

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.

Rifampicin

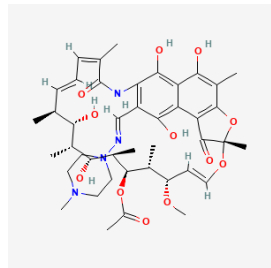
Evidence Summary

Rifampicin is an important tuberculosis drug and is effective against several types of drug-susceptible bacterial infections. Clinical trials have not found a benefit of rifampicin for neurodegenerative diseases.

Neuroprotective Benefit: Preclinical work suggests that rifampicin is anti-inflammatory and inhibits aggregation, but clinical trials report no benefit or even harm. Some animal work has tested intranasal rifampicin to try to improve efficacy and safety.

Aging and related health concerns: Rifampicin has not been explored for use in aging or health related conditions.

Safety: GI events and orange-colored bodily fluids are often reported for rifampicin. Rifampicin interacts with many drugs, and concomitant medication should be carefully assessed. Hepatotoxicity and hypersensitivity reactions are potential serious events.

Availability: Rx	Dose: Doses should not exceed 600 mg per day for infectious disease. Trials in neurodegenerative disease have tested doses of 300 mg per day. Rifampicin is available orally or by intravenous injection.	Chemical formula: $C_{43}H_{58}N_4O_{12}$ MW: 822.9 g/mol  Source: PubChem
Half-life: Approximately 1 to 5 hours, depending on dosing, frequency of dosing, and liver function.	BBB: At least partly penetrant.	
Clinical trials: The largest identified meta-analysis of use of rifampicin for a CNS indication included 4,640 patients with tuberculous meningitis.	Observational studies: The largest meta-analysis of observational studies identified included over 1.3 million patients with tuberculosis.	

What is it?

Rifampicin, also called rifampin, is an ansamycin antibiotic that is derived from a class of compounds known as rifamycins. Rifampicin has activity against a range of bacterial species via binding to DNA-dependent RNA polymerase and physically inhibiting RNA elongation ([Hardie & Fenn, 2022](#)). It is approved for use against both latent and active tuberculosis as well as for asymptomatic carriers of *N. meningitidis*; it is not approved for use for active meningococcal infection ([FDA](#)). Rifampicin is used off-label for other infections such as leprosy and severe gram-positive infections such as anthrax, osteomyelitis, and endocarditis, and as a prophylactic for carriers of *H. influenzae* who may transmit infection to young children and infants. Antimicrobial-impregnated catheters are sometimes used for cerebrospinal shunts and drains as well as central lines, and rifampicin is one agent used for this purpose ([Patel & Rosani, 2023](#)).

Rifampicin is a critical piece of the standard treatment for drug-susceptible tuberculosis; the treatment involves a 6-month course of rifampicin and isoniazid with the addition of pyrazinamide and ethambutol in the first two-month intensive phase. This treatment is considered effective, with a cure rate of 85% or



more in some settings. However, the treatment is not always well-tolerated, and the length of treatment introduces challenges for adherence ([Marais et al., 2027](#)). A significant challenge in treating tuberculosis is the rise of rifampicin-resistant tuberculosis, and resistance can develop quickly if rifampicin is administered alone ([Hardie & Fenn, 2022](#)). Proper use of rifampicin involves appropriate protocols to minimize antibiotic resistance, such as administration with other antimicrobials and/or testing for drug susceptibility ([Patel & Rosani, 2023](#)).

As rifampicin is an antibiotic, research into use of the drug primarily focuses on bacterial infections. Rifampicin is also thought to have more broad anti-inflammatory activity (reviewed briefly in [Haferland et al., 2022](#)). Given this, and theories that bacterial infections are involved in the pathogenesis of neurodegenerative diseases like Alzheimer's disease, there has been some research into the potential effects of rifampicin in neurological disorders ([Vaezipour et al., 2025](#)).

As a note on nomenclature: rifampin and rifampicin are two names for the same drug. Rifampin is more commonly used in the United States, whereas rifampicin is more commonly used in Europe and Australia. This report will use rifampicin for consistency.

Neuroprotective Benefit: Preclinical work suggests that rifampicin is anti-inflammatory and inhibits aggregation, but clinical trials report no benefit or even harm. Some animal work has tested intranasal rifampicin to try to improve efficacy and safety.

Types of evidence:

- 3 meta-analyses or systematic reviews
- 6 randomized controlled clinical trials
- 5 open label studies
- 3 observational studies
- 4 reviews
- Numerous laboratory studies

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

It is not known whether rifampicin prevents dementia or decline.

Few studies have assessed the effects of rifampicin on cognition. A systematic review by [Vaezipour et al., 2025](#) described six studies performed in non-dementia populations. Of these studies, three were in patients with tuberculous meningitis; one in patients with bacterial meningitis; one in patients with multiple sclerosis (MS); and one in patients with mycobacterial infection. Of the studies in patients with infectious diseases, two were in children and three were in adults. Overall, the researchers report that the systematic review was hampered by the heterogeneity of the studies in terms of dose, duration, cognitive assessment tool, and study population. Rifampicin is also prescribed as a combination therapy for infectious disease in an effort to combat antibiotic resistance, which complicates interpretation of findings. Moreover, it is difficult to untangle the neurological benefits of rifampicin in reducing or clearing pathogen load in the CNS vs. the potential direct neuroprotective effect of the drug. The included studies reported the following findings:

- An open-label study of 37 children with tuberculous meningitis tested three different antibiotic regimens. All participants received standard isoniazid and pyrazinamide and then either 1) high-dose rifampicin + ethambutol, 2) high-dose rifampicin + levofloxacin, or 3) standard-dose rifampicin + ethambutol for two months. All participants then received the standard therapy of isoniazid + standard-dose rifampicin for 10 months. In this study, high-dose rifampicin was 30 mg/kg, and standard-dose rifampicin was 15 mg/kg. The study found that those receiving high-dose rifampicin have significantly better fine motor, receptive language, and expressive language compared to patients receiving standard-dose rifampicin ([Paradkar et al., 2022](#)).
- An RCT of 40 children with bacterial meningitis assessed the impact of a single dose of rifampicin (20 mg/kg) before treatment with ceftriaxone, a different antibiotic, compared to treatment with ceftriaxone alone. The primary outcome measures were inflammatory markers such as TNF- α , calcium-binding protein B (S100B) and neuron-specific enolase (NSE). The researchers reported that children who received rifampicin + ceftriaxone had significantly lower markers of inflammation on day 1 and 5 compared to the group who received ceftriaxone alone. There was a trend towards reduced morbidity and neurological events at 3 months in the rifampicin + ceftriaxone group compared to ceftriaxone alone, but this did not reach statistical significance ([Uppal et al., 2017](#)).
- An RCT of 817 adults with tuberculous meningitis tested the standard treatment cocktail including rifampicin (10 mg/kg) compared to an intensive regimen with a higher dose of rifampicin (15 mg/kg) plus levofloxacin. After 9 months of treatment, there was no difference between groups in the primary outcome measure of death or in the secondary outcome of neurological disability ([Heemskerk et al., 2016](#)).



- An open-label RCT of 120 patients with tuberculous meningitis compared treatment with rifampicin (10 mg/kg, maximum 450 mg per day) to levofloxacin. Patients in both treatment arms also received standard therapy of isoniazid, pyrazinamide, and ethambutol. They also received prednisolone and acetyl salicylic acid. The trial reported that the levofloxacin arm had a significant survival benefit over the rifampicin arm. There was no significant difference in neurological outcomes as defined by activities of daily living and brain MRI changes at 6 months. There were significantly more seizures in the levofloxacin group than the rifampicin group and numerically more neurological events like encephalopathy in the levofloxacin group; the RCT study team interpreted these as adverse events of levofloxacin ([Kalita et al., 2014](#)).
- An RCT of 8 women with relapse-remitting MS used a 6-month treatment with rifampicin (600 mg/day) + azithromycin compared to placebo to test the hypothesis that a bacterial pathogen called *C. pneumoniae* might be involved with MS pathogenesis. The participants received monthly MRIs. The study failed to meet its primary outcome of benefit of antibiotic treatment on lesion parameters. While there were benefits or trends towards benefit of the antibiotics on other MRI parameters such as reduced brain atrophy in the antibiotic group, the small size of the trial hinders full evaluation. It is also impossible to ascribe any potential benefit to rifampicin vs. azithromycin ([Siram et al., 2005](#)).
- A retrospective study collected data on 77 patients who were older than 65, had a mycobacterial infection treated with rifampicin, did not have dementia, and had at least 2 FDG-PET scans. Some patients received 300 mg per day of rifampicin while others received 450. The durations also varied between 6 months of treatment and 12+ months of treatment. The researchers then focused just on the 40 patients in this sample who had AD-type hypometabolism on at least one PET scan. They first reported a significant correlation between reduced standardized uptake value ratios (SUVR) in the posterior cingulate cortex and poorer performance on MMSE in these patients. Of the 77 patients, 26 had FDG-PET scans before and after rifampicin treatment and 51 had scans only after treatment initiation. In those who received pre- and post-treatment scans, the researchers found that the SUVR and MMSE scores were stable in those who received at 12 months of 450 mg/day of rifampicin but declined in those who received 450 mg/day of rifampicin for 6 months. In the group that received their PET scans after rifampicin treatment, all patients showed a decline in SUVR. Patients who received 12+ months of rifampicin had a milder decline in SUVR and MMSE than those who received treatment for 6 months. Dose also significantly influenced SUVR changes, with higher doses appearing to be more beneficial. One limitation of this study is the variable time between PET acquisitions, as this variability significantly influenced changes in SUVR. Perhaps more



importantly, the duration of treatment of rifampicin is based on the type of infection. Patients with tuberculosis typically receive 6 to 9 months of treatment in their hospital, and patients with mycobacterium avium complex typically receive 12 months of treatment ([Iizuka et al., 2017](#)).

The other studies discussed in the systematic review involved patients with AD and are thus described in the following section.

Rifampicin is sometimes used to treat leprosy. [Namba et al., 1992](#) examined the neurofibrillary tangle load in brain samples from 16 patients with leprosy compared to 140 elderly individuals without dementia and reported that there was a lower plaque load in those who received rifampicin compared to age-matched controls. However, follow-up studies have not found an association between rifampicin treatment and AD incidence in patients with leprosy ([Endoh et al., 1999](#)).

Human research to suggest benefits to patients with dementia:

One of the many hypotheses of the etiology of AD is involvement of a bacterial infection such as *C. pneumoniae* (reviewed in [Subedi et al., 2024](#)). Preclinical work has also suggested that rifampicin, along with other antibiotics, may inhibit A β aggregation

Therefore, an RCT was run to test the effects of a 3-month treatment of rifampin (300 mg) + doxycycline (200 mg) vs. placebo followed by a 9-month follow-up period in 101 patients with mild to moderate AD (MMSE scores of 11 to 25). Serology for *C. pneumoniae* was not required for this study due to the lack of standardized serological criteria for chronic *C. pneumoniae* infections. The primary outcome measure was the Standardized Alzheimer's Disease Assessment Scale (SADAS) cognitive subscale (SADAScog) at 6 months. The trial met this primary endpoint; there was significantly less decline as measured by SADAScog at 6 months in the group that received antibiotics vs. placebo (-2.75 points; 95% CI -5.28 to -0.22, $p=0.034$). There was a trend towards benefit at 12 months for the antibiotic group that did not reach statistical significance (-4.31 points; 95% CI -9.17 to -0.56, $p=0.079$). In the antibiotic group there was a significant improvement in dysfunctional behavior as measured by the Dysfunctional Behavior Rating Instrument at 3 months but not at later timepoints. There was no significant difference at any timepoint in MMSE, measures of daily living, or symptoms of depression. There was no indication that any benefit stemmed from treatment of chronic *C. pneumoniae* infection; there was no significant difference in IgA or IgG antibody titer levels in either group at 6 months, nor any difference in drug effect based on baseline titer levels ([Loeb et al., 2004](#)).

Based on these preliminary results, a larger multicenter trial known as the Doxycycline and Rifampin for Alzheimer's Disease (DARAD) trial was initiated. This study randomized 406 patients with mild to moderate AD (MMSE of 14 to 26) 1:1:1:1 to receive either doxycycline (200 mg/day) + placebo, rifampicin (300 mg/day) + placebo, doxycycline (200 mg/day) + rifampicin (300 mg/day), or placebo + placebo for 12 months. Randomization was designed to balance gender, age, MMSE score at baseline, and current use of symptomatic AD drugs, and the trial was well-balanced. The protocol specified that an interim analysis would be conducted by a Data Monitoring Committee after two-thirds of the total sample completed the 1-year follow-up. At this interim analysis, the trial was determined to be futile and stopped early. Patients in all groups (n=305) showed a decline in cognitive function as assessed by SADAS-cog. There was significantly more decline in both the rifampicin ($p<0.001$) and doxycycline groups compared to placebo. There was no difference between the decline with rifampicin, doxycycline, or the combination. In secondary outcomes, there was either no significant difference between placebo or either antibiotic as with the CDR-SB, or there was a significantly greater decline in the active treatment groups compared to placebo as with activities of daily living and a measure of depressive symptoms. The researchers concluded that "The results of this study leave little doubt that neither doxycycline nor rifampin, whether alone or in combination, has any beneficial effects on cognition or function in patients suffering from AD", citing the consistent results of no benefit or worse outcomes with antibiotic treatment and in particular, with treatment with rifampicin. One potential explanation may be that rifampicin, as a CYP3A4 inducer, affected the levels of concomitant AD medications such as donepezil, though it may be that rifampicin is either not effective or actively harmful for neurodegenerative diseases ([Molloy et al., 2013](#)).

An RCT tested the effects of 600 mg per day of rifampicin for 12 months in 100 patients with multiple system atrophy (MSA), which is a synucleinopathy that is characterized by autonomic failure, cerebellar ataxia, and parkinsonism, among other symptoms. The trial was negative; rifampicin did not slow or halt the progression of MSA. A prespecified interim analysis of 30 patients who completed dosing found that the trial met futility criteria and the trial was stopped; the mean rate of change in USMARS, an assessment of MSA disease severity, was 0.62 points per month in the rifampicin group, and 0.47 points in the placebo group. Scores on this assessment are expected to increase as the disease progresses. As the trial had recruited rapidly and completed recruitment by the time of the futility analysis, an exploratory analysis of the primary and secondary aims was possible. At the time of trial halt, 79 patients had completed the full 12-month dosing, 82 had completed 9 months, 90 had completed 6 months, and 99 had completed 3 months of treatment. In the exploratory analysis of the primary

endpoint, there was no difference in mean rate of change in USMARS between groups (mean rate of change 0.5 points in each group) ([Low et al., 2014](#)). The researchers concluded that despite an earlier open label study of 450 mg/day for 6 months rifampicin in patients with MSA that reported potential delay in disease progression with rifampicin treatment ([Ohyagi et al., 2013](#)), that rifampicin did not provide any benefit to patients with MSA.

A commentary article about the RCT conducted by Low and colleagues suggested potential issues with powering, disease type and stage variability, and timing of the intervention, though the commentary does not discard the possibility that this is one of many failures of translation between animal models and human disease ([Wenning et al., 2014](#)).

A meta-analysis by [Song et al., 2026](#) assessed potential AD therapeutics that were derived from natural sources. They report that rifampicin improved MMSE scores, but the meta-analysis only included the smaller pilot study from [Loeb et al., 2004](#) and not the larger follow-up study by [Molloy et al., 2013](#).

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

The main hypotheses of mechanism of action for neuroprotection for rifampicin are that rifampicin is anti-inflammatory and prevents aggregation of different proteins associated with neurodegeneration (reviewed by [Yulug et al., 2018](#)).

Several preclinical studies have reported the rifampicin inhibits aggregation of different proteins, including A β in cell-free and cell culture models ([Tomiya et al., 1994](#)), tau and A β in AD mouse models ([Umeda et al., 2016](#)), and α -synuclein in both cell-free systems ([Umeda et al., 2016](#)) and in animal models of Parkinson's disease (PD) ([Umeda et al., 2021](#)). Preclinical work has also suggested that rifampicin can mitigate behavioral signs of disease. [Kaur & Sodhi, 2015](#) report that administration of rifampicin in an aluminum chloride rat model of AD mitigated memory and locomotor deficits as well as improved histopathological parameters. In [Umeda et al., 2016](#), rifampicin was administered for 1 month to three different AD mouse models: APP_{OSK} mice, which model A β oligomers; Tg2576 mice, which are an AD model; and tau609 mice, which are a tauopathy model. In 17-month-old APP_{OSK} mice and 13-month-old Tg2576 mice, rifampicin reduced deposition of A β oligomers and tau hyperphosphorylation and mitigated synaptic loss and microglial activation. In 14- to 15-month-old tau609 mice, rifampicin reduced accumulation of tau oligomers and tau hyperphosphorylation as well as synaptic loss and microglial activation. In both the APP_{OSK} mice and the tau609 mice, treatment with rifampicin mitigated



memory deficits. [Zhu et al., 2021](#) examined the impact of a 7-day treatment with rifampicin on a mouse model of LPS-induced cognitive decline. Rifampicin reduced accumulation of A β 42, neuronal loss in the hippocampus, and mitigated cognitive impairment. They also reported that rifampicin promoted autophagy. [Bi et al., 2021](#) published further results from the same lab using a similar experimental design. In these experiments, they found that rifampicin treatment reduced levels of inflammatory markers like TNF- α , IL-1 β , and nitric oxide, mitigated microglial activation, and inhibited NF- κ B signaling. Rifampicin also mitigated cognitive and motor impairment in the LPS-treated mice. In a model of a synucleinopathy known as multiple system atrophy, rifampicin treatment reduced levels of monomeric and oligomeric α -synuclein as well as phosphorylated (pS129 α -synuclein) and prevented neuronal loss ([Ubhi et al., 2008](#)).

Later studies from the same group as in [Umeda et al., 2016](#) assessed the effects of alternate administration routes of rifampicin such as intranasal administration in animal models. Their hypothesis was that alternative administration routes might mitigate drug-drug interactions and liver adverse events while still efficiently delivering the drug to the brain.

[Umeda et al., 2018](#) reports on the effects of 1-month oral, subcutaneous, and intranasal rifampicin in 11-month-old APP_{OSK} mice. They found that while subcutaneous and intranasal rifampicin both had greater positive impacts on memory than oral rifampicin at the same doses. All routes reduced signs of neuropathology such as tau phosphorylation and synapse loss as assessed by synaptophysin staining, and intranasal and subcutaneous rifampicin appeared to have greater reductions in phosphorylated tau and mitigated loss of synaptophysin. When the researchers looked at liver enzyme levels, they found that subcutaneous rifampicin showed no increase in liver enzymes; a trend towards increase with intranasal rifampicin; and a significant increase in AST but not ALT with oral rifampicin. Brain concentrations of rifampicin were higher with both intranasal and subcutaneous rifampicin than with oral rifampicin. [Umeda et al., 2021a](#) explored the use of rifampicin in an A53T α -synuclein mouse model at 6 months, which is a timepoint when the mice have cognitive but not motor impairment in their laboratory. The group thus proposes that this is a model of dementia with Lewy bodies (DLB) at this stage. They treated the 6-month-old animals with rifampicin or vehicle once per day for 1 month. They found that rifampicin treatment mitigated memory deficits as measured by Morris water maze and also reduced levels of pS129 α -synuclein and microglial activation. [Umeda et al., 2021b](#) tested 1-month regimens of rifampicin, resveratrol, or the combination in transgenic mice lines expressing APP, tau, or α -synuclein. Both drugs were administered intranasally. They reported that while both drugs individually mitigated cognitive deficits, the combination therapy was the most effective in all models at reducing

cognitive impairment. They also found that the combination reduced accumulation of oligomers, and reduced loss of synaptophysin. [Umeda et al., 2022](#) reported on the effects of rifampicin on tau spread. They used a mouse model called tau264 that express wild-type human tau and do not show behavioral or pathological signs of disease even at 24 months. They prepared tau oligomer-rich samples from brain tissue from AD patients and injected the preparations into the hippocampus of the tau264 mice. A week later, they initiated treatment with either rifampicin or vehicle three times a week for 24 weeks. Treatment with rifampicin abrogated tau spread and neurofibrillary tangle formation, mitigated neuronal, synapse loss, and microglial activation as measured by NeuN, synaptophysin, and Iba1 staining, respectively. Rifampicin treatment also prevented cognitive decline, as the active treated mice had a similar performance on the Morris water maze as their non-transgenic and sham-operation control mice whereas the vehicle treated mice had significantly poorer performance. [Hatanaka et al., 2022](#) of the same group reported that intranasal rifampicin treatment also mitigated memory deficits, synapse and neuronal loss, microglial activation, and neuropathological protein accumulation in a *C9orf72* mouse model of FTD and ALS.

Other preclinical studies have suggested that rifampicin is a hydroxyl free radical scavenger. Rifampicin is also known to induce the efflux transporter P-glycoprotein. It has been proposed that upregulation of P-glycoprotein leads to increased clearance of A β from the brain (reviewed in [Yulug et al., 2018](#)). Preclinical work that reported rifampicin treatment reduced amyloid deposition and oxidative stress also reported that these effects were reversed when a P-glycoprotein inhibitor was used. The group hypothesized that the benefits they reported of rifampicin treatment might be in part due to increased efflux of A β across the BBB via P-glycoprotein, though they caution that this is speculative ([Kaur & Sodhi, 2015](#)).

There are some caveats for mechanism of action hypotheses for rifampicin. At least one preclinical study reported that rifampicin does not inhibit amyloid formation but rather interferes with thioflavin-T staining ([Meng et al., 2008](#)). However, animal work discussed above used immunohistochemistry rather than thioflavin-T staining. The blood-brain barrier (BBB) penetrance of rifampicin is also a topic of some debate. Rifampicin is used for CNS infections like tuberculous meningitis, but there are concerns that there is insufficient BBB penetration ([Donald 2010](#); [Te Brake et al., 2015](#)). It is clear that at least some rifampicin crosses the blood-brain barrier in animal models of neurodegeneration ([Umeda et al., 2018](#)) and in humans without CNS infections ([Mindermann et al., 1998](#)), but it is unclear whether sufficient concentrations accumulate in the brain in healthy individuals and/or in individuals with cognitive impairment for various biological effects. Finally, any study assessing the anti-inflammatory effects of

rifampicin in models or humans with microbial infections has the inevitable confounder of the relative contributions of a direct anti-inflammatory effect of rifampicin vs. the indirect effect of its bactericidal properties.

APOE4 interactions:

It is not known whether rifampicin has differential effects based on APOE4 status.

Aging and related health concerns: Rifampicin has not been explored for use in aging or health related conditions.

Types of evidence:

- 1 professional resource

Rifampicin is an essential component of the standard treatment for tuberculosis and has bactericidal activity against a range of bacterial species ([Patel & Rosani, 2023](#)). No studies exploring the use of rifampicin in aging or other related health concerns were identified.

Safety: GI events and orange-colored bodily fluids are often reported for rifampicin. Rifampicin interacts with many drugs, and concomitant medication should be carefully assessed. Hepatotoxicity and hypersensitivity reactions are potential serious events.

Types of evidence:

- 2 meta-analyses or systematic reviews
- 2 pilot studies
- 2 professional resources
- 2 reviews
- 2 laboratory studies

Rifampicin is considered generally well-tolerated in patients, but there are several potential adverse events that can be serious. Hepatotoxicity is a concern, particularly for individuals who have pre-existing liver conditions. Hypersensitivity reactions including hives, flu-like symptoms, thrombocytopenia,



hemolysis, and renal failure have been reported. These reactions are more common with intermittent and/or extended use of rifampicin, and intermittent use of rifampicin is not recommended. Cases of rifampicin induced pneumonitis have been reported. Other adverse events include gastrointestinal events such as nausea, loss of appetite, and diarrhea ([Patel & Rosani, 2023](#)). The FDA label also includes warnings about severe cutaneous adverse reactions (SCARs), vitamin-K dependent coagulation disorders and bleeding, and pulmonary toxicity, and notes that headache, dizziness, drowsiness, muscle weakness, balance problems, numbness, confusion, and trouble concentration have also been reported ([FDA](#)).

Patients should be counseled that rifampicin treatment often leads to red or orange discoloration of tears, sweat, and urine. This is a common and harmless reaction but can be alarming if patients are not forewarned of this side effect ([Patel & Rosani, 2023](#), [FDA](#), [CDC](#)).

The safety profile of rifampicin in patients without bacterial infections, as well as the use of rifampicin alone as opposed to a combination therapy of antibiotics, is less well studied. [Loeb et al., 2004](#) describes an RCT of 101 patients with mild to moderate AD who were randomized to receive either rifampicin (300 mg/day) + doxycycline (200 mg/day) or placebo for 3 months. There was no significant difference in percentage of patients reporting adverse events or trial discontinuation between the groups. Of the trial discontinuations, 3 patients in the antibiotic group discontinued due to adverse events while no placebo patients withdrew for adverse events. There were two deaths in the antibiotic group and one in the placebo group; these deaths due to congestive heart failure, respiratory failure, and pneumonia were judged to be unrelated to study drug. In the antibiotic group, 22 (43%) of the patients reported a total of 56 adverse events; 17 (34%) of the placebo group patients reported a total of 22 adverse events. The most common complaints were loss of appetite (8 vs. 3), sleep disturbances (8 vs. 6), nausea (6 vs. 0), headache (0 vs. 7), weight loss (6 vs. 0), and diarrhea (4 vs. 6) in the antibiotic group and placebo group, respectively. There were no reports of bodily fluid discoloration in the study.

[Molloy et al., 2013](#) details the larger follow-up trial to the pilot trial by [Loeb et al., 2004](#); the larger trial was known as DARAD. DARAD randomized 406 patients with mild to moderate AD to receive either doxycycline (200 mg/day) + placebo, rifampicin (300 mg/day) + placebo, doxycycline (200 mg/day) + rifampicin (300mg/day), or placebo + placebo for 12 months. There were significantly more gastrointestinal and weight loss adverse events in both the rifampicin group vs. the non-rifampicin group and the doxycycline group vs. the non-doxycycline group. There were also more adverse events based on blood lab results in the rifampicin group compared to the non-rifampicin group; some examples of this type of adverse event were anemia, hyperlipidemia, and hypokalemia. No patient in

the placebo group withdrew due to an adverse event; 2 patients in the rifampicin only, 3 in the doxycycline only, and 1 in the combination group withdrew due to adverse events. There were 3 deaths in each single antibiotic group and 6 in the rifampicin + doxycycline group compared to 1 death in the placebo group. The difference in mortality was not statistically significantly different, and no deaths were judged to be related to study drug.

[Low et al., 2014](#) reports on an RCT of 600 mg/day of rifampicin for 12 months in patients with MSA. The trial was terminated early due to futility, but a large percentage of the participants completed at least 6 months of the trial. Of the 100 participants in each group, 3 discontinued due to adverse events in each group. There were three serious adverse events in 3 participants in the rifampicin group, and 15 serious adverse events in 12 participants in the placebo group. All serious adverse events were determined to be definitely or probably not related to study drug. There were 7 total deaths, 2 in the rifampicin group and 5 in the placebo group. There was no significant difference between types of adverse events or attribution to study drug between the two groups. The most common systems for adverse events to occur in were gastrointestinal or hepatic, genitourinary, constitutional or other, and neurological. This trial noted that rifampicin causes a yellow-orange discoloration of tears and urine, and they selected riboflavin as a placebo as it causes a dark yellow discoloration to bodily fluids.

There has been preclinical research interest into whether alternative routes of administration like intranasal or subcutaneous dosing may reduce the risk of hepatotoxicity and drug-drug interactions by avoiding first-pass metabolism in the liver ([Umeda et al., 2021](#)). Use of intranasal rifampicin appears to be relatively unexplored in humans; the only clinical study investigating intranasal rifampicin was for the purpose of reducing *M. leprae* populations in the nose to reduce transmission of leprosy ([Mamidi et al., 1996](#)).

Given rifampicin's importance in treating tuberculosis, the leading cause of death from a single infectious agent in the world, safe use of rifampicin should also consider how to minimize risk of development of rifampicin resistance ([Patel & Rosani, 2023](#)).

Drug interactions:

Rifampicin is a potent cytochrome P450 inducer, particularly of CYP3A4, and also induces P-glycoprotein. Drug-drug interactions must be carefully reviewed for rifampicin ([Patel & Rosani, 2023](#)). Some drugs should not be taken with rifampicin. It is very important to discuss all concurrent



medications, vitamins, and supplements with your doctor before and while you take rifampicin. Rifampicin is known to have interactions with at least 808 other drugs. Of these interactions, 320 are major, 427 are moderate, and 61 are minor. Rifampicin can interact with many drugs, including those used for infections, tuberculosis, depression, birth control, hormone replacement, high cholesterol, high blood pressure, seizures, or common over the counter pain medications such as acetaminophen, ibuprofen, and naproxen sodium ([Drugs.com](https://www.drugs.com)).

As absorption of rifampicin are affected by food, patients should take rifampicin at least 1 hour before or 2 hours after eating ([Drugs.com](https://www.drugs.com)).

Rifampicin is associated with liver damage. Deaths due to liver damage have occurred, particularly in patients with pre-existing liver disease or in patients taking other hepatotoxic medication. Rifampicin should be administered with caution and with extremely careful medical oversight in patients with history of liver disease or alcoholism ([Drugs.com](https://www.drugs.com)).

Research underway:

There are currently 119 ongoing studies of rifampin / rifampicin registered on clinicaltrials.gov. These trials largely focus on patients with tuberculosis or other infections. No trial is investigating the effects of rifampicin on cognition or dementia.

Search terms:

Pubmed, Google: rifampicin, rifampin

- Tuberculosis, dementia, cognition, MSA, Alzheimer's disease, blood-brain barrier, ApoE4

Websites visited for rifampicin:

- [Clinicaltrials.gov](https://clinicaltrials.gov)
- [Drugs.com](https://www.drugs.com)
- [WebMD.com](https://www.webmd.com)
- [PubChem](https://pubchem.ncbi.nlm.nih.gov)
- [DrugBank.ca](https://www.drugbank.ca)

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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](#).