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.

Baricitinib

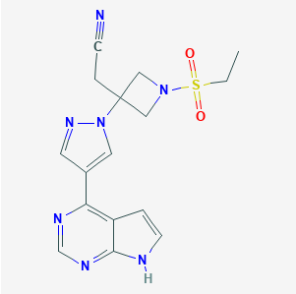
Evidence Summary

Baricitinib is approved for the treatment of rheumatoid arthritis, but benefits for neurodegenerative diseases and other age-related diseases are unknown. It is associated with some serious adverse events.

Neuroprotective Benefit: A machine learning study identified baricitinib as one of the kinase inhibitors potentially promising for repurposing in Alzheimer's disease. No studies have tested the neuroprotective potential of baricitinib except for one study in mice.

Aging and related health concerns: Baricitinib is effective in reducing pain, stiffness, and swelling in people with rheumatoid arthritis who have not achieved improvement in first-line therapies. Efficacies for other conditions are under investigation.

Safety: Baricitinib increases risks of serious infections and venous thromboembolism and the 4 mg dose is associated with more serious adverse events than the 2 mg dose. Baricitinib also interacts with many medications and vaccines.

Availability: Rx	**Dose**: In people with rheumatoid arthritis, baricitinib is taken 2 mg once daily, orally, as monotherapy or in combination with methotrexate or nonbiologic disease-modifying antirheumatic drug(s).	**Chemical formula:** $C_{16}H_{17}N_7O_2S$ **MW**: 371.4  Source: PubChem
Half life: 12.5 hours	**BBB**: penetrant	
Clinical trials: Numerous meta-analyses have included many randomized controlled trials, with some studies including thousands of rheumatoid arthritis patients.	**Observational studies**: None available.	

What is it? Baricitinib (marketed as Olumiant by Eli Lilly and Company) is a selective and reversible Janus kinase 1 and 2 (JAK1 and JAK2) inhibitor. JAKs belong to the tyrosine protein kinase family and transduce cytokine-mediated proinflammatory signals via the JAK-STAT pathway. This pathway is overactivated in autoimmune disorders such as rheumatoid arthritis. Baricitinib is approved for the treatment of adult patients with moderate to severe active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor antagonist therapies (Drugs.com). Baricitinib is also being studied for use in treating COVID-19. The FDA has authorized emergency use of Baricitinib in combination with remdesivir to treat people hospitalized with COVID-19 (Drugs.com).

Neuroprotective Benefit: A machine learning study identified baricitinib as one of the kinase inhibitors potentially promising for repurposing in Alzheimer's disease. No studies have tested the neuroprotective potential of baricitinib except for one study in mice.

Types of evidence:

- No clinical trials or meta-analyses testing baricitinib
- 1 clinical study examining gene expressions in AD, FTD, and HD
- 1 machine learning drug repurposing study identifying drugs for Alzheimer's disease
- 1 laboratory study testing baricitinib
- Several laboratory studies examining the roles of JAK-STAT in neurodegeneration

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:
None available.

Human research to suggest benefits to patients with dementia:
No clinical trials have tested whether baricitinib provides benefit to patients with dementia.

A machine learning framework called Drug Repurposing in AD (DRIAD) identified the top 15 FDA-approved drugs and top 15 preclinical drugs among 80 kinase inhibitors as potentially promising candidates for repurposing in Alzheimer's disease, of which baricitinib was included (Rodriguez et al., 2021). The DRIAD approach used machine learning to quantify the association between the stage of Alzheimer's disease (early, mid, and late, defined by Braak staging) and biological processes or responses characterized by mRNA expression profiles of postmortem brain specimens obtained from the Accelerating Medicines Partnership - Alzheimer's Disease (AMP-AD). Eighty FDA-approved and clinically tested drugs were administered to differentiated human neural cell cultures and RNAseq was used to measure gene expression responses in these cells. This approach identified differentially expressed genes to generate drug-associated gene lists. High-scoring drugs in DRIAD had some features in common, including inhibition of one or more members of the JAK family, comprised of JAK1, JAK2, JAK3, and TYK2 and modulate pathways related to interferon signaling, autophagy, and microtubule formation and function. While these kinase inhibitors are known to have off targets or multiple targets, compounds having higher binding affinity for members of the JAK family appeared earlier in the DRIAD ranking, and this correlation was statistically significant. This suggests that the downstream transcriptional changes induced by JAK inhibitors inversely correlate with Braak stage severity.

The advantage of this DRIAD approach was the unbiased assessment of biological processes or drug candidates in a disease where the etiology is not clearly defined. In this study, the authors focused on kinase inhibitors because of their strong transcriptional signatures. The drugs that rose to the top had target proteins in signaling networks regulating innate immunity, autophagy, and microtubule dynamics. This approach can be extended to other classes of drugs with other mechanisms of actions such as G-protein coupled receptor inhibitors. While this approach may identify candidate drugs for repurposing, validation in relevant model systems followed by clinical trials is necessary.

Gene expression profiling of choroid plexus tissue from Alzheimer's, frontotemporal dementia, Huntington's disease patients, and healthy controls reported that Alzheimer's patients have significant enrichment of genes related to metabolic and immune-related pathways including cytokine and

interferon signaling, cell adhesion, and JAK-STAT and mTOR signaling pathways (Stopa et al., 2018). The choroid plexus is a complex tissue that not only produces and regulates the cerebrospinal fluid, but it also provides a permeability-regulating blood-CSF barrier. The authors of this study argue that the blood-CSF barrier undergoes harmful but also adaptive changes in neurodegenerative diseases. The JAK-STAT and mTOR pathways are enhanced in these conditions, which in turn help the choroid plexus in adaptive transcription and epithelial repair, respectively. In Alzheimer's disease and Huntington disease (but not frontotemporal dementia), several neuroimmune-modulating interferons were significantly upregulated (e.g., in Alzheimer's disease: IFI-TM1, IFN-AR1, IFN-AR2, and IFN-GR2).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Only one study in mice has studied the effects of baricitinib on neuroprotection.

In a mouse model of HIV-associated neurocognitive disorders (intracranial injection of HIV-1 infect human monocyte-derived macrophages), baricitinib treatment (10 and 50 mg/kg, once daily) for 6 days reversed behavioral abnormalities as measured by the object recognition task (Gavegnano et al., 2019). Baricitinib was also detected in brain samples, demonstrating blood-brain barrier penetrance in this mouse model. Baricitinib treatment significantly reduced the HIV-induced neuroinflammation marked by glial activation (measured by MHCII+/CD45+ activated microglia and GFAP+ astrogliosis). This study suggests that in this HIV-associated neurocognitive disorder model, blocking the JAK/STAT pathway reverses cognitive deficits and curtails inflammatory markers.

Other studies in rodents provide indirect evidence for the potential neuroprotective effects of baricitinib. In rats exposed to Aβ-42, treatment with the RAGE inhibitor, azeliragon (5, 20, 50 mg/day), for 5 days reversed the overexpression of NLRP1 inflammasome, neuronal damage, and cognitive dysfunction (Yang et al., 2021). The azeliragon-mediated alleviation of Alzheimer's pathology was regulated through the JAK/STAT signal pathway; the neuroprotective benefit of azeliragon was eliminated when inhibitors for JAK (tofacitinib) and STAT (fludarabine) were co-administered.

In mouse models of Alzheimer's disease (APP/PS1 mice, 3xTg-AD mice), the JAK/STAT3 pathway was activated in reactive astrocytes (Haim et al., 2015). A lentiviral vector that specifically targets astrocytes *in vivo* to overexpress the endogenous inhibitor of the JAK/STAT3 pathway (suppressor of cytokine signaling 3; SOCS3), prevented astrocyte reactivity, and decreased microglial activation in these mouse models.

In microglia isolated from the brain of an Alzheimer's model mice (APP/PS1 mice), administration of a JAK2 inhibitor (TG101209) attenuated IFN-γ-induced changes such as increased expressions of TNF-α, IL-1β, IL-6, and iNOS (Jones et al., 2015).

In contrast to the above findings, there are studies associating inactivation of JAK2/STAT3 axis in aging and in Alzheimer's disease (Chiba et al., 2009). In Alzheimer's patients and in a mouse model of Alzheimer's, phospho-STAT3 levels are decreased in hippocampal neurons (Chiba et al., 2009). In a model of Alzheimer's (Tg2576 mice), intracerebroventricular administration of Aβ-42 downregulated phospho-STAT3 levels. Pharmacological inhibition of the JAK2/STAT3 pathway also induced spatial working memory impairment along with downregulation of the acetylcholine synthesizing enzyme (choline acetyltransferase). Thus, inhibition of the JAK2/STAT3 pathway does not always confer neuroprotection and the effects may be context-dependent.

APOE4 interactions: Unknown.

Aging and related health concerns: Baricitinib is effective in reducing pain, stiffness, and swelling in people with rheumatoid arthritis who have not achieved improvement in first-line therapies. Efficacies for other conditions are under investigation.

Types of evidence:

- 11 meta-analyses or systematic reviews, mostly in rheumatoid arthritis
- Numerous clinical trials
- Several laboratory studies

Rheumatoid arthritis: BENEFIT

Cytokines are critical drivers of inflammation in rheumatoid arthritis. The recommended first-line therapies are synthetic disease-modifying anti-rheumatic drugs (DMARDs)(e.g., methotrexate). However, for those who do not achieve sustained remission or improvement after 6 months, these medications can be changed or used in combination with a biologic DMARD, or a targeted synthetic DMARD such as JAK inhibitors. JAKs are a family of intracellular tyrosine kinases that function as mediators of proinflammatory signaling. Numerous meta-analyses have examined the comparative efficacies of various treatments for rheumatoid arthritis including JAK inhibitors.

In a Bayesian network meta-analysis of 9 randomized controlled trials including a total of 3,577 rheumatoid arthritis patients, JAK inhibitors and non-TNF biologics achieved a significant American College of Rheumatology 20% (ACR20) response relative to placebo (Sung et al., 2021). For ACR20, JAK inhibitor treatment was most likely to achieve the highest response rate, followed by non-TNF biologics and placebo. The ACR50 rate displayed similar patterns as the ACR20 response rate, but for ACR 70 response rate, non-TNF biologics had a higher value than JAK inhibitors.

In a network meta-analysis of 21 randomized controlled trials in rheumatoid arthritis patients, efficacy outcomes for JAK inhibitors (baricitinib, peficitinib, and tofacitinib) were compared (Tanaka et al., 2021). At 12 weeks of treatment, efficacy outcomes including disease activity (as measured by SDAI) and reduction in progression of joint damage (as measured radiographically) were comparable across baricitinib (2 and 4 mg, daily), peficitinib (150 mg, daily), and tofacitinib (5 mg, twice daily). A different Bayesian network meta-analysis of 5 randomized controlled trials comprising 1,547 patients reported that tofacitinib, baricitinib, upadacitinib, filgotinib, and peficitinib as monotherapy showed a significantly higher efficacy (ACR20) compared with placebo (Lee and Song, 2020). The ranking probability indicated that peficitinib 150 mg had the highest probability of being the best treatment for achieving the ACR20 response rate, followed by peficitinib 100 mg, filgotinib 200 mg, filgotinib 100 mg, tofacitinib 5 mg, upadacitinib 15 mg, baricitinib 4 mg, and placebo.

Systemic lupus erythematosus: DECREASES CYTOKINE LEVELS
In a phase 2 double-blind randomized controlled trial of 274 patients with systemic lupus erythematosus (SLE), baricitinib treatment (2 or 4 mg, daily) for 24 weeks reduced mRNA expression of STAT1-target, STAT2-target and STAT4-target genes and multiple IFN responsive genes (Dorner et al., 2020). At baseline, gene expression profiling demonstrated that in SLE patients, STAT1, STAT2, serum cytokines IFN-α, IFN-γ, interleukin (IL)-12p40 and IL-6 were elevated above healthy controls. Baricitinib treatment (at the 4 mg dose) significantly decreased serum IL-12p40 and IL-6 cytokine levels at week 12. Baricitinib treatment significantly reduced RNA expression of a network of genes associated with the JAK/STAT pathway, cytokine signaling, and SLE pathogenesis.

Safety: Baricitinib increases risks of serious infections and venous thromboembolism and the 4 mg dose is associated with more serious adverse events than the 2 mg dose. Baricitinib also interacts with many medications and vaccines.

Types of evidence:

- 11 meta-analyses or systematic reviews
- 1 comparative clinical study
- Prescribing information for Olumiant (baricitinib)

U.S. Boxed Warning: The use of baricitinib increases risk for developing serious infections that may lead to hospitalization or death (Drugs.com). Most patients who developed these infections were taking concomitant immunosuppressants (e.g., methotrexate or corticosteroids). Reported infections include active tuberculosis, invasive fungal infections, bacterial, viral, and other infections due to opportunistic pathogens. Lymphoma and other malignancies have been observed in people treated with Baricitinib. Additionally, baricitinib use increases the incidence of serious, sometimes fatal thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis.

Meta-analyses and clinical trials: In a meta-analysis of 20 double-blind randomized controlled trials including 8,982 rheumatoid arthritis patients, the overall incidence of adverse events was higher in groups receiving any JAK inhibitor compared to placebo (RR=1.09; 95% CI, 1.05 to 1.13; p<0.001)(Wang et al., 2020). Adverse events with baricitinib at the 2 mg daily dose were similar to placebo but adverse events for the 4 mg daily dose was significantly elevated compared to placebo (RR=1.13; 95% CI, 1.02 to 1.24; p=0.02). However, there was no difference in the frequency of serious adverse events compared with placebo. The risk for infection was increased with baricitinib at the 4 mg daily dose (RR=1.28; 95% CI, 1.12 to 1.45; p<0.001), but not at the 2 mg daily dose (RR=1.06; 95% CI, 0.72 to 1.57). Across all treatment groups (baricitinib, tofacitinib, upadacitinib), the overall incidence of serious infections (excluding herpes zoster infection) was not statistically different from placebo (RR=1.42; 95% CI, 0.93 to 2.17, p=0.10). A statistically higher risk for herpes zoster infection was observed only with baricitinib at the 4 mg daily dose (RR=3.81; p=0.01) compared with placebo and not with baricitinib at the 2 mg daily dose (RR=2.32; p=0.44) or other JAK inhibitors (tofacitinib or upadacitinib). Although JAK inhibitors and the different doses used showed no significant increase in risk for upper respiratory tract infection, the overall estimated RR was significantly higher than for placebo (RR=1.32; 95% CI, 1.07 to 1.63; p=0.01). Because there were only 7 trials reporting on malignancy, the overall incidence of serious malignancy was not statistically different from placebo (RR=1.68; 95% CI, 0.57 to 4.95; p=0.34); however, the risk

was numerically higher, and a greater number of studies and longer-term follow-up may be needed to properly examine this association.

A systematic review and indirect meta-analysis including 59 studies (involving 14,335 patients treated with tofacitinib or baricitinib, and 11,612 patients treated with another active drug or placebo) reported that the odds ratio for venous thromboembolism risk for baricitinib 2 mg dose was 3.05 (95% CI, 0.12 to 75.43) and for baricitinib 4 mg dose was 3.64 (95% CI, 0.59 to 22.46)(Poderos et al., 2020). For tofacitinib, the odds ratio was 0.29 (95% CI, 0.10 to 0.84).

In a meta-analysis of 26 randomized controlled trials testing JAK inhibitors in a total of 11,799 rheumatoid arthritis patients, risk for cardiovascular events was not statistically elevated with baricitinib treatment (RR=1.21; 95% CI, 0.51 to 2.83; p=0.66)(Xie et al., 2019). However, risks of all cardiovascular events, major adverse cardiovascular events, and venous thromboembolism events were found to be significantly lower for baricitinib at 2 mg daily dose compared to the 4 mg daily dose (OR=0.19; 95% CI, 0.04 to 0.88; p=0.03). JAK inhibitors when grouped together did not show significantly elevated risks for major adverse cardiovascular events (OR=0.80; 95% CI, 0.36 to 1.75; p=0.57) or venous thromboembolism events (OR=1.16; 95% CI, 0.48 to 2.81; p=0.74).

In a meta-analysis of 6 randomized controlled trials including 3,552 patients with rheumatoid arthritis, the effects of baricitinib treatment (1, 2, and 4 mg/day; duration of 6-52 weeks) on LDL and HDL cholesterol were evaluated (Qiu et al., 2019). Results showed that baricitinib significantly increased LDL-c levels (net mean increase by 13.15 mg/dl; 95% CI, 8.89 to 17.42). HDL-c also increased with baricitinib with the net mean increase of 5.40 mg/dl (95% CI, 3.07 to 7.74). Subgroup and meta-regression analysis demonstrated that these effects of baricitinib occurred in a dose-response manner. In this meta-analysis, risks for cardiovascular events and major cardiovascular events were not statistically different across different drugs. For major cardiovascular event risk, baricitinib versus placebo showed a relative risk (RR) of 1.08 (95% CI, 0.10 to 11.42), baricitinib versus methotrexate showed an RR of 3.03 (95% CI, 0.28 to 33.19), and baricitinib versus adalimumab showed an RR of 0.74 (95% CI, 0.07 to 8.10). There were also no significant differences of cardiovascular risk scores (as measured by the Framingham risk score and the Reynolds risk score) between baricitinib treatment and placebo.

In a meta-analysis of 4 randomized controlled trials comparing two baricitinib doses (2 mg versus 4 mg, daily), no significant differences at 12 weeks were observed for the 4 mg dose compared to the 2 mg dose of baricitinib for serious adverse events (RR=1.33; 95% CI, 0.63to 2.78; p=0.46), any adverse events after the start of therapy (RR=1.09; 95% CI, 0.98 to 1.21; p=0.13), discontinuation of drugs due to

adverse events (RR=1.19; 95% CI, 0.61 to 2.34; p=0.60), malignancies (RR=3.03; 95% CI, 0.12 to 73.90; p=0.50), and major adverse cardiac events (RR=2.95; 95% CI, 0.12 to 71.91; p=0.51)(Huang et al., 2018). However, at 24 weeks, serious adverse events (RR=1.84; 95% CI, 1.02-3.30; p=0.04) were significantly higher with baricitinib at the 4 mg dose compared with the 2 mg dosage. Total adverse events after the start of therapy (RR=1.07; 95% CI, 0.98 to 1.17; p=0.11), discontinuation of drug due to adverse events (RR=1.33; 95% CI, 0.73 to 2.42; p=0.35), malignancies (RR=3.98; 95% CI, 0.45 to 35.48; p=0.22), major adverse cardiac events (RR=4.92; 95% CI, 0.24 to 101.66; p=0.30), infections (RR=1.08; 95% CI, 0.78 to 1.51; p=0.63), herpes zoster infections (RR=1.23; 95% CI, 0.50 to 3.02; p=0.65), and serious infections (RR=1.65; 95% CI, 0.61 to 4.50; p=0.32) were not significantly different between 4 mg and 2 mg doses of baricitinib.

Other meta-analyses have shown that adverse events for JAK inhibitors were comparable to other drug classes or placebo. In a meta-analysis of 21 randomized controlled trials in rheumatoid arthritis patients, safety outcomes for JAK inhibitors (baricitinib, peficitinib, and tofacitinib) were compared and no significant differences between the drugs and the different doses were observed at 12 weeks (Tanaka et al., 2021). There was not enough data to evaluate the risks of adverse events and severe adverse events at 24 weeks.

In a Bayesian network meta-analysis of 9 randomized controlled trials including a total of 3,577 rheumatoid arthritis patients, JAK inhibitors and non-TNF biologics were compared (Sung et al., 2021). At 12 weeks, there were no statistically significant differences in adverse events or serious adverse events across drug classes, including comparison with placebo. With regards to adverse events and associated withdrawals, placebo was likely to be the safest intervention, followed by JAK inhibitors and non-TNF biologics. JAK inhibitors were associated with fewer adverse events and associated withdrawals than non-TNF biologics, but this difference was not statistically significant. But for serious adverse events, placebo was likely to be the safest therapy, followed by non-TNF biologics and JAK inhibitors, though again, the differences between the latter two classes were not statistically significant. Because this study only assessed safety at 12 weeks, it does not rule out differences in significant safety issues such as death, major adverse cardiac events, Herpes zoster, opportunistic infection, pneumonia, and deep vein thrombosis.

However, it is worth noting that there may be differences in the safety profiles between different JAK inhibitors as baricitinib is a JAK1/JAK2 inhibitor, tofacitinib is a JAK1/JAK3 inhibitor, and filgotinib and upadacitinib are selective JAK1 inhibitors—and JAK isoform selectivity may affect adverse events such as

risk of herpes zoster infection (Olivera et al., 2020). Thus, studies that group all JAK inhibitors as a comparator may not be able to detect differences in adverse events that are specific to a select drug.

In a real-life multicenter prospective study of 446 patients with rheumatoid arthritis, 58 patients (13%) discontinued baricitinib due to adverse events, including thrombotic events and herpes zoster reactivation (Guidelli et al., 2020).

Drug interactions: Baricitinib has 240 major drug interactions and 107 moderate drug interactions. These drugs include biologic disease-modifying antirheumatic drugs (DMARDs), chloramphenicol (ophthalmic), cladribine, clozapine, deferiprone, denosumab, dipyrone, echinacea, fingolimod, immunosuppressants, leflunomide, natalizumab, nitisinone, nivolumab, pidotimod, pimecrolimus, roflumilast, BCG, live vaccines, and inactivated vaccines (see full list of drugs at Drugs.com).

Sources and dosing: Baricitinib is a prescription medication used to reduce pain, stiffness, and swelling in people with rheumatoid arthritis. It is marketed as Olumiant (Eli Lilly and Company). In people with rheumatoid arthritis, baricitinib is taken 2 mg once daily as monotherapy or in combination with methotrexate or nonbiologic disease-modifying antirheumatic drug(s).

Research underway: There are currently 44 ongoing clinical studies testing baricitinib (ClinicalTrials.gov). These trials are testing baricitinib in conditions such as arthritis (11), dermatitis (7), systemic lupus erythematosus (3), graft-versus-host disease (2), alopecia (2), type 1 diabetes (1), arteritis (1), uveitis (1), and COVID-19 (8).

Search terms:
Pubmed, Google: baricitinib, Janus kinase

- + cognitive, + Alzheimer, + dementia, +ApoE, + memory, + meta-analysis

Websites visited for baricitinib:

- Clinicaltrials.gov
- DrugAge (0)
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.