

**The use of nanotechnology in the  
treatment and diagnosis of Alzheimer's  
disease and Dementia**

**By  
Nick Williams  
Anil Krishan  
Kiran Sabharwal**

**PASS WITH MERIT**

**Research Paper Based On Pathology  
Lectures at Medlink 2010**

## **Abstract**

For generations, the human race has been trying to use drugs to help cure illness. Now in the 21<sup>st</sup> century we have the technology to create a completely new form of drug, a drug using Nanotechnology. We have the technological ability to create particles that are a mere 50 atoms in diameter and are able to combine drugs within these intricate structures. In this paper we aim to outline the basics of nanotechnology and the treatment and diagnosis of Alzheimer's disease. We will then further discuss how it may be possible for nanotechnology to improve and expedite the treatment and diagnosis of Alzheimer's disease at an early stage.

## **Introduction**

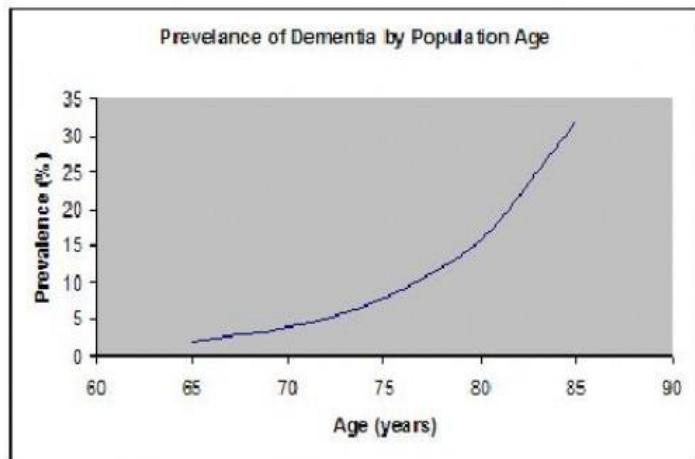
### **Alzheimer's Disease and Dementia**

Alzheimer's disease is a neurodegenerative disease affecting around 465 000 people in the UK and is the most common cause of dementia. It is thought that in the approximately 60 000 deaths are attributed to dementia in UK every year. Not only is Alzheimer's an emotionally taxing disease but also it has major economical consequences. In *World Alzheimer's Report 2010* it was estimated that \$604 billion was spent worldwide on treatment and support, furthermore 70% of that was from Western Europe and North America.

There is no sole cause of Alzheimer's disease but it is believed that the condition is linked to a person's health and lifestyle as well as age and genetics. One of the key factors is age, and nearly all the data suggests that the older you get the more likely you are to get Alzheimer's disease and hence dementia, seen in *Figure 1*. The probability of Alzheimer's in a person 65 years of age is about 1 in 1. This rises to 1 in 7 by the age of 80

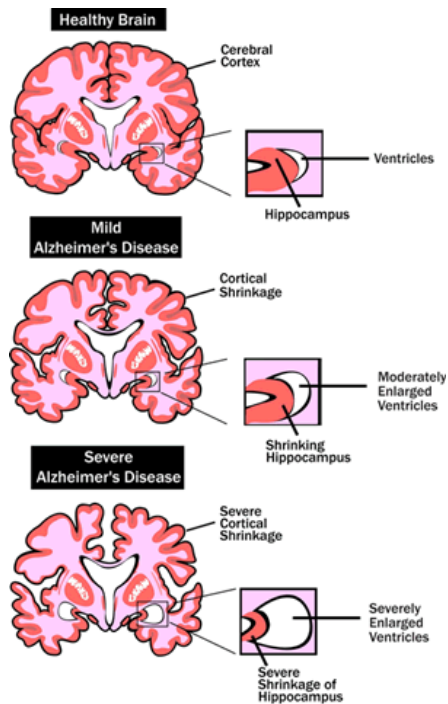
The generics of Alzheimer's disease are somewhat subtle. Quite often conditions are inherited and passed down through the generations, this is not the case for Alzheimer's. Research has shown that if someone has a member of their immediate family with the disease then it only slightly increases the chance of developing the disease.

The other contributing influence on this indisposition is a person's health and lifestyle. If an individual has a history of severe head injuries, scientists have shown that this increases their probability of developing the condition. Smoking and a high serum



*Figure 1* shows a graph comparing the prevalence of Dementia to age

cholesterol have also been shown to increase the probability of having the disease in later life.



Patients who suffer from Alzheimer's tend to suffer from dementia, mood swings and may lose the ability to speak. Alzheimer's disease is a progressive disease meaning it is slow and systematically gets worse. If the brain of an Alzheimer's sufferer was to be looked at, atrophic changes develop over time within the cerebral cortex and hippocampus. As the condition progresses more and more of the brain atrophies. In *Figure 2* it can be seen that the cerebral cortex and the hippocampus are diminishing in size as the disease progresses. The hippocampus is the part of the brain used for memory and the cerebral cortex for language and problem solving and hence the consequences that are seen in dementia.

*Figure 2 shows the stages of Alzheimer's in the brain*

## Nanotechnology

### What is Nanotechnology?

Nanotechnology is defined as the study and application of molecules 1nm and 100nm in size. This technology can be used in all manner of things such as: medical purposes, energy storage, self-cleaning windows and even to alter the taste of the food we eat.

### Why Nanotechnology?

When elements are on a nanoscale they behave differently to the way in which they behave on a macro scale. The reason the particles act so differently is because on a nano scale the particles have a greater surface area to weight ratio. Due to this varying ratio, the nanotechnological particles have a higher reactivity.

### The different Nanoparticles

The beauty of this technology is that there are so many different forms of nanoparticles. The three of the prominent forms that are used in medical development are: Quantum Dots, Buckyballs (Buckminsterfullerene) and Carbon Nanotubes. Each have their unique properties, which will be explained in due course.

### Carbon Nanotubes

Nanotubes are, in essence, a sheet of graphite (graphene) rolled up to form a tube, seen in *Figure 3*. These structures are unique in the way that they have the highest known strength to weight ratio, making them ideal for use in a compound needing to be exceptionally strong. Due to this property of nanotubes, NASA is currently attempting to use these nanoparticles in the production of space aircrafts.

QuickTime™ and a decompressor are needed to see this picture.

Another unique characteristic of carbon nanotubes is that they have the ability to penetrate easily through membranes such as cell walls. Their nanoscopic diameter results in the tubes acting like fine nanoneedles. This trait makes them excellent for medical purposes because it provides a means to supply drugs to places in the body, which are somewhat inaccessible.

*Figure 3 shows a Carbon Nanotube*

### Buckyballs (Buckminsterfullerene)

A Buckminsterfullerene, or more commonly known as a Buckyball, is  $C_{60}$  and is a “patchwork” of 12 pentagons and 20 hexagons of carbon, seen in *Figure 4*. The one fundamental physical property of a buckyball is that it is hollow inside and therefore chemicals or drugs can be placed for more specific drug delivery.

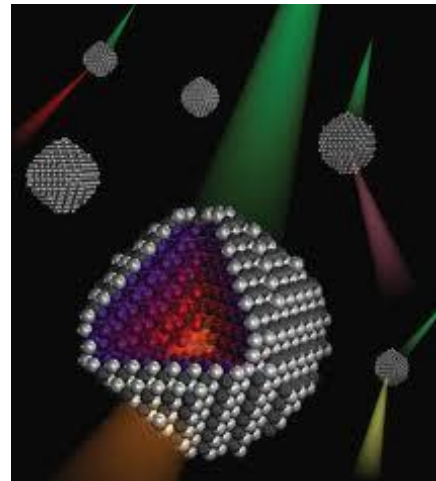
QuickTime™ and a decompressor are needed to see this picture.

The fullerene is also an incredibly strong and stable structure and so has been used to create body armour that is tremendously strong. The armour when created could survive 250 tonnes/cm<sup>2</sup>, which is the equivalent of having the weight 4 locomotive trains on the area of one fingernail.

*Figure 4 shows a Buckminsterfullerene (C<sub>60</sub>)*

### Quantum Dots

Quantum dots are nanoparticles, generally cadmium or zinc chalcogenides, which are between 2nm and 10nm in diameter, seen in *Figure 5*. These particles are particularly noteworthy due to their unique optical and electrical properties.



The quantum dots emit photons, which is seen as light to the naked eye. The colour of the light produced depends on the size of the quantum dot. In this knowledge it is possible to tailor the various colours because quantum imaging and the monitoring of various chemicals in that body.

*Figure 5 shows a Quantum Dot*

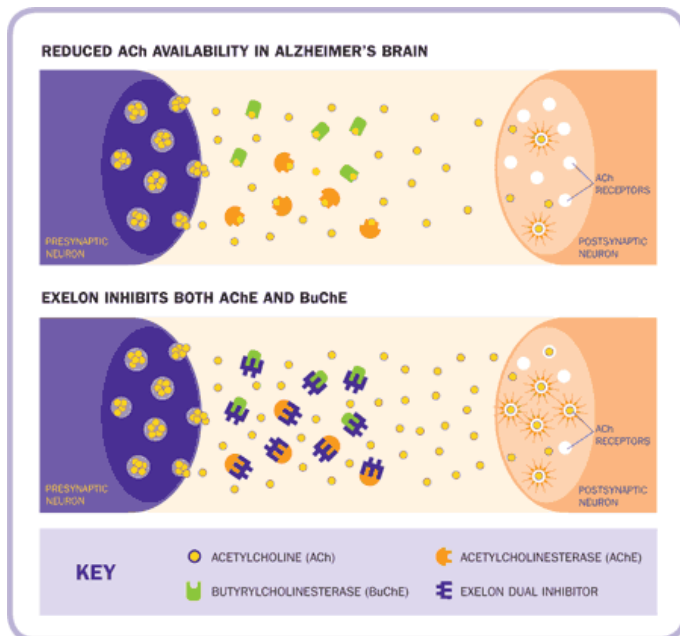
Another way in which these nanoparticles are employed is in solar panels. As quantum dots are generally not harmful to the environment it makes them a favourable candidate for use in solar panels.

### **Drug Treatment for Alzheimer's Disease**

At present there is no cure for Alzheimer's disease, which is why research into new technologies such as nanotechnology is of such great importance.

Before analysing future possible treatments/managements for Alzheimer's disease using nanotechnology it would be interesting to look into the current management of this incurable, degenerative, and terminal disease.

Drug treatments have been developed that do not cure the disease but can help to alleviate symptoms and also decelerate their progression in some cases. The four main drugs used are Aricept, Exelon, Reminyl and Ebixa which fall under two distinct categories. Aricept, Exelon and Reminyl are known as acetylcholinesterase and butyrylcholinesterase inhibitors whereas Ebixa blocks glutamate (a messenger chemical). Consequently Aricept, Exelon and Reminyl all work in the same way. Existing research has found that people with Alzheimer's disease show a loss of nerve cells in the brain that use acetylcholine as a neurotransmitter. The extent of the loss of these nerve cells is associated to the severity of cognitive impairment that people experience. Therefore acetylcholinesterase and butyrylcholinesterase inhibitors are employed to reduce the rate at which acetylcholine is broken down. This is important because the concentration of acetylcholine in the brain increases and it helps to counter the loss of acetylcholine caused by the loss of cholinergic nerve cells. Therefore symptoms of Alzheimer's Disease are controlled e.g. memory loss, mood swings and general loss of living skills



*Figure 6 Illustrates how AChE and BuChE are inhibited between neurones by Exelon.*

The most prevalent side-effects are vomiting and nausea which occur in about 10-20% of users and are known to be mild to moderately severe. Muscle cramps, bradycardia and increased gastric acid production are rare secondary side-effects.

Ebixa (chemical name Memantine) is recommended for managing Alzheimer's Disease in people with a moderate form of the disease who are intolerant to acetylcholinesterase inhibitors or for those with severe Alzheimer's Disease. It is an N-methyl-D-aspartate (NMDA) receptor antagonist. The NMDA receptors are the receiving targets of glutamate molecules released from nerves. Glutamate molecules function as neurotransmitters when they interact with NMDA receptors. In Alzheimer's Disease when neurones get damaged large amounts of glutamate leak out of them; leading to excessive interaction with the NMDA receptors. Consequently the "receiving" nerve cells get damaged and die.

Ebixa works by interacting with the NMDA receptors and blocking them to prevent glutamate from interacting with them. This reduces the toxicity of excess glutamate. Messages are now transmitted normally between nerve cells and the decline of memory and cognition is slowed down.

Ebixa can also be used in combination with cholinesterase inhibitors such as Aricept or Exelon. Research in progress suggests that combining cholinesterase inhibitors with Ebixa seems to significantly enhance outcomes. Nevertheless, more and larger-scale drug trials are required to substantiate these promising early results.

However the problem with all these drugs is that they only stabilise the symptoms associated with the disease rather than curing the disease as they do not affect the underlying degenerative development of the disease.

### **Current Alzheimer's Disease Diagnosis**

Diagnosing Alzheimer's Disease is very difficult, especially early on. A certain diagnosis of the cause of the disease may only be confirmed at post mortem or through a brain biopsy.

The time taken for a diagnosis can vary between four weeks to twelve months depending on the stage of the disease for that person. Firstly a GP will assess the person to see if dementia is suspected by analysing background information such as symptoms and medical history, physical examinations such as blood and urine tests and mental tests that test memory and thinking skills.

The next step is referral to a specialist who has a deeper knowledge and experience of dementia than a GP. These can include neurologists, geriatricians or psychiatrists.

The final step of diagnosis is assessment. The specialist will carry out assessment through:

- Analysis of relevant background information
  - Physical examination
  - Memory assessments
  - Scans

The memory assessment will be more detailed and will assess memory, verbal and non-verbal capacity. These tests can determine the nature of the person's problem and also can act as a baseline for measuring any changes/decline over time in a person's mental and cognitive ability. This information is therefore very useful for making a diagnosis.

The person might be given a brain scan to identify conditions, for example strokes, brain tumours and hydrocephalus.

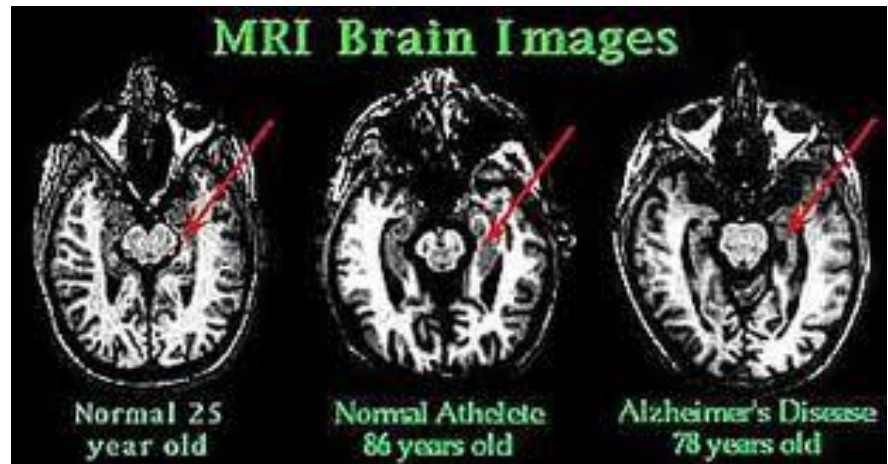
– Computerised

tomography scans use X-rays to take pictures of the brain using X-rays

– Magnetic resonance

imaging scans also use a computer to create an image of the brain using radio signals produced by the body due to the effects of a very strong magnet contained within the scanner. The person lies inside a large, cylinder-shaped magnet and radio waves are then sent through the body which forces the nuclei into a different position. When the nuclei move back into position they send out radio waves. The scanner picks up these waves and a computer produces a picture.

CT and MRI scans may show shrinkages of the brain (atrophy). However a scan that shows no unexpected changes in the brain does not rule out Alzheimer's disease especially because in the early stages of the disease the changes are difficult to recognise.



*Figure 7 shows an MRI scan with people with and without Alzheimer's disease.*

## Discussion

### Drug Treatment

Alzheimer's, being a neurological disease, requires drugs that are capable of accessing specific parts of the brain. Drugs normally travel through the blood stream and then diffuse through into the brain. However, there is one thing that often stops drugs getting to the brain, the Blood Brain Barrier (BBB).

The primary purpose of the BBB is to protect the brain from potentially harmful substances. It is a physiological barrier, which inhibits movement of certain substances into the brain.

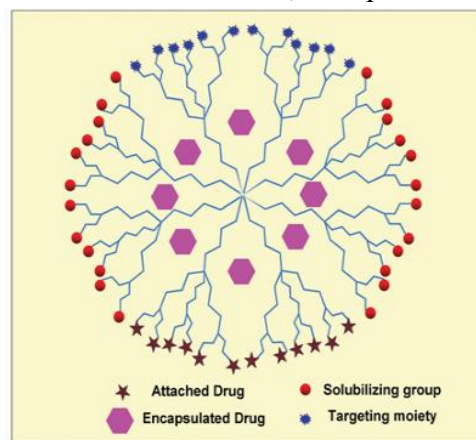
The BBB is a single layer of endothelial cells, which line the inside of blood capillaries in the brain. The BBB is semi permeable as a result only some substances can pass through. Normally an endothelium lines the inner surface of capillaries; however in the brain endothelial cells are packed together with high electrical resistance, they meet each other at 'tight junctions' so substances cannot diffuse out of the blood capillaries. Some substances can be actively transported out of the capillaries e.g. glucose. Large or lipid insoluble molecules cannot pass into the BBB easily; also molecules that have a particular charge cannot pass through. Lipid soluble molecules such as caffeine and nicotine can affect the brain as they are able to pass through the BBB.



*Figure 8 shows a capillary and the BBB*

As not all drugs can pass through the BBB, this is where nanotechnology can help in the medical advancement of drugs. As previously discussed, singular of the unique feature of nanotubes is that they have the ability to penetrate through nearly all membranes. Coupled with the ability to contain drugs within its structure this makes them an ideal solution for inserting drugs into the brain. If a drug could be synthesised with nanotubes not only would it be more efficient at applying the drug to it's desired location but also less evasive, compared to the present use of trepanning.

The other way in which nanotechnology could help get around the problem of the BBB is by using bucky balls. Bucky balls not only can have the drug stored on the inside of the ball but chemicals can be attached to the outside of the bucky ball. As caffeine is able to pass through the BBB, it may be possible to take full advantage of this characteristic of caffeine. A drug could be designed whereby the drug, intended for the brain, was put on the inside of the nanosphere and then on the outside caffeine was attached to the drug. The concept is similar to a Trojan horse.



### Diagnosis

An early diagnosis and effective treatment, like many other progressive diseases e.g cancer will result in a better prognosis. Due to the lack of a conclusive test to determine whether a patient has Alzheimer's, invariably it is difficult to diagnose with 100% certainty. Nanoparticles could be used to detect biological markers that indicate Alzheimer's even at very low concentrations, which could lead to more conclusive screening to determine whether a patient has Alzheimer's.

One of the chemicals present in the Cerebro Spinal Fluid (CSF) in Alzheimer's sufferers is Amyloid- $\beta$ -Derived Diffusible Ligands (ADDLs). If the presence of this chemical could be detected it would mean that Alzheimer's could be diagnosed earlier and thus treated better, even cured. Once again this is where nanotechnology provides us with the possibility to do these things.

Quantum dots are an incredibly clever and unique branch of nanotechnology and in this case have the properties to help diagnose Alzheimer's disease. Quantum dots emit different coloured light, all depending on its size. Furthermore they are capable of having chemicals attached to its surface. With this in mind it might be possible to synthesise quantum dots so that in the presence of ADDLs they emit light or change the colour of light they emit. If this could be made then a sample of CSF was taken from a patient then they could be tested for Alzheimer's disease.

*Figure 9 shows the concept of a Buckminsterfullerene drug*

A large build up of neuritic plaques are thought to be a significant part the cause of Alzheimer's disease. Plaques are insoluble products formed from the breakdown of  $\beta$ -amyloid. Neuritic plaques can be used as a target for a nanoparticle carrying a tracer, presence of  $\beta$ -amyloid could be used as a biomarker for Alzheimer's.

Radiotracers are radioactive isotopes, which can be easily identified with the use of gamma rays. A radiotracer bound to  $\beta$ -amyloid would be highlighted through PET scans. Radiotracers could be deployed through use of nanoparticles to transport them while bound to a lipophilic molecule such as caffeine. The most likely nanoparticle that would be used would be a buckminsterfullerene. All provided the radiotracer has a half-life longer than the time it would take to circulate to the BBB and to prepare a PET scan, it would be viable.



*Figure 10 shows the different colours produced by Quantum Dots*

## **Ethics and Complications**

The nature of nanotechnology requires research into funding to determine possible toxicity of particles in altering environments as hypothetically an idea may be sound yet a small change in the structure of a nanoparticle could result in a potential hazard. The reactivity of a molecule is invariably affected by its surface area, as nanoparticles are so tiny, collectively they have a very large surface area which may easily interact with unintended tissues. This would raise questions as to whether the drugs did more harm than good.

Being very small, airborne nanoparticles are able to enter the body through inhalation. Asbestos has a thin fibre-like structure which irritates cells in the lung, it is a known carcinogen. Carbon nano tubes share a similar shape if isolated, single tubes could pose a threat to health.

In the past, chemicals have been used to make weapons, an example of this is anthrax. Nanotechnology has the potential to be used in a military capacity; the employment of toxic nanoparticles could prove disastrous. This question is whether, if as well as further research being done medically; research may also be done on biological weapons. Nanotechnology can be very expensive and if a course of treatment was formulated, utilising nanoparticles, it may be expensive. If the drug treatment was significantly expensive then questions would be raised as to how much better this new drug is compared to the previous one and whether the drug was actually cost-effective.

## **Conclusion**

Nanotechnology provides tremendous potential for future medical treatment and diagnosis. The exclusive properties of nanotechnology give researchers the opportunity to experiment with new ideas to further our treatment of Alzheimer's Disease and Dementia.

Firstly the use of bucky balls to carry drugs seems to be very useful and may offer a more efficient drug delivery system. One concept that makes them more efficient than current drugs is the fact they can be used as a Trojan horse. On the exterior of a buckminsterfullerene, chemicals can be placed in order to disguise the drug as something else in order to get through cell membranes, such as the BBB. An example of this idea is using caffeine to conceal the drug and allow it to pass through the BBB.

The other way in which drugs might be carried to their designated locations is by using carbon nanotubes. Due to the fact the nanotubes are so narrow, they act somewhat like nanoscopic needles penetrating through membranes. Once again with BBB causing problems with drug delivery to the brain, drugs could be placed inside of the carbon nanotubes and then the nanotubes could penetrate through the BBB making it possible to apply the drugs in question.

Quantum dots, with their unique aptness to emit photon and give off natural light, are an ideal solution to helping diagnose Alzheimer's disease. If the quantum dots were to bind with either ADDLs or even neuritic plaques, it might help identify the early stages of Alzheimer's.

Finally it does not seem ill-conceived that nanoparticles, either bucky balls or nanotubes, could be used to detect neuritic plaques, a potential biomarker for Alzheimer's. If a radioactive compound was attached to the nanoparticles and then they located the plaques, a PET scan could be used to show up how many plaques were present. If a large number were present, then it might indicate the onset of Alzheimer's Disease and then Dementia.

## **References**

<http://alzheimers.org.uk/>

<http://biomed.brown.edu/>

<http://www.neurologychannel.com/>

<http://mirrorreflections.wordpress.com/>

<http://pubs.acs.org/doi/full/10.1021/ja044087q>

<http://www.pnas.org/content/102/7/2273.full>

[http://www.azonano.com/details.asp?ArticleID=1698#\\_Regenerative\\_Medicine](http://www.azonano.com/details.asp?ArticleID=1698#_Regenerative_Medicine)

[http://www.medscape.com/viewarticle/587001\\_5](http://www.medscape.com/viewarticle/587001_5)

[http://www.medscape.com/viewarticle/731630\\_2](http://www.medscape.com/viewarticle/731630_2)

<http://www.nanowerk.com/spotlight/spotid=5262.php>

<http://www.nanowerk.com/spotlight/spotid=6269.php>

<http://nanotechnologytoday.blogspot.com/2010/08/researchers-develop-drug-delivery.html>

<http://www.understandingnano.com/>

<http://www.nanocotechnologies.com/content/AboutUs/AboutQuantumDots.aspx>

<http://www.isracast.com/article.aspx?id=28>

[http://www.alzheimers.org.uk/site/scripts/documents\\_info.php?documentID=260](http://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=260)

[http://www.netdoctor.co.uk/health\\_advice/examinations/mriscan.htm](http://www.netdoctor.co.uk/health_advice/examinations/mriscan.htm)

<http://www.alzheimers.org.uk/site/scripts/documents.php?categoryID=200346>

[http://www.alzheimers.org.uk/site/scripts/documents\\_info.php?documentID=147](http://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=147)

<http://en.wikipedia.org/wiki/Acetylcholine>

<http://en.wikipedia.org/wiki/Alzheimer%27s#Pharmaceutical>

[http://www.alz.org/national/documents/statement\\_genericdrugs.pdf](http://www.alz.org/national/documents/statement_genericdrugs.pdf)

[http://exelon.co.nz/exelon\\_treatment/how.htm](http://exelon.co.nz/exelon_treatment/how.htm)

<http://www.medlink-uk.org/Site/documents/Alzheimers2010/McIntoshA&RossE.pdf>

[http://www.lundbeck.com/products/our\\_products/ebixa/default.asp](http://www.lundbeck.com/products/our_products/ebixa/default.asp)

<http://www.alzheimer.ca/english/treatment/treatments-ebixa.htm>