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## Minocycline

### Evidence Summary

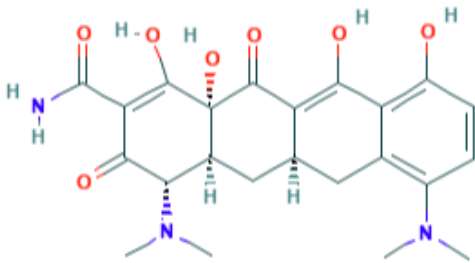
Minocycline is potentially beneficial for aging and cardiovascular disease while having mixed effects for neurodegenerative disease; however, case studies have reported some potentially serious side effects with long-term use.

**Neuroprotective Benefit:** Some potential benefits in Alzheimer's models; however, minocycline accelerated functional decline in ALS patients.

**Aging and related health concerns:** Minocycline is associated with life-extension in model organisms and has some cardioprotective features.

**Safety:** Use of minocycline up to one year may be associated with mild side effects; however, long-term use is associated with serious side effects in some case reports.



<b>Availability:</b> As a generic prescription	<b>Dose:</b> 100-200mg/day	<b>Chemical formula:</b> C <sub>23</sub> H <sub>27</sub> N <sub>3</sub> O <sub>7</sub> <b>MW:</b> 457.483g/mol  <b>Source:</b> <a href="#">Pubchem</a>
<b>Half life:</b> 11-22 hours	<b>BBB:</b> Penetrant (in animals)	
<b>Clinical trials:</b> 1 ongoing in Alzheimer's	<b>Observational studies:</b> None	

### What is it?

Minocycline is a broad-spectrum tetracyclic antibiotic commonly used for acne and bacterial infections, such as Lyme disease and sexually transmitted diseases. Beyond its anti-biotic effects, it is reported to be anti-inflammatory, anti-apoptotic, and inhibit proteolysis, angiogenesis, and tumor metastasis ([Garrido-Mesa et al, 2013](#)).

Its antibiotic properties are due to its ability to inhibit protein synthesis by binding to the bacterial 30S ribosomal subunit ([Garrido-Mesa et al, 2013](#)). In fact, its life extension properties in model organisms is also reported to be due to its ability to inhibit protein synthesis (see below). It was initially commercialized in 1971, and thus has long use in humans.

**Neuroprotective Benefit:** Some potential benefits in Alzheimer's models; however, minocycline accelerated functional decline in ALS patients.

### Types of evidence:

- 10 preclinical Alzheimer's studies
- 1 clinical trial in ALS patients
- 1 meta-analysis for acute stroke

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

None

Human research to suggest benefits to patients with dementia:

None

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

Minocycline was investigated in many preclinical Alzheimer's animal studies. A summary of the results is below:

↑ (increase/improvement); ↓ (decrease); ↔ (no change); n.s. (non-significant).

Presumably good; presumably bad

Study	Population	Treatment started	Dose	Length	Amyloid	Tau	Inflammation	Other	Cognition
<a href="#">Parachikova et al, 2010</a>	3xTg-AD	8 months	55mg/kg/day	4 months	↔ soluble AB40/42 ↔ insoluble AB42 ↓ insoluble AB40 ↓ amyloid fibrils ↔ amyloid oligomers	↓ p25 (involved in tau phosph) ↑↓↔ ptau	↓ Astrogliosis ↓ Microgliosis (n.s.)		↑
<a href="#">Biscaro et al, 2012</a>	APP/PS1	11 weeks of age	25-50mg/kg/day	5 weeks	No change in AB40/42		↓ Microgliosis ↓ TNF-a (n.s.) ↓ IL-6 (n.s.) ↓ iNOS	↑ Neurogenesis ↔ Dendritic Morphology	↑
<a href="#">Seabrook et al, 2006</a>	APP	8 and 12 months (before and after AB deposition)	55mg/kg/day	3 months	↑ Young ↔ Old		↔ Astrogliosis		↑ Young animals ↔ Old animals



<a href="#">Noble et al, 2009</a>	htau	young and old (3-4 months and 12 months)	10mg/kg/day	14 days		↓ Cleaved tau (young and old) ↓ ptau (young) ↔ ptau (old) ↓ tau aggregation (young and old)		↓ Caspase 3 (apoptosis marker)	
<a href="#">Garwood et al, 2010</a>	htau	3-4 month	10mg/kg	14 days			↓ Astrogliosis ↔ TNF-α, MCP-1, IL-1B ↓ IL-10, IL-6		
<a href="#">Garcez et al, 2017</a>	ICV amyloid	Just after	Mino (50mg/kg)	17 days			↓ IL-1B, TNF-α, IL-4 ↓ BDNF, NGF		↑
<a href="#">Choi et al, 2007</a>	ICV amyloid	Just after	45mg/kg/day	3 weeks				↓ p-IF2a (stress response protein)	↑
<a href="#">Cai et al, 2013</a>	Diabetes by HFD and IP STZ rats	Just after	50mg/kg/day	4, 6, and 8 weeks	↓ AB40, AB42	↓ ptau ↔ tau	↓ TNF-α, IL-1B		
<a href="#">Ferretti et al, 2012</a>	McGill-Thy1-App (a model with pre-plaque inflammation associated with intracellular AB oligomers)	2 months	50mg/kg/day	1 month (before plaques developed)	↓ BACE1 activity in transgenic ↑ BACE1 activity in non-transgenic		↔ Microgliosis ↓ iNOS, Cox2, IL-1B ↑ NFkB (n.s.) in non-transgenic ↓ NFkB (n.s.) in transgenic		
<a href="#">El-Shimy et al, 2015</a>	in vitro AB oligomers						↑ phagocytosis of AB ↓ CD68		



In conclusion, based on animal studies, minocycline has mostly beneficial effects. In most situations it reduces inflammation and improves cognition. Its effects on amyloid and tau are mixed, and in a few situations may be detrimental (especially in young or non-transgenic animals).

These results are reflected in a meta-analysis of animal studies in Parkinson's disease, Huntington's disease, and stroke, showing mostly benefits with large effect sizes in animal models ([Li et al, 2013](#)).

In a meta-analysis of 7 RCTs in patients with acute stroke (ischemic and hemorrhagic), minocycline demonstrated a favorable trend for functional independence (RR = 1.31; 95%CI 0.98-1.74) and a significant benefit for functional independence in patients with acute *ischemic* stroke (RR = 12.37; 95%CI – 5.60-19.14) ([Malhotra et al, 2018](#)). However, although minocycline was beneficial in animal models of amyotrophic lateral sclerosis (ALS), a phase 3 clinical trial in 412 ALS patients reported that minocycline accelerated functional decline, regardless of dose (up to 400mg/day), questioning whether these preclinical studies will translate to clinical findings ([Gordon et al, 2007](#)).

#### APOE4

None

#### **Conclusion**

Although minocycline was somewhat effective in many animal models, the acceleration of functional decline in ALS patients questions whether we know what effects it will have in human studies. Specifically, we don't really understand what function inflammation has in neurodegenerative diseases. If inflammation is a sign that microglia in the brain are removing pathology, and we inhibit this function, further cognitive decline may be accelerated.

**Aging and related health concerns:** Minocycline is associated with life-extension in model organisms and has some cardioprotective features.

#### *Types of evidence:*

- 4 lifespan studies in model organisms
- 8 preclinical studies for cardiovascular disease
- 1 clinical and 6 preclinical studies for neuropathy

### Lifespan

Worms induce stress signaling pathways (SSPs) in response to stressors such as oxidative stress and misfolded proteins. [Solis et al, \(2018\)](#) reported that worms lose their ability to induce SSPs after the age of 8 days. In an effort to find drugs that extend lifespan when given later in life, they tested 21 molecules that were previously reported to extend lifespan in worms ([Ye et al, 2014](#)), and found that only one, minocycline, was effective when started at day 8 (lifespan extension of 22% when started at day 8 and 48% when started at day 1). Life extension was independent of its antibiotic activity, autophagy, and the integrative stress response (ISR). Minocycline also protected from a-synuclein aggregation and amyloid-induced paralysis. The reported mechanism of action was a reduction in cytoplasmic translation of proteins, especially highly expressed proteins. This effect was also present in human cell cultures. Notably, the EC<sub>50</sub> for life extension was 22uM with an optimal concentration of 50-100uM, while serum concentrations of minocycline in therapeutic doses in humans is only 5-10uM.

Minocycline (at 0.87mM) also increased lifespan in both male and female flies and increased activity (a marker of health span) in male but not female flies ([Oxenkrug et al, 2012](#)). In two other fly strains, minocycline (at 0.05mM) increased median lifespan by 17-27% in males and 14-23% in females (less life extension was seen at a higher dose of 0.36mM), and this was independent of its antibiotic effects (though the effects were less pronounced in germ-free conditions) ([Lee et al, 2017](#)).

Interestingly, minocycline reduced growth and reproduction in worms ([Solis et al, 2018](#)) and reduced reproduction in flies ([Oxenkrug et al, 2012](#)), suggesting a potential negative effect when given earlier in life.

### Cardiovascular disease

#### *Myocardial Ischemia/reperfusion (I/R)*

In a rabbit models of ischemia/reperfusion (I/R) and I/R injury with cardioplegia, acute minocycline treatment reduced plasma levels of malondialdehyde (but not tissue levels in one study) (malondialdehyde is a marker of oxidative stress), soluble ICAM (a marker of inflammation), ischemic size, and the number of apoptotic cells, while increasing plasma SOD levels and improving functional recovery, suggesting it has anti-oxidant, anti-inflammatory, and anti-apoptotic effects ([Huang et al, 2012](#); [Yamaki et al, 2017](#); [Salameh et al, 2015](#)). In a rat model of I/R, acute treatment with minocycline before ischemia reduced infarct size, reduced tissue expression of malondialdehyde, and increased tissue SOD expression ([Hu et al, 2010](#)).



### *Myocardial Infarction*

In a rat model of myocardial infarction, minocycline treatment over 28 days improved cardiac function, reduced the number of apoptotic cells, reduced PARP-1 levels, and reduced inflammation (NF-kB and IL-1 $\beta$  expression) ([Zhao et al, 2018](#)).

### *Carotid Artery Injury*

In a rat model of carotid artery injury, high doses of minocycline (70mg/kg/day – 14 days) reduced intima thickness, but increased liver toxicity and death (1/2 of the animals died). At lower doses (35mg/kg/day – 5 days), minocycline was still effective at reducing intima thickness but still induced hepatotoxicity ([Pinney et al, 2003](#)).

### *Atherosclerosis*

In a rabbit model of induced vulnerable plaques, 4-week treatment with minocycline reduced the expression of matrix metalloproteinases, improved plaque stability (increased fibrous cap and decreased intima-media thickness), and reduced the incidence of plaque rupture (14.3% vs. 66.7% for minocycline and placebo, respectively) ([Gao et al, 2013](#)). In a mouse model of atherosclerosis, minocycline over 20 weeks reduced plaque size, lipid content of plaques, and vascular stenosis (it had no effect on other markers of plaque morphology including necrotic core, fibrous cap, or plaque rupture). It also reduced the proliferation of vascular smooth muscle cells and inhibited PARP-1 ([Shahzad et al, 2011](#)).

### *Neuropathy*

In an RCT in patients with diabetic neuropathy (n=50), 6-week treatment with minocycline (100mg/day) improved 3 out of 5 measures of neuropathy in only the treatment group (vibration perception threshold – VPT; Leeds Assessment of Neuropathic Symptoms and Signs – LAANS; and Pain Disability Index – PDI), and both the minocycline and placebo group improved on the other two measures (Visual Analog Scale – VAS; beck depression inventor – BDI). The two groups were not statistically compared against each other, rather the investigators looked at whether the treatments were significant from baseline which complicates the interpretation ([Syngle et al, 2014](#)).

This clinical study is supported from preclinical data. 2-week treatment with minocycline prevented the development of diabetic neuropathy (thermal allodynia and thermal and chemical hyperalgesia) in a rat model and reduced levels of IL-1 $\beta$ , TNF $\alpha$ , lipid peroxidation, nitrite, and increased SOD activity ([Pabreja et al, 2011](#)). However, in another rat diabetic neuropathy study, minocycline treatment reduced thermal allodynia and hyperalgesia after 2 weeks but not 3 weeks ([Zychowska et al, 2016](#)). In another rat diabetic neuropathy study, 7-week treatment with minocycline attenuated mechanical allodynia, but



had no effect on cold allodynia, mechanical hyperalgesia or heat hypoalgesia ([Amorin et al, 2017](#)). These results suggest that the effects of minocycline in diabetes-induced neuropathy may be transient.

The effects of minocycline on neuropathy may depend on the type of neuropathy and when treatment commences. In a nerve transection rat model, minocycline reduced neuropathy if started before injury but not if started after injury. At both time points, IL-1 $\beta$  and TNF $\alpha$  were reduced ([Raghavendra et al, 2003](#); [Padi et al, 2008](#)). Additionally, in a model of peripheral nerve resection then reimplantation, minocycline treatment initially reduced Wallerian degeneration of axons but subsequently reduced nerve regeneration, possibly due to decreased infiltration of macrophages ([Keilhoff et al, 2007](#)).

### Cancer

Preclinical studies suggest that minocycline may reduce cancer metastasis, possibly due to inhibition of matrix metalloproteinases ([Garrido-Mesa et al, 2013](#)). A couple of clinical trials for cancer are ongoing.

**Safety:** Use of minocycline up to one year may be associated with mild side effect; however, long-term use is associated with serious side effects in some case reports.

### *Types of evidence:*

- 2 meta-analyses of RCTs in schizophrenia and depressed patients
- Case reports for other side effects

In two meta-analyses of schizophrenia and depressed patients (total ~550 patients), minocycline was not associated with serious adverse effects compared to placebo. The only adverse effect observed with minocycline was headache. Most studies were small, used 100-200mg/day, and ranged from 12-52 weeks in length ([Solmi et al, 2017](#); [Rosenblat and McIntyre, 2018](#)).

However, there are case reports of individuals that long-term minocycline use may lead to systemic autoimmune syndromes, such as drug-induced lupus, autoimmune hepatitis, and systemic vasculitis ([Baratta et al, 2015](#)).

Other side effects that have been reported to occur include nausea, vertigo (especially in women), and dizziness, but these disappear after discontinuation ([Garrido-Mesa et al, 2013](#)). There are also case reports that long-term minocycline use may be associated with skin discoloration ([La Placa et al, 2017](#)).





For more potential side effects, see [drug.com](http://drug.com).

**Drug interactions:**

Minocycline has 11 major and 265 moderate drug interactions. Minocycline is commonly used for acne, and other acne drugs are potential drug interactions (e.g. Vitamin A and other retinoids). Other major drug interactions include lomitapide, leflunomide, and tretinoin. For other interactions, see [drug.com](http://drug.com).

**Sources and dosing:**

Available as a generic. Most studies use 100-200mg/day.

**Research underway:**

There are current ongoing clinical trials using minocycline in Alzheimer's disease ([in the EU](#), 100mg/day for 24 months in 560 patients), two studies for hypertension, and two studies for cancer.

**Search terms:**

Pubmed:

Minocycline + lifespan, Alzheimer, atherosclerosis, microbiome, DNA damage repair, neuropathy, cancer, neurodegeneration, hypotension

Websites visited for

- Clinicaltrials.gov (58)
- Examine.com (0)
- DrugAge (5)
- Drugs.com
- DrugBank.ca
- Labdoor.com (0)



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