimulating Hormone, TSH. The pituitary gland is considered to be the “thermostat” for the production of thyroid hormones; it tells the thyroid gland when to produce more hormones. When the thyroid hormones get too low, the pituitary gland will “turn on” and produce TSH, which will then excite the thyroid gland to produce more hormones. Every cell in the body is dependent on these two hormones in order for the bodies’ metabolism to stay regulated. The hormones produced by the thyroid gland have chemical structures as follows:

\[ \text{T}_3 \text{ Thyroid Hormone (Triiodothyronine)} \]
\[ \text{Chemical Formula- } C_{15}H_{12}I_3NO_4 \]
\[ \text{IUPAC Name: } (2S)-2\text{-amino-3-[4-(4-hydroxy-3-iodo-phenoxy)-3,5-diiodo-phenyl]propanoic acid} \]

\[ \text{T}_4 \text{ Thyroid Hormone (Thyroxine)} \]
\[ \text{Chemical Formula- } C_{15}H_{11}I_4NO_4 \]
\[ \text{IUPAC Name: } 3,5-3,5\text{-tetraiodothyronine} \]

The normal thyroid gland produces 80% of T₄ and approximately 20% of T₃. The production of T₃ is lower because it contains more hormones than the T₄ does. In fact it contains about four times as more hormones than the T₄, and therefore fewer T₃ hormones need to be produced.
The thyroid gland is very important to almost every aspect of your health and life. It affects your metabolism, the rate at which your heart beats, how quickly your body burns calories, how much you weigh, and how warm you feel. Unfortunately, your thyroid may not always produce normal amounts of thyroid hormones and may actually produce too much of the thyroid hormone thyroxine, T4, this is how Hyperthyroidism develops.

**Symptoms**

The signs and symptoms that are caused by the over production of the thyroid hormone is medically termed Hyperthyroidism. The increase of the thyroid hormone causes the metabolism to increase and causes an increase in appetite and cravings for mostly carbohydrates while maintaining or even losing weight. Although many may experience weight loss, there are those rare cases where weight is actually gained due to the increase in appetite. Hyperthyroidism may also cause the person to become heat sensitive and may feel hotter than those around them. Fatigue is also often experienced and despite feeling exhausted, insomnia occurs. Nervousness, trembling of hands and irregular heart palpitations may also develop. Heat intolerance and irregular heart palpitations may cause the person to become irritable and easily upset. Here is a list of the most common symptoms felt by a patient:

- Irregular Heart Palpitations
- Heat Intolerance
- Increased Appetite
- Irritability, Anxiety, and/or Nervousness
- Moodiness or Depression
- Irregular Menses, light or absent menstrual cycles; infertility
- Fatigue
- Insomnia
- Weight Loss
- Increased Bowel Movements
- Hair Loss
- Muscle Deterioration
- Breathlessness

If Hyperthyroidism is gone undetected, symptoms may become more severe. Most people don’t notice they have this disease for months and sometimes even years which make the symptoms worsen over time. Hyperthyroidism mainly affects women. The symptoms may be completely different from one age group to the next. In fact, older women may not experience many of the symptoms normally experienced in younger women, if any at all. Elder women often just become anorexic, causing them to lose weight, and become depressed. They often feel fatigue while engaging in ordinary activities.

Symptoms of Hyperthyroidism can always be mistaken for other diseases or disorders such as anxiety disorders or psychological disorders like manic behavior. In
Living Well With Graves’ Disease and Hyperthyroidism, by Mary J Shomon, a patient that was misdiagnosed for years stated,

“I felt off, nothing so serious that I was suffering terribly, but just not feeling myself. I started a job and soon was plagued by anxiety, stomach problems, heart palpitations, mood swings, and hot flashes. The doctors— I was sent to a gastroenterologist, a psychologist, a general practitioner, a gynecologist, and an allergist—did not have a clue to what was wrong with me. They wrote it off to stress and having a “sensitive” stomach. I continued to endure the symptoms and hoped that they would go away. I tried to change things about my life in hopes that it would help. But five years after making dietary changes, lifestyle changes, changing my career, and moving cross-country, things got worse. I had even worse heart palpitations, achy joints, breathing problems, and I could not keep weight on. I ate enormous amounts of food that barely allowed me to maintain my weight. My gynecologist claimed I just had monthly water weight and should take more water pills; the allergist claimed I had asthma and gave me an inhaler. The inhaler nearly killed me one day while exercising because it sent my already skyrocketing heart rate into the stratosphere. Finally, all my symptoms and the fact that my hands were shaking violently clicked with my general practitioner and she gave me a thyroid blood test. I was suffering with sever hyperthyroidism that had gone undetected for years.”

Millions of people in the United States, mostly women, suffer from Hyperthyroidism. Many of them go undetected for years or actually get misdiagnosed, just like the one stated above, causing people to think that they are going mad. There have been misdiagnosis’ that have caused many more health issues and could potentially be termed fatal; which could have been avoided if diagnosed and treated properly from the beginning. The cause of such a disease is not quick understood. Although not medically proven, it is believed that Hyperthyroidism may be genetic or even caused by stress.

Diagnosis

There are many diseases diagnosed from Hyperthyroidism a few being: Multinodular Goiter (Plummers’ Disease), Follicular Adenoma, and Subacute Thyroiditis. Thyroid Storm is also a disease that affects a small percentage of people with Hyperthyroidism. Unfortunately, this condition is very dangerous and even more dangerous for those who go untreated. During Thyroid Storm, the heart, blood pressure, and body temperature become uncontrollably high and this life threatening condition requires treatment within hours in order to avoid fatal complications such as a stroke or heart attack.

Although there are many other diseases caused by Hyperthyroidism, the most common diagnosis is Graves’ Disease. Graves’ Disease is an autoimmune disorder that affects about eight women to every one man. It is most common in women in their early twenties and thirties; however it has also affected infants, children, and the elderly. It is an autoimmune disorder that causes the thyroid gland to work overtime, producing way
more thyroid hormones than needed. This surplus of thyroid hormones speed up the rate at which your body uses energy and the antibodies that are normally produced to fight away viruses and bacteria begin to attack the thyroid gland and the bodies' organs and tissue in which it normally protects. There are three apparent characteristics of Graves' Disease: overactivity of the thyroid gland, inflammation of the tissues around the eyes which tend to cause swelling and positive thickening of the skin over the lower legs. The eyes of patients who have been diagnosed with Graves' Disease are affected slightly, and sometimes not at all. Their eyes may feel irritated or they may even look like they are staring, however, the majority of patients are not affected. Statistics have shown that only one out of twenty people with this disease will suffer more severe eye problems such as bulging of the eyes, severe inflammation, double vision, or even blurred vision causing them to be incapable of driving at night. If this is gone undetected and not treated, the eyes can become damaged permanently and can even cause blindness. If the disease is detected and treated in sufficient time, the eye problem can slowly be corrected once treatment has begun.

Hyperthyroidism is usually detected by your physician, if noticeable. A physical examination can reveal that the thyroid gland is enlarged or that there is a goiter. If an enlarged thyroid gland is detected, the physician normally checks to see if you have trembling hands, moist skin, and/or a rapid pulse rate. Like mentioned earlier, not all patients possess these symptoms, so the detection of Hyperthyroidism may be a little more difficult. If there are any questions to whether you have Hyperthyroidism, accurate blood tests can be ran to confirm or rule out the possibility. There are a few common tests that can be done to detect Hyperthyroidism. One test would be the thyroid stimulating hormone, TSH, which is produced by the pituitary gland. If this test results in the TSH hormone being low or suppressed, then the diagnosis of Hyperthyroidism is always associated. If the test results in no change in the amount of TSH hormone or over production of the TSH hormone, then more tests need to be run. A second test that can be used to detect Hyperthyroidism would be to actually test the thyroid hormones T₃ and T₄. If the test proves that there are high levels of the thyroid hormones then that signifies that your thyroid gland is overactive. If this occurs the physician may want to run one more test, which brings us to the third test that can be done to detect Hyperthyroidism. This test is the iodine thyroid scan. This scan looks at the complete thyroid gland and detects if the thyroid gland is overactive or if there is possibly something else that is causing the gland to be enlarged.

Treatment

There are several treatments readily available for Hyperthyroidism. The treatment in which your physician chooses will be based on your age, the severity of your disorder, as well as any preexisting medical conditions that may be affecting your health. There are three major treatments used to treat Hyperthyroidism. The two most common treatments are the administration of antithyroid drugs and radioactive iodine treatment. The third treatment is a thyroidectomy. This option should be the last measure of treatment because it is a permanent removal of your thyroid gland and patients will have to be on medication for the remainder of their lifetime. This method of treatment is only used
when the antithyroid drugs are intolerable and the patient doesn’t want to go through radioactive iodine therapy. Beta blockers can also be given to patients that have high blood pressure due to the effects of the thyroid hormone on your body. This will only slow down the rate at which your heart beats and prevent future heart palpitations, it will not have any effect on the amount of thyroid hormones being produced by the overactive thyroid gland. This medication is taken until the normal thyroid level is reached.

Methimazole (Tapazole®) and Propylthiouracil (PTU) are the two most common medications used in the administration of an antithyroid agent treatment. These two drugs inhibit the thyroid gland from producing more hormones. They do this by blocking the thyroid peroxidase which catalyze both the assimilation of iodine into the thyrosine residue and the pairing of the outer phenol ring to the inner phenol ring. The normal synthesis of the thyroid hormones with the inhibitors of PTU and Tapazole is shown below:

![Biosynthesis of Thyroid Hormones Diagram]

Methimazole (1-methylimidazole-2-thiol) is the most commonly prescribed medication in the US for treatment of Hyperthyroidism. This medication is normally administered primarily before any of the others. It is inexpensive and does not harm the thyroid gland as much as other treatments. This medication is used to return the patients’ overactive gland to a normal metabolic state. Methimazole inhibits the synthesis of the
thyroid hormones by blocking the oxidation of iodine in the thyroid gland and by blocking the ability of iodine to react with the thyrosine to form T₄ or T₃. Methimazole is a white crystalline substance that is freely soluble in water. It differs chemically from the drugs of the thiouracil series primarily because it has a 5-membered ring instead of a 6-. It is administered orally and absorbed in the Gastrointestinal (GI) tract and is excreted in the urine. It metabolizes quickly and therefore requires often administration. It is also ten times more potent than Propylthiouracil. Methimazole should not be taken if pregnant because it can cause harm to the fetus and therefore other forms of treatment should be administered. Methimazole can also be excreted in the milk of nursing mothers and therefore, nursing is not advised while taking Methimazole. There can be major side effects to this medication and therefore use should be discontinued if side effects occur. Some of the major side effects are: anemia, fever, severe liver problems, sore throat, unusual bruising or bleeding, vomiting, and/or yellowing of the skin or eyes. The chemical structure is as follows:

\[
\begin{align*}
\text{HN} & \quad \text{HS} \\
\text{S} & \quad \text{HS} \\
\text{CH₃} & \quad \text{CH₃}
\end{align*}
\]

\text{Methimazole} \\
\text{(Tapazole)}

PTU is the second most commonly prescribed medication in the US. It is also used for the soothing treatment of Hyperthyroidism in order to prepare the patient for surgical treatment or radioactive iodine therapy. The mechanism of action is to inhibit the enzyme thyrperoxidase, which normally acts in thyroid hormone synthesis to add iodide to the hormone precursor thyroglobulin, thus forming thyroxine. It makes so the hormones are blocked and the oxidation of iodine in the thyroid gland inhibits the production of thyroxine and triiodothyronine. PTU also acts by inhibiting the enzyme 5'-deiodinase, which converts T₄ to the active form T₃. PTU has a half-life of two hours and is administered orally. It is also absorbed in the GI tract and metabolized by the liver. It normally takes up to two to three months to normalize the concentrations of T₃ and T₄. Side effects may occur in one and every one hundred patients. The most common side effects are: swelling, nausea, vomiting, heartburn, loss of taste, numbness, headaches, abnormal loss of hair, as well as, irritations to the skin like rash, itching, hives. If any of the side effects are noticed discontinue use and contact your doctor. PTU is usually not administered as often as the others due to its cost; therefore, the treatment of radioiodine is most desirable.
The chemical structure is:

![Chemical structure of Propylthiouracil (PTU, USA)](image)

In addition to their activity in the Thyroid Follicular cells, Methimazole and PTU are suspected to inhibit the conversion of $T_4$ to $T_3$ in the liver. Since $T_3$ is the active form of the hormone, inhibiting this process also inhibits the thyroid hormone activity.

**Conclusion**

Hyperthyroidism was new to me, in fact I had no idea that it even existed until about two years ago. Hyperthyroidism affects many women and some men, children, and elderly. It is very crucial to detect early on in the beginning stages of the disease in order to avoid any major side effects that may term fatal. The proper functioning of the thyroid is extremely important to your body and your life. If it is not functioning properly medical attention should be sought after immediately. In fact, if any of the above symptoms for Hyperthyroidism are noticed and haven’t been detected by your physician, return to your doctor and insist that your thyroid hormones are tested. Too many women go through there life not knowing what is wrong with them, they may believe their physician when they are told that they have a depression problem or that they have a psychological problem, but still continue to live with the major side effects of Hyperthyroidism no matter what medication their doctor prescribes.

I myself am an advocate of the disease caused by Hyperthyroidism, Graves’ Disease. I have been suffering the effects for many years and in fact I am one who went about 4 years without knowing. I was misdiagnosed at first for anemia and was also tested for depression. I was told to take iron pills so that my iron could regain its normalcy. I was constantly moody, one minute I would be happy and the next angry. I thought I was going crazy. I rapidly lost weight despite what I ate. I was heat sensitive and always hot even in the middle of the winter. I noticed that my heart rate was always high especially when I worked out, but I thought it to be a good thing, the higher the heart rate the better the workout. Between the heat and the mood swings I also experienced anxiety. It wasn’t until I went to the doctor for a pregnancy test that the problem was finally noticed. I thought for sure I was pregnant due to months without a menstrual cycle after being newly married but the pregnancy test came back negative. While sitting up on the bed in the doctors office, the doctor stated “wow it looks like your thyroid gland is swollen, we should take a blood test to test your thyroid activity.” It took 4 years and many doctors to finally receive the proper diagnosis. The regulation of the thyroid gland is so critical in controlling moods, weight, and mental and physical energy levels that
with any of these signs a blood test should always be taken to detect over activity of the thyroid gland. Due to the increased heart rate caused by Hyperthyroidism, if this condition would have gone any longer undetected it could have been fatal. I could have been running or exercising somewhere and my increased heart rate could have caused me to have a heart attack. I am very grateful to the doctor that finally noticed my enlarged thyroid gland and had enough knowledge to say “let’s take a blood test and test your thyroid activity”.
Bibliography


Imatinib (Gleevec®)

Treatment for Leukemia and Lymphoma

by George Rivello

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CHM 236

Instructor: Dr. Mancini

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Abstract:

Today's treatments for leukemia, lymphoma and myeloma include chemotherapy and radiation therapy, sometimes in combination. The progress in treatment and survival for patients with blood cancers is largely due to the development of chemotherapy drugs over the past 40 years. The number of chemotherapy agents available has soared since their first usage in the 1940s. Today, drugs that target the cancer producing proteins such as Imatinib are available and may be used to achieve maximum cancer cell fighting ability. Unfortunately, Chemotherapy used to treat leukemia, lymphoma and myeloma may be accompanied by undesirable side effects.

History of Chemotherapy Drugs:

Chemotherapy dates back to the 1940s. The first efforts were related to nitrogen mustard, which was intended to be a chemical warfare agent, until it was discovered upon autopsy that people exposed to mustard gas had lymphoid cell and myeloid cell suppression. (Lymphoid cells originate from the lymph nodes and myeloid cells from the bone marrow. These terms are often used when describing types of blood cancers.) Working for the Department of Defense at the time, the pharmacologists Louis Goodman and Alfred Gillman reasoned that nitrogen mustard could be used in the treatment of blood cancers. After experimentation on animals, the two pharmacologists then tried treating a patient with non-Hodgkin’s lymphoma, working with a surgeon named Gustav Linskog. Both Hodgkin’s and non-Hodgkin’s diseases are lymphomas, cancer that originates in a subset of white blood cells called lymphocytes. The difference between Hodgkin’s and non-Hodgkin’s lymphoma is in the specific lymphocytes involved. The nitrogen mustard treatment had some tangible results. There was a reduction in the patients’ overall tumor masses. This was the first step in treating cancer with pharmaceuticals.

In the late 1940s, pathologist Sidney Farber studied the effects of folic acid on leukemia patients. Folic acid was discovered in 1937, and it seemed to stimulate lymphoblastic leukemia cells in children with lymphoma. Farber designed these drugs to work antagonistically with folates. They blocked folate requiring enzymes by binding to the site and inhibiting the use of that enzyme. Remissions were quite brief, but the general idea of using antifolates to suppress the spread of malignant blood cells was demonstrated.

Later a doctor named Joseph Burchenal worked with Dr. Farber, making an alkaloid based anti-cancer drug called 6-mercaptopurine. This proved to be an effective anti-leukemia drug. This drug changed the metabolites a cell needed to divide, thus inhibiting its production. Then Eli-Lilly pharmaceuticals experimented with an alkaloid drug based on the Madagascar periwinkle flower, Vinca rosea. They found that it blocked the spread of tumor cells. Although quite by mistake, later understanding of this drug revealed that the plant inhibited microtubule polymerization, required for tumor cell division and proliferation.
In 1955 the US government established an agency called the National Cancer Chemotherapy Service Center (NCCSC), in response to some of the aforementioned successes with chemical treatment. At the time, private pharmaceutical companies didn’t have much interest in cancer fighting drugs. The NCCSC would be responsible for some major pharmaceutical breakthroughs and techniques such as cell lines and animal models used in the development of chemotherapeutic drugs. The NCCSC would also develop drugs based on natural products from plant and marine sources, with anti-cancer qualities.

The Madagascar Periwinkle, a plant with anti-cancer qualities.

In 1965 James Holland, Emil Freireich and Emil Frei experimented with cancer therapy using the antibiotic therapy for tuberculosis as a model. At the time tuberculosis was treated with multiple simultaneous drugs, each with a different mechanism of action. By giving the drugs concurrently, it would be more difficult for the cancer cell to mutate and become resistant to the treatment. The doctors Holland, Freireich and Frei came up with a combination drug treatment using a methotrexate (an antifolate), incrusting (an alkaloid based on the periwinkle flower), 6-mercaptopurine, and prednisone. This regimen reduced leukemia in children, and had a much longer term remission than earlier treatments. Once thought incurable, acute lymphoblast leukemia became a treatable disorder. Similar concurrent regimens were used successfully with similar blood disorders Hodgkin’s and non Hodgkin’s lymphoma. Today almost all cancer chemotherapy treatment involves the same technique of multiple drugs given simultaneously.

As a part of a government contract, researcher John Montgomery synthesized an important drug nitrosourea, an alkylating agent that crosslinks DNA. Nitrosourea compounds include a nitroso (R-NO) group and a urea (NC(=O)N). These drugs cross the blood brain barrier and are effective at treatment for chronic lymphatic leukemia.
During the 1970s, a period of discovery was taking place. The pharmaceutical industry was undergoing a period of more extensive clinical trials before releasing a drug to the market. Also, higher doses and different combinations of drugs were being tested. It was during this period of time that a greater understanding of how cancer works was taking place. One important contribution during this period was a special process of harvesting bone marrow, administering chemotherapy, then returning the harvested bone marrow a few days later. This process, called *autologous bone marrow transplantation*, was thought to be a cure for many types of cancer, but it didn’t prove to be effective for tumors. It is currently used for Hodgkin’s patients who have failed traditional chemotherapy treatment.

The 1990s brought about the introduction of targeted therapy. Unlike its predecessors, these drugs would specifically target the cancer cells and suppress them, instead of causing a system wide slowdown of new blood cell production. The advancements in understanding of how cancer works that took place in the 1970s and 1980s paid dividends. Understanding how signaling networks worked between cells showed that the signaling networks were quite different in cancer cells. Knowing this difference allowed scientists to isolate the specific cancer producing proteins. Imatinib, or Gleevec®, was one of the first of such a targeted drug. Imatinib was specifically engineered for a purpose, unlike other chemotherapy drugs which had historically been discovered by happenstance. Brian Druker, working at Oregon University, had researched an abnormal enzyme kinase in chronic myelogenous leukemia (CML). He wanted to make a drug that would inhibit this special kinase and no other. It was the research of those before him that enabled Druker to make such a connection by understanding exactly how the leukemia cells work. Druker worked with Novartis chemist Nick Lydon, who had done similar work with enzyme inhibitors. Novartis Pharmaceuticals then produced Gleevec® was the end product of their efforts.

**Chronic Myeloid Leukemia**

Chronic myelogenous leukemia (CML) is one of the four main types of leukemia. Chronic leukemia progresses very slowly over a period of years. An alternate form, acute leukemia, progresses in a matter of months. Myeloid refers to the type of white blood cell being overproduced. There are three phases of CML. The chronic phase, the accelerated phase, and the blast crisis phase. Most patients are in the chronic phase of CML. Imatinib is usually taken during the chronic phase of CML.¹

CML starts with a change to a stem cell. The change occurs by way of a chromosomal crossover known as the Philadelphia Chromosome. (Ph chromosome). The Ph chromosome is made by a translocation between chromosome 9 and chromosome 22. The break on chromosome 9 is a gene called ABL. The break on chromosome 22 is a gene called BCR. The special gene that is made by the crossover makes a protein that causes CML. The oncogene (cancer) gene is called BCR-ABL. In some cases, high doses of radiation can cause the BCR-ABL gene to occur by mutation. It can also occur naturally by a miscoded gene.
CML is somewhat difficult to diagnose because initially it presents itself as a high white blood cell count, which isn’t deterministic of CML.

**Imatinib Description**

Imatinib is a drug that is used to treat certain types of cancer. It is currently marketed by Novartis Pharmaceuticals as Gleevec® in the USA. It is used primarily in treating CML, gastrointestinal stromal tumors and a few other disorders. It is the first drug to selectively target cancer creating cells, rather than reduce overall new cell production, as with traditional chemotherapeutic drugs.\(^5\)

Imantib mesylate is a white to off white to brownish or yellowish tinged crystal powder. Its molecular weight is 589.7. Imatinib mesylate is soluble in aqueous buffers less than pH 5.5. In non-aqueous solvents, the drug substance is soluble in dimethyl sufixed, methanol, and ethanol, but is insoluble in acetone, n-octanol, acetone, and acetonitrile. There are other inactive ingredients used in making the drug, such as tablet coating and binding agents.
Imatinib Mechanism of Action:

While traditional cancer treatments such as chemotherapy or radiation kill all dividing cells, Imatinib acts on a molecular target by a lock and key mechanism that is specifically targeted to the cancer cells.\(^3\)

In chronic myelogenous leukemia, the Ph chromosome contains the BCR-ABL gene, which leads to the cancer causing protein.\(^5\) The enzyme complex is a tyrosine kinase. Tyrosine kinase is an enzyme that can transfer a phosphate group from ATP to a tyrosine residue in a protein. Tyrosine kinases are a subgroup of the larger class of protein kinases. Phosphorylation of proteins by kinases is an important mechanism in regulation of enzyme activity. The problem occurs when the tyrosine kinase becomes continually active, and has no regulation mechanism. The active sites of tyrosine kinases each have a binding site for ATP. Imatinib works by binding to the ATP binding site of BCR-ABL. If the BCR-ABL cannot bind ATP, the BCR-ABL protein cannot carry out its kinase activity, and is therefore shut down.\(^4\)

Imatinib is remarkable because it is selective for BCR-ABL, and it doesn’t inhibit other tyrosine kinases. Imatinib also inhibits the ABL protein of other non-cancerous cells. However, as if almost by luck, these non-cancerous cells have additional redundant tyrosine kinases which allow them to continue to function normally even when the abl tyrosine kinase is blocked. The tumor cells, however, have a BCR-ABL dependence to perform enzymatic phosphorylation.
Side effects

Traditional chemotherapy drugs have serious side effects such as nausea, weight loss, hair loss and severe fatigue. Imatinib was designed as a specific inhibitor, so it has less fewer side effects. In the United States, the FDA has approved Imatinib as the first line of treatment for chronic myelogenous leukemia (CML). Long term side effects of Imatinib have not been determined because of the short amount of time the drug has been available to patients. Studies show that the drug is very well tolerated in the liver (low liver toxicity).  

Nausea is one of the most common side effects with Gleevec therapy, sometimes accompanied by vomiting. Swelling around the eyes (periorbital edema) and/or of the lower legs occurs frequently. If this happens, patients are sometimes given a diuretic, or the dosage is reduced. Muscle cramps are another common symptom, but they are usually mild. Muscle cramps are usually treated with a calcium supplement. Diarrhea is common with patients who take Imatinib. Diarrhea is usually mild and can be managed with over-the-counter medications. Also, hemorrhage can result from the use of this drug. Generally the drug is completely removed from the regimen if there are signs of this occurring. Some patients taking Gleevec develop a skin rash. Patients may be given an additional medication, such as hydrocortisone, to reduce the signs and symptoms of rash. There are other symptoms, such as headaches and joint pain. Sometimes side effects are more severe, and at that point, the medication may be stopped or the dosage reduced.

This drug should never be taken by women who are pregnant or planning to become pregnant. Like other chemotherapeutic drugs, this drug can cause teratogenic effects in babies, or even death.

Drug Interactions

The body metabolizes many drugs in the liver with enzymes. When Imatinib is taken at the same time as other drugs, enzymes may be forced to put the other drugs aside while they break down Imatinib. This can result in higher or lower than expected levels of the other drugs in the bloodstream. Similarly, certain drugs may take priority and force the enzymes to put Imatinib aside, which can result in higher or lower than expected levels of Imatinib in the bloodstream. In particular, acetaminophen, birth control pills, blood thinners, herbal products (e.g., St. John's Wort), erythromycin, and similar drugs are all broken down by the same enzymes that metabolize Imatinib.
In some cases, resistance to Imatinib can be developed within the patient. There are two types of resistance, primary and secondary. Primary resistance is when the patient does not respond to the drug after the first six months of treatment. With secondary resistance, the patient is in the chronic phase of leukemia, takes the drug and goes into remission, then once off the drug begins to develop a resistance to the drug. In the case of secondary resistance, Imatinib is no longer effective against chronic myelogenous leukemia. The way the resistance works is that the BCR-ABL gene mutates to protect itself against the competitive inhibition with Imatinib. When this happens, the drug is no longer effective, because it is no longer a lock and key fit with the new, mutated substrate. Imatinib does not fit in the enzyme site, and the BCR-ABL gene can propagate new cancerous proteins. Because this type of drug is so new, very few alternatives are available if a patient becomes resistant to the drug, but new alternatives such as Dasatinib and AMN107 are being screened by the FDA chain to be released on the market.

**Legal Debate on Imatinib**

This year, Gleevec® fell under a heated legal debate. Gleevec® became a test case through which Novartis challenged India’s patent laws. India, which is a largely impoverished country, relies on generic drugs to provide front line healthcare for its peoples. This would make it harder for Indian companies to produce generic versions of the drug still manufactured under patent in other parts of the world. A change in the Indian law, some advocates argue, would make it impossible for Indian companies to provide cheap anti-AIDS medication, which in turn endangers the sale of drugs in third world countries. This debate is ongoing. It is by no means isolated to Gleevec® alone, but Gleevec® is the landmark case which Novartis has decided to make a patent claim on. In the legal world, one case provides a precedent for another, if the patent laws are decided in Novartis’ favor, then it could have a huge impact on healthcare in the third world countries.

**Conclusion**

Imatinib is the first of its kind, and the cumulation of many years of research. Chronic myelogenous leukemia is an especially difficult disorder to remedy, because it is in the blood cells, the disorder is system wide throughout the entire body. Because the blood cells that are being overproduced are receiving instructions from the bone marrow, the entire chain of how the defective gene codes for protein needs to be completely understood in order to create an effective remedy to the disorder. The years and years of research were built upon to come up with Imatinib, which represents the future of anticancer drugs because it targets the cancer creating proteins, instead of damaging the cells of the entire body. The future of chemotherapy lies here, and the hope is that other drugs will follow this pattern of specific enzyme inhibition. This means less suffering for those diagnosed with blood cancers, and a greater probability of surviving.
1 Wikipedia, (05, May 20). History of Cancer Chemotherapy


Other References

   by Gerald P. Murphy (Author), Lois B. Morris (Author), Dianne Lange (Author)
Encompassing Features of Acetylsalicylic Acid: Aspirin

By Jeff Robertson
Organic Chemistry 236
Section 2232
April 15, 2007
Abstract:

Although most households have aspirin in their medicine cabinet, many individuals have little or no understanding of its true function. How does aspirin work once inside the human body? Are there any side effects associated, or is it a relatively safe drug? What does the molecular structure of aspirin look like? What type of chemical, structural, and physical properties does it possess? These questions along with other insights will be the focus of discussion in this paper.

Introduction:

Aspirin, or a similar derivative, has been in use for many years. Some of the earliest applications have been tracked to the time of Hippocrates (wikipedia.org). Although the applications of aspirin throughout time have been similar, the composition and knowledge of the molecule have evolved from the earliest uses. The properties, formation, and effects of aspirin will be further investigated. Exploring how this drug has been used, and the side effects that are possible will allow greater awareness. Understanding its chemical and physical properties, applications, history, and uses allows us additional knowledge into the workings of this drug.

History:

Functional purposes of aspirin have been utilized for thousands of years. Some of the earliest applications were used for many of the same reasons it is used today. The first documented example occurred in the 5th century when Hippocrates utilized bark and leaves of a willow tree (wikipedia.org). This lead to the documentation that Hippocrates made of salicylic acid a powdery extract used that would relieve aches and reduce fevers (howstuffworks.com). This salicylic acid caused a side effect of upset stomach. From this point until much later, the advances were modest but the uses still evident. That all changed in the 1800’s when advances were made which lead to the discovery of aspirin as we know it today. In 1897, Felix Hoffman, a young chemist synthesized the first pure and stabilized form of the molecule (wikipedia.org). The stability came from transforming one of the acidic portions of the molecule with an acetyl group (howstuffworks.com). As a result of this transformation, the salicylic acid was changed to Acetylsalicylic acid. Due to these discoveries, the Friedrich Baker & Co. began to distribute aspirin. Many of the advances made by Hoffman were due to his desire to find a remedy for his father’s rheumatoid arthritis (aspirin.com). Dr. Hoffman was interested in finding a medication that would be better tolerated than the previously prescribed salicylic acid (aspirin.com). In the 1970’s, the mechanism for how aspirin truly works in the body was finally discovered. John Robert Vane in 1971 showed a breakthrough in the understanding of the way aspirin works and as a result was awarded The Nobel Prize in 1982 (wikipedia.org).
1899 saw the naming of acetylsalicylic acid to aspirin as a trademark. In many countries the term Aspirin is a registered trademark of the Bayer Company (aspirin.com). This trademark was held true for many years in the U.S. until that purchase was expired in 1917 (wikipedia.org). In 1918 the trademark was purchased by Sterling Drug from the U.S. Government (wikipedia.org). Today there are many manufacturers of aspirin as a result of a court ruling in 1921 which allowed reproduction of the drug. Bayer purchased Sterling in 1994 but the result still did not restore the U.S. trademark (aspirin.com). Thus in pharmacy, and virtually every household counter, we see aspirin today. Acetylsalicylic acid is produced by various manufacturers, many of which are in generic form.

Uses for Acetylsalicylic Acid

There are several historical features surrounding aspirin. Aspirin has been known to be used as a pain reliever or fever reducer (howstuffworks.com). Hoffman understood the exceptional ability of aspirin to act as a pain reliever as he searched for a more tolerable medication to treat arthritis (wikipedia.org). Often, as Hoffman discovered, acetylsalicylic acid was useful in the relief of those diagnosed with arthritis due to its ability to alleviate inflammation (aspirin.com). Actually, acetylsalicylic acid is a member of a larger class of drugs known as non-steroidal anti-inflammatory drugs. Due to certain properties of aspirin, it is often used on a daily bases for those at risk of heart attacks (howstuffworks.com). Typically the dosage for this type of preventive care is lower than what may be a suggested use in other circumstances. Higher doses may be given to patients that have just experienced a heart attack. Other treatments include aches and pain, migraines, rheumatic fever, menstrual pain, toothache or headache (aspirin.com). There may be other applications of aspirin use depending on circumstance and doctor or pharmacist recommendation. The situations and prior medical history are important in determining whether to take the medication or not. It is important to understand the mechanisms by which aspirin works in the human body. These mechanisms will be investigated further within. Although there are many uses for acetylsalicylic acid, the possibility of side effects may occur.

Possible side effect of a higher dose of aspirin could include stomach bleeding or ulcers. Due to aspirin having a thinning effect on the blood, it can cause extensive bleeding. Dr. Hoffman discovered another possible side effect of salicylic acid. When he prescribed it for his ailing father, it caused upset stomach (howstuffworks.com). Although there may be additional isolated side effects use must be determined by the benefit over possible side effects. Warnings advise to stop use if asthma, stomach problems, ulcers, or bleeding problems exist (wikipedia.org). In addition to those possible contradictions, aspirin should not be used if prescriptions treating diabetes, gout, arthritis, or an anticoagulant are being taken (wikipedia.org). Individuals exceeding the recommended dose (for adults over 12 years of age taking one to two tablets repeated every four hours) overdose can occur. In these cases it is suggested to contact poison control to determine if additional medical attention is necessary. Serious problems arising from aspirin use have been associated with Reye’s syndrome. This syndrome affects children that have taken aspirin and may be recovering or still compromised by a viral infection (mayo.com). Effects can be relative to the brain, liver, or blood. With this
syndrome comes a spike in the level of acidity and ammonia in the blood. In addition a
drop in the blood sugar levels occurs (mayo.com). Swelling may then occur in both the
brain and liver. This can cause seizure activity or even death depending on the severity.
Due to public awareness of the health risks of using aspirin for children, few cases of
Reyes syndrome have been reported (mayo.com). The ultimate reason behind how and
why aspirin acts the way it does is due to the defining characteristics, both physical and
chemical.

**Chemical and Physical Properties:**

As with any organic molecule aspirin has defining characteristics that set it apart
from many other drugs. Many of the simple properties such as molecular weight or
chemical formula allow to the building of the greater compound as a whole. The
chemical formula of aspirin is C9H8O4 (chemfinder.com). This gives rise to a molecular
weight of 180.160g/mol. This number is derived from taking the weight of each molecule
and multiplying by the corresponding amount present. The results of this are shown
below:

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<th>Atom</th>
<th>Amount Present</th>
<th>Weight per Atom</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon(C)</td>
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<td>12.011</td>
<td>108.099</td>
</tr>
<tr>
<td>Hydrogen(H)</td>
<td>8</td>
<td>1.008</td>
<td>8.064</td>
</tr>
<tr>
<td>Oxygen(O)</td>
<td>4</td>
<td>15.999</td>
<td>63.997</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>180.160</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In addition to these chemical properties, it is also helpful to identify the molecule
based on a family or root to which they belong. This would classify
acetylsalicylic acid as a member of the salicylates family. In
addition, it contains as a major functional group, a benzene ring.
From the total molecular formula the ring itself constitutes C6H4.
This would qualify it as a benzene type compound obtained from
chemfinder.com as pictured to the right with removal of the 2
substituents:

The two substituents that protrude off the benzene ring compromise two major groups.
To begin, at the number one carbon, a carboxylic acid group appears which is composed
of COOH (Wade, 2006). The carbon is double bonded to the oxygen and an additional
bond on the carbon is formed with an OH group. This functionally has the structure
contained within the box that is positioned at the number one carbon:
Finally a last functionality of C₂O₂H₃ exists. This has a methyl group along with a carbon to oxygen double bond. The carbon with the double bonded oxygen and methyl group is attached to the benzene ring with oxygen. This functionality looks structurally as pictured in the box:

All of these structural functional groups come together to encompass aspirin as a whole. As this occurs the structure completed takes on an appearance shown below from chemfinder.com:

Additionally, the structure and different functional groups can be seen clearly and 3-dimensionally (left) complements of wikipedia.org or in the exaggerated form (right) from howstuffworks.com (2001).

It is important to notice the conformation of the benzene ring. As the substituents hang off they are in an ortho configuration. This simply means that the functionalities are on the number one and two carbons. These many properties constitute only a portion of characteristics displayed by aspirin. Aspirin also has properties evident physically.

The properties of acetylsalicylic acid constitute a smaller overall amount of physical characteristics rather than chemical or structural. According to Chemfinder.com the density of aspirin is 1.40g/cm³. The melting range of aspirin is found to be between 138-140°C. Oddly enough, the boiling range in a decomposed form equates to 140°C (chemfinder.com). Acetylsalicylic acid displays solubility in water of 1mg/mL at 20°C. One characteristic of aspirin, that gives lead to reactions, is found within the dissociation factor as an acid. According to wikipedia.org, aspirin has a pKₐ value of 3.5 at 25°C.
This constitutes a fairly weak acid thus giving rise to dissociation equilibrium. This equilibrium can be visualized from wikipedia.org.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{O}^- \\
\text{O}^- & \quad \text{H}^+
\end{align*}
\]

The many chemical, physical, and structural properties of acetylsalicylic acid give rise to the ability of reactions. For example, understanding its melting range or density may assist in reactions or synthesis. In many examples this includes particular target portions of a molecule in which the ability to react and synthesis end products is present. This may also include being able to utilize pressure, acid or base, temperature or various other techniques to accomplish the end goal: aspirin.

**Reactions/Synthesis:**

As previously stated, a large disadvantage in taking salicylic acid is due to the side effect of upset stomach. This lead Hoffman to find an alternative that was much better. As a result, aspirin was synthesized and thus discovered. This simple process of taking salicylic acid in a reaction with an acetyl group at the site of the acidic portion results in the product of aspirin. In the described reaction above the acetyl group is derived from acetic anhydride. This reaction can be followed simply as seen below (Wade, 2006).

![Salicylic Acid](image1)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{O}^- \\
\text{O}^- & \quad \text{H}^+
\end{align*}
\]

Salicylic Acid

Acetic anhydride

Acetylsalicylic acid

A typical catalyst of choice for the synthesis of aspirin could include phosphoric acid (H₃PO₄) or sulfuric acid (H₂SO₄) (Williamson, 2003). These would be acceptable catalysts over HCl due to the percent of water contained in each. H₃PO₄ and H₂SO₄ both contain small amounts of water. HCl on the other hand contains up to 80% water. The effects of water could interfere with the formation of the acetyl group, causing salicylic acid and acetic acid production (Williamson, 2003). Although the reaction seems simple, the intermediate formations become much more complex. As salicylic acid reacts with acetic anhydride the alcohol portion of the salicylic acid contains the oxygen with unpaired sets of electrons. One set attacks the carbonyl portion of the acetic anhydride. This results in the formation of intermediates that transfer electrons and charges to finally produce the acetylsalicylic acid. The first intermediate can be seen below as the reaction proceeds:
As the rearrangement continues another intermediate is created. This occurs by hydrogen leaving and creating unpaired electrons on oxygen. This removes the positive charge on the oxygen. Additionally an intermediate is created from this that takes the oxygen with a negative charge and creates a double bond with carbon. This in turn kicks a bond off carbon and causes CH$_3$COO$^-$ to leave. These two intermediate structures are seen below:

The resulting product from the final intermediate is acetylsalicylic acid. Along with this comes CH$_3$COO$^-$. This may be but one of many examples of an ability to exchange the OH group on salicylic acid with an acetyl group (Williamson, 2003). Although the experimental result may seem simple the molecule configures into the different transition states to obtain the end product. On March 27, 2007 this exact experiment was utilized in Paradise Valley Community College Organic Chemistry lab. Some of the results of that lab will be reported below to explore further capabilities and effectiveness of the experiment.

As the experiment proceeded in the making of aspirin, outlined above, many distinguishing results were obtained from the final data. To begin the melting range of the acquired product was 94.3-109.3°C. This result compared to actual melting range (128-137°C) seemed low. This may have been due to incomplete dryness or the factor of not re-crystallizing the product. The percent yield obtained seemed to be fairly large. Overall from a beginning salicylic acid weight of 0.1386g to an acetylsalicylic acid weight of 0.1520g the amount obtained resulted in an 84.4% yield. This would lead to an assumption that a good percentage of product may be obtained from the starting material. This is important for cost effectiveness. These results were obtained via micro-scale techniques. But how is aspirin synthesized for commercial purposes? Does it follow a similar mode of action?

Acetylsalicylic acid is synthesized utilizing a two step process (wikipedia.org). This process takes phenol and treats it with sodium base to produce sodium phenoxide. The sodium phenoxide is reacted with carbon dioxide under high temperature and
pressure conditions then finally acidified with sulfuric acid resulting in salicylic acid (wikipedia.org). The synthesis process is called the Kolbe-Schmitt reaction (Williamson, 2003). This reaction process can be seen below as described in wikipedia.org.

\[
\begin{align*}
\text{phenol} + \text{H}_2\text{SO}_4 & \rightarrow \text{salicylic acid} \\
\text{CO}_2 + \text{H}_2\text{O} + \text{NaOH} & \rightarrow \text{Na}_2\text{CO}_3 + \text{H}_2\text{O}
\end{align*}
\]

The process from this point follows the path explained above, in that the salicylic acid is treated with acetic anhydride to form acetylsalicylic acid (wikipedia.org). A distinguishing feature of the synthesis of acetylsalicylic acid is the possibility of the aspirin to smell of vinegar. Usually this is seen in high concentrations of aspirin (wikipedia.org). The reason for this is due to the possibility of the acetylsalicylic acid undergoing autocatalytic degradation; in which exposure to moist conditions results in the molecule separating (wikipedia.org). The products obtained in this case are salicylic acid and acetic acid. The factors surrounding the reaction and synthesis of aspirin lay the foundation for the investigation into the actions contained within the human body.

**Effects on the body:**

John Robert Vane was credited with showing the mechanism of action of aspirin within the human body in 1971 (wikipedia.org). This knowledge led to an understanding that aspirin works as an inhibitor. Specifically, the inhibition occurs with prostaglandins (aspirin.com). These prostaglandins function as a hormone-like substance involving the regulation of processes such as pain, fever or inflammation (aspirin.com). Aspirin also works to suppress thromboxanes (wikipedia.org). The effectiveness of aspirin is due to the noncompetitive and irreversible inhibition of cyclooxygenase enzyme (wikipedia.org). This enzyme also known as COX enzyme is a requirement for prostaglandin and thromboxane synthesis according to wikipedia.org. Aspirin works to attach its acetyl group covalently to the serine residue of the enzyme’s active site (howstuffworks.com). The effectiveness of aspirin in suppression is due to the role that prostaglandins and thromboxanes exhibit. Prostaglandins function as hormones that have a range of duties including transmission of pain to the brain, inflammation, and control of hypothalamic thermostat (wikipedia.org). On the other hand thromboxanes work in the aggression of platelets (wikipedia.org). As aspirin works it functions to inhibit cyclooxygenase. It can accomplish this in one of two ways. The two different types of cyclooxygenase, COX-1 and COX-2 are affected differently by aspirin. First aspirin works to modify the enzyme activity of COX-2 and inhibits the COX-1 activity (wikipedia.org). Recently it has been discovered that certain COX-2 inhibitors have been linked to increase risk of heart attacks and thus have been withdrawn (wikipedia.org).

The path that aspirin follows in these modes of action helps to see the workings exposed. First the aspirin is swallowed and enters the stomach. Here it is dissolved and enters the digestive tract. While in the stomach aspirin binds with the COX-1
prostaglandin which is utilized in thickening the stomach lining (howstuffworks.com). The result is a thinning of the stomach lining which explains the occurrence of upset stomachs with use (howstuffworks.com). After the aspirin has entered the digestive tract and has been absorbed by the body, it enters the blood stream where it is spread into the entire body. Aspirin functions to seek out the prostaglandins close to the site of pain, resulting in relief (howstuffworks.com).

Although these modes of action seem to cover the general uses of aspirin, there are additional properties. According to wikipedia.org aspirin also functions in two other roles. Namely acetylsalicylic acid works to uncouple oxidative phosphorylation in cartilaginous mitochondria. This occurs by diffusion from the inner membrane space buffering and assisting in the transport of protons (wikipedia.org). Most recently, aspirin was discovered to activate the formation of NO radicals (wikipedia.org). This was an important observation made by Dr. Derek W. Gilroy because these radicals in the body enable the white blood cells to work more effectively in the fight of infection (wikipedia.org). These recent discoveries into the workings of aspirin have led to a better understanding into the mode of action in the human body.

**Conclusion:**

Many individuals have been made aware of aspirin’s evolving functions due to numerous researchers and their discoveries. These contributions to the field of medicine have laid the foundation for further research. The ability of aspirin to effectively work in the human body will continue to change as greater understanding of the drug advances.
Works Cited


Chantix®
(Varenicline)

Prepared for
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Paradise Valley Community College

Prepared by
Ashley Sanford
CHM 236
April 20, 2007
Abstract

Chantix® (Varenicline) is a prescription medication approved by the FDA in May 2006 to help adults stop smoking. Varenicline is different than bupropion (Zyban) and nicotine replacement therapy (NRT). This paper will discuss the history and differences of smoking cessation, how Chantix works, and the future of Chantix.

Difference between Chantix and Zyban

Chantix (varenicline) and Zyban (bupropion) are the two most popular prescription drugs which help adults get rid of the smoking routine. They are both licensed to help smokers quit. Pfizer developed a smoking cessation drug Chantix that reduces the nicotine craving and withdrawal effects while Zyban, manufactured by GlaxoSmithKline, has been approved as an antidepressant used for treatment of a condition called major depressive disorder. Zyban was approved in 1997 by the FDA whereas Chantix was approved in May 2006. Both drugs were approved for the same cause but vary in many ways. Chantix works on the nicotine receptor sites in the brain to create less of an urge to smoke whereas Zyban boosts chemical levels in the brain to create less of an urge to smoke. A study done of 1000 smokers from June 2003 to April 2005 found that Chantix was more effective in helping people quit smoking. Researchers found that 24% of those taking Chantix were able to quit immediately, compared to 18% taking Zyban and just 10% given placebo. It was also found that 20% of those taking Chantix and 11% taking Zyban were able to quit if they continued on the medication for up to three months. According to studies, Chantix is more effective than Zyban and three times as effective as a placebo. Chantix is a 1mg dose twice daily and is more effective compared to Zyban’s 150mg twice daily.

Description

The active ingredient in Chantix (varenicline tablets) is varenicline (tartrate salt). Varenicline is partially selective for α4β2 nicotinic acetylcholine receptor subtypes. Varenicline is a powder with the chemical name of: 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine,(2R,3R)-2,3-dihydroxybutanedioate (1:1) and is highly soluble in water. Chantix is a selective α4β2 nicotinic acetylcholine receptor partial agonist, providing a low to moderate level of dopamine stimulation to reduce the craving. It also withdraws the symptoms simultaneously, blocking the action of
nicotine. Chantix is admitted orally in two strengths-0.5mg and 1mg. The molecular formula for varenicline is \( \text{C}_{13}\text{H}_{13}\text{N}_3\cdot\text{C}_4\text{H}_6\text{O}_6 \) with the molecular weight of 361.35 Daltons and chemical structure of:

![Chemical structure of varenicline](image)

**Mechanism**

Varenicline is highly selective and binds to \( \alpha_4\beta_2 \) receptors better than to other common nicotinic receptors, as well as to non-nicotinic receptors. Varenicline is partial agonist at \( \alpha_4\beta_2 \) neuronal nicotinic acetylcholine receptors. Nicotine exerts its effects when binding to these receptors. Cravings are stimulated during periods of abstinence by low levels of mesolimbic dopamine. Varenicline is effective by partially stimulating \( \alpha_4\beta_2 \) receptors to produce a low level of mesolimbic dopamine thus diminishing nicotine cravings and withdrawal symptoms. The benefit of varenicline is its blocking effects on nicotine by occupying receptor sites. By varenicline blocking the receptors, it reduces the pharmacologic reward of nicotine in cases where a patient relapses and uses tobacco.

**Pharmacokinetics**

*Absorption and Distribution:*

Maximum absorption of varenicline into the blood occurs typically within 3-4 hours after being administered orally and a steady-state is reached in about 4 days after multiple doses. Food does not affect the varenicline oral bioavailability. Twenty percent or less of varenicline is plasma protein bound and is independent of both age and renal function.

*Metabolism and Elimination:*

Varenicline has an elimination half-life of approximately 24 hours. Varenicline undergoes minimal metabolism with 92% excreted unchanged in the urine. Elimination via the kidneys is primarily through glomerular filtration along with active tubular secretion by the human organic cation transporter, OCT2.
Clinical Studies

There were six clinical trials demonstrated on the efficacy of Chantix in smoking cessation. Over 3659 chronic cigarette smokers were studied. Abstinence from smoking was determined at weekly visits by the patients giving a self-report and verified by measurement of exhaled carbon monoxide. The completion rate was 65% of patients treated by Chantix enrolled in these studies. The patients were treated for 12 weeks and then followed for 40 weeks post-treatment. Most of the patients being studied were Caucasian (79% - 96%) and equal numbers of men and women. The average age of the subjects was 43 years. The subjects, on average, smoked about 21 cigarettes per day for approximately 25 years.

The patients were provided an informational booklet on smoking cessation and received smoking cessation counseling at each weekly treatment for about 10 minutes. The patients were required to set a stop smoking date with dosing starting 1 week before this date.

Study 2: In this study, there were 627 subjects comparing 1mg per day of Chantix vs. 2mg per day of placebo. Chantix was given in two divided doses. Dosage was titrated up over the course of one week. Full dosage started with the second week of dosing. Forty five percent of subjects receiving 1mg per day of Chantix and 51% of subjects receiving 2mg per day had confirmed continuous abstinence during weeks 9-12 compared to 12% of the subjects taking placebo.

Study 3: This study, containing 312 subjects, examined the effect of patient directing dosing strategy of Chantix or placebo. After the initial week of 0.5mg per day, the subjects could adjust their dosage as often as they wished between 0.5mg and 1mg per day. Sixty-nine percent of the patients used the maximum allowable dose at any time during the study. Forty four percent selected 1mg for over half of the study. Forty percent confirmed abstinence during weeks 9-12 compared to the 15% of patients that took placebo. Twenty-nine percent of patients treated with Chantix were continuously abstinent from the end of the first week to the end of the treatment compared to 9% of the patients that took placebo.

Study 4: Subjects that were treated with Chantix had a superior rate of abstinence during weeks 9-12 (44%) compared to patients that were treated with bupropion SR (30%) or placebo (17%). Bupropion quit rate was also superior to placebo. Twenty nine percent of the patients treated with Chantix were abstinent from the end of the first week to the end of the treatment compared to 11% of patients treated with placebo and 23% of patients treated with bupropion.

Study 5: Study five was very similar to study four. The percentage varied by 1%.
Figure 1: Continuous Abstinence, Weeks 9 through 12

![Figure 1: Continuous Abstinence, Weeks 9 through 12](image)

Table 1: Continuous Abstinence, Week 9 through 12 (95% confidence interval) across different studies

<table>
<thead>
<tr>
<th>Study</th>
<th>CHANTIX 0.5 mg BID</th>
<th>CHANTIX 1 mg BID</th>
<th>Flexible</th>
<th>Bupropion SR</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 2</td>
<td>45% (39%, 51%)</td>
<td>51% (44%, 58%)</td>
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<td>12% (6%, 18%)</td>
<td>12%</td>
</tr>
<tr>
<td>Study 3</td>
<td>40% (32%, 48%)</td>
<td>30% (25%, 35%)</td>
<td>40%</td>
<td>17% (13%, 22%)</td>
<td></td>
</tr>
<tr>
<td>Study 4</td>
<td>44% (38%, 50%)</td>
<td></td>
<td></td>
<td>18% (14%, 22%)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2: Continuous Abstinence, Weeks 9 through 52

![Figure 2: Continuous Abstinence, Weeks 9 through 52](image)

Table 2: Continuous Abstinence, Weeks 9 through 52 (95% confidence interval) across different studies

<table>
<thead>
<tr>
<th>Study</th>
<th>CHANTIX 0.5 mg BID</th>
<th>CHANTIX 1 mg BID</th>
<th>Flexible</th>
<th>Bupropion SR</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 2</td>
<td>19% (13%, 24%)</td>
<td>23% (18%, 28%)</td>
<td></td>
<td>12% (6%, 18%)</td>
<td>12%</td>
</tr>
<tr>
<td>Study 3</td>
<td>22% (16%, 29%)</td>
<td></td>
<td></td>
<td>17% (13%, 22%)</td>
<td></td>
</tr>
<tr>
<td>Study 4</td>
<td>31% (25%, 36%)</td>
<td></td>
<td></td>
<td>20% (16%, 24%)</td>
<td>10%</td>
</tr>
<tr>
<td>Study 5</td>
<td>22% (17%, 26%)</td>
<td></td>
<td></td>
<td>18% (13%, 23%)</td>
<td>12%</td>
</tr>
</tbody>
</table>
Study 6: This was the last study and it was assessed based on the effect of the additional 12 week Chantix therapy on the likelihood of long-term abstinence. The patients in this study were treated with the open label of Chantix which is 1mg for 12 weeks. Patients who had stopped smoking by week 12 were randomized to double-blind the treatment with Chantix or placebo for another 12 weeks and then followed by another 28 weeks post-treatment. The abstinence rate with the patients from week 13-24 was higher for the patients that were being treated with Chantix (70%) than for the patients being treated with placebo (50%).

In figure 3 the x-axis represents the study week for each observation allowing a comparison of groups at similar times after discontinuation of Chantix. Post-Chantix follow-up begins at week 13 for the placebo group and week 25 for the Chantix group. The y-axis represents the percent of subjects who had been abstinent for the last week of Chantix treatment and remained abstinent at the given time.

Drug Interactions

There are no clinical drug-drug interactions that have been identified. On the other hand, physiological changes from smoking cessation may alter the pharmacokinetics of some drugs. Dosage adjustments for these drugs may be necessary. Safe and effective uses of varenicline in combination with other smoking cessation therapies have not yet been established. The steady-state of pharmacokinetics of bupropion or transdermal nicotine was not tainted with varenicline when used in a combination. There was a considerable increase in the reactions such as nausea/vomiting, headache, dizziness, dysguesia, abnormal dreams, and fatigue when varenicline was combined with nicotine replacement therapy, instead of just nicotine replacement therapy by itself. Since varenicline can cause drowsiness and fatigue patients should be warned about driving and operating machinery.
Precautions

If a patient has renal disease, renal impairment, or renal failure, varenicline should be used with caution. Varenicline is excreted significantly into the kidneys and if one has impaired renal function, there is a risk of toxic reactions. There have not been any studies on pregnant women and children under 18 years of age. Pharmacokinetics of varenicline in healthy elderly patients was very similar to those of younger patients. There were no overall differences in safety or effectiveness in elderly or younger patients. Elderly patients are susceptible to decreased renal function. Care should be taken in dose selection and monitor renal function due to the excretion in the kidneys and the risk of toxic reaction.

Side Effects

Nausea was the most common side effect with the Chantix treatment. Nausea was generally illustrated as mild to moderate. In some patients, the nausea continued for the several months during treatment with Chantix. Nausea was initiated by increased dosage. The percentage of patients experiencing nausea treated with 1mg of Chantix was 30% and 16% with those patients treated with 0.5mg of Chantix. If the nausea is intolerable, there should be a consideration of dosage reduction.

How Chantix Works

Chantix works by partially blocking the $\alpha_4\beta_2$ nicotinic receptors in the brain which is the main nicotine receptor. Nicotine attaches to this receptor within 10-19 seconds after a single puff from a cigarette. There is a large increase in dopamine once the receptor is triggered. Once the dopamine is release, the smoker is then satisfied with gratifying sensation. Chantix attaches to the receptor and by occupying the receptor, it prevents nicotine from attaching. This will break the cycle of addiction by blocking the reward reinforcement associated with a large increase in dopamine.

Future of Chantix

The future for Chantix looks bright. Chantix is a new drug on the market and so far the clinical data shows that Chantix ranks towards the top compared to Zyban, placebo, and all other quit smoking aids. Chantix has a bright future for staying on the market due to the way Chantix works on the $\alpha_4\beta_2$ brain receptors.

Conclusion

Although Chantix is a new prescription drug on the market, if taken correctly, it is a great way to quit your smoking habit with minimal side effects, the worst being nausea.
With Chantix being so new there was very little information on the prescription drug. The information collected was very informative. I look forward to learning more about this drug in the future and monitor how it has progressed.
References

   Prescribing information
Abstract

Nuvaring, a new form of birth control, is a ring that is inserted in the vagina to suppress the body's ability to become pregnant. This report looks at the many methods of birth control available, Nuvaring as a birth control, and how Nuvaring is projected to last in the future. The many methods of birth control looks at methods of preventing unwanted births before and after contraception. In the description of Nuvaring as a birth control, the report discusses how Nuvaring works, what Nuvaring looks like on a molecular level, and compares Nuvaring to other forms of hormonal birth controls. Finally, the projection of Nuvaring looks at several studies to give an estimation of how Nuvaring is doing.

Introduction: What is Nuvaring and What is it For

Nuvaring is a clear, flexible ring that is 54mm in diameter and contains two major components, etonogestrel and ethinyl estradiol. These components are released in a steady stream over the course of three weeks with etonogestrel, a progesterone, releasing approximately 0.12 mg per day and ethinyl estradiol, an estrogen, releasing an average of 0.015 mg per day. The ring itself is composed of a combination of ethylene, vinyl acetate copolymers, and magnesium stearate that creates an almost transparent ring. The ring needs to be kept in a refrigerated climate of two to eight degrees Celsius, or thirty-six to forty-six degrees Fahrenheit, until use. See Figure 5 for a picture of Nuvaring at its approximate size.

Nuvaring is a prescription only vaginal contraceptive used by women who have reached puberty. The ring is folded in half and inserted in the vagina using one of several methods described in the patient handout once a month and left in for three weeks, with a one week break between taking out the old ring and inserting the new ring to allow for menstruation. Once inserted in the vagina, many patients no longer are aware of the Nuvaring, and, when questioned, a minimal number of the patients sexual partners where aware of the Nuvaring during intercourse. Nuvarings main use is to prevent unwanted pregnancies without the need to take a daily pill, use a patch, or receive an injection.

The Prevention of Conception and Unwanted Births

Prior to the invention of Nuvaring there were many other methods available to women for the prevention of unwanted pregnancies. These methods fit into approximately seven categories of pregnancy prevention. The categories are as follows: sterilization, post intercourse, intra-uterine, anti-estrogen, barrier, behavioral and hormonal.

Sterilization is the surgical process of making a patient unable to conceive. This usually involves a process that ties off the Fallopian tubes in women, making it impossible for the egg to reach the uterus for fertilization. In men the vas deferens is cut making it impossible the sprem to leave the testicles. Both processes can be reversed.

Post intercourse pregnancy prevention includes a couple of options. The first option available is an abortion. Abortions have been available to patients for several years, and have been refined to a quick and easy procedure. Another option includes taking a large dose of oral contraceptive within seventy-two hours of intercourse, better known as the morning after pill, Plan B. Finally, a patient can choose to bear the child full term and terminate the fetus as it emerges from the birthing canal.
Intra-uterine devises are also used for pregnancy prevention. This device, known as an IUD or coil, is considered to be the most popular form of reversible contraceptive. The devise is placed within the uterus by a medical procedure and is left there until pregnancy is desired. This method may also be used as a form of post intercourse prevention.

Anti-estrogen pregnancy prevention involves using Ormeloxifene products to interfere with the implantation of any fertilized eggs. The drug works by speeding the travel of the egg and by making the lining on the uterus develop more slowly; making the environment inhospitable to fertilized eggs.

The barrier method involves the use of diaphragms and condoms. Diaphrams are worn by the female, inserted in the vagina in a similar fashion as the Nuvaring. Condoms are worn by the male over the erect penis. Both of these methods act as physical barriers to prevent the sperm from ever reaching the site of fertilization. The condom also works as a prevention against most sexually transmitted diseases. Also included in this category are spermacide, sponges, and female condoms.

Behavioral prevention includes two different options. The first is choosing to abstain from sex until pregnancy is desired. The second involves counting the days of the cycle and relying on a constant ovulation in the exact center between menstruations.

Hormonal prevention is the category that Nuvaring falls into. There are many other forms of hormonal prevention available that include pills, patches, and shots. This method works by preventing the egg from becoming fertile.

How Nuvaring Works on the Body

Nuvaring works in the body to prevent pregnancy by suppressing the gonadotropins, which in turn inhibits ovulation. Nuvaring also makes the vagina inhospitable to sperm, and prevents against the implantation of a fertilized egg into the uterine wall. The two drugs that make up the chemical composition of Nuvaring, etonogestrel and ethinyl estradiol, work in different methods that are as follows.

Etonogestrel is a synthetic form of progesterone, a hormone that is used in the process of conception. Once in the body, etonogestrel starts working by binding to both progesterone and estrogen receptors located in the reproductive track, mammary gland, hypothalamus, and pituitary. The drug then slows the release of the gonadotropins from the hypothalamus and stems the luteinizing pre-ovulatory surge associated with contraception.

Ethinyl estradiol is used to treat the vasomotor symptoms that accompany menstruation and menopause, as well as working as a contraceptive. Once in the body Ethinyl estradiol, a synthetic derivative of estrogen, interacts with a protein receptor on the target cells. Target cells are located in the reproductive track, mammary gland, hypothalamus, and pituitary, as they were with etonogestrel. Once attached, the drug suppresses the follicle stimulating hormone, and increases the production of sex hormone binding globulin and thyroid binding globulin. When ethinyl estradiol is used with a progesterone suppresser, such as etonogestrel, it also helps decrease the secretion of the gonadotropin-releasing hormone.
Nuvaring’s Path Through the Body

Nuvaring is composed of two synthetic chemicals that pass through the body in similar patterns.

Ethynyl estradiol is rapidly absorbed into the body through the vaginal wall. Once it has been absorbed it has a bioavailability of 56 percent. Approximately 95 percent of the ethynyl estradiol then binds with albumin in the blood. Once attached it travels through the body until it is metabolized. The process of metabolism starts in the liver where cytochrome P450, a hemoprotein, breaks down its targets and instigates the metabolic process. The ethynyl estradiol is metabolized into either 3-O-glucuronide or 3-O-sulfate metabolites, and is processed further by aromatic hydroxylation to its end product. Finally, ethynyl estradiol is excreted from the body by urine, feces, and bile.

Etonogestrel travels through the body in a very similar manner as ethynyl estradiol. After absorption, etonogestrel has a bioavailability of 100 percent. Once in the body etonogestrel binds 32 percent with the sex hormone globulin and 66 percent with albumin. After it binds, the etonogestrel travels through the body until it is metabolized. Though the exact metabolism of etonogestrel is unknown, it is believed to be processed in the same manner as the ethynyl estradiol; through aromatic hydroxylation. Finally, etonogestrel is excreted from the body through bile, urine, and feces.

Figure 1 depicts the concentration of the two components of Nuvaring over the course of its three week life.

![Figure 1](image)

Chemical Structures and Mechanisms of Nuvaring

Nuvaring is composed of two different drugs, etonogestrel and ethynyl estradiol. These different components come together to create a system that effectively prevents pregnancy.

Etonogestrel has an IUPAC name of 13-ethyl-17-ethynyl-17-hydroxy-11-methylidene-2,6,7,8,9,10,12,13,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-one. It has a molecular weight of 324 grams per mole and a molecular formula of C_{22}H_{28}O_{2}. See figure 2 for the chemical structure of etonogestrel.
Ethinyl estradiol has an IUPAC name of 17-ethynyl-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol. The molecular weight is 296 grams per mole and the molecular formula is C_{20}H_{24}O. Ethinyl estradiol has a melting point of 183 degrees Celsius. The solubility of it in water is 11.3 mg/L and its half-life is approximately thirty six hours. The structure of ethinyl estradiol can be found in figure 3.

**Nuvaring Versus Other Forms of Hormonal Contraceptives**

With many other options for hormonal contraceptives, Nuvaring provides a new method for preventing pregnancy.

The first reason Nuvaring is different then other contraceptives is because of the convenience. A patient only has to remember Nuvaring twice a month as opposed to oral contraceptives, which must be taken on a daily basis. Nuvaring is inserted in the vagina, as opposed to the worry of possibly having a patch fall off or become exposed. Finally, Nuvaring is a physical structure that the patient can see and feel, making it easier to work in comparison to a shot that is never handled by the patient. Also, with the shot, the patient must return to the doctor’s office every time one is needed, which may prove costly in the long term.

A second reason that Nuvaring is a strong candidate for hormonal contraceptives is that it is almost impossible to overdose or under dose on the medication. With a pill, it is easy to forget to take it. It is just as easy to have already taken it, forget, and take it twice. This is especially true if the patient does not use the Sunday start day and forgets which day they used. Although unlikely, a professional may inaccurately dose a patient for the shot, which could potentially have long lasting effects.
A final reason that Nuvaring is different from some of its competitors is the overall estrogen delivery consistency. Figure 4 demonstrates that Nuvaring has little fluctuation throughout the month, indicating a steady, low dose of hormone. The other methods all have multiple peaks that affect the concentration of the medication within the patient. This means that while on Nuvaring the patient should suffer fewer of the side effects associated with taking contraceptives.

![Figure 4: Estrogen Delivery](image)

**Nuvaring and the Future**

Nuvaring shows great potential to become a more favored form of hormonal contraceptive. Within the United States there are different sources that clearly show Nuvaring’s expansion. Several recent studies show that some college campuses are slowly starting to favor the oral contraceptives and patches less and less because of the inconveniences associated with taking daily pills or having to return to the doctors office. Another indicator that Nuvaring is slowly expanding is that studies being performed at other campuses at this time are beginning to hypothesize Nuvaring as the preferred method of patients as well. Finally, many online sites and articles are also becoming available to patients that state Nuvaring is a great option for hormonal birth control. Some websites that allow patients to rank the medication and Nuvaring posted outstanding marks in comparison to some of the other methods of hormonal birth control.

Nuvaring is slowly being introduced to other countries as well. Due to differences in many countries’ willingness to accept new methods, it is taking much longer for Nuvaring to be used by the patients outside of the United States. Yet recent studies in the Netherlands have shown similar results to the studies performed in America. These studies are indicating that Nuvaring is preferred to oral contraceptives after the patient has tried the medication. This correlation between America and the Netherlands shows that Nuvaring is progressing forward with the expansion into European countries.

Nuvaring, with its convenience and availability, is becoming a more commonly requested form of birth control. Price is not proving to be an issue, as oral contraceptives have similar costs to Nuvaring through most insurance companies, and the newer oral
contraceptives that work with lower doses of the medication like Nuvaring can even prove more costly. The ability to get Nuvaring is no more restricted than any other form of hormonal contraceptive; and the new research is pushing Nuvaring to the forefront of birth controls. With time, Nuvaring, or future vaginal rings like it, could come to be one of the top selling types of hormonal birth control.

Figure 5: Approximate Size of Nuvaring
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Prednisone

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Synopsis

This paper will discuss the widely used corticosteroid known as Prednisone. It will shed light on the history, chemical composition, synthesis process and of course it’s many uses in medicine. Finally it will cover the future of Prednisone and where it is going in the medical fields.

History

For many years the primary treatment for rheumatoid arthritis had been the administration of cortisone. However the side effects were very unpleasant to those already suffering from a debilitating disease. Some of these side effects included water retention, high blood pressure and muscle weakness. In 1950 a chemist by the name of Arthur Nobile succeeded in using bacteria to oxidize cortisone to prednisone. This new drug gave a new effective treatment for a wide variety of ailments with greatly reduced negative reactions. Prednisone was one of the most significant advances in medicine during the mid 20th century. It has risen to treat many autoimmune diseases such as Addison’s disease and lupus as well as inflammatory diseases including severe asthma, poison ivy dermatitis, ulcerative colitis and Crohn’s disease. It also is used to treat various kidney diseases including nephrotic syndrome and even prevent and treat organ transplantation rejection. It also ushered in a new era of chemical synthesis using microbes to manufacture new and better drugs.

Figure 1. Arthur Nobile

Side effects

With every drug there are side effects. Although prednisone has provided relief to millions of people suffering from a gamut of illnesses, it too has side effects that can range from unpleasant to debilitating and even fatal. These range from the short-term side effects such as high blood glucose levels, especially in those already living with diabetes to fluid retention, insomnia, euphoria and rarely mania. Other side effects that are more common include weight gain, headache, growth of facial hair, irregular periods, thinning of skin, easy bruising, aseptic necrosis, fatigue, facial swelling, nervousness, acne, rash, increased appetite and hyper activity. Some of the more serious side effects come with prolonged use, or severe adverse reaction to prednisone include depression, abdominal pain, blurred vision, peptic ulcer, infections, painful hips or shoulders, osteoporosis, acne breakouts, cataracts, glaucoma, insomnia and reduced libido. With prolonged use of prednisone the adrenal glands can begin to atrophy and stop producing natural cortisol. Patients are advised to not suddenly stop taking prednisone as to not
put them selves at risk for an adrenal crisis. This can include nausea, vomiting and shock. People who have to take high does of steroids for long periods of time can develop abdominal striae (Fig. 2) which can be disfiguring. (14, 6, 11.)

![Abdominal Striae](image)

**Figure 2 Abdominal Striae**

**Structure**

Prednisone is a non-synthetic corticosteroid and it is considered a prodrug. (2) Prodrugs are a pharmacological substance that are administered in an inactive form and are metabolized within the body (in this case the liver) into the active compound. The active compound formed within the liver is called prednisolone and it is considered a steroid and it is the active drug. (3)

![Prednisone](image)

**Figure 3. Prednisone**
The difference between prednisone and prednisolone can be seen in Fig.2 and Fig.3. There is an oxidation that occurs on Carbon number 11 within the liver to transform from one to the other. In fig. 4 the change has been identified and color coded.

The formation of prednisone is through the transformation of cortisone into prednisone by the use of two mycobacteria, Mycobacterium album and Mycobacterium globiforme and the surfactant antifoamsilane.\(^1\) A surfactant is simply a wetting agent that is used to make the combination of two or more compounds easier. Although cortisone may seem like the same molecule as prednisolone at first glance, the difference is between the first and second carbon. Cortisone lacks a double bond between carbons 1 and 2, circled in Fig. 5. \(^1, 5\)
In the body

To understand how and where prednisone came from it is important to understand how its natural cousins work within the human body. Cortisone is a steroid that is naturally produced within the body by the adrenal cortex or it can be manufactured synthetically. The adrenal cortex synthesizes hormones from cholesterol within our bodies. (7, 8)

Adrenal Gland

Cholesterol is transported into the inner mitochondrial membrane (12) (Fig. 8) within our cells where it is then converted into pregnenolone, the natural version of the active ingredient in prednisolone. Pregnenolone is not itself a hormone, but is the precursor for the production of all human steroid hormones, including progesterone, estrogen, testosterone, cortisol (Fig. 9), aldosterone and cortisone. (9)
Cortisol has a much greater glucocorticoid activity than cortisone which means cortisone can be considered an inactive metabolite of cortisol; much like prednisone is an inactive form of prednisolone. Cortisol is released from the adrenal gland by ACTH (Adrenocorticotropic hormone) signaling from the brain. ACTH is secreted by the pituitary gland in the brain, when cortisol levels are low; the pituitary secretes ACTH to prompt the adrenal glands to produce cortisol. Then from there the cortisol is converted to cortisone by 11-beta-steroid dehydrogenase, which is a type of enzyme that acts as a catalyst in the conversion of inert keto-products to active cortisol. Cortisol is more commonly referred to as hydrocortisone. Within the body it responds to stress by increasing blood pressure, blood sugar levels, immune system suppression and even infertility in women. However it can be used to treat allergies and manage inflammation processes but the side effects can be severe and more bothersome than the symptoms of the condition being treated. Prednisone has a much lower occurrence of side effects and for this reason it is favored over Cortisone. (9)

Dosages

Prednisone is an oral tablet. Less than 7.5 mg per day is generally considered a low dose. A moderate dose would be up to 40 mg a day and more than 40 mg is considered a high dose. Occasionally a very large dose of steroids are given for a short period of time. This is referred to as a ‘pulse steroid treatment’ and involves giving 1000mg of methyl-prednisone intravenously each day for three days.
The Future

There are many avenues that prednisone has already taken from its original intent of alleviating rheumatoid arthritis. It is commonly prescribed today to treat severe asthma, IBS, hay fever, Lupus, transplantation rejection (in conjunction with newer drugs like cyclosporine and tacrolimus) blood disorders, certain cancers, eye problems, severe allergies, immune system disease and skin diseases. The use of prednisone is making its way into many unexpected Treatments regiments as well as being used to boost the effects of other drugs. More and more it is seen being used for non-Hodgkin’s lymphoma (in conjunction with Oncovin, methotrexate, l-asparaginase, and 6-mercaptopurine), Vasculitis, thyroid and intestinal disorders and Duchenne dystrophy. Dushenne dystrophy is the most common of muscular dystrophies. About one in every 3,500 boys is born with Duchenne dystrophy. It is caused by a gene mutation that causes muscle cells to die. There is no cure for Duchenne dystrophy and it is eventually fatal but treatment consists of physical therapy, surgery, braces and breathing aids. Prednisone is used to slow the progression of the disorder and reduce muscle weakness. Prednisone has made its mark within the pharmaceutical industry from being the first mycobacterium-synthesized drug to being one of the more versatile treatments for so many illnesses and many more to come.
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Apricot Seeds and Cancer Treatment

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Abstract

Amygdalin/ Laetrile, two byproducts that are found in the synthesis of apricot seeds have sparked much controversy in the history of medicine. Supporters of amygdalin/Laetrile as an anti-cancer agent propose that its use is a natural method to cure or prevent cancer. Those that oppose the use of amygdalin/Laetrile consider it to be ineffective as well as highly toxic, yielding high levels of hydrogen cyanide which can lead to severe neurological, and cardiovascular issues, and can also cause death. This paper is an investigation into the history, of amygdalin and Laetrile, and the proposed mechanism by which each substance breaks down and is thought to kill cancer cells, and toxicity of the cyanide produced. Finally, a review of the studies that have evaluated its effectiveness will be discussed.

History

Amygdalin is a naturally occurring cyanogenic glycoside found in many edible plants, including the kernels of peaches, plums, cherries, nectarines, apples, almonds, and particularly apricots. Purified amygdalin was first isolated in the 1830’s by French chemists Robiquet and Boutron from the bitter almond. Therefore, the name amygdalin is appropriate after the scientific name of the bitter almond. However, more recently amygdalin has been extracted from the kernels of apricots. The chemical properties of amygdalin were described by German chemists Liebig and Wholer in 1837 who found that amygdalin can be split by the specific enzyme emulsin into hydrogen cyanide, benzaldehyde, and glucose. The first recorded use to treat cancer was reported in 1845 by T Inosmetzeff, a professor at the Imperial University of Moscow.

The synthesis of amygdalin was first reported in 1924 in the United States. In the late 1940’s, Ernest T. Krebs, Jr. used the term Laetrile to describe a purified derivative of amygdalin. The name Laetrile is a pharmaceutical abbreviation of laevomandelonitrile and was registered with the US patent office June 30, 1953. Krebs Jr. designated Laetrile as Vitamin B17 and has further proposed the term nitrilosides to describe Vitamin B17. Nitrilosides were defined by Krebs Jr. to be water soluble, non-toxic, edible compounds comprised of glucose molecules, hydrogen cyanide and benzoic acid.

In the 1970s, Laetrile gained popularity as an anticancer agent and more than 70,000 individuals were treated with it in the United States. A majority of those individuals received treatment in Mexican clinics. During this time, Laetrile was legalized and considered a promising cancer therapy. In the 1980s, the FDA banned Laetrile/amgdalin, and it was no longer authorized for sale as a medicinal product. “Laetrile supporters viewed this reversal as an attempt by the US government to block access to new and promising cancer therapies, and pressure mounted to make Laetrile available to the public”. Laetrile continues to be manufactured in Mexico, Switzerland, and Germany.

Amygdalin is administered by ingesting raw apricot pits. Laetrile is administered through tablet and or by injection. Most treatments are also combined with other
metabolic therapies which include enzymes and high dosages of vitamins, particularly vitamin C.\textsuperscript{1,10}

Chemical Structure

Considerable confusion exists concerning the relationship between the nomenclature and the structure of amygdalin and Laetrile. Although the names are often used interchangeably, these compounds are not chemically identical.\textsuperscript{1,5,10} Other terms used to describe amygdalin and Laetrile include vitamin B17, mandelonitrile, and prunasin.

The Chemical Structure of Amygdalin:

Amygdalin is an optically active compound that has a dextrorotatory (R) configuration, which is considered to be its natural active form.\textsuperscript{10} Therefore in most of the literature, the composition of amygdalin is D-mandelonitrile-b-D-glucosido-6-b-D-glucoside. Neo-amygdalin, L-mandelonitrile-\beta-D-gentiobioside, is the inactive (S) isomer which does not occur naturally.\textsuperscript{10} Neo-amygdalin is produced during the decomposition process by the enzyme emulsin. Isoamygdalin is a racemic mixture comprised of 56.25\% of (R)-amygdalin and 43.75\% neo-amygdalin.\textsuperscript{6}

![Chemical structures of R-Amygdalin, Neo-Amygdalin, and Iso-Amygdalin](image)

R-Amygdalin: R1=H, R2=CN
Neo-Amygdalin: R1=CN, R2=H
Iso-Amygdalin

Identifying these structures is of biological and therapeutic importance because the R configuration is considered to be therapeutically inactive in cancer therapy, whereas the S configuration is the therapeutically active form.\textsuperscript{6,9} “It is therefore imperative that the highest level of quality control be employed in the production of amygdalin.”\textsuperscript{6}
The Chemical Structure of Laetrile

US patented Laetrile is D-mandelonitrile-β-glucuronide, a semi-synthetic derivative of amygdalin. It differs from the Laetrile produced in Mexico which is made from crushed apricots. Crushed apricot pits have the chemical composition of D-mandelonitrile-s-gentiobioside. This substance is also called prunasin. Prunasin contains one less glucose molecule than amygdalin.

Although Laetrile is similar in structure to prunasin with one less glucose molecule, it differs by having a COOH group, making it a glucuronide rather than a glucoside, thus demonstrating the difference in chemical composition.

Both amygdalin and Laetrile break down further into a mandelonitrile before producing the end products of two glucose molecules, hydrogen cyanide, and benzaldehyde. They are also both considered to be members of the class of beta-cyanogenic glucosides and are often referred to as nitrilosides.
Mechanism for Treating Cancer: Selective Toxicity

The precise mechanism for how amygdalin/Laetrile works is not known but there are a number of proposed theories that have been presented.

The first theory involves the hydrolysis of amygdalin to form glucose and prunasin. In the kernel, amygdalin seems to be completely harmless as long as it is relatively dry. These seeds, however, contain an enzyme, emulsin, that is capable of catalyzing a hydrolytic reaction when the seeds are crushed and moistened.\(^4\) "A study performed by Tuncel et al. (1995) reported that grinding of apricot kernels, followed by soaking in water resulted in approximately 70% release of amygdalin into water."\(^14\) Amygdalin is further broken down by β-glucosidase found in intestinal bacteria to form mandelonitrile.\(^3,14\) Mandelonitrile is both spontaneously and enzymatically reduced to form the final products consisting of 2 glucose molecules, cyanide, and benzaldehyde.\(^3,5,14\)

\[
2 \text{ H}_2\text{O} + \quad \begin{array}{c}
\text{Water} + \text{ amygdalin} \\
\end{array} \longrightarrow \quad \begin{array}{c}
\text{2 glucose} + \text{ cyanide} + \text{ benzaldehyde}
\end{array}
\]

The Hydrolysis of Amygdalin

The toxic effect on cancerous cells is believed to be caused by a synergistic effect of the combination on cyanide and benzaldehyde. Benzaldehyde is a normal metabolic byproduct of amygdalin and has been demonstrated to have anticancer activity in laboratory animals and acts as an analgesic.\(^6\)

A second theory is that selective toxicity begins in the liver. It is theorized that the prunase glucoside can be catalyzed in the liver to form a glucuronide by a two-step oxidative mechanism.\(^6\) In order for the glucuronide to produce hydrogen cyanide (HCN) and benzaldehyde, the enzyme β-glucuronidase must be present. This enzyme has been found in cancerous tissue at a rate of 100-3600 times greater than non-cancerous tissue.\(^6\) The liver also contains the enzyme rhodanase (transulfurase) which is known to convert toxic HCN to thiocyanate. Thiocyanate is a normal metabolic byproduct resulting from ingestion of cyanide-containing foods, also called nitrilosides.\(^6\)

Thiocyanate is proposed to be a cancer inhibitor.\(^6\) Rhodanase also appears to be actively involved in the formation of cyanocobalamin or vitamin B12, and is also known to be part of the detoxification process of the body.\(^6,7\) Normal cells contain high levels of
rhodanase and low levels of β-glucuronidase, where cancer cells are high in β-glucuronidase and low in rhodanase. The presence of these enzymes has been seen by tumor cells producing human chronic gonadotropin (HCG). HGC present in tumor cells inhibit rhodanase thereby blocking HCN to convert to thiocyanate. Therefore tumor cells have less of a protective mechanism and are more sensitive to the effects of the cyanide which leads to cell death of the cancerous cells. The purpose of the glucuronide molecules was to concentrate its toxic effect against cancer cells and not the host. Since cancer cells contain higher levels of β-glucuronidase this enzyme would act upon the glucuronide and release the cyanide ion against the cancer cell. Since normal cells contain large quantities of rhodanase and relatively low quantities of β-glucuronidase the rhodonase would detoxify the cyanide ion forming thiocyanate which is a nontoxic cancer inhibitor.⁶,⁷

Cyanide Metabolism

Laetrile contains a cyanide ion, which is not the same as chemical cyanide.⁶ When it is metabolized by the body it is converted to thiocyanate, a relatively non-toxic product that has an inhibitory effect against cancer.⁶ Cyanide absorption is affected by the presence of food in the gut, the pH of the gut, and the lipid solubility of the cyanide compound.¹⁵ Absorbed cyanide is principally excreted as thiocyanate in the urine, as CO₂ in the air, and as B-thiocyanalanine in saliva and sweat.¹⁵
“Cyanide is metabolized by one major route and several minor routes. The major route is detoxification in the liver by the mitochondrial enzyme rhodanase, which catalyzes the transfer of the sulfane sulfur of thiosulfate to the cyanide ion to form thiocyanate. About 80% of cyanide is detoxified by this route. The rate-limiting step is the amount of thiosulfate. While rhodanase is present in the mitochondria of all tissue, the species and tissue distributions of rhodanase are highly variable. In general, the highest concentrations are found in the liver, brain and muscle, but the supply of thiosulfate is limited.”

“Cyanide and thiocyanate can also be metabolized by several minor routes including the combination of cyanide with hydroxycobalamin (vitamin B12) and the non-enzymatic combination of cyanide and cysteine forming 2-iminothiazoline-4-carboxylic acid which appears to be excreted without further change.”

Pathways for Cyanide Metabolism
Cyanide Toxicity

One of the arguments held against the use of amygdalin for cancer treatment is the concern of cyanide toxicity. Ingested amygdalin does release hydrogen cyanide and can cause serious cyanide poisoning.3 "One to 10 grams have been given parenterally in humans apparently without acute toxicities. Cyanide containing breakdown products possess well defined toxicities and amounts equivalent to 500 mg of mandelonitrile, and 50 mg of hydrogen cyanide can be fatal. With oral dosing, a toxic potential is manifest, b-glucosidase is present in the gastric lumen. Oral Laetrile could be 40 times more toxic than parenterally doses due to the free HCN released by that enzyme present in the gut."2 "This reaction takes place slowly in an acid environment. However, in an alkaline solution the reaction occurs rapidly and hydrolysis is complete within minutes. This degradation process is the key to the intoxication."4

Acute cyanide exposure is dominated by the central nervous system (CNS) and cardio disturbances. Cyanide poisoning can lead to the symptoms of tachypnoea, headache, and vertigo, lack of motor coordination, weak pulse, cardiac arrhythmias, vomiting, stupor, convulsions, and coma.3,15 "The mechanism of the production of hydrocyanic acid from amygdalin is important in trying to explain the symptomatology in cases where cyanide poisoning has occurred.4

The limiting factor in cyanide metabolism is the low concentration of sulfur containing substrates in the body, primarily thiosulfate but also systine and cysteine. The rate of spontaneous detoxification of cyanide in humans is about 1uk/kg body weight per minute, with a half life values in humans as 4 hours, 2 days, and 2.7 days. If there is renal insufficiency, the mean half life is 9 days.15 Another concern is that laetrile does not undergo rapid conversion to cyanide, and it may take at least two hours to develop symptoms.3

"Acute exposure to cyanide has occurred by oral route (accidental poisonings due to ingestion of apricot kernels or almond seeds). Death occurred after absorption of an average 1.4 mg HCN/kg body weight the lowest fatal dose was 0.54 mg/body weight. In most poisoning cases, a large part of the ingested cyanide remained in the GI tract, thus using dose ingested as an indicator of the lethality of cyanide is misleading. Some individuals ingesting 1-3 grams of cyanide salts have survived."15

Clinical signs are often confounded by dietary deficiencies, including lack of protein, iodine, and vitamin B12.2 In protein deficient populations where low levels of sulfur containing amino acids are present will cause cyanide to break down to cyanate which causes neurodegenerative diseases.15

Although apricot pits are eaten often, intoxication rarely occurs.4 But in a few rare circumstances cyanide poisoning has taken place, which has become one of the major reasons eating apricot seeds in not advised and considered harmful by the FDA.
Research

In the late 70’s, the National Cancer Institute (NCI) conducted a retrospective survey where questionnaires were sent to 385,000 physicians and 70,000 other health professionals, they received only 67 replies. The results showed that no definite conclusions could be drawn concerning Laetrile’s anti-cancer activity. Although they concluded this, they continued to investigate Laetrile. “The NCI investigated the effectiveness of Laetrile, but the results of their study did not support the anti-cancer activity of Laetrile: out of 22 suitable cases, only 6 patients experienced a positive response. In the 1980s, two clinical trials were sponsored by the NCI with the approval of the FDA. The results did not show the efficacy of Laetrile.” In 1982, the NCI concluded that laetrile was not effective as a cancer treatment and could be harmful.

“In a single arm, phase II trial, 179 patients with advanced, untreatable cancer and measurable lesions were treated with Laetrile. Patients also received vitamins and enzymes as well. Only one patient met the criteria for a partial response; 90% of patients had disease progression within three months. The median survival was 4.8 months.” Again, Laetrile was concluded to be ineffective.

Recently, new research conducted outside of the United States has begun to reevaluate Amygdalin and its use for cancer treatment. Park et al. (2005) found Amygdalin to have an anticancer effect via down regulation of cell cycle genes in colon cancer cells and concluded that it might be used as an anticancer drug.

Another study evaluating the effectiveness against cancer was performed by Paoletti et al. in 2005. It was found that amygdalin had immunomodulatory effects on human kerinocyte cells which may be promising for the treatment of psoriasis.

Conclusion

Although many studies have shown that Amygdalin is ineffective to cure cancer, there are numerous studies that have also reported positive effects from the use of amygdalin. There are also many case studies that have reported positive results from ingesting or using amygdalin/Laetrile. Its use continues to receive national attention as a treatment for cancer despite the fact that neither its safety nor the effectiveness has been demonstrated. Those in favor of its use believe that there are underlying motives protecting the vested interests of the pharmaceutical industry. Furthermore, many believe that adults should have a fundamental right to seek medical treatments beyond the scope of current conventional practice. “In the United States in 2004, 563,700 US patients died of cancer. According to the World Health Organization, worldwide incidence could increase by 50% to 15 million by the year 2020”. Despite considerable improvement in survival rates, the prognosis remains poor for many cancer diagnoses. “Under such circumstances, there is a pressing need for an expanded (not constricted) list of treatment options”. “The role of the government should be to facilitate, rather than restrict, the exercise of freedom of choice by its citizens. There is simply no room for dogmatism in medicine. Even Laetrile, now widely scorned, may someday have to be reevaluated.”
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Atarax®
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Abstract

Hydroxyzine hydrochloride is a generic prescription medication used to treat itching due to hives, eczema, and allergic reactions, as well as anxiety and tension. It is in the class of drugs known as sedating antihistamines. Hydroxyzine hydrochloride is indexed as brand names such as Atarax, Vistaril, Atazine, Dovaril, Hycam, Vistacot, and Vistawin. This paper will discuss the history of antihistamines specifically Atarax, its mechanism of action, its side effects and its future.

History of Histamine and Antihistamines

Histamine is chemically classified as an amine, an organic molecule based on the structure of ammonia (NH₃). It is formed by the decarboxylation of the amino acid histidine. The English scientists George Barger and Henry H. Dale first isolated histamine from the plant fungus ergot in 1910, and in 1911 they isolated the substance from animal tissues.¹

In humans, histamine is found in nearly all tissues. It is stored primarily in the granules of tissue mast cells. Once released from its granules, histamine produces many varied effects within the body, including the contraction of smooth muscle tissues in the lungs, uterus, and stomach. However, the effect histamine has on blood vessels is crucial to its role in the immune response, which is most clearly followed by inflammation and allergic reaction. This reactions cause visible symptoms, including a runny nose, watery eyes, constriction of bronchi, tissue swelling, and itching.

The search for blocking the activity of histamine in human body led to the development of various chemicals called antihistamines, which can prevent the binding of histamine to its receptors: H₁, H₂, and H₃. The development of antihistamines dates from about 1937, when French researchers discovered compounds that protected animals against both the lethal effects of histamine and those of anaphylactic shock. The first antihistamines were derivatives of ethylamine; aniline-type compounds, tested later and found to be more potent, were too toxic for clinical use. In 1942, the forerunner of most modern antihistamines (an aniline derivative called Antergan) was discovered; subsequently, compounds that were more potent, more specific, and less toxic were prepared.²

In the early 1950’s the Company called UCB founded by Emmanuel Janssen, a Belgian businessman with a long-term vision set up a research center where a new antihistamine named Atarax® (hydroxyzine hydrochloride) was developed.³

FDA records indicate that Atarax was first approved on April 12, 1956 under the company name PFIZER in tablet form. The Liquid form of Atarax was approved shortly after its initial approval under the company name ROERIG on May 31, 1956.⁴ Soon more than 100 antihistaminic compounds became available for treating patients.³
Description

Atarax occurs as a white, odorless powder which is very soluble in water. It is prepared in tablets: 10mg, 25mg, 50mg, and 100mg. Capsules are available in 25mg, 50mg, and 100mg. Syrup contains 10mg per teaspoon.

Chemical formula: C_{21}H_{25}Cl_{3}N_{2}O_{2}
Molar mass: 447.825 g/mol

Pharmacokinetic data:
Bioavailability: High in-vivo
Protein binding: 93%
Metabolism: Liver
Half life: 20 to 25 hours
Excretion: Urine, feces

Therapeutic considerations:
Legal status: Prescription only
Routes: Oral, Intramuscular injection

Mechanism of Action

The way in which Atarax (hydroxyzine hydrochloride) works is not fully known. It is known that when histamine which is stored in almost all tissue cells of human body reacts to a foreign substance (an allergen e.g. flower pollen), it is released and then may bind at the So-called H_1 receptor sites in many areas of the body, causing an increase in blood flow to the area of the allergy and the release of other chemicals that add to the allergic response. This
stimulates the symptoms of an allergic reaction, such as rashes, itching of the skin, eyes or nose, nasal congestion or narrowing of the airways.

Atarax acts by blocking the binding sites of histamine to the receptors specifically H₁ receptors, therefore; its designated H₁-blocking agent and acts on all of histamine except gastric secretion. Atarax enters the brain in significant quantities and prevents or relieves the typical symptoms of an allergic reaction. For the same reason, it is more likely to cause drowsiness than non-sedating anti-histamines. Atarax also acts as a calmative and pain reliever by affecting other natural substances (e.g., acetylcholine, serotonin) or by acting directly on certain parts of the brain.² Atarax may also be used for the short-term treatment of common anxiety, nervousness and tension that may occur with certain mental/mood disorders. In other cases, the usage of hydroxyzine hydrochloride is that of a non-barbiturate tranquilizer used in the treatment of neurological disorders, such as psychoneurosis and other forms of anxiety or tension. It may also be used to prevent/treat motion sickness, nausea, and vomiting related to certain conditions (e.g., traveling, after surgery). It is therefore prescribed as a means of regulating normal function of the body.³

Hives which is a common form of allergic symptoms is medically known as urticaria. Hives are smooth, raised pink or white bumps that appear on or beneath the skin and are usually accompanied by itching.
As a sedative antihistamine Atarax may also be used for the short-term treatment of insomnia. Comparing benzodiazepines which work by slowing down central nervous system, as Non-benzodiazepines, Atarax may be better tolerated and have less risk of abuse or dependency and have fewer adverse effects.

**Pharmacokinetics and Metabolism**

As mentioned above, Atarax can be administered orally or via intramuscular injection. When given orally it is rapidly diffused in the body and metabolized in the liver; the main metabolite (45%) through oxidation of the alcohol moiety to a carboxylic acid is cetirizine, and overall effects are observed within one hour of administration. It has a half-life of average for around 7-10 hours in adults, 6-7 hours in children, and 18-21 hours in the elderly, or those with renal insufficiency. In a 10mg dose, 70% of the drug is excreted unchanged in the urine within 72 hours and 10% excreted within feces. Atarax can be taken with or without food.

Administration of hydroxyzine hydrochloride in geriatrics differs from younger patients. Patients over the age of 60 years are especially sensitive to the sedatory effects of hydroxyzine hydrochloride so doses should be reduced. According to the FDA, as of 2004 there have not been significant studies which include population groups over 65, and therefore distinction cannot be determined between elderly aged patients and younger groups: any hydroxyzine administered should be done with doses at the small end of the dosage range and be carried out with the knowledge that any existing concomitant disease, decrease in the function or lessened excretion, in hepatic, renal or cardiac cases.

Similarly, the use of sedatives in accordance with hydroxyzine hydrochloride can cause over-sedation and confusion if administered in large amounts. Any form of treatment alongside sedatives should be done under supervision of the doctor.

![Atarax 25mg](image)

**Clinical Studies**

Chemically Atarax is unrelated to phenothiazines, reserpines, meprobamates, or the benzodiazepines. It is not a cortical depressant, but its action may be due to a suppression of activity in certain key regions of the subcortical area of the central nervous systems. Primary skeletal muscle relaxation has been demonstrated experimentally. Bronchodilator activity and anti-histaminic and analgesic effects have been demonstrated experimentally and confirmed
clinically. An antiemetic effect, both by the apomorphine test and the veriloid test, has been demonstrated. Clinical studies also indicate that hydroxyzine in therapeutic dosages does not increase gastric secretion or acidity and in most cases has mild antisecretory activity.⁶

As a sedative, when used as premedication and following general anesthesia, hydroxyzine may potentiate meperidine (Demerol®) and barbiturates, so their use in pre-anesthetic adjunctive therapy should be modified on an individual basis. Atropine and other belladonna alkaloids are not affected by the drug. Atarax is not known to interfere with the action of digitalis in any way and it may be used concurrently with this agent.⁶

The effect of hydroxyzine has also been tested on the ability of humans in the registration and storage of memory, and was used in comparison with relatively safe drugs, such as lorazepam, to illustrate the effects of benzodiazepines, which are thought to have adverse effects on the capacity of memory storage. Hydroxyzine was found to have no adverse effects on memory in relation to benzodiazepines such as lorazepam, which caused several deficiencies in the capacity of memory storage. In comparison to lorazepam, patients involved a study on memory that had taken hydroxyzine experienced sedative effects similar to drowsiness, but recalled that they felt capable, attentive and able to continue with a memory test under these conditions. Conversely, those under the effects of lorazepam felt unable to continue due to the fact they felt out of control with its effects; 8 out of 10 patients describing tendencies of problems with balance and control of simple motor functions.⁵

The effectiveness of hydroxyzine as an antianxiety agent for long term use, which is more than 4 months, has not been assessed by systematic clinical studies. The physician should reassess periodically the usefulness of the drug for the individual patient.⁶

**Drug Interactions**

Hydroxyzine hydrochloride exaggerates the sedating effects of alcohol and other drugs that can cause sedation such as the benzodiazepine class of anti-anxiety drugs (e.g., Valium, Ativan, Klonopin, Xanax), the narcotic class of pain medications and its derivatives (e.g., Percocet, Vicodin, Dilaudid, Codeine, Darvon), the tricyclic class of antidepressants (e.g., Elavil, Tofranil, Norpramin), and certain antihypertensive medications (e.g., Catapres, Inderal). Hydroxyzine can also intensify the drying effects of other medications with anticholinergic properties (e.g., Bentyl, Urecholine, Probanthine, Elavil, Thorazine.) When using these drugs, the dose of hydroxyzine may require reduction.⁷

**Contraindications**

Using Atarax alone, with other medicines, or with alcohol may lessen patients’ ability to drive or to perform other potentially dangerous tasks. Alcohol should also be avoided while using this medicine. The syrup form contains sugar, and therefore should be used with caution by people who have diabetes. This medicine should not be used if patient is allergic to one or any of its ingredients. If overdose is suspected, patient should contact the local poison control center or emergency room immediately. Symptoms of overdose may include unusual drowsiness and dizziness. Drug interactions can result in unwanted side effects or prevent a medicine from doing
its job. Some medicines or medical conditions may interact with this medicine. Doctor or pharmacist should be informed of all prescriptions and over-the-counter medicines that a patient is taking. The safety of Atarax during pregnancy and breastfeeding is not established. So it is not recommended for use during pregnancy or breastfeeding.

Side effects

Medicines and their possible side effects can affect individuals in different ways. Reported side effects of Atarax are generally mild and transitory in nature. The following effects are known to be associated with this medicine:

- dry mouth, nose, and throat
- upset stomach
- drowsiness
- dizziness
- chest congestion
- headache
- reddening of skin
- difficulty breathing
- muscle weakness
- increased anxiety

A side effect being stated here does not mean that all people using this medicine will experience it or any of them.\(^6\)

Future of Atarax

Labeling Atarax as an anti allergic drug is correct. Labeling Atarax as a "psych drug" is also correct. As a tranquilizer with no benzodiazepine structure, Atarax may well be the first choice of anxiety treatment, avoiding the risk of replacing the addiction with a benzodiazepine. So it is believed that Atarax is still and will continue to be used in the future despite the plethora of new and more specified pharmacological substances on the market.

Conclusion

Atarax (hydroxyzine hydrochloride) is prescribed as both antihistamine for the treatment of allergic conditions, and for general anxiety disorders. As a result, it is used as a means of regulating normal function in the body. Drugs that combat both allergies and anxieties enable patients to cope more effectively with life's vicissitudes and lead more rewarding lives. In comparison to drugs in the benzodiazepine class (i.e. alprazolam, diazepam) the non-benzodiazepine drugs including Atarax have some advantages. The most significant advantage is the absence of the potential for abuse, which renders these drugs safe for long-term treatment of chronic problems such as generalized anxiety disorder. Although Atarax has some sedative side effects, comparing other antihistamine but people still use it because it's a great anti allergy drug.
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Fluvoxamine ®: An Analysis into Retarding the Repetitive Nature of Obsessive Compulsive Disorder

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Organic Chemistry Professor
Paradise Valley Community College
Abstract

Fluvoxamine® (Luvox®, Faverin®, Fevarin® and Dumyrox®) is an antidepressant which acts as a selective serotonin reuptake inhibitor (SSRI). The Food and Drug Administration approved the drug in December 1994 under priority to relieve the signs and symptoms of depression and anxiety disorders (Dissociative Identity Disorder, Obsessive Compulsive Disorder, Panic Disorder, Social Phobia, and Post Traumatic Stress Disorder). Fluvoxamine® differs from other selective serotonin reuptake inhibitors class in that the structure is monocyclic. This paper will address the history of SSRI's, the pharmacodynamics of fluvoxamine®, clinical trials, drug interactions, side effects, and future possibilities.

Serotonin

Serotonin is the primary neurotransmitter that the class of drugs known as selective serotonin reuptake inhibitors act upon. Known as 5-hydroxytryptamine (5-HT), serotonin plays a crucial role in the regulation of several emotional and physical states. The pharmaceutical industry has taken an interest in serotonin to provide a positive pharmacotherapy to individuals diagnosed with clinical disorders associated with low levels of serotonin. Tryptophan hydroxylase (TPH) and amino acid decarboxylase (DDC) are several possible metabolic pathways to synthesize serotonin. Serotonergic neurons are the primary location for serotonin production. The central nervous system (CNS) houses the serotonergic neurons. Key structures that are primarily responsible for serotonin release in the central nervous system are the brain stem (specifically the midbrain), hypothalumus, limbic system, cerebellum, pineal gland, and spinal cord. After the initial release of serotonin, 5-hydroxytryptamine receptors are activated. The receptors are located in the nervous system on dendrites, cell bodies, and presynaptic terminals of adjacent neurons.

Figure 1

Serotonin effect

Figure 2
History of Selective Serotonin Reuptake Inhibitors

The search for a "new wonder drug" lead to the development of the selective serotonin reuptake inhibitor family. The older tricyclics and monoamine oxidase inhibitors (MAOI) were recognized as a powerful class prescribed for the treatment of depression in the early 20th century. The downfall to these primitive classes was that they interfered with neurotransmitters and receptor sites throughout the brain that disrupted deeper brain functions. This inspired pharmacologists and biochemists to search for a newer, more innovative antidepressant.

It wasn't until 1988 that Eli Lilly introduced the first SSRI called Prozac (fluoxetine) to treat depression9. Scientists realized the innovation behind this new class of drugs was their characteristic of being specific. Without affecting deeper brain functioning, SSRI's can zero in and target serotonin only. Rapidly becoming popular among physicians and patients, the class gained fame over previous generation antidepressants due to fewer side effects. Since its introduction in 1988, over 17 million people in the United States have been prescribed Prozac9. The Food and Drug Administration approved Prozac to be effective toward treating obsessive compulsive disorder in July 1993. In March of 2001, Prozac Weekly was approved as a 90mg tablet administered once a week. Since its first appearance on the market, the Food and Drug Administration has approved the drug for the treatment of certain eating disorders specifically bulimia.

Paxil (paroxetine) soon followed Prozac's release into the market by its manufacturer GlaxoSmithKline. Approved by the Food and Drug Administration on December 29, 1992, Paxil was meant to target the symptoms of depression9. Relief was in sight for individuals needing a cost effective medication who were clinically diagnosed with obsessive compulsive disorder. Luvox (fluvoxamine) was introduced to the general public in 1994 for adult patients and for pediatric therapy in 1997. Celexa (citalopram) is distributed by Forest Pharmaceuticals, Inc. and was approved for depression in 1998. Lexapro (escitalopram) to date is the most recent selective serotonin reuptake inhibitor on the market. Distributed by Forest Pharmaceuticals, Lexapro was approved in August 2002 for major depression and in December 2003 for generalized anxiety disorder (GAD)9.

Questions have been raised in recent years about the negative effects selective serotonin reuptake inhibitors produce in the body. On August 21, 2001, a lawsuit was filed against the major pharmaceutical mogul GlaxoSmithKline indicting them on charges of conspiring to conceal important statistical data during clinical trials that Paxil lead to physical dependencies or addiction9. New evidence has surfaced with GlaxoSmithKline with new charges of conspiring to conceal critical data during previous clinical studies of risks about suicidal tendencies and self-inflicting harm. October 6, 2006, was a landmark day in the United States legal system. A settlement of $63.8 million was preliminarily approved for American consumers whose children were prescribed Paxil7. On March 9, 2007, the US Court system voted on its approval. GlaxoSmithKline is still under investigation and lawyers are waiting for their chance at another lawsuit.
Description

Fluvoxamine Maleate tablets are available in 25mg, 50mg, and 100mg strengths for oral administration. Fluvoxamine is chemically designated as 5-methoxy-4′-(trifluoromethyl)valerophenone-1-(E)-O-(2-aminoethyl)oxime maleate. The product is a white to off white crystalline powder. Fluvoxamines' solubility depends on the solvent the drug is exposed to. In water, the drug is soluble and freely soluble in ethanol and chloroform. However, when exposed to diethyl ether, the drug is practically insoluble. Fluvoxamine is innovative in its chemical property characteristics. In the family of selective serotonin reuptake inhibitors, it belongs to a new series entitled aralkylketones. The new chemical series are 2-aminoethyl oxime ethers. Fluvoxamine does not contain a chiral center. It has a molecular weight of 434.4 and a chemical structure as follows:

![Chemical structure of Fluvoxamine Maleate](image)

Figure 3
Chemical Formula C_{15}H_{21}F_3N_2O_2

Dosage and Administration

Fluvoxamine maleate is available by prescription only and should be taken only as directed by your physician. The route of administration is PO (by mouth) only. The initial starting dose for both adult and pediatric patients differs. Typically, adult patients are prescribed a single dose of 50mg when beginning fluvoxamine. Patients are to take 1 T PO QHS (take 1 tablet by mouth every night at bedtime). QHS can be substituted for QPM (every night). Every four to seven days the dose is increased by 50mg. 300mg is the maximum recommended daily dose for adult patients and two separate doses should be administered if prescribed more than 100mg per day. Pediatric demographics are defined as being 8 to 17-years-old. Physicians start children and adolescents at 25mg tablets of fluvoxamine. Pediatric patients are to take 1 T PO QHS as a single dose. Over a four to seven day period, fluvoxamine doses can be increased by 25mg increments. The maximum allowable daily dose is separate for children and adolescents. Children ages 8 to 11 should only receive a maximum daily dose of 200mg and adolescent maximum levels are 300mg per day. If the cumulative dose is more than
50mg per day, two divided doses should be administered to the patient. If a patient misses or skips a dose, he/she should consult a physician for advice to maintain a regular schedule of drug administration. Patients on a single dose per day regimen should skip a missed dose and return to their original schedule. If adults who are prescribed more than 100mg per day and children and adolescents who are taking more than 50mg per day, the procedure for missed doses changes. Take the missed dose as soon as possible and continue on with your planned schedule. Patients need to be cautious not to take two doses at one time.

Pharmacokinetics (Bioavailability/Distribution/Metabolism/Elimination)

The administration route of fluvoxamine is orally. Ranging from three to eight hours after ingestion, the maximum plasma concentrations peaked at a steady state of 546ng/mL. In clinical trials, this steady state was achieved after seven days of continuous dosing. Peak plasma levels (Cmax) after administration of 100mg/day was 73ug/L. The area under the curve (AUC) for a dosage of 100mg/day was 927ug/L per hour. When fluvoxamine tablets are taken with food, peak plasma levels are not affected.

The main organ primarily responsible for the metabolism of Fluvoxamine is the liver. Bioavailability in the human body has been identified through two metabolic pathways. The main routes discovered are oxidative demethylation and deamination. In urinary excretion, researchers have been able to isolate nine metabolites. Analysis of metabolites reveals all nine make-up 85% of urinary waste. Constituting 70% of overall consistency is two primary metabolites, fluvoxamine acid and fluvoxethanol. Fluvoxamine acid, in a synergistic relationship with N-acetylated analog, constitutes 60% of the metabolites while fluvoxethanol accounts for 10%. Pharmacodynamic analysis revealed fluvoxamine half-life (t1/2) for patients ranged from 14 to 22 hours. However, the mean value calculated was 15.6 hours after repeated doses.

Synthesis

In the laboratory, synthesis of Luvox® (fluvoxamine®) is prepared by the following reactions of Grignard reaction, hydrolysis, and oximation from 4-trifluoromethylbenzonitrile.

Clinical Studies

Clinical trials of Fluvoxamine demonstrated significant reduction of moderate to severe obsessive compulsive tendencies compared to placebo trials. To be approved to participate in the study, participants were chosen based on scores from both the adult and children’s Yale-Brown Obsessive Compulsive Scale (Y-BOCS and CY-BOCS). Composite scores in adult patients averaged 23 units and pediatric scores averaged 24 units. Fluvoxamine was evaluated in two parallel group studies in both adult and pediatric outpatients. The duration of both clinical studies were given in 10 week durations. The demographics of the children and adolescent pediatric trials were
analyzed in ages ranging from 8 to 17. Dosing for adult outpatients began at 150mg/day over the first scheduled two week period. Based off of participant response and tolerance to administered dosing, dosages were increased to 100 to 300mg/day twice a day (BID) throughout the remainder of the 10 week clinical trial. Doses in adult patients proved beneficial with mean reductions of four to five units on the Y-BOCS compared to two units with placebo trials on the Y-BOCS scale. Pediatric trials for relief of obsessive compulsive symptoms began at lower dosing than adult patients. During the first two week period, pediatric participants were given 100mg/day. Based off of children and adolescent response and tolerance to fluvoxamine, the administered dosing was increased to 50 to 200mg/day BID. Doses in pediatric patients proved beneficial with mean reductions of six units on the CY-BOCS scale.

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**Figure 4**

**Drug Interactions**

- The combination of monoamine oxidase inhibitors (MAOI) and selective serotonin re-uptake inhibitors in patients may increase the risk of adverse drug reactions, both serious and possibly fatal. Patients may experience hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations/changes in vital signs.

- A sudden decrease in systolic and diastolic blood pressure will occur from a combination of a single dose of tizanidine 4mg and a dosage of 100mg/day PO QD for 4 days. Pharmacokinetic analysis saw a decrease in average heart rate by four beats/minute when doses were combined.

- If prescribed Lotronex™ (Alosetron), warn your physician you are taking fluvoxamine. It is recommended alosetron and fluvoxamine not be administered together. Lotronex™ (Alosetron) mean plasma levels (AUC) increased 6-fold and half-life increased 3-fold.

- The initial stages of fluvoxamine therapy to children and adolescents need to be monitored closely. This stage of drug administration is critical for parents or legal guardians to be observant of warning signs for clinical worsening, suicidal tendencies, and unusual changes in behavior.

- People who smoke compared to non-smokers saw an increase in 25% of fluvoxamine maleate metabolism.

- Patients on Warfarin (Coumadin), an anticoagulant (blood thinner), need their prothrombin time monitored and dosage of anticoagulants adjusted.
Side Effects

The most common adverse effects are nervousness, restlessness, unable to sit still, insomnia, drowsiness, weakness, urinating more than usual, loss of appetite, weight gain or loss, nausea, vomiting, diarrhea, decreased sex drive, impotence, dry mouth, difficulty having an orgasm, upset stomach, and unpleasant taste in your mouth\(^1\). A physician should be notified if these serious side effects occur: tremors, shivering, muscle stiffness or twitching, seizures, problems with balance or coordination, unusual thoughts or behaviors, confusion sweating, fast heartbeat, mood changes, anxiety, panic attack, irritability, aggressiveness, severe restlessness, mania, and suicidal tendencies\(^8\). Allergic reactions can occur with fluvoxamine. Individuals who have developed allergic reactions (skin rash, hives, difficulty breathing, and swelling of lips, tongue, face, and throat) should stop taking fluvoxamine and consult a physician\(^1\).

Bulimia Nervosa Cure?

Scientific work in placebo-controlled studies suggests selective serotonin re-uptake inhibitors specifically fluvoxamine maleate had the potential to prevent urges to binge and overall bulimic behavior. The Hospital for Behavioral Medicine in Prien, Germany led the study consisting of 72 participants diagnosed with bulimia nervosa. The trial was given over a 15 week duration broken into two divisions of scheduled phases. The first phase was over a two to three week period directly for inpatient titration. The remainder of the double blind study was over a twelve week period specifically for maintenance\(^4\). Researchers identified the maintenance phase as the outpatient relapse-prevention program. Individuals were randomly assigned to receive dosing of fluvoxamine or a placebo. The foundation of the study revolved around assessing the psychotherapy aspects of bulimia nervosa and providing an effective pharmacotherapy for treating variables involved with eating disorders. The Eating Disorder Inventory (EDI), Psychiatric Status Rating Scales for Bulimia Nervosa, and Structured Interview for Anorexia and Bulimia nervosa (SIAB) were analyzed to prove the success of the study\(^4\). Expert analysis of these professional scales found fluvoxamine to have a positive impact in decreasing the return of bulimic behavior. Possible error could have been present in the case due to recent evidence discovered in the study that revealed 19 out of 37 participants in the fluvoxamine group dropped out\(^4\). Sudden withdrawals from a drug therapy can lead to dependencies and a final off-medications phase was implemented to test for effects of discontinuation of fluvoxamine\(^9\). Researchers found no evidence of harmful effects in the body after discontinuation.

Conclusion

Although there have been cases of increased potential for self-inflicting harm and suicidal tendencies, fluvoxamine, if monitored closely, is a great medication for obsessive compulsive disorder. Because it is the most unique selective serotonin reuptake inhibitor due to its monocyclic structure, fluvoxamine will continue to shine in the market for antidepressants. Unless another class of antidepressants is discovered, fluvoxamine will be dispensed. Due to its popularity among physicians and patients, people will continue to use it no matter what the cost.
Bibliography


Stem Cell Research
Scientific Report

Prepared for
Dr. Mancini

By
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April 20, 2007
Abstract

A relatively new scientific discovery is that of human stem cells. Research of these master cells has shown that they can be found in many locations throughout the human body. Stem cells are very unique cells that pose specific characteristics that are different than other cells throughout the human body. Over the years scientists have been able to separate these cells and grow them in a laboratory setting. Stem cells hold such great potential; however, they can also be considered quite controversial.

Introduction

Stem cell research is the study of stem cells in the body. It is considered to be a relatively new scientific study. Most scientists would agree that the surface has only been scratched regarding stem cell research. Stem cells are cells that have the natural ability to replicate and to evolve into specific cells through the body. These stem cells are said to one day be able to cure countless diseases such as: diabetes, heart disease, Parkinson’s disease, Alzheimer’s disease, cancer, muscular dystrophy, and osteoporosis. There are many different areas where one would find stem cells. Some are said to be more useful, and some are said to be controversial.

Types of Stem Cells

Stem cells are incredibly different from other types of cells within the body. As stated earlier stem cells are types of cells that have the ability to replicate indefinitely. Stem cells are considered to be unspecialized cells. This is due to the fact that stem cells do not contain tissue specific structures that permit them to perform those particular functions. Also, stem cells have the ability to turn into nearly every type of cell necessary to produce any type of tissue in the human body. There are many different locations where these magnificent cells can be located.

One of the locations where stem cells are found is in human embryos. The two main methods scientist’s uses to retrieve stem cells from an embryo are: by cloning them from human cells, or they can use spare frozen embryos from fertility clinics. “Embryonic stem cells are derived from the inner cell mass of a blastocyst. Embryonic stem cells are also known as pluripotent stem cells. Pluripotent cells are capable of generating every cell type that the
body produces, but they are not able to form a functioning organism.\footnote{1}

Another location of stem cells is in adults. Adult stem cells are known as multipotent stem cells. Multipotent stem cells can give rise to a restricted number of cell types. Stem cells can be found in most adult tissue such as skin, intestine, liver, brain, and bone.\footnote{1}

“Adult stem cells are also called organ or tissue specific cells. The main function of these cells is to replenish cells lost from normal turnover or disease in specific organs or tissues where they are found. Adult stem cells occur in mature tissue. Also, adult stem cells just like embryonic stem cells have the ability to replicate. However, unlike embryonic stem cells, adult stem cells are very difficult to expand in culture.”\footnote{1} Adult stem cells are limited in their ability to evolve into countless types of cells. They can only evolve into a handful of different cell types unlike embryonic stem cells. Adult stem cells are also extremely difficult to work with because there is not a large number of them. They can be rather difficult to find and to isolate. “Another drawback of adult stem cells is that they have been exposed to a lifetime of toxins and have also accumulated a lifetime of genetic mutations.”\footnote{2}

Blood stem cells are another location where one can find stem cells in adults. This is the most studied location of adult stem cells. The blood generation process is called hematologist. This occurs largely in bone marrow. The hematopoietic stem cells can replicate into multiple types of mature blood cells. Blood stem cells, just like the adult stem cells, are also incredibly difficult to isolate.\footnote{1} This is due to the low number of blood stem cells located in the human body.

Another type of stem cells that is beginning to steal focus is neural stem cells. These are multipotent stem cells that can produce nerve cells. These neural stem cells have been found in areas of the adult brain such as the sub-ventricular zone, and ventricle zone.\footnote{3} “These brain ventricles are composed of small hollow space filled with cerebrospinal fluid. Another location of brain stem cells is in the hippocampus. The hippocampus is a small structure of the cerebral cortex. Stem cells isolated from these areas are able to divide and give rise to nerve cells, and neuron-supporting cell types in culture.”\footnote{3}

Another location where stem cells can be retrieved is the umbilical cord blood. The umbilical cord is typically discarded as waste material after birth. It is now known that the umbilical cord and placenta are a source of stem cells. “Umbilical cord blood refers to the small amount of blood remaining in the placenta and blood vessels of the umbilical cord. The umbilical cord can be used as a source material of stem cells for transplantation. Unfortunately, there is a very limited number of stem cells located in the umbilical cord.”\footnote{3}

A new location of stem cells was just recently discovered. The new source of stem cell retrieval can be found in amniotic fluid. The placenta and amniotic fluid contain a large number of cells shed by the developing embryo. The amniotic fluid-derived stem cells have the added bonus of avoiding ethical issues that are derived from the use of embryonic stem cells. This is due to that the retrieval processes of amniotic fluid-derived stem cells. These cells can be retrieved after birth, or through amniocentesis. This avoids
harm to the embryo. “About one percent of the amniotic fluid cells were found to be pluripotent cells. These newly discovered cells have characteristics that fall somewhere between adult and embryonic stem cells.”

**How Embryonic Stem Cells are Grown**

In order to understand how embryonic stem cells are grown, it is first important to understand the structure of an embryonic stem cell. As stated earlier, there are a few ways that embryonic stem cells can be retrieved. The most common retrieval processes is using spare embryos that are donated to the laboratories. The embryos that are generally used are in the range of four to five days old. This few day old cell ball is known as a blastocyst. The blastocyst can be divided into multiple layers. The trophoblast is the layer of cells that coat the outside of the blast cyst. The next structure layer of the blastocyst is known as the blastocoel which is an unfilled hole within the structure of the blastocyst. The final piece of the blastocyst is known as the inner cell mass. The inner cell mass is a cluster of cells that is in the region of thirty cells at one side of the blastocoel.

Cell culture is the process of growing cells in a laboratory. “Human embryonic stem cells are isolated by transferring the inner cell mass into a plastic laboratory culture dish that contains a nutrient broth known as culture medium. The cells divide and Cell Culture spreads over the surface of the dish. The inner surface of the culture dish is typically coated with mouse embryonic skin cells that have been treated so they will not divide. This coating layer is known as a feeder layer. The reason for having the mouse stem cells in the bottom of the culture dish is to give the inner cell mass cells a sticky surface to which they can attach. Also, the feeder cells release nutrients into the culture medium.”

Within the next few days, the inner cell mass multiply and begin to overtake the culture dish. Once this begins, the cells are then carefully transferred into many new culture dishes. This process is then repeated several times over the course of a few months and is known as sub-culturing. “After six months or more, the original thirty cells of the inner cell mass yield millions of embryonic stem cells. Embryonic stem cells that have proliferated in cell culture for six or more months without differentiating are pluripotent, and appear genetically normal and are referred to as an embryonic stem cell line. Once the cell lines are established, or even before that stage, batches of them can be frozen and shipped to other laboratories for further culture and experimentation.”

In order to create cultures of specific types of cells such as blood cells, nerve cells, or heart muscle cells, scientists will then attempt to control the differentiation of the embryonic stem cells. “They change the chemical composition of the culture medium,
alter the surface dish, or modify the cells by inserting specific genes.” By successfully being able to control the cells differentiation of the embryonic stem cells into specific cells, scientists may be able to use the resulting, differentiated cells to treat countless diseases in the future.

In November of 1998, the first ground breaking stem cell experiment occurred. “Scientists at the University of Wisconsin and Johns Hopkins University announced that they isolated human embryonic stem cells.” These stem cells were then used to give rise to heart tissues.

Figure 3²
Isolating stem cell diagram

Advantages and disadvantages of adult and embryonic stem cells

Pluripotent, or embryonic stem cells can differentiate into multiple types of cells. Whereas adult stem cells are awfully restricted with the number of cells that they can differentiate. Also embryonic stem cells can effortlessly be grown in culture. “Adult stem cells are rare in mature tissues and methods for expanding their nature numbers in cell culture have not yet been worked out.” One advantage for using a patient’s own adult stem cells would avoid possible rejection from the patient’s immune system. While embryonic stem cells from a donor may pose the problem of a patient’s immune system rejecting them. “However, whether the recipient would reject donor embryonic stem cells has not been determined in human experiments.” The purpose of adult stem cells is to repair and maintain the tissue in the human body. Even though embryonic stem cells seem to contain the most medical potential, they also come with the most controversial
issues. Regardless, adult and embryonic stem cells have their own advantages and disadvantages.

**Potential Uses of Human Stem Cells**

“Studies of human embryonic stem cells may yield information about the complex events that occur during human development. A primary goal of this work is to identify how undifferentiated cells become differentiated. Some of the most serious medical conditions, such as cancer and birth defects are due to abnormal cell division and differentiation.”

Once scientist can better comprehend the process of cell differentiation, it can unlock many doors. “Once a better understanding of genetic and molecular controls of these processes may yield information about how such disease arise and suggest new strategies for therapy.”

**Stem Cells’ Unlimited Potential**

Researchers believe that human embryonic stem cells can be grown into a variety of body parts, enabling them to fight many common afflictions.

<table>
<thead>
<tr>
<th>Cells Derivable From Stem Cells</th>
<th>Target Diseases</th>
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<tbody>
<tr>
<td>Insulin-producing cells</td>
<td>Diabetes</td>
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<tr>
<td>Nerve cells</td>
<td>Stroke, Parkinson’s disease, Alzheimer’s disease, Spinal cord injury</td>
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<tr>
<td>Heart muscle cells</td>
<td>Heart attacks, Congestive heart failure</td>
</tr>
<tr>
<td>Liver cells</td>
<td>Hepatitis, Cirrhosis</td>
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<td>Blood cells</td>
<td>Cancer, Immunodeficiencies</td>
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<td>Bone cells</td>
<td>Osteoporosis</td>
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<td>Cartilage cells</td>
<td>Osteoarthritis</td>
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<td>Eye cells</td>
<td>Macular degeneration</td>
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<tr>
<td>Skin cells</td>
<td>Burns, Wound healing</td>
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<tr>
<td>Skeletal muscle cells</td>
<td>Muscular dystrophy</td>
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Source: Genen Corp.

Another potential use of human stem cells would be for testing new drugs. “For example, new medications could be tested for safety on differentiated cells generated from human purport cell lines.” It is known that other stem cell lines have been used in the testing of drugs. One example of that is cancer cell lines which are used to investigate possible anti-tumor drugs.

One of the most important prospective treatments of human stem cells is the ability to create tissues that could be used for cell based therapies. “Stem cells, directed to differentiate into specific cell types offer the possibility of a renewable source of replacement cells and tissues to treat diseases.” Stem cell therapies could
revolutionize the medical field. Some of the diseases include diabetes, stroke, Parkinson’s disease, Alzheimer’s disease, heart attack, congestive heart failure, cancer, burns, osteoporosis, osteoarthritis, and muscular dystrophy. For example, it may be possible to generate healthy heart muscle cells in the laboratory and then transplant those cells into patients with chronic heart disease. Studies have shown that when transplanting bone marrow stem cells into a damaged heart of an animal, the stem cells create heart muscle cells and effectively reproduce the heart tissue.

“Other recent studies in cell culture systems indicate that it may be possible to direct the differentiation of embryonic stem cells or adult bone marrow cells into heart muscle cells.” Another example is in people who undergo Type I diabetes. With this disease the pancreas cells are not able to produce insulin. “New studies indicate that it may be possible to direct the differentiation of human embryonic stem cells in cell culture to form insulin producing cells that eventually could be used in transplantation therapy for diabetes.”

**Funding**

**Support for Research Is Growing**

Fifty-six percent of Americans believe the potential benefits of embryonic stem cell research outweigh concerns about the destruction of human embryos involved in the research, up from 43 percent in 2002. At the same time, the percentage who said they didn’t know about the issue dropped by 7 percentage points, reflecting the growing interest and awareness in stem cell research.

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<tr>
<th>Attitudes About Embryonic Stem Cell Research</th>
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<tr>
<td>It is more important to...</td>
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<td>March 2002</td>
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<tr>
<td>Conduct research 43%</td>
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<tr>
<td>Protect embryos 38%</td>
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<tr>
<td>Don't know 19%</td>
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Source: The Pew Research Center for The People & The Press, May 23, 2005; survey results are based on telephone interviews with a nationwide sample of 2,000 adults age 18 and older.

Due to its controversial cells characteristics, embryonic stem cells have been a heated debate over the past few years. The question is when does human life begin? There have been many debates between religion and science. “On July 19, 2006, President George Bush, for the very first time, used his power to veto a bill that would have increased federal funding for embryonic stem cells.” However, recently there has been a change of minds with many members of Congress that are now leaning favorably to embryonic stem cell research. Support of embryonic stem cell research among Americans over the years is also growing in popularity. “Fifty-six percent of Americans believe that potential benefits of embryonic stem cell research outweigh concerns about the destruction of human embryos involved in research, up from forty-three percent in 2002.” Even without governmental support, stem cell research still continues with the support of private funding and state funding. California leads the way in state funding with many more
states to follow. California is allowing three billion dollars in donations to embryonic stem cell research over the course of ten years. Mayor Michael Bloomberg leads the private donation section. So far Michael Bloomberg has donated one hundred million dollars to Johns Hopkins University to perform studies on stem cell research. There are also many countries outside of the United States that are allowing stem cell research to continue. “More than thirty nations have explicit policies permitting at least some research into embryonic stem cells.”

<table>
<thead>
<tr>
<th>States, Foundations Provide Research Funding</th>
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<tr>
<td>A growing number of foundations and states are providing funding for research on human embryonic stem cells (ESCs) in response to President Bush’s July 19 veto of stem cell funding legislation.</td>
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<th>Non-Federal Funders of ESC Research</th>
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<td>State commitments</td>
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<tr>
<td>California</td>
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<th>Private Donations That Include Support for ESC Research</th>
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<tr>
<td>Donor</td>
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<td>Mayor Michael Bloomberg</td>
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<td>Starr Foundation</td>
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<td>Broad Foundation</td>
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<td>Ray and Dagmar Dolby</td>
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<td>Sue and William Gross</td>
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<tr>
<td>Stowers Medical Institute</td>
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<td>Leon D. Black</td>
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<td>Private individuals</td>
</tr>
</tbody>
</table>

Figure 6

State and Private funding

Although scientists still do not know much about these cells, what they do know shows strong potential. Even though embryonic stem cells may be controversial to some, it is gradually growing support in the United States. In America although there is no governmental funding for stem cell research, there is funding through other sectors. Stem cell research is the largest scientific discovery science DNA, and the research has only just begun.

Conclusion

There are many locations of human stem cells. Some can be found in embryos, amniotic fluid, umbilical cords, or in adult tissues. Some are considered pluripotent, and some are considered multipotent. This depends on the cells ability to differentiate. Pluripotent cells are able to differentiate into a mass number of cells; whereas multipotent cells are extremely limited in their ability to differentiate. There are many assumptions to the multiple benefits in human stem cells. Stem cells hold the promise of many medical advantages.
References

Internet Resources


The Ingestion of Ethanol and Alcoholism

(Fig. 1)

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CHM236
20 April 2007
Abstract

Ethanol (ethyl alcohol) is the second simplest alcohol and is the alcohol found in alcoholic beverages. Sometimes referred to as grain alcohol due to its fermentation of grain or other organic material, ethanol is responsible for a wide range of health effects when misused or abused. This paper will discuss the history of ethanol, provide scientific information about the effects of the ingestion of ethanol on the human mind and body, and will finish with information about recovery of alcoholism and speculation about the future.

The History of Ethanol Consumption

The consumption of ethanol or alcoholic beverages is known to have originated extremely early in the history of mankind. Throughout the history of this intoxicating beverage, mankind has used it socially in many arenas from gaining courage on a battlefield to the seduction of a lover. The Norse, the Celts, Ancient Greeks, Babylonians, and Ancient Egyptians have records of habitual production and consumption of ethanol.¹

Since the production of alcohol relies on grain or other organic material, agriculture plays a key role in the origin of alcoholic beverages. The Sumerians were one of the first civilizations to center around agriculture around 4000 BC. Ancient engravings in Sumerian text on stone tablets reveal recipes of a drink made with bread that had intoxicating qualities. Egyptians, around 1600 BC, invented the first straws which they used to drink beer that contained corn husks in it. In addition, social problems stemming from drunkenness have been revealed in some of their hieroglyphics and texts. In addition, the Babylonians were the first to write laws that regulated the consumption of alcohol.¹

Distilled spirits originated in China and India around 800 BC. The product of fermenting wine or beer from fruit or grain is taken and distilled to yield a more potent alcoholic beverage. Distillation has produced beverages such as Brandy, Cognac, and Sake. Oddly, this technique did not find its way to Europe until the eleventh century. The Greeks and Romans were among the first to try different flavors using herbs and spices. Both civilizations worshiped a God of wine. The Greeks worshiped Bacchus while the Romans worshiped Dionysus. Both Gods were documented in mythology and for the first time drinking alcohol was immortalized and glamorized.¹

The Romans introduced beer to Northern Europe around 55 BC. The beers and Ales that followed were rich with protein and high in carbohydrates. In the 8th and 9th century hops were introduced into beer for a better taste. The use of hops persists today in beer making worldwide. In the Middle Ages alcohol consumption continued to grow, especially in monasteries. Beer was accepted as a nutritional drink with meals and was even permitted during fasting. Amazingly, monks were permitted to consume up to 5 liters of beer per day. That is equivalent to more than 14 twelve ounce beers per day. Taverns, public houses, and inns began to sprout up everywhere and by the end of the Middle Ages; most of the world was starting to master the process of distillation and brewing.¹
Nearly everything during the age of enlightenment, the Renaissance, became an art. Distillation and brewing were no different. The use of different techniques and spices paved the way for many brewers of the future, all of whom tried to master the craft in search of the perfect flavor. This period was also beneficial in the expansion of knowledge in the sciences. Microbiology became a widely studied science that contributed to more healthy ways to make alcoholic beverages. In addition, the industrial revolution yielded steam power, refrigeration, and more efficient methods of distillation that produced even more potent alcohol.¹

During the American Revolution, drunkenness was not a major concern for Americans. Liquor became a driving force in colonial commerce. However, some regulations were implemented within the army during the war. Traditional control over drunkenness began to diminish as America’s consumption continued to grow. Congress attempted to tax spirits in the late 1700’s. This outrage resulted in the Whiskey Rebellion of 1794. Saloons at this time were in much need of profit, so the introduction of gambling and prostitution promoted drinking and kept many saloons in business.¹

A popular belief of personal perfection began to emerge in the United States and these saloons were considered offensive by many Americans. The Prohibition emerged and the eighteenth amendment to the constitution revoked the business license of brewers, distillers, wholesalers, and retailers of alcoholic beverages. In order to save grain for food during World War I, the Wartime Prohibition Act led to complete prohibition in thirty three states. Along with a decrease in consumption came bootleggers and Cartels. People were not willing to be separated from drinking. Law and order began to break down while the corruption swept the United States. Prohibition was repealed in 1933 and slowly the consumption levels were on the rise again.¹

Clearly ethanol has impacted human life for centuries. The real question becomes, why? An understanding of what ethanol is, what happens when it is ingested, and the short and long term effects, may explain our history and possibly our future with alcoholic beverages.

**What is Ethanol?**

Ethanol is a two carbon alcohol and is the alcohol found in alcoholic beverages. The molecule consists of the alkyl ethyl group (CH₃CH₂-) attached to the hydroxyl functionality, or an oxygen bonded to a hydrogen atom (OH).

![Chemical structure of ethanol](Fig. 2)

This hydroxyl group participates in hydrogen bonding mainly in the liquid phase. These hydrogen bonded pairs of ethanol molecules make ethanol more viscous than other
polar molecules of similar atomic masses. It is a colorless, flammable, and volatile liquid formed by the fermentation of sugars. Ethanol is the most widely abused depressant in the world and is responsible for many biochemical and pathological phenomena.\(^2\)

Ethanol is also used as a source of fuel, a solvent, and in hand sanitizer as an antiseptic. Although it does not kill bacterial spores, ethanol kills other organisms such as most bacteria, fungi, and many viruses by denaturing their proteins and dissolving their lipids.\(^2\) However, the overwhelming majority of health problems associated with ethanol stem from ingestion.

**The Ingestion of Ethanol, Physical Addiction, and Consequences**

Ethanol chemically affects the body in a highly complex manner. Alcohol’s primary target is the central nervous system, where it influences neurotransmission to produce intoxication. William Boggan, Ph.D. is an instructor of psychology at the University of North Carolina at Chappell Hill and an expert on alcoholism. Boggan described the ingestion of ethyl alcohol as it is taken in “from the mouth down the esophagus and into the stomach and on into the small intestine.” At any given point it may transfer to the blood stream. However, most of the alcohol is soaked up from the small intestine and stomach. The faster one drinks, the higher the blood alcohol concentration (BAC). This concentration is a measure of the milligrams of ethanol in 100 milliliters of blood.\(^3\)

Ethanol is a poisonous substance. However, it is the least toxic alcohol. In fact the term intoxicated refers to a case of ethanol poisoning. Our bodies must detoxify ethanol or it will accumulate and poison the brain. The liver produces the enzyme alcohol dehydrogenase (ADH) to detoxify ethanol. The ADH is a catalyst in an oxidation reaction involving oxidized nicotinamide adenine dinucleotide (NAD\(^+\)) and ethanol. The oxidation involves the removal of two hydrogen atoms in the ethanol molecule. The oxidized form of NAD\(^+\), NAD\(^{2+}\), is reduced to NADH while ethanol is ironically oxidized to an even more toxic substance, acetaldehyde.\(^4\) Acetaldehyde is readily detoxified by aldehyde dehydrogenase (ALDH) to the non-toxic acetic acid and acetate, a salt of acetic acid. However, when too much acetaldehyde is produced and all of it cannot be detoxified, it collects in the blood stream and poisons the body. The typical hangover symptoms such as headache, vomiting, and malaise are a product of this poisoning and dehydration.

![Chemical diagram showing the conversion of ethanol to acetic acid and acetate.](Fig. 3)

About 90% of alcohol ingested is oxidized to acetic acid in the liver. It is well known that long term abuse of alcohol may result in liver disease. The liver damage
comes from both the ethanol and from the substances produced when ethanol is metabolized. The most severe type of liver disease is alcohol cirrhosis. This cirrhosis is identified by “extensive scar tissue (fibrosis) that stiffens blood vessels and distorts the internal structure of the liver”.  

In addition to a number of organs being damaged, such as the kidneys and brain, heavy drinkers also may have heart complications. The potential heart problems in heavy drinkers are described as an increased risk “for heart muscle disease (cardiomyopathy), disturbed heart rhythm (arrhythmia), high blood pressure, and hemorrhagic stroke”.  

In relation to the brain, alcohol works as a depressant and diminishes the function of the nervous system. More specifically Boggan stated, “Ethanol acts at specific sites on a specific subset of GABA and glutamate receptors (protein molecules upon which the neurotransmitters act). By influencing the action of these receptors, ethanol “slows down” the functioning of the nervous system. Thus, ethanol is called a central nervous system (CSN) depressant”.  

This leads us straight to alcoholism. Alcohol has been known to cause depression and anxiety. In addition, it can create episodes of craving, loss of control, physical dependence, and tolerance.  

The NIAAA website defines these terms as follows:

- **Craving:** A strong need, or compulsion, to drink.
- **Loss of control:** The inability to limit one’s drinking on any given occasion.
- **Physical Dependence:** Withdrawal symptoms, such as nausea, sweating, shakiness, anxiety, occur when alcohol use is stopped after a period of heavy drinking.
- **Tolerance:** The need to drink greater amounts of alcohol in order to “get high.”

Marc A. Schuckit, M.D., Director of Alcohol Research and the Alcohol and Drug Treatment Program is a professor of psychiatry at UCSD, School of Medicine. In an article that appeared in *Alcohol Health & Research World* he described this anxiety and depression:

“As a typical depressant, alcohol affects the brain in many ways, and it is likely that high doses will cause feelings of sadness (i.e., depression) during intoxication that evolve into feelings of nervousness (i.e., anxiety) during the subsequent hangover and withdrawal. The greater the amounts of alcohol consumed and the more regular the intake, the more likely a person will be to develop temporary anxiety and depressive symptoms. As consumption increases even more, these symptoms also are likely to intensify.”

After understanding the chemistry behind alcohol ingestion, it becomes easier to comprehend the biochemical basis of alcohol addiction. The two main processes that contribute to this addiction are a modified reward process and neuroadaptation.

1. **A modified reward process:** The rewarding aspects of ethanol use such as the taste of the alcohol itself or the relaxed feeling gained from drinking ethanol. The rewarding aspects of ethanol use involve the brain’s reward system. This system is comprised of brain structures and circuitry (e.g. ventral tegmental area, extended amygdala and the nucleus accumbens) that appears to be important in the reinforcing (rewarding) properties of a variety of drugs.
2. **Neuroadaptation**: The process by which the brain attempts to compensate for something (ethanol) which influences normal functioning. Just as there is adaptation upon the presence of something new, there is neuroadaptation when the compound leaves the brain. Thus, through neuroadaptation the brain is able in many instances to up-regulate (increase) or down-regulate (decrease) its function to compensate for the presence or absence of ethanol.

(Fig. 4)

Dr. William Boggan clarifies the confusion of these processes, symptoms, and the urge to keep drinking:

If a person chooses to drink more regularly (chronic intake), the brain attempts to adapt to the increasing amounts of ethanol. Generally, neuroadaptation can take place up to a point. After chronic consumption and ongoing adaptation, it will now take more ethanol to produce the same effect as the first drink. When this is the case, **tolerance** has developed and substantial adaptation has taken place. If the person now chooses to quit drinking the body tries to return to its original state in doing so causes a number of **withdrawal signs** including tremors, seizures, nausea, and negative emotional states. Since further drinking will delay, diminish, or prevent withdrawal, the person often chooses to drink again. Even if the person stops drinking, the neuroadaptations that took place in the brain may persist for a period of time well beyond the time when ethanol is no longer present in the body. It has been speculated that these may be the source of the urges to drink again.³

It is apparently easy to let drinking get out of control. With the brain constantly adapting to our choices of what we consume, are we really in control? When drinking does get out of control, few actually recover and live a happier life. Others try to recover and fail miserably.
Recovery and the Future

People have been drinking since near the beginning of our existence. Obviously alcohol has been a problem for centuries. The advantage we possess now is enhanced knowledge about drinking and of course, technology. The highway to a sober state is long, winding, and treacherous. At any given point, if one drinks or fails in moderation, they must return to the beginning and start again. Therefore, it is essential that the program chosen is one that is right for the individual. Motivation seems to be the biggest factor in a successful recovery. In a Harvard Mental Health Letter the importance of motivation was acknowledged as follows: “Because alcoholism, like all addictions, is a disorder of motivation, a full commitment to change is not only a cause of recovery but often the largest part of recovery itself.” 7 After the realization of the importance of motivation, selecting an appropriate process becomes the next step.

The most popular program in the United States is Alcoholics Anonymous. Their famous 12 step program relies on a faith in God rather than a medical regimen. Although it is very popular and successful, it is not right for everyone. Some people need to abstain from drinking while others are successful in moderation, medical help, and simply changing their diets.

The Harvard Mental Health Letter discussed the two sides of the abstinence controversy. It is widely accepted by AA and health professionals that “abstinence is necessary because alcoholics will inevitably lose control once they start to drink.” 7 Many therapists in favor of controlled drinking believe that “most alcoholics are not powerless over the drug; they can change their “drinking behavior” without giving up alcohol entirely.” 7

The importance of nutrition is overlooked in our society. Doctors David A. Arneson and Angela Pinkhasova wrote an article entitled “Nutritional treatment for detoxification and recovery from alcoholism: the functional/molecular medicine approach. The article acknowledges treatments for alcoholism such as medical, counseling, and spiritually-based approaches. However, the Doctors criticize these programs when they are not used simultaneously and when the holistic approach is ignored. Nutrition plays a huge role in the detoxification and recovery of an alcoholic. Nutritional intake “including water, proteins, carbohydrates, fats, vitamins, and minerals—is the absolute basis of our health and mental well-being.” 8 Arneson continued with the importance of water in that, “[p]roper hydration may be the most important factor since every biochemical process in the human body operates in a fluid matrix. Fluid is essential in transporting nutrients and removing waste products in and out of cells.” 8

Nutritional deficiencies are extremely common in heavy drinkers. Rather than proteins, carbohydrates, vitamins, and fats, alcoholics get most daily energy from ethanol. Ethanol is not a nutrient, but “contains approximately 7 calories per gram and represents about 3% to 5% of the daily energy intake of the adult American population” (Arneson 4). The problem with treating alcoholism is getting a sufficient amount of nutrients into the body for organ repair so the organ may effectively utilize nutrients. In addition, nutritional deficiencies make alcohol cravings worse and “promote complications in alcoholics such as heart disease, liver disease, high blood pressure, diabetes, osteoporosis, and increased cancer risk.” 8
The nutritional/medical path of recovery seems to make the most sense. Certain drug treatments (if prescribed by a doctor) may be helpful as well. Many anti depressants are prescribed to aid in recovering alcoholics. For example, selective serotonin reuptake inhibitors (SSRIs) like fluoxetine (Prozac) and sertraline (Zoloft) are effective in managing anxiety. In addition, buspirone (Buspar) is commonly prescribed to help alcoholics.

Based on what we have seen throughout history, it does not appear that mankind is willing to stop drinking. In the United States in 1850, 1.05 gallons of ethanol were consumed per capita. From 1906-1919 an average of 2.37 gallons were consumed per capita. After the prohibition it slowed down to 1.94 gallons. However, since prohibition ethanol consumption has been on the rise reaching record levels. From 1978-1982 an average of 2.72 gallons per capita were consumed. Since 1982 we have slowed down a little. In 2004 the amount consumed was 2.23 gallons per capita. These numbers are totals from beer, wine, and spirits based on a minimum age of 14.5

The numbers do not lie. We are on a steady increase of ethanol consumption since prohibition. With advances in technology and medicine fewer people die every year of liver cirrhosis. This certainly will not keep people from drinking. Ethanol will continue to be consumed at record levels unless the majority of people take the responsibility to learn about what they are really doing to themselves.

Conclusion

Mankind has consumed alcoholic beverages for centuries. We have learned a great deal about the biochemistry of the metabolism of ethanol and its effect on our brain. In addition we have made huge leaps in medicine and technology to help with this problem. It is tough to argue that drinking is good for people with the knowledge we have obtained. There have been many programs and regimens to try to limit or stop excessive drinking. However, as the numbers continue to climb, human beings will continue to repeat history.
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Illustrations


Figure 2. “Exaggerated line – Ethanol” sciencegeek.net. 15 April 2007. <http://www.sciencegeek.net>

