

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.

COMT inhibitors

Evidence Summary

COMT inhibitors may benefit or harm cognitive functions depending many factors. Currently available drugs have problems with liver toxicity and dopaminergic side effects.

Neuroprotective Benefit: COMT inhibitors may benefit or harm cognitive functions depending on many factors. The relationships between COMT Val158Met polymorphism and AD risk is mixed, counter-intuitive, and depend on factors such as age.

Aging and related health concerns: No studies have tested COMT inhibitors in treating or preventing age-related conditions. In Parkinson's patients, COMT inhibitors appeared to reduce plasma homocysteine levels.

Safety: Currently approved COMT inhibitors have problems with liver toxicity and other dopaminergic side effects such as dyskinesia, diarrhea, and sleep disorders.

Availability: tolcapone and entacapone are available with prescription; oricapone was recently approved in Europe	Dose: for Parkinson's patients, initial dose of tolcapone is 100 mg orally, 3 times per day, then increased to 200 mg orally, 3 times per day	Chemical formula: $C_{14}H_{11}NO_5$ (tolcapone); $C_{14}H_{15}N_3O_5$ (entacapone) MW: 273.244 (tolcapone); 305.29 (entacapone)
Common brand: tolcapone (Roche); entacapone (Orion)		
Half life: tolcapone has a short half-life of 2-3.5 hours	BBB: tolcapone has low penetration; entacapone and oricapone are not penetrant	
Clinical trials: a meta-analysis of 2 clinical trials included a total of 349 Parkinson's patients	Observational studies: no studies with COMT inhibitors; numerous studies with COMT Val158Met polymorphism	

What is it? Catechol-O-methyltransferase (COMT) is one of several enzymes that degrades catecholamines by catalyzing the transfer of a methyl group from S-adenosylmethione. For example, dopamine is metabolized by COMT and monoamine oxidase (MAO). COMT regulates and optimizes prefrontal cortical levels of dopamine and alterations in its activity is associated with different neuropsychiatric disorders ([Perkovic et al., 2018](#)). COMT acts as a modulator of various brain functions, especially in the prefrontal cortex as there are few dopamine transporters in this region. COMT is widely expressed in the CNS, but also in the periphery (liver, kidney, adrenal and lungs). There are two main isoforms of COMT: membrane bound (MB-COMT) and soluble (S-COMT). The longer membrane bound isoform, MB-COMT, is the dominant type in the brain, while in other tissues the soluble cytoplasmic S-COMT isoform is abundant. In humans, most tissues express both COMT mRNA transcripts, but in the brain, only the longer transcript (MB-COMT) is detectable.

COMT inhibitors are a class of medications (e.g., tolcapone, entacapone, opicapone) that are used with carbidopa-levodopa therapy in the treatment of Parkinson's disease ([DrugBank.ca](#)). Carbidopa-levodopa therapy alleviates the motor symptoms of Parkinson's, while COMT inhibitors slow the breakdown of levodopa and extend the effectiveness of the carbidopa-levodopa therapy.

The COMT Val158Met polymorphism affects the COMT enzyme activity and is thought to also affect cognitive performance associated with dopamine, as well as reward-related and emotional processing

([Gennatas et al., 2012](#); [Perkovic et al., 2018](#)). The Val allele confers greater stability of the COMT enzyme, while the Met allele produces a COMT that is more thermo-labile with lower activity at physiologic temperature. Carriers of the Met allele have ~25% of COMT activity compared to Val allele carriers.

Neuroprotective Benefit: COMT inhibitors may benefit or harm cognitive functions depending on many factors. The relationships between COMT Val158Met polymorphism and AD risk is mixed, counter-intuitive, and depend on factors such as age.

Types of evidence:

- 1 meta-analysis of observational studies examining COMT Val158Met genotype and risk for Alzheimer's
- 2 clinical trials testing tolcapone in healthy adults
- 3 clinical trials testing tolcapone or entacapone in Parkinson's patients
- 4 observational studies on COMT Val158Met genotype that are not included in the above meta-analysis
- Numerous review articles
- Numerous laboratory studies

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

Clinical trials: BENEFIT/HARM DEPENDS ON BASELINE PERFORMANCE AND/OR GENOTYPE
There have been 2 studies that have tested the effects of tolcapone on cognitive functions in healthy adults.

The most recent study from 2017 was a double-blind randomized controlled trial in 27 healthy men and women aged 18-35 years old who were homozygous for either the Met/Met or Val/Val genotype of COMT ([Bhakta et al., 2017](#)). No significant main effects of tolcapone (single dose of 200 mg) or COMT genotype were found on cognitive battery scores. Post hoc analyses of each cognitive domain showed only a significant tolcapone x baseline performance interaction for the visual learning domain ($p=0.03$), with tolcapone-induced improvement in low-baseline performers and tolcapone-induced impairment in high-baseline performers. A post hoc analysis revealed a significant main effect of tolcapone on verbal fluency ($p=0.03$) but no significant main effect of genotype.



No significant main effects of tolcapone or COMT genotype were found on early, middle, and late peak amplitudes in the electroencephalogram-based 5-Choice Continuous Performance test. Post hoc comparisons showed a strong effect of tolcapone-enhanced P200 amplitude at centroid 1 in low-baseline performers and a modest opposite effect in high performers. Also, tolcapone increased frontal P300 amplitude in Val/Val individuals but had an opposite effect in Met/Met individuals.

In an older 2007 double-blind randomized controlled crossover trial in 47 healthy people, tolcapone treatment (200 mg, 3 times daily) for one week significantly reduced COMT enzyme activity in whole-blood by about 25% (consistent across genotype)([Apud et al., 2007](#)).

Three of the tests of executive cognition showed positive effects of tolcapone, though none of these tasks showed a main effect of drug status or a main effect of genotype. On the trail making test, a significant effect of tolcapone ($p < 0.05$) was observed, such that while on tolcapone, subjects performed the trail making test more rapidly than while on placebo. No order ($p > 0.05$) nor genotype ($p > 0.05$) effects were found. For the N-Back test, a drug x test interaction ($p < 0.05$) was present on the reaction time measure, such that reaction times for 2- and 3-back conditions improved with tolcapone, whereas reaction times for the less demanding 0- and 1-Back conditions showed little change. No genotype ($p > 0.05$) or order ($p > 0.05$) effects were seen. For intra-dimensional set shifting, a significant drug x genotype interaction ($p < 0.05$) was present, such that individuals with Val/Val genotypes markedly improved while receiving tolcapone, whereas individuals with Met/Met genotypes worsened. Tolcapone also showed a trend for an effect on verbal episodic memory in the form of a drug x genotype interaction ($p = 0.1$), such that individuals with the Val/Val genotype improved while receiving tolcapone, whereas individuals with the Met/Met genotype worsened. No statistical corrections were performed for multiple comparisons, so some of these significant findings may have occurred by chance.

In the fMRI study, a significant main effect of tolcapone was found on the efficiency of information processing during the N-Back working memory test, with greater activation in brain regions subserving working memory, particularly in the dorsolateral prefrontal cortex (Brodmann's area, 9/46) bilaterally on placebo compared with tolcapone ($p = 0.02$ and 0.03 in right and left DLPFC, respectively).

Associations between COMT genotype, Alzheimer's risk, and cognitive functions: MIXED.

The COMT Val158Met polymorphism affects the COMT enzyme activity and is thought to also affect cognitive performance associated with dopamine ([Perkovic et al., 2018](#)). Carriers of the Met allele have ~25% of COMT activity compared to Val allele carriers. Numerous observational studies have examined

the relationship between COMT Val158Met polymorphism and Alzheimer's risk, but the evidence is mixed, inconsistent, sometimes counter-intuitive, and may depend on many factors such as age.

The most recent and largest study was a 2016 meta-analysis of 10 case-control studies that included 2,777 Alzheimer's cases and 2,839 controls total ([Yan et al., 2016](#)). There was no significant association between COMT Val158Met polymorphism and susceptibility to Alzheimer's disease for the entire population, or for Caucasian people. In Asian populations, however, decreased risk for Alzheimer's was found with the Val allele. For example, the pooled odds ratio (OR) for Val/Val or Val/Met compared to Met/Met was 0.66 (95% CI, 0.50 to 0.87), and the pooled OR for Val/Val compared to Met/Met was also 0.66 (95% CI, 0.50 to 0.89). This meta-analysis suggested that COMT Val allele (associated with greater COMT activity and dopamine metabolism) was associated with a decreased risk of Alzheimer's in the Asian population, but not in the Caucasian or the overall population (ORs ranging from 0.96 to 1.24).

A longitudinal study of 2858 Caucasian and African-American elderly people evaluated the associations between COMT genotype and cognitive functions over a follow-up period of 8 years ([Fiocco et al., 2010](#)). Stratified by race and adjusted for covariates, no association were found between COMT genotype and baseline cognitive function in Caucasian and African-American subjects. In Caucasian subjects, COMT genotype was associated with a different magnitude of change in cognitive functions as measured by 3MS (Met/Met: -2.3, Met/Val: -1.7, and Val/Val: -1.2) and digit symbol substitution test (Met/Met: -5.60, Met/Val: -4.80, Val/Val: -4.00). In African-American subjects, COMT genotype was associated with a different magnitude of change in the digit symbol substitution test (Met/Met: -4.10, Met/Val: -4.80, Val/Val -2.60). No consistent COMT-by-APOE and COMT-by-sex interactions on cognitive function were observed ($p = 0.10$). These findings suggest that the Val allele has a protective impact on cognitive decline in late life. It is not clear whether the genotype association is a direct or indirect effect. It is worth noting that middle-aged white men with the Met/Met genotype displayed the highest waist-to-hip ratio and sagittal abdominal diameter compared to other genotypes. Met/Met subjects were also found to have higher blood pressure and heart rate compared to Val/Val carriers. All of these factors are risk factors for cognitive impairment, though in this study, they adjusted for cardiovascular risk factors and disease and the associations still remained.

Findings from [Fiocco et al., 2010](#) are in contrast to previous studies that reported that the Val/Val genotype was associated with a detrimental effect on cognitive function ([de Frias et al., 2004](#); [Starr et al., 2007](#)). In 2 studies ([de Frias et al., 2004](#); [de Frias et al., 2005](#)) that assessed the association between COMT and cognitive function in a group of men without dementia, aged 35–85, Met/Met individuals



performed better than Val carriers (Val/Val + Met/Val) on baseline tests of episodic and semantic memory ([de Frias et al., 2004](#)) as well as on tests of executive function and visuospatial abilities ([de Frias et al., 2005](#)). Interestingly, the genotype association with visuospatial ability was limited to middle-aged participants and was not found in older adults (50–85 years of age), suggesting that the association between COMT genotype and cognitive function may be age-dependent. Optimal prefrontal function is achieved with a balanced, moderate dopaminergic activity as it follows an inverted U-shaped model ([Perkovic et al., 2018](#)).

There were also many other observational studies that have reported a lack of association between COMT genotype and Alzheimer's risk (e.g., [Zhang et al., 2015](#); [Shibata et al., 2015](#)) or cognition ([Gennatas et al., 2012](#)).

Human research to suggest benefits to patients with dementia:

Alzheimer's disease: No clinical trials have tested the efficacy of COMT inhibitors in Alzheimer's patients. In an observational study of 232 Alzheimer's patients, COMT Val/Val or Val/Met genotypes were significantly associated with a "psychosis endophenotype" ([Borroni et al., 2006](#)). COMT Val carriers had a lower risk of developing the "frontal" endophenotype (marked by disinhibition and euphoria). The odds ratios of COMT Val was 6.30 for hallucinations and 0.14 for disinhibition.

Dementia: In an observational study of 46 patients with dementia and 65 healthy older adults, carriers of the Met/Met genotype had significantly lower cognitive scores (measured by MMSE) and performed worse on the Visual Association Test (longer time to respond, average response to numbers, etc.) when compared to Met/Val or Val/Val genotypes ([Nedic et al., 2011](#)). Although the Met/Met genotype with more dopamine available in the frontal cortex would be expected to be associated with better neuro-cognitive functions compared to the Met/Val or Val/Val genotype, data from this study did not support this notion.

Parkinson's disease: Several clinical trials have been carried out in Parkinson's patients.

In a very small study, 8 patients with advanced Parkinson's were treated with levodopa + decarboxylase + selegiline at entry, then introduced to tolcapone therapy (200 mg, 3 times daily) while L-dopa levels were progressively reduced ([Gasparini et al., 1997](#)). The statistical analysis showed significant improvements in auditory verbal short-term memory ($p = 0.039$), cued recall ($p = 0.031$) and in visuospatial recall ($p = 0.015$). Significant differences were also found in the drawing test ($p = 0.039$). For

the Trail Making test, significant differences were found in part B, both for time of execution ($p = 0.023$) and number of alternating errors ($p = 0.026$). No differences were found in auditory verbal long-term memory ($p = 0.156$), verbal fluency ($p = 0.109$), Tower of London thinking time ($p = 1.00$) or the number of problems ($p = 0.28$). Because the treatment regimen involved changes in multiple drugs and doses, it is not possible to pin-point whether tolcapone was responsible for the observed improvements.

In a small clinical study of 13 Parkinson's patients treated with levodopa, tolcapone treatment (100 mg, 3 times daily for 2 days) significantly reduced plasma levels of S-adenosylhomocysteine (SAH) and total homocysteine ([Muller and Kuhn, 2006](#)). COMT inhibition may hypothetically be neuroprotective in patients undergoing long-term levodopa treatment due to a reduction of homocysteine levels.

In a cross-sectional study of 57 Parkinson's disease patients, people who were on levodopa alone had a higher mean plasma homocysteine level compared to those receiving a combination of levodopa and entacapone, a COMT inhibitor, or in the control group receiving anti-Parkinson's medications other than levodopa or COMT inhibitors ([Valkovic et al., 2005](#)). Concentrations of serum vitamin B12 and serum folate were on average normal in all groups, but levodopa-treated subjects (with or without entacapone therapy) were more prone to have low B12 levels (45%) than controls on dopamine agonists (6%). In the levodopa group, 37% suffered from low B12 levels, whereas 52% of the levodopa + entacapone group had low B12 levels. Concentrations of serum folate were normal in all but one subject, and there was no significant group effect. Levodopa causes hyperhomocysteinemia in Parkinson's patients, but patients on the combination therapy levodopa/entacapone had mostly normal plasma homocysteine levels.

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

Several preclinical studies have suggested possible mechanisms of neuroprotection with COMT inhibition, while others suggested harm.

In an *in vitro* study, entacapone and tolcapone potently inhibited α -synuclein and A β oligomerization and fibrillogenesis, and they also protected against extracellular toxicity induced by the aggregation of both proteins in PC12 cells ([Di Giovanni et al., 2010](#)). Given the poor CNS penetrance of entacapone and low brain penetrance of tolcapone, it is not clear whether these drugs would produce these effects in the brain.

In a tau mouse model with COMT deletion, acute reboxetine treatment (norepinephrine reuptake inhibitor) which promotes dopamine efflux in the hippocampus significantly increased tau

phosphorylation spread throughout brain regions ([Koppel et al., 2019](#)). It is difficult to extrapolate data from a gene deletion model to what might be expected from pharmacological inhibition of the enzyme as there may be deleterious and/or compensatory mechanisms involved in gene deletions. But it remains possible that having excess dopamine may increase tau phosphorylation.

APOE4 interactions: It is unknown whether APOE4 carriers respond differently to COMT inhibitors compared to non-carriers. In an observational study of 248 healthy subjects, 276 Alzheimer's patients, and 70 subjects with mild cognitive impairment (MCI), neither COMT alleles nor genotypes were independently associated with the risk of Alzheimer's or MCI ([Lanni et al., 2012](#)). However, there was an association between COMT Val/Val genotype and APOE4 carrier status and the risk of Alzheimer's and MCI. Specifically, when the Val/Val genotype was included into the analysis, the risk of Alzheimer's and MCI due to APOE4 allele is increased by about 2-3 fold. The risk conferred by the combination of the Val and APOE4 alleles was more pronounced in men.

A different observational study also reported a synergistic effect between COMT genotype and APOE4 allele, based on 345 Alzheimer's patients, 223 MCI subjects, and 253 healthy controls ([Martinez et al., 2009](#)). Although COMT alleles and genotypes did not show independent risk for Alzheimer's or MCI, the Val/Val and Val/Met genotypes (with high COMT activity) showed a synergistic effect with the APOE4 allele, increasing the risk of Alzheimer's (OR = 5.96; 95% CI 2.74 to 12.94; $p < 0.001$, and OR = 6.71; 95% CI 3.36 to 13.41; $p < 0.001$, respectively). In Alzheimer's patients this effect was greater in women.

In another observational study of 634 people, APOE4 carriers with high Alzheimer's genetic risk score (computed using genotypes for clusterin, complement receptor 1, PICALM) had poorer executive function performance at the age of 75 and steeper 9-year decline with increasing cognitive aging genetic risk score (computed based on genotypes for COMT and BDNF) ([Sapkota and Dixon, 2018](#)). Interestingly, this association was not present in APOE4 carriers with low Alzheimer genetic risk score. In other words, APOE4 carriers with high Alzheimer genetic risk scores were at an elevated risk of cognitive decline when they also possessed higher cognitive aging genetic risk scores.

Aging and related health concerns: No studies have tested COMT inhibitors in treating or preventing age-related conditions. In Parkinson's patients, COMT inhibitors appeared to reduce plasma homocysteine levels.



Types of evidence:

- 2 clinical studies in Parkinson's disease patients evaluating homocysteine levels

Homocysteine is a non-protein homologue of the amino acid cysteine, derived from the metabolism of the amino acid methionine. Several distinct B vitamins are required for homocysteine metabolism and vitamin supplementation may lower homocysteine levels. These B vitamins include B9 (folate), B12 (cobalamin) and B6 (pyridoxal phosphate). High homocysteine levels have been implicated in a wide variety of age-related problems including vascular disease, stroke, depression, dementia, functional decline, and osteoporotic fractures ([Kuo et al., 2005](#)). High levels are much more common in people over 65 (eg. 30% vs 5-10% of the population).

Levodopa, frequently used to treat Parkinson's disease patients, can elevate plasma homocysteine levels by interfering with the metabolism of homocysteine by consuming methyl groups in the transmethylation reaction ([Valkovic et al., 2005](#)). Levodopa is methylated to 3-O-methyldopa by COMT while using up a methyl group on S-adenosylmethionine (SAM). When SAM loses the methyl group, it becomes S-adenosylhomocysteine (SAH), which after hydrolysis will turn to homocysteine.

In Parkinson's patients, addition of a COMT inhibitor (tolcapone or entacapone) to standard therapy of levodopa significantly reduced plasma levels of S-adenosylhomocysteine (SAH) and total homocysteine ([Muller and Kuhn, 2006](#); [Valkovic et al., 2005](#)). COMT inhibition may hypothetically be neuroprotective in patients undergoing long-term levodopa treatment due to a reduction of homocysteine levels.

Safety: Currently approved COMT inhibitors have problems with liver toxicity and dopaminergic side effects such as dyskinesia, diarrhea, and sleep disorders.

Types of evidence:

- 1 Cochrane meta-analysis comparing COMT inhibitors with active comparators in Parkinson's
- Several clinical trials
- Reviews on COMT inhibitors

A 2004 Cochrane meta-analysis that compared the efficacy and safety of COMT inhibitors versus active comparators in Parkinson's patients reported that the frequency of adverse events and withdrawals from treatment were similar between COMT inhibitors and their comparators (e.g., pergolide, bromocriptine) ([Deane et al., 2004](#)). One patient had significantly elevated liver enzymes

while on tolcapone, but otherwise the frequency of adverse events and withdrawals from treatment were similar across medications.

In a double-blind randomized controlled trial in 27 healthy adults with either Met/Met or Val/Val genotypes of COMT, short-term treatment with tolcapone (200 mg, orally, for 2 days) was well tolerated, though liver function tests revealed a small but statistically significant increase in total bilirubin and alanine transaminase levels one week after treatment ([Bhakta et al., 2017](#)). In an older 2007 clinical study in 47 healthy adults, tolcapone treatment for 1 week (100 mg, 3 times daily on day 1; 200 mg, 3 times daily on days 2-7) resulted in urine discoloration (in all subjects), dizziness (10%), nausea (10%), diarrhea (10%), loss of appetite (5%), stiffness (5%), sleep difficulties (5%), muscle spasms (2%), and irritability (2%) ([Apud et al., 2007](#)).

The greatest problem with COMT inhibitors is their liver toxicity ([Perkovic et al., 2018](#)). Other common adverse effects include dyskinesia and diarrhea. Details are listed for tolcapone and entacapone below.

Tolcapone: There is a US black box warning on tolcapone due to liver toxicity ([Drugs.com](#)). Cases of severe hepatocellular injury, including fulminant liver failure resulting in death, have been reported in post-marketing use. As of May 2005, 3 cases of fatal fulminant hepatic failure have been reported from over 40,000 patient-years of worldwide use. This incidence is thought to be 10- to 100-fold higher than the incidence in the general population. It is possible that there is underestimation of risk associated with tolcapone due to underreporting of cases. All 3 cases were reported within the first 6 months of initiation of tolcapone treatment.

Adverse reactions associated with tolcapone include: dyskinesia (42 to 51%), nausea (28 to 50%), diarrhea (16 to 34%), drowsiness (14 to 32%), sleep disorder (24 to 25%), hallucination (8 to 24%), dystonia (19 to 22%), increased dream activity (16 to 21%), muscle cramps (17 to 18%), dizziness (6 to 13%), confusion (10 to 11%), and headache (10 to 11%) ([Drugs.com](#)).

Other warnings and precautions include: abnormal thinking and behavioral changes, CNS depression (falling asleep without warning while engaging in activities of daily living), hematuria, impulse control disorders, orthostatic hypotension, and others ([Drugs.com](#)).

Entacapone: Adverse reactions associated with entacapone include: dyskinesia (25%), nausea (14%), diarrhea (10%), urine discoloration (10%), hyperkinesia (10%), hypokinesia (9%), dizziness (8%), and others ([Drugs.com](#)). Other warnings and precautions include: abnormal thinking and behavioral

changes, hallucinations, impulse control disorders, orthostatic hypotension, somnolence (falling asleep while engaging in activities of daily living), and others.

Drug interactions: There are [19 major drug interactions](#) and [577 moderate drug interactions](#) with tolcapone ([Drugs.com](#)). There are [16 major drug interactions](#) and [578 moderate drug interactions](#) with entacapone ([Drugs.com](#)).

Sources and dosing: Tolcapone (Tasmar®, Roche) was approved in 1998 as an adjunct to levodopa/carbidopa therapy for the symptomatic treatment of Parkinson's disease ([Drugbank.ca](#)). The initial dose of tolcapone is 100 mg orally, 3 times per day, then increased to 200 mg orally, 3 times per day ([Drugs.com](#)). Entacapone (Comtan®, Orion) is also taken orally, 200 mg per dose, up to 8 times a day, concomitantly with levodopa-carbidopa ([Drugs.com](#)).

Research underway: There are currently 10 ongoing clinical trials testing the COMT inhibitor tolcapone ([ClinicalTrials.gov](#)). These trials are testing the efficacy of tolcapone in diseases including brain injuries (3 trials), alcohol abuse and impulsive behavior (3 trials), neuroblastoma (1 trial), amyloidosis (1 trial), obsessive-compulsive disorder (1 trial). and nicotine dependence (1 trial).

Search terms: COMT inhibitor, tolcapone

Pubmed, Google:

- + Alzheimer, + APOE, + dementia, + cognitive, + meta-analysis

Websites visited for COMT inhibitor:

- [Clinicaltrials.gov](#)
- Examine.com (o)
- DrugAge (o)
- Geroprotectors (o)
- Drugs.com ([tolcapone](#), [entacapone](#))
- WebMD.com ([tolcapone](#), [entacapone](#))
- PubChem ([tolcapone](#), [entacapone](#))
- DrugBank.ca ([COMT inhibitors](#), [tolcapone](#), [entacapone](#))

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