*Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.*

# Valacyclovir

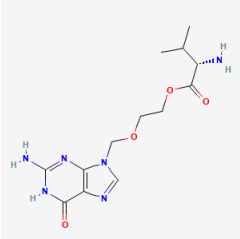
**Evidence Summary**

Observational studies suggest treating viral infections with valacyclovir may be associated with lower incidence of dementia. Clinical trial data is needed.

**Neuroprotective Benefit:** Some epidemiological studies report associations between herpesvirus infection and dementia risk, particularly in APOE4 carriers. Studies also report that valacyclovir treatment may be associated with lower dementia risk.

**Aging and related health concerns:** Chronic viral infection, particularly CMV, might accelerate aging and mortality risk but direct evidence for anti-viral benefits is not available.

**Safety:** Common side effects include headache and gastrointestinal complaints. Rare but serious adverse events include nephro- or neurotoxicity, especially in individuals with renal disease, and aberrant blood clotting, especially in immunocompromised people.

| | | |
|---|---|---|
| **Availability**: Rx | **Dose**: The medication dose varies by indication; generally, dosing is 1 to 3 grams. An ongoing trial is testing up to 4 grams daily in AD patients. Valacyclovir can be administered orally or via IV infusion. | **Chemical formula:** $C_{13}H_{20}N_6O_4$ **MW**: 324.34 g/mol  Source: PubChem |
| **Half-life**: 2.5 to 3.3 hours. | **BBB**: Penetrant. | |
| **Clinical trials**: Clinical development included over 10,000 patients in total. | **Observational studies**: Largest observational study included over 215,000 patients who received acyclovir / valacyclovir. | |

**What is it?**

Valacyclovir, also called valaciclovir, and acyclovir (aciclovir) are guanosine nucleoside analog anti-viral drugs used to manage the various types of herpesviruses, including herpes simplex virus 1 and 2 (HSV1 and 2), varicella zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV). Valacyclovir is often used for treatment of cold sores, genital herpes, including in immunocompromised populations, reduction of viral transmission, shingles, and chickenpox (Drugbank.ca). As the report on the shingles vaccine discusses literature on varicella zoster virus and its association with dementia, this report will focus on other herpesviruses such as HSV-1 and/or the specific effects of valacyclovir so as not to be redundant.

Valacyclovir is a prodrug that is more orally bioavailable than acyclovir. Valacyclovir gets broken down into acyclovir by the liver before further chemical modifications that occur only in virally infected cells. This specificity is possible because one step in the metabolism of the drug is carried out only by a virally expressed enzyme (NIDDKD). The final active compound potently inhibits viral DNA replication.

Herpes simplex virus 1 is a common and contagious virus that is best known for causing cold sores in humans. In between outbreaks, the virus can hide from the immune system inside neurons. During an outbreak, the latent virus reactivates and is transported down the neuronal axon to the skin, where new cold sores form. More than half of infected people who have the virus in their nervous system show no

peripheral signs of the disease like cold sores (reviewed in Itzhaki 2014). HSV-1 DNA is commonly found in the brains of elderly people although less so in younger people. Some researchers hypothesize that HSV-1 periodically reactivates in the brain, for example during stress or inflammation or immune suppression, causing focal but cumulative damage. This periodic reactivation is assumed to be quite mild, or it would lead to herpes simplex encephalitis, a rare but often fatal outcome.

Cytomegalovirus is another virus in the herpesvirus family. In people with healthy immune systems, CMV infections often go unnoticed but, particularly in the elderly, the latent infection is hypothesized to sometimes become chronic, leading to accelerated aging and inflammation. Varicella zoster virus, which causes chickenpox and shingles, and HSV-2, which causes genital herpes, also are latent in neurons after the initial infection and can reactivate periodically. Some researchers speculate that chronic latent infections by these viruses can directly contribute to the development of Alzheimer's disease as well as inflammaging and immunosenescence (Harris & Harris, 2018; Noronha et al., 2021; Zhu et al., 2023). This is due in part to epidemiological studies that have reported associations between infection with a herpesvirus like HSV-1 or VZV and incidence of dementia.

**Neuroprotective Benefit:** Some epidemiological studies report associations between herpesvirus infection and dementia risk, particularly in APOE4 carriers. Studies also report that valacyclovir treatment may be associated with lower dementia risk.

*Types of evidence:*

- 3 systematic reviews and meta-analyses
- 1 systematic review
- 1 randomized controlled trial
- 1 open label study
- 12 observational studies
- 3 reviews
- 4 commentary articles
- 1 study protocol for an ongoing randomized controlled trial
- 2 laboratory studies

It is hypothesized that infections such as HSV-1 and HSV-2 may be linked to dementia (Itzhaki et al., 2016). Many studies have been carried out to investigate this hypothesis. There is controversy in the field as to whether any observed relationship between herpesviruses and dementia is due to infection

with a herpesvirus, reactivation of the herpesvirus, a correlational rather than a causational relationship, or another explanation entirely.

There are several complicating factors to consider when evaluating the research. First, a high percentage of the world's population is thought to have been infected with different herpesviruses; for instance, approximately 90% of the world is thought to be infected with HSV-1, HSV-2, or both (Wald & Corey, 2007). This makes it difficult to compare infected to truly uninfected individuals in epidemiological studies. How researchers define infection with HSV is another important point. Cold sores, the common physical manifestation of HSV-1, can be so minor as to not be reported, diagnosed, or treated, and so may not be accurately reflected in the medical records that epidemiological studies often rely on. Whether or not cold sores reflect neuronal reactivation of the virus is also not known, or whether neuronal reactivation is necessary to increase the risk of dementia. These factors do not rule out HSV or other herpesviruses as a potential contributing factor to dementia; they simply make it more challenging to compare results from different groups or tease apart causes from incidental bystanders in the pathological landscape of dementia (Itzhaki et al., 2021).

The laboratory tests used to assess HSV infection is another potentially confounding factor in assessing the relationship between infection and dementia. The presence of anti-HSV IgG antibodies, for instance, is thought to reflect latent infection, whereas presence of anti-HSV IgM antibodies is thought to reflect a primary infection or recent reactivation. It is possible that the prevalence of seropositivity or titer level of one class of antibodies is associated with incidence of dementia and not the other, as perhaps reactivation of the virus or severity of the infection are more associated with disease risk than presence of latent infection. It is also important to note here that it is unclear whether these tests reflect viral action in the central nervous system or not – and whether that is relevant for dementia association studies (Itzhaki et al., 2021).

***Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function***:

Many studies have evaluated the association of dementia incidence with infection with a herpesvirus and subsequent treatment with antivirals like valacyclovir. Many of these studies cannot individually assess the antiviral treatment, but valacyclovir is typically the most commonly prescribed antiviral treatment for herpesviruses.

Lindman et al., 2021 describe a matched cohort study using national registries in Sweden to assess the interaction between herpesvirus infection and/or antiviral treatment and dementia diagnosis. The authors followed 265,172 individuals with an HSV or VZV diagnosis or had received antiviral medications. Some of these patients had HSV and/or VZV and did not receive antiviral treatment; some had HSV and/or VZV and did receive antiviral treatment; and some received antiviral drugs, irrespective of diagnosis. Each of these three groups was age and sex matched to the same number of control subjects in the population who had neither an HSV / VZV diagnosis, nor antiviral treatment. Valacyclovir was the most common antiviral treatment, used in 52.8% of the patients; a vast majority of the remaining patients received acyclovir (42.6%).

The below table indicates the incidence rates of dementia and the calculated HRs, based on diagnosis and treatment, compared to their respective control group with neither HSV/VZ diagnosis nor antiviral drug prescription. It is important to note that as each group was 1:1 age and sex matched, each control group is different.

| Group | Incidence Rate of Dementia | HR |
|---|---|---|
| Herpes diagnosis, no antiviral treatment vs. their controls | 12.9 and 10.2 per 1000 person-years, respectively | 1.50; 95% CI 1.29 to 1.74 |
| Herpes diagnosis, antiviral treatment vs. their controls | 8.5 and 9.4 per 1000 person years, respectively | 0.90; 95% CI 0.82 to 0.98 |
| Antiviral treatment, irrespective of diagnosis, vs. their controls | 6.6 and 7.4 per 1000 person years, respectively | 0.89; 95% CI 0.86 to 0.92 |

When the authors compared the incidence of dementia in patients with herpes diagnosis based on whether they had antiviral treatment or not, they found that antiviral treatment was associated with a decreased incidence of dementia (HR=0.75; 95% CI 0.68 to 0.83). Overall, the authors found an 11% lower risk of dementia diagnosis in those who received antiviral therapy compared to controls, and a 50% higher risk of dementia incidence for those with a herpes diagnosis who did not receive treatment compared to controls. It is important to note that the authors did not match by underlying medical condition at baseline. The authors provided prevalence information on several health conditions but did not run statistical analyses. It appears that the group with herpesvirus infection but no antiviral treatment had numerically higher incidence of conditions like stroke and anti-diabetic medication prescription, and the group with herpesvirus infection and antiviral treatment had numerically higher

incidence of heart attack, for example. How these health conditions intersect with the results is not clear.

Young-Xu et al., 2021 utilized data from the VA healthcare system records to compare the incidence of dementia in 87,687 symptomatic HSV+ veterans and 217,865 matched controls with no reported HSV symptoms. The authors found an overall adjusted HR of 0.80 (95% CI 0.78 to 0.83) for dementia diagnosis of symptomatic HSV individuals compared to their matched control individuals with no reported sign of infection. This HR appears to be driven by patients who received antiviral treatment. The 25,911 individuals who did not take antiviral medications had an adjusted HR of 0.94 (95% CI 0.88 to 0.99) compared to their matched controls. The 61,776 individuals who did receive treatment for HSV had an adjusted HR of 0.75 (95% CI 0.72 to 0.78) compared to their matched controls. The authors did not compare the individual antiviral prescriptions, but valacyclovir and acyclovir were the two most common medications prescribed. The authors did not directly statistically compare the dementia incidence for symptomatic HSV+ patients who received antiviral therapy to those who did not.

Tzeng et al., 2018 used national healthcare records from Taiwan to compare the dementia incidence in 8,362 individuals 50 years and older with new HSV-1 or HSV-2 infections or reactivations of infections who had at least three outpatient visits for HSV infections in a one-year study period to 25,086 age- and sex-matched controls. When they compared dementia incidence in patients with new HSV infections compared to controls, they found an adjusted hazard ratio of 2.564 (95% CI 2.351 to 2.795, $p<0.001$). When they looked at antiviral usage and dementia diagnosis, they found an overall adjusted hazard ratio of 0.092 (95% CI 0.079 to 0.108, $P < 0.001$) in patients who took antiherpetic medications as opposed to those who did not. A vast majority of patients took antiherpetic medications (7,215 of 8,362 patients). Longer-term use of anti-herpetic medications (30 days or more) was associated with reduced HRs. For valacyclovir, the overall adjusted HR was 0.153 (95% CI 0.096 to 0.317); the HR for 1 to 29 days of use was 0.618 (95% CI 0.154 to 0.997) and the HR for 30 days or more was 0.099 (95% CI 0.045 to 0.268). The HSV positive individuals included in this study may have more severe HSV disease, given that they had multiple office visits for the condition, and this might account for how significant the HR is compared to other studies.

Hemmingsson et al., 2021 discusses a nested case-control study in a subset of participants in a larger prospective population-based cohort study in Sweden. The authors identified 262 HSV-1 seropositive individuals who ultimately developed AD during study follow up period, and age, sex, and APOE-status matched them to 262 HSV-1 seropositive individuals who did not develop AD during follow-up. The

average follow-up period ranged from 9 to 14 years. The authors examined the medical records of the patients for presence of antiviral prescriptions and found that such prescriptions were more common in the healthy controls than in the participants who developed AD (2.3% vs. 7.6%, p=0.006) and found a lower incidence of AD diagnosis among those who received an antiviral prescription (OR=0.287; 95% 0.102 to 0.809, p=0.18).

Bae et al., 2020 found a protective association of antiviral treatment for shingles and dementia diagnosis in their study of 34,505 patients with shingles infection in a national healthcare records database from South Korea. Antiviral treated patients with shingles had a covariate-adjusted HR of 0.79 (95% CI 0.69 to 0.90) compared to untreated patients with shingles. Valacyclovir and acyclovir were two of the three included antiviral medications that were inclusion criteria for the study. Chen et al., 2017 also found a lower incidence of dementia in patients with shingles who were treated with antivirals compared to those who were not (adjusted HR=0.55; 95% CI 0.40 to 0.77), using national healthcare records from Taiwan.

Not all studies found strong links between antiherpetic treatment and incidence of dementia. Schnier et al., 2021 report on a multicenter observational cohort study that used health data from a total of 2.5 million individuals from Denmark, Germany, Scotland, and Wales to assess the association between antiherpetic medication and incidental dementia. A vast majority of the antiherpetic prescriptions were for valacyclovir and/or acyclovir. The authors report heterogeneous results. Exposure to one or more doses of antiherpetic medication was significantly associated with a lower dementia incidence in the Denmark sample. They calculated the HR for one, two, and three+ treatments: HR=0.91; 95% CI 0.89 to 0.93, p<0.001; HR=0.93; 95% CI 0.88 to 0.98, p=0.008; HR=0.89; 95% CI 0.83 to 0.95, p<0.001, respectively. In the Wales sample, one dose of antiherpetic medication was also associated with lower incidence of dementia (adjusted HR=0.91; 95% CI 0.86 to 0.97). The authors did not observe any significant associations in the samples from the two other countries, and as a whole were skeptical of their findings, stating that "short term antiherpetic medication is not markedly associated with reduced subsequent dementia incidence". Linard et al., 2022, similarly found significant associations of at least one dose of antiherpetic medications and lower incidence of AD (aHR=0.85; 95% CI 0.75 to 0.96, p=0.009) in a study of 68,291 people 65 years and older in a French medical records database, 6,642 of whom received oral antiherpetic medications. The authors also stated that their results should be viewed with caution given that most participants did not receive regular treatment, and they suggested it was implausible that a single dose of antiherpetic medication could have a biologically significant effect.

Multiple epidemiological studies have also reported an association between infection with a herpesvirus and dementia, though there are conflicting results. This may stem in part from the different ways studies define infection, particularly with HSV-1 and/or HSV-2. A systematic review and meta-analysis of 57 studies of herpesvirus infection and dementia from Warren-Gash et al., 2019 generally found that IgG seropositivity for herpesviruses was not associated with dementia incidence. They found some hints that recent infection and/or reactivation of herpesviruses as measured by anti-HSV IgM antibodies, titer levels of IgG, or symptomatic disease might be associated with higher incidence of dementia, but the results were not consistent. Elhalag et al., 2023 describes a systematic review and meta-analysis of 19 studies comprising 342,535 patients in studies of the relationship between HSV and MCI and AD. The authors reported that increased anti-HSV IgG titer was associated with MCI and AD but did not find a statistically significant association between anti-HSV IgM titer and MCI or AD. Wu et al., 2020 also found that HSV-1 infection was a potential risk factor for AD (pooled OR=1.40; 95% CI 1.13 to 1.75) but they did not separately analyze different HSV diagnosis techniques. This meta-analysis included 21 studies and a total of 3,566 patients.

Some of the discrepancy between results of the relationship between HSV infection and dementia is likely driven by the definition of HSV infection used. Other confounding factors include whether the study looked at antiviral prescriptions. For instance, Murphy et al., 2021 describes a study of HSV IgG seropositivity and cognitive function and dementia in 1,915 individuals in the Rotterdam Study; the authors found no association between anti-HSV IgG seropositivity and incidence of dementia. However, the authors did not have data on whether participants took antiviral medication, which could theoretically influence the results as in Young-Xu et al., 2021.

More research – specifically, randomized controlled trials – is needed to fully address the question of whether valacyclovir can affect incidence of dementia.

***Human research to suggest benefits to patients with dementia***:

An open-label pilot study was conducted in Sweden to assess the safety and possible efficacy of valacyclovir treatment in HSV positive, APOE4 carriers with early-stage AD. The study enrolled 33 patients who had at least one APOE4 allele, an early-stage AD diagnosis, and serum or plasma IgG antibodies against HSV. Participants took 500 mg of valacyclovir three times daily, orally, for the first week; for the remaining three weeks of dosing, they took 1000 mg three times daily. All participants

completed the study; one participant required a dose reduction. The primary outcome measures were feasibility, tolerability, safety, and change in CSF total tau as well as neurofilament light chain (NfL), thought to be a marker of neurodegeneration. Secondary outcomes included change in cognitive function as assessed by MMSE, anti-HSV IgG levels, and CSF levels of a variety of other AD biomarkers such as Aβ42, p-tau, GFAP, and other markers of inflammation.

The authors did not find a significant change in either CSF tau or CSF NfL over the course of the study. They did report a significant improvement in MMSE score from baseline to end of treatment (mean change=0.88 ±1.96 points, p=0.23). The authors recognize that without a placebo group that these results are difficult to interpret; the improvement could, for instance, be a training effect, though whether that effect would be significant in cognitively impaired individuals 4 weeks apart is not clear (Weidung et al., 2022).

***Mechanisms of action for neuroprotection identified from laboratory and clinical research***:

Many studies have found associations between infection with herpesviruses such as HSV1 and incidence of dementia, and/or association between treatment with antiherpetic drugs such as valacyclovir and incidence of dementia. There are several hypotheses for how these viral infections could increase risk of AD; the mechanism of action of valacyclovir would be by mitigating viral replication and concomitant consequences of viral infection.

HSV1 DNA has been detected in 90% of the plaques of Alzheimer's patients (Wozniak et al., 2009). It is present in the brains of Alzheimer's patients at a slightly higher frequency than age-matched controls (in one study, estimated at 74% in AD and 73% of elderly controls; Jamieson et al., 1991). While this difference in infection rate does not appear immediately compelling, investigators argue that infection is sometimes asymptomatic. In other words, it is the highly variable response of the individual to the virus and the probability of a given strain to reactivate that leads to damage in some people but not others. While this explanation is credible, there is little strong evidence to back it.

The association between viral reactivation and Alzheimer's disease risk might reflect direct damage to the brain by the virus. However, it might also be an artifact of residual confounding. Viral reactivation is known to be triggered by stress, inflammation, and immune suppression, all of which might also reflect an overall poor state of health.

In laboratory cells, HSV1 and HSV2 infection has been reported to cause beta-amyloid aggregation and tau phosphorylation (Kristen et al., 2015). Treating cells with antiviral medications such as acyclovir reduced HSV1 particles as well as Aβ and p-tau accumulation (Wozniak et al., 2011). HSV1 may also inhibit autophagy, disrupt apoptosis regulation, trigger the release of proinflammatory cytokines, and increase oxidative stress (reviewed in Harris & Harris, 2018).

***APOE4 interactions***:

There is substantive epidemiological evidence that suggests that APOE4 and HSV-1 infection may interact. The APOE gene is thought to be involved in viral infection. APOE4 is thought to increase susceptibility to HSV-1 infection (Chen et al., 2023), and APOE4 carriers reportedly have a higher risk of recurrent reactivation of HSV-1 cold sores and HSV-2 genital herpes (Jayasuriya et al., 2008). Individuals who are both HSV-1 positive and APOE4 carriers appear to have higher incidence of dementia compared to HSV-1 negative or non-carriers (Corder et al., 1998, Lindman et al., 2019, Linard et al., 2020). APOE4 carriers with HSV-1 infections have also been reported to have increased cognitive decline compared to non-carriers (Lövheim et al., 2019). Preclinical work indicates that APOE4 may increase the HSV-1 viral load in the brain (Harris & Harris, 2018).

While the effects of valacyclovir and APOE4 have been tested but not fully delineated (see "Human research to suggest benefits to patients with dementia" section), it is possible that antiviral treatment may have greater effects in this higher-risk population. Ongoing trials are also exploring the interaction of valacyclovir and APOE4 (see "Research Underway" section).

**Aging and related health concerns:** Chronic viral infection, particularly CMV, might accelerate aging and mortality risk. Direct evidence for anti-viral benefits is not available.

*Types of evidence:*

- 2 observational studies
- 2 reviews
- 4 laboratory studies

No direct evidence is available to suggest that anti-viral drugs like valacyclovir can promote longevity or slow the rate of aging per se. Long-term (12-month) treatment with valacyclovir reduced the prevalence of immunesenescence in mice with an established CMV infection. For example, it protected against a 60% reduction in the proportion of naïve CD8 T cells and improved immune function in the elderly mice (Beswick et al., 2013).

As a therapeutic target, chronic viral infections like CMV or HSV-1 have been linked to an increased risk of immunesenescence as well as inflammaging and even premature mortality (reviewed in Deleidi et al., 2015). For example, all-cause mortality was 43% higher over nine years in (Roberts et al., 2010) and biomarkers of suppressed immune function associates with a higher risk of death in elderly people (Ferrando-Martinez et al., 2015). However, some data is inconsistent. CMV-infected individuals were not more likely to have weak grip strength which might indicate frailty or mortality risk (Goldeck et al., 2016) and CMV infection was not associated with a risk of inflammaging in a 10 year prospective study (Bartlett et al., 2012). It has been speculated that CMV and HSV infections become chronic rather than latent in elderly individuals, leading to chronic inflammation and damage.

**Safety:** Common side effects include headache and gastrointestinal complaints. Rare but serious adverse events include nephro- or neurotoxicity, especially in individuals with renal disease, and aberrant blood clotting, especially in immunocompromised people.

*Types of evidence:*

- 1 systematic review
- 1 case report
- 3 book chapters or professional resource pages
- 3 reviews

Valacyclovir is rapidly converted to acyclovir, which has been tested in trials up to 10 years long. Common adverse events attributable to acyclovir and valacyclovir include malaise, nausea, headache, and diarrhea. When taken intravenously, there can be infusion reactions.

While valacyclovir is typically well-tolerated, less common but serious adverse events can occur. Nephrotoxicity is a known and serious concern, specifically in individuals who are not well hydrated or have underlying kidney issues, as valacyclovir is excreted by the kidneys. There have been reports of

thrombotic microangiopathy, though these have been most often reported in individuals on very high doses of valacyclovir and/or or are immunosuppressed, such as transplant patients (Tyring et al., 2002). There has been one case report of thrombotic thrombocytopenic purpura in an immunocompetent individual (Bukhari et al., 2020).

Central nervous system events, or neurotoxicity, characterized by symptoms such as confusion, psychiatric symptoms, dizziness, drowsiness, or coma, have also been reported, though it is rare. A study that included 119 individuals who had neurotoxicity secondary to acyclovir and/or valacyclovir administration indicated that a vast majority of the patients (83.2%) had documental renal impairment before drug administration. Some of these patients had end-stage renal disease. Other contributing factors included too-high dosage for the individual patient's renal status and increasing age. Of the 119 patients with neurotoxicity, 73.9% of them received acyclovir and 29.4% received valacyclovir; some patients received both drugs (Brandariz-Nuñez et al., 2021). Neurotoxicity may also be more common with intravenous administration of the medication. Maintaining fluid intake may help prevent against neurotoxicity (Asahi et al., 2009).

One open-label pilot trial assessed the effects of valacyclovir treatment in patients with early-stage AD. All participants had at least one APOE4 allele and were serum or plasma positive for anti-HSV IgG antibodies. The participants took 500 mg of valacyclovir orally three times daily for the first week; for the remaining three weeks of the trial, they took 1000 mg three times daily. All the 33 enrolled patients completed the study; 1 required a dosage decrease due to an adverse event (headache). Overall, there were 14 adverse events in 11 participants, and 2 serious adverse events in 1 participant. Of these, 10 adverse events and no serious adverse events were judged to be related to the valacyclovir treatment. Fatigue and headache, reported by 2 participants each, were the most common treatment related adverse events; others included thirst, nausea, gastrointestinal complaints, mild depressive symptoms, and polyurea, each reported by one participant (Weidung et al., 2022).

***Drug interactions***:

Valacyclovir is known to interact with 66 drugs; 23 are major, 37 are moderate, and 6 are minor interactions. Many of the interactions are either other similar-action antivirals, which should not be combined, or medications or imaging contrast agents that can be nephrotoxic (Drugs.com). Drug classes

that interact with valacyclovir include chemotherapy, injected antibiotics, medicine for blood pressure, injectable osteoporosis medication, and certain pain or arthritis medications (Drugs.com).

Almost all of valacyclovir is converted to two metabolites, acyclovir and L-valine, in the intestines and/or liver. Acyclovir is primarily excreted through the renal system and can interact poorly with existing renal conditions. Cases of acute renal failure and corresponding neurological side effects have been reported in patients taking other nephrotoxic medications, and in patients with pre-existing renal disease who received too-high doses of valacyclovir. Proper dosage is essential, and if a patient who is on dialysis needs valacyclovir, they should receive this medication after a dialysis session. Acute renal failure has also been reported in individuals taking valacyclovir who became dehydrated, as acyclovir may precipitate in renal tubules when the concentration of acyclovir gets too high (Drugs.com).

Valacyclovir may also reduce the activity of certain varicella virus vaccines; your doctor can help you identify the best timing for your specific vaccination, antiviral treatment, and specific indication (Drugs.com, CDC).

**Research underway:**

There are a total of 26 ongoing studies that reference valacyclovir in the clinicaltrials.gov database. Three of them involve dementia or Alzheimer's disease.

NCT03282916 is an ongoing study that has enrolled 120 participants with probable AD who also have serum antibodies for HSV1 or HSV2. Participants will be randomized to either the treatment group, receiving eight 500 mg caplets of valacyclovir daily for a total dose of 4 g, or the same number of 500 mg sugar pills daily. The double-blinded study will last for 78 weeks. The primary outcome is change in cognitive function as measured by ADAS-COG11 from baseline to week 78. Secondary outcomes include measures of daily functioning and change in amyloid and tau PET from baseline to week 78. Exploratory analyses include brain changes as measured by MRI, antiviral antibody titers, CNS penetration of valacyclovir in this population, and CSF biomarkers for AD such as Aβ42, tau, and p-tau. APOE status information will also be collected, and APOE as a moderating factor will be tested as an exploratory outcome. An in-depth protocol for this study has been published (Devanand et al., 2020).

NCT04710030 is a currently recruiting study that is seeking to enroll 50 participants with mild cognitive impairment who also test positive for HSV1 or HSV2 antibodies. Like the above study, this is a double-blinded trial where patients will be randomized to either eight 500 mg caplets of valacyclovir daily for a total dose of 4 g, or the same number of 500 mg sugar pills daily. The trial will last for 52 weeks. The primary outcome measures are change in amyloid load as measured by amyloid PET and change in cognitive and daily functioning from baseline to end of study. Exploratory outcomes include MRI, viral antibodies, and plasma tau and p-tau, as well as whether APOE4 status interacts with the findings.

NCT05894954 is investigating whether a precision medicine approach can mitigate the decline of cognitive function in patients with mild cognitive impairment or early dementia. The 9-month long study aims to enroll 72 patients who will be randomized to either standard of care or to the personalized medicine approach. The personalized medicine approach will involve a battery of testing to create a personalized treatment plan including diet, sleep habits, stress management, and mental and physical exercise. One of the many potential treatments in the intervention group is valacyclovir treatment, if applicable. The study is scheduled to start recruitment in the near future.

**Search terms:**

Pubmed, Google: alacyclovir, acyclovir, HSV

- Dementia, AD, APOE4, mortality, longevity, cardiovascular, diabetes

Websites visited for valacyclovir

- Clinicaltrials.gov
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca

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