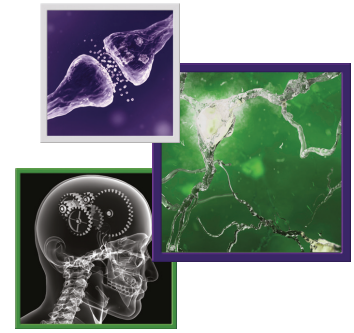
Plain Language Summary of Publication

Neurodegenerative Disease Management



A study of once-a-week donepezil transdermal system's bioequivalence to oral donepezil in healthy volunteers: a plain language summary

Rene Braeckman[1] and Charles Oh[2]

[1]Zevra Therapeutics, Inc., Celebration, FL, USA; [2]Corium, LLC, Boston, MA, USA

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Summary

What is this summary about?

This is a plain language summary of an article published in the *Journal of Alzheimer's Disease*. It describes an adhesive patch placed on the skin's surface, also referred to as a **transdermal** delivery system (or TDS), that delivers **donepezil** (called donepezil TDS going forward) through the skin of patients with mild, moderate, and severe dementia of the Alzheimer's type. This summary focuses on how fast and how much of the medication donepezil enters the body through the skin, and how it compares with taking a pill form of donepezil by mouth (oral donepezil). This summary also looks at how much donepezil is circulating through the body with the use of the once-a-week donepezil TDS versus the once-a-day donepezil pill. We show that the same amount of donepezil circulates through the body when donepezil TDS is used once a week as when a participant takes an oral donepezil pill once a day.

How to say (double click sound icon to play sound)...

- **Adlarity:** Ad-lar-eh-tee
- **Acetylcholine:** uh-see-tuhl-kho-leen
- **Acetylcholinesterase:** uh-see-tuhl-kho-luh-neh-str-ays
- **Alzheimer's:** aalz-hai-mrz
- **Bioequivalence:** bahy-oh-i-kwiv-uh-lunze
- **Dementia:** duh-men-shia
- **Donepezil:** don-neh-puh-zil
- **Pharmacokinetics:** faar-muh-ko-kuh-neh-tiks
- **Transdermal:** tranz-der-mul

Why is this study important?

Dementia is a term used to describe a person's decreasing ability to remember, think, or make decisions necessary to successfully complete daily activities. **Alzheimer's** disease is a disorder that progresses slowly, with the symptoms of dementia getting worse over many years. When viewed under a microscope, the visible features of Alzheimer's disease within the brain are protein deposits called plaques between brain cells and protein strands within brain cells that appear as tangles. One of the many features that cannot be seen with the naked eye in the Alzheimer's brain is the low level of a chemical called **acetylcholine** that allows certain nerve cells in the brain involved with memory to communicate with one another. Donepezil, a drug that is widely used to treat dementia associated with Alzheimer's disease, increases the amount of acetylcholine in the brain. Donepezil is usually in pill form and taken by mouth. However, one problem with taking oral donepezil is that it can cause stomach or intestinal side effects like diarrhea, nausea, and vomiting. These side effects may be bad enough that people stop taking their medication.

Future Medicine part of fsg

In 2022, for the first time, the United States Food and Drug Administration approved a donepezil TDS marketed under the name **Adlarity**. Donepezil TDS is for use in patients who have mild, moderate, and severe dementia caused by Alzheimer's disease. It is applied once a week to skin on the patient's back, upper buttocks, or thigh. Donepezil TDS allows the drug donepezil to be absorbed into the body directly through the skin, which means that the drug does not go through the digestive system. This means that many stomach and intestinal side effects (the undesirable effects of the drug) can potentially be reduced.

What were the results?

In healthy volunteers, we showed that donepezil TDS allows a similar amount of the drug into the body as the oral donepezil pill. This is done using a type of examination known as **pharmacokinetics** (how much, how fast, and how steadily donepezil is taken into the bloodstream). In healthy participants, donepezil TDS had overall fewer stomach and intestinal side effects (like constipation, diarrhea, nausea, and vomiting) than the oral donepezil pill, although more participants reported abdominal pain with donepezil TDS than with oral donepezil. Donepezil TDS also had fewer instances of nervous system side effects (like dizziness and sleepiness) than the oral donepezil pill. These findings support using donepezil TDS to treat patients with Alzheimer's disease.

Where can I find the original article on which this summary is based?

The original article is called "Comparison of Steady-State Pharmacokinetics of Donepezil Transdermal Delivery System With Oral Donepezil."

You can read the original article, published in the *Journal of Alzheimer's Disease*, for free at: https://content.iospress.com/articles/journal-of-alzheimers-disease/jad220530

Who is this article for?

The authors of the original article developed this summary to help patients, caregivers, patient advocates, health care professionals, policy makers, and insurance providers to understand the results of their study.

What is Alzheimer's disease?

Alzheimer's disease is a progressive and fatal disease, with symptoms of dementia that slowly worsen until the person ultimately dies from the disease. However, a person may live many years after diagnosis of Alzheimer's disease.

Alzheimer's disease is separated into 3 stages: **mild, moderate, and severe disease**

Mild disease

The person can do most things independently, like still being able to drive, but may notice some memory lapses, like repeatedly **losing common objects such as car keys**. Family and close friends begin to notice memory problems during conversation.

Moderate disease

The longest stage. The person will show even greater memory loss and seem **confused about where they are and what day it is**. The person becomes noticeably agitated, frustrated, and angry. At this stage, the person can manage daily activities with some help.

Severe disease

Memory and thinking skills continue to worsen, and it becomes **harder to communicate**. Swallowing becomes difficult, and the person **needs constant assistance with daily activities**. Family, friends, or caregivers may struggle because of the constant needs of their loved-one with Alzheimer's disease.

- People living at home with Alzheimer's disease need help taking their medications, and this **responsibility falls on their family, friends or caregivers**
- **In 2020, more than 11 million family members and other caregivers provided care to people with Alzheimer's disease or other dementias**

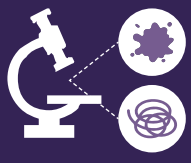
Who is at risk of getting Alzheimer's disease?

Most people who develop Alzheimer's disease are aged 65 years or older. The underlying reasons why some people get the disease and others do not is still being determined.

How many people have Alzheimer's disease?

In 2021, an estimated 6.2 million Americans aged 65 years and older were living with Alzheimer's disease, and the numbers will increase as more people in the "baby boom" generation live beyond 65 years.

Besides memory and behavior, what are the other features of Alzheimer's disease?



Alzheimer's disease can be detected in a sample of a patient's spinal fluid and by brain imaging. Evidence of Alzheimer's disease can also be seen under a microscope on a sample of brain tissue from a patient with Alzheimer's disease. Evidence includes protein plaques that look like "gooey" clumps, protein tangles that look like twisted strands of thread, and large gaps in the folds of the brain that occur because the brain cells have died.

Experimental treatments used at very early stages of Alzheimer's disease target the proteins causing the plaques and tangles.

One of the many features that cannot be seen microscopically in the Alzheimer's brain is the change in brain chemistry as levels of a chemical called acetylcholine become low; acetylcholine allows certain nerve cells in the brain involved with memory to communicate with one another, so when acetylcholine levels drop, nerve cell communication breaks down and memory is impaired.

What is donepezil?

Many treatments increase the levels of acetylcholine and, in doing so, reduce some symptoms of dementia. Donepezil is one such treatment.

How does donepezil work?

A protein called acetylcholinesterase breaks down acetylcholine. The idea is that by giving a patient with Alzheimer's disease a medication called an acetylcholinesterase inhibitor, the acetylcholinesterase protein is blocked, which stops the breakdown of acetylcholine. This allows levels of acetylcholine in the brain to increase so nerve cells can continue communicating with each other, helping with memory.

Donepezil is the most widely used acetylcholinesterase inhibitor. It was originally available as oral donepezil, which is in pill form and taken by mouth once a day.

Do people with Alzheimer's disease have any problems taking oral donepezil?

Oral donepezil at **higher doses can cause stomach or intestinal problems** like diarrhea, nausea, and vomiting. These side effects may become so bad that they can cause patients to stop taking their medication.

When oral donepezil is taken once a day, **the level of medication in the body goes up and down throughout the day.**

People with Alzheimer's disease often **forget to take their medicine** and must **rely on a caregiver constantly** to remember to give the medication. If they miss the once-a-day dose of their medicine, patients do not get the full benefit of the treatment.

What is donepezil transdermal delivery system, and how is it different?

In 2022, the United States Food and Drug Administration approved, for the first time, a donepezil patch applied to the skin, called donepezil TDS, and marketed under the name Adlarity.

- **Donepezil TDS** is approved for use in patients with **mild, moderate, and severe** dementia of the Alzheimer's type.
- **Donepezil TDS** is applied **once a week to skin on the patient's back, upper buttocks, or thigh**. Donepezil TDS lets the drug donepezil be absorbed into the body directly through the skin.
- The idea is that the drug does not pass through the digestive system, so the **stomach and intestinal side effects overall associated with the oral donepezil pill can be reduced**.
- Because donepezil TDS is a patch applied once a week to a patient's skin, the **level of medication remains more constant** in the patient's body.
- **Donepezil TDS** is **used once a week** compared with the donepezil pill, which must be taken by mouth once a day.

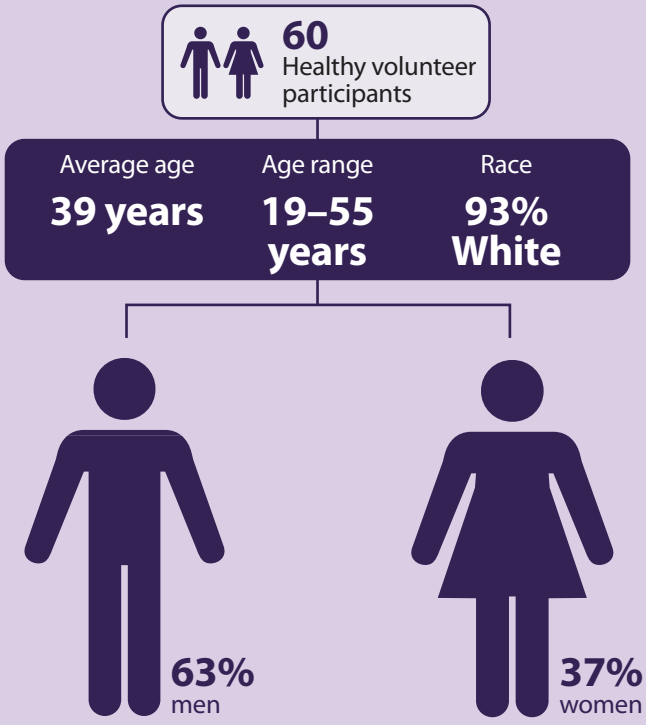
Why was this study done?

The study's aim was to compare **how much, how fast, and how steadily donepezil is absorbed into the bloodstream** of healthy volunteer participants when they were given the donepezil TDS or the oral donepezil pill.

We analyzed **how well donepezil TDS stayed on the skin** (skin adhesion) for 1 week and the **safety of using donepezil TDS**, including looking at gastrointestinal side effects.

For the United States Food and Drug Administration to approve the use of donepezil TDS for patients, it was important to show that **the same amount of donepezil was circulating through the body with use of the once-a-week donepezil TDS** as it is when a patient takes 1 pill of oral donepezil once a day.

Who took part in this study?



How was it carried out?

Open-label study
The participants were aware they received donepezil TDS or the oral donepezil pill.

3 Periods
The study was separated into 3 periods, 1 for each treatment.

Randomly assigned
The sequence in which the 10-mg oral donepezil pill and the 10-mg donepezil TDS was given was chosen randomly for each participant.

3 Treatments
Participants received each of the 3 treatments in turn, with 2 treatment options for periods 2 and 3.

Period 1

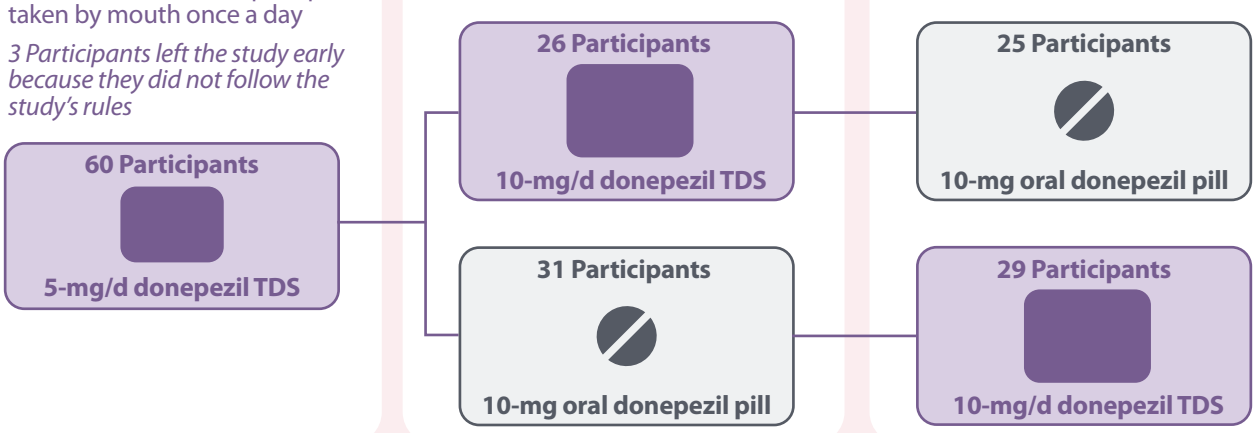
- **60 Participants** entered the study and started with the **donepezil TDS at a dose of 5 milligrams per day (abbreviated here as "mg/d") applied to skin once a week for 5 weeks**. After 5 weeks, they were randomly assigned to receive 10 mg either as a donepezil TDS applied to skin once a week or a donepezil pill taken by mouth once a day
- *3 Participants left the study early because they did not follow the study's rules*

Period 2

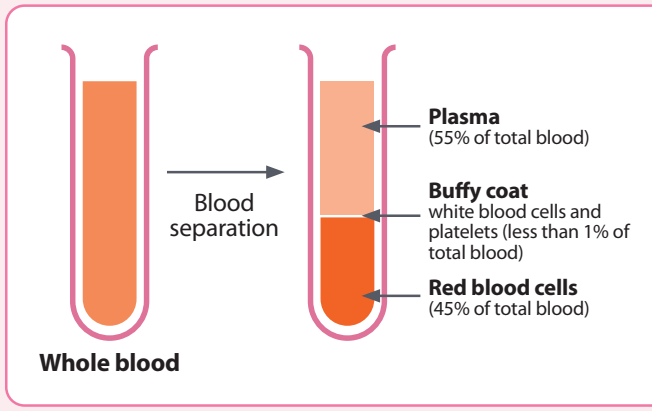
- **26 Participants** were given **10-mg/d donepezil TDS once a week for 5 weeks**
- **31 Participants** were given the **10-mg oral donepezil pill once a day for 5 weeks**
- *3 More participants left the study (2 for not following the study's rules and 1 for not wanting to be in the study)*

Period 3

- Of those given the 10-mg/d donepezil TDS in period 2, **25** were given the **10-mg oral donepezil pill once a day for 5 weeks**
- Of the participants given the 10-mg oral donepezil pill in period 2, **29** were given the **10-mg/d donepezil TDS once a week**



- Blood samples were taken before the participants received any treatment and then taken during the 3 treatment periods throughout the study
- Plasma, which is the liquid portion of blood without the blood cells, was used to examine the level of donepezil in the participants' bodies
- How much of the donepezil TDS remained attached to the skin was examined throughout the study; it was important to understand during the 1-week use period if all of the donepezil TDS stayed attached to the skin, or if part of the donepezil TDS detached from the skin, or if all of the donepezil TDS detached from the skin
- The skin was examined for any problems that might be caused by the donepezil TDSs
- Any problems with the participants' health, such as digestive problems and other adverse effects caused by the treatments, were clearly recorded for each participant during the entire study



What was examined in the plasma?

The plasma from the participants was examined in a laboratory to see how much and how fast donepezil entered a person's bloodstream. This type of examination is called **pharmacokinetics**.

Pharmacokinetics

Pharmacokinetics is the study of a drug's journey through a person's body, including examining the amount of drug in a person's plasma during a set timeframe (in this case, 0 to 168 hours). The total amount of drug, the peak level of the drug, and the time it takes to reach the peak level in person's plasma are important to understand the drug's safety and effectiveness.

Steady-state

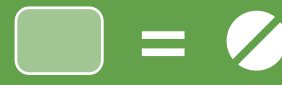
Pharmacokinetic measurements are done at a **steady-state**, which is when the amount of drug being absorbed into a person's body is the same amount that is being removed by the body when the drug is given continuously or repeatedly.

Dose normalization

To make an "apples-to-apples" comparison of the 5-mg/d donepezil TDS with 10-mg/d donepezil TDS, the pharmacokinetic results were dose normalized. **Dose normalization** is a math calculation that is used for pharmacokinetic measurements to compare 2 different doses of the same drug. In this case, the normalization factor was 2 because of the 2-fold (double) difference in the doses.

Bioequivalent

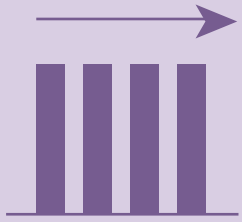
For the United States Food and Drug Administration to approve the use of donepezil TDS for patients, it was important to show that the same amount of donepezil was circulating through the body with use of the once-a-week donepezil TDS as it is when a patient takes 1 pill of oral donepezil once a day. This is called **bioequivalence** or **bioequivalent**.



Donepezil TDS **Oral donepezil**

What did the results show?

1 The donepezil TDS keeps a constant level of donepezil in the blood.



At steady-state, the levels of donepezil in plasma were relatively constant for the donepezil TDS used once a week.

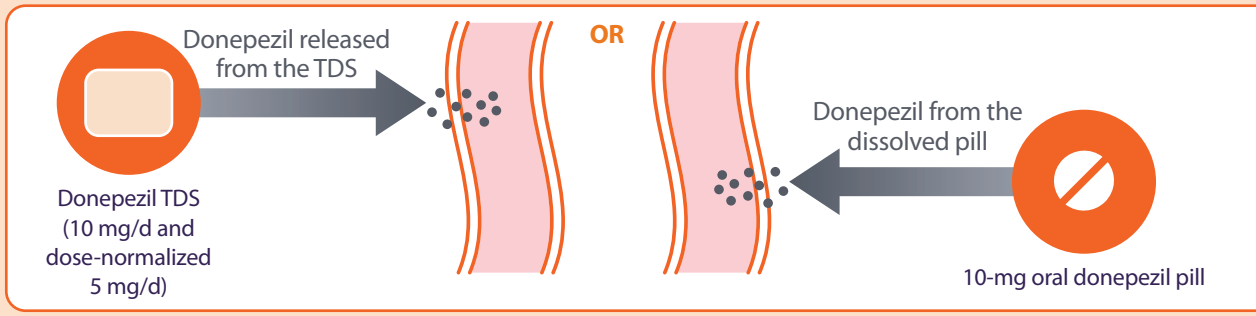
Whereas

The level of donepezil went up and down when participants were given an oral donepezil pill once a day.

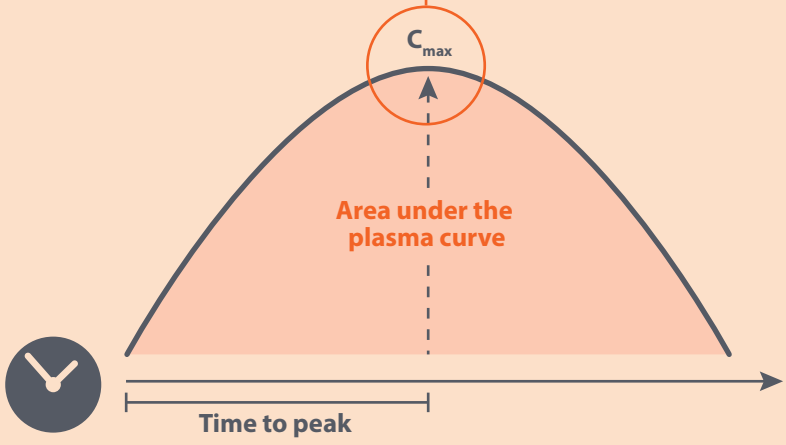
2 The donepezil TDS keeps a constant level of donepezil in the blood.

Donepezil TDS (10 mg/d and dose-normalized 5 mg/d) applied to skin once a week were found to be bioequivalent to the oral donepezil pill (10 mg) taken by mouth once a day for 5 weeks. In other words, the same amount of donepezil was found to be circulating through the body with use of the donepezil TDS once a week as when a participant took oral donepezil once a day.

We use specific pharmacokinetic measurements to show bioequivalence. When the same type of drug is given to people in different ways (for example, using a patch or swallowing a pill), having the same pharmacokinetic measurements shows that the drugs are bioequivalent, and we expect the drugs to have the same effectiveness.



Studying the peak concentration of a drug – also known as C_{max} – is important because levels that are too high could cause side effects. In this study, **C_{max} was similar between the 10-mg/d and dose-normalized 5-mg/d donepezil TDSs and the 10-mg oral donepezil pill**.

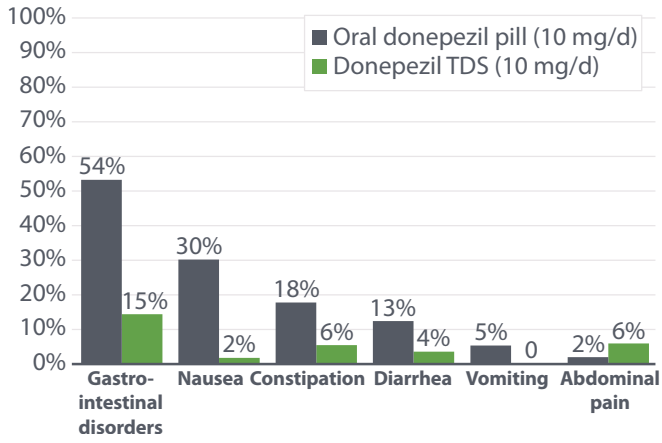


The amount of drug in the bloodstream is described by a measurement called the area under the plasma concentration–time curve, or AUC. We use the AUC and the peak level of a drug to describe how the drug becomes distributed through the body. These measurements show how well the drug works and whether the drug is likely to have side effects.

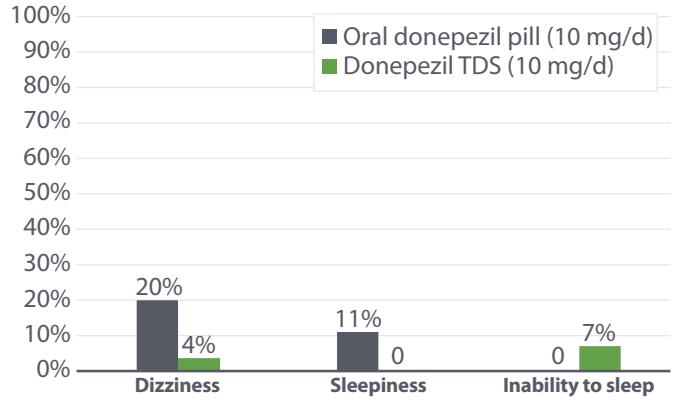
The amount of drug in the bloodstream, or the AUC, for donepezil over the time that people were treated was similar when comparing donepezil TDSs (dose-normalized 5 mg/d and 10 mg/d) with oral donepezil pill (10 mg/d).

3 In healthy participants, donepezil TDS had fewer overall gastrointestinal and central nervous system side effects than the oral donepezil pill that often cause people to stop taking donepezil.

Compared with the oral donepezil pill, fewer participants using the donepezil TDS had **nausea**, **constipation**, **diarrhea**, and **vomiting**.



Participants using donepezil TDS also had fewer central nervous system side effects, such as **dizziness** and **sleepiness.**

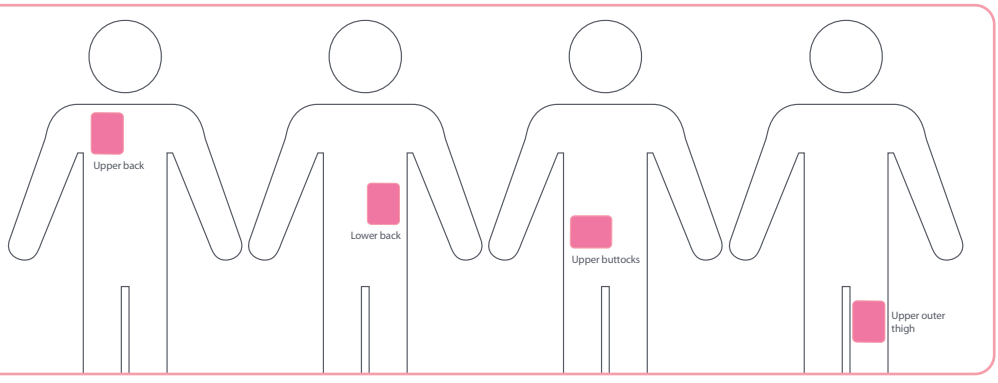


However, **6%** of participants using the donepezil TDS had **abdominal pain** compared with only 2% using the oral donepezil pill.

However, **7%** of participants using donepezil TDSs (either 5 or 10 mg/d) had **insomnia (**an inability to fall asleep**)**. This did not occur with use of the oral donepezil pill.

- When people use donepezil as a TDS, the drug is not swallowed and, therefore, does not travel through the gastrointestinal system, which helps avoid gastrointestinal side effects. In addition, the donepezil TDS allows more even and constant dosing, which means that people are less likely to experience central nervous system side effects
- Of participants who wore the 10-mg/d donepezil TDS, 9% experienced itchiness at the application site, and 6% had mild skin inflammation (swelling)

4 The donepezil TDS remained stuck to the skin during the 1-week use period.



When measuring how well the donepezil TDS stuck to the skin, on average, more than 90% of the donepezil TDS surface area remained attached to the skin. Both doses of donepezil TDSs stuck to the skin during the 1-week period of wear during the course of 5 weeks. Only about 1% of donepezil TDS completely detached from the skin. Participants were not allowed to tape over the donepezil TDS, nor reinforce or press on areas that were detaching.

Some potential weaknesses of this analysis are that:

- The study was done in healthy volunteers, not in people with Alzheimer's disease, and in a controlled setting in which the people involved followed study directions. Additional studies will need to be done in a real-world setting, such as in an assisted living facility on residents with Alzheimer's disease
- Although the participants did not know ahead of time which treatment they were getting, they knew what they got once they received it

What do the results of this study mean?

- These results in healthy volunteers show that once-a-week donepezil TDS is equivalent to the once-a-day oral donepezil pill in getting the drug donepezil into the body
- Overall fewer side effects of the digestive and/or central nervous systems developed with donepezil TDS compared with those for the oral donepezil pill
- Minimal itchiness and swelling occurred at the site of the TDS application
- During use, the donepezil TDS remained stuck to the participants' skin

Where can readers find more information on this study and Alzheimer's disease?

Original publication citation
Tariot PN, Braeckman R, Oh C. Comparison of steady-state pharmacokinetics of donepezil transdermal delivery system with oral donepezil. *J Alzheimers Dis.* 2022;90(1):161-172. doi:10.3233/JAD-220530 (https://content.iospress.com/articles/journal-of-alzheimers-disease/jad220530).
The clinical trial number is NCT04617782 and additional information on the clinical trial can be found at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT04617782).

Educational resources
For more information on Alzheimer's disease, visit these websites: Alzheimer's Association (https://www.alz.org) and National Institutes of Health – National Institute on Aging (https://www.nia.nih.gov/health/alzheimers).
For more information on donepezil TDS (trade name ADLARITY®), visit: https://www.adlarity.com.

Acknowledgments
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Ethical conduct of research
The study was approved by an independent ethics committee and conducted in accordance with relevant clinical guidelines. All study participants provided written informed consent.

Financial & competing interests disclosure
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