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# A systematic review of the cognitive effects of the COMT inhibitor, tolcapone, in adult humans

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**Review**

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## Abstract

**Objective.** The catechol-*o*-methyltransferase (COMT) inhibitor tolcapone constitutes a potentially useful probe of frontal cortical dopaminergic function. The aim of this systematic review was to examine what is known of effects of tolcapone on human cognition in randomized controlled studies.

**Methods.** The study protocol was preregistered on the Open Science Framework. A systematic review was conducted using PubMed to identify relevant randomized controlled trials examining the effects of tolcapone on human cognition. Identified articles were then screened against inclusion and exclusion criteria.

**Results.** Of the 22 full-text papers identified, 13 randomized control trials were found to fit the pre-specified criteria. The most consistent finding was that tolcapone modulated working memory; however, the direction of effect appeared to be contingent on the COMT polymorphism (more consistent evidence of improvement in Val–Val participants). There were insufficient nature and number of studies for meta-analysis.

**Conclusion.** The cognitive improvements identified upon tolcapone administration, in some studies, are likely to be due to the level of dopamine in the prefrontal cortex being shifted closer to its optimum, per an inverted U model of prefrontal function. However, the results should be interpreted cautiously due to the small numbers of studies. Given the centrality of cortical dopamine to understanding human cognition, studies using tolcapone in larger samples and across a broader set of cognitive domains would be valuable. It would also be useful to explore the effects of different dosing regimens (different doses; and single versus repeated administration).

## Introduction

Dopamine is a neurotransmitter found abundantly in the brain. It is a key regulator in reward and learning pathways as well as for movement. Dopamine has been reported to play an important role in multiple brain processes, including motivation, mood, attention, working memory, and learning[1] and well as having a key role in neuromodulation[2] in humans. The maintenance of these pathways is crucial for physiological processes and imbalances in them have been implicated in neurodegenerative illnesses and psychiatric conditions.[3] Dopamine plays a key role in the mesocortical pathway,[4] connecting the ventral tegmentum and basal ganglia to the prefrontal cortex (PFC), forming extensive connections that are important in a range of processes, including motivation and executive functions.[5–7] The mesocortical dopamine receptors are found in the PFC and are involved in the regulation of executive functions, for example, working memory, planning, and attention. Despite considerable inroads into understanding the role of dopamine in cognition, it has proven relatively difficult to disentangle specific roles for cortical—as opposed to subcortical dopamine.[8]

Tolcapone is a brain penetrant catechol-*o*-methyltransferase (COMT) inhibitor that is used clinically as an adjunctive treatment in some cases of Parkinson's disease[9] but which is also being explored as a candidate novel treatment for mental health disorders such as those with impulsive and/or compulsive features.[10,11] Tolcapone was chosen for this systematic review due to its increased ability to penetrate the blood–brain barrier when compared to other COMT inhibitors, for example, entacapone.[12] By inhibiting the COMT enzyme, which is the main mechanism responsible for the breakdown of dopamine in the prefrontal cortices, tolcapone can selectively enhance dopamine transmission in this region, with a relative lack of effects on subcortical dopamine systems. As such, it constitutes a potentially useful selective pharmacological challenge or "probe" to explore the role of cortical dopamine in human cognition. For example, a study using functional magnetic resonance imaging (fMRI) reported that tolcapone significantly improved the efficiency of information processing in the PFC during a working memory task.[13]

Tolcapone was initially thought to predominantly work within the periphery; however, the results of several animal studies[14–16] and a human study examining patients with Parkinson's disease [17] demonstrated additional central activity. Tolcapone is thus largely used in research studies to manipulate dopamine levels primarily within the PFC [13,18] as well as other areas in the brain to explore different cognitive domains.[19–21]

There is evidence that tolcapone has mitigated cognitive dysfunction in several preclinical models.[22–24] These studies suggest a positive influence of tolcapone on cognition, including improvements in memory, spatial working memory, and recognition memory processes. Relatively few studies have explored the effects of tolcapone in humans; however, a few have reported its benefits on working memory in healthy participants as well as participants with varying levels of post-traumatic stress disorder (PTSD).[13,19–21]

A particular genetic polymorphism within the COMT gene has been found to be important in relation to the dopaminergic system in humans, and therefore, the effects of tolcapone due to it being a dopaminergic medication. An amino acid substitution of valine (Val) to methionine (Met) in the COMT gene leads to different levels of COMT activity due to the differing thermostabilities of the enzyme. Individuals with the Met/Met variant can show up to a 40% reduction in enzymatic activity than those with the Val/Val variant.[25] Those homozygous for the Met allele have a lower COMT activity, leading to a higher concentration of dopamine in the PFC. However, Val/Val individuals show relatively lower dopamine concentrations due to the higher COMT activity, and thus, a higher breakdown of dopamine.[20] COMT inhibition will therefore, theoretically, tend to move Val/Val subjects closer to the optimum dopamine level, enhancing performance, but could have no effect (or even impair cognition) in Met/Met subjects.[19] However, it is important to note that other polymorphisms have been identified to influence dopamine availability (eg number of tandem repeat dopamine transporter [DAT1] polymorphisms) building a complex network of gene × phenotype interactions.[26]

While studies have examined the effects of tolcapone in humans, to the best of our knowledge, there has been no systematic review of this area to date. Therefore, we conducted a preregistered systematic review of studies examining the cognitive effects of tolcapone in randomized controlled trials. We hypothesized that due to tolcapone increasing the dopamine concentration in the PFC, there would generally be improvements in cognition in the cognitive tasks when individuals received tolcapone in comparison to when they received a control condition (eg placebo). It was further hypothesized that the effects of tolcapone on cognition would be greater in people with the Val/Val variant (ie those individuals with a putatively lower bioavailability of baseline dopamine in the cortex[27]), as compared to the Met/Met variant.

## Methods

The aim of this study was to perform a systematic review with the potential of carrying out a meta-analysis looking into the cognitive effects of the COMT inhibitor tolcapone, compared to an appropriate control, in humans. The protocol was preregistered using the Open Science Framework (OSF) (see https://osf.io/yh523/).

### *Search strategy*

Following discussion among the research team, the search string was "(tolcapone OR tasmar) AND (cogn*)." Tasmar was included as this is a brand name of tolcapone. A literature search was then conducted on 09/09/2022 using this string. Following the initial identification of studies, the titles and abstracts were read by a member of the research team to check against the inclusion and exclusion criteria as below. The literature search was rerun on the 11/10/2023 to identify any new relevant studies, but this did not identify any new data studies of relevance since the original search was conducted.

#### Inclusion criteria

1. Participants received at least one oral dose of tolcapone at any dose.
2. Randomized control trials examining the effects of tolcapone in humans that had an appropriate control condition, for example, placebo.

#### Exclusion criteria

1. Studies with an age focus on children or young people <18 years old (non-adults).

Once all the studies were screened based on titles, abstracts were then read by a member of the study team against the above criteria.

### *Data extraction and reporting*

Key information from each included study was compiled, including: study design (crossover or parallel), cognitive test(s) used, and the domain being measured, dose of tolcapone administered, number of participants (and ratio of male to female), condition of participants, mean age, and summary of results.

After performing the relevant data extractions, the findings from each study were summarized.

### *Quality assessment*

In order to assess the quality of studies, a list of criteria was made compiling both a broad, standard set of questions as well as some more specific ones to our systematic review. The papers were given one point for each question included in the study so that a numerical comparison could be made between the studies. Two raters reviewed the studies and created independent quality assessment tables. The IRR was 0.90, and the differences between the scores were discussed and resolved with a consensus to create one final table, as shown in Table S1 in the Supplementary Material.

## Results

The PRISMA flowchart showing the number of studies at each stage is shown in Figure 1, and Table 1 provides a summary of the included studies. After carrying out a quality assessment of each study, the mean score out of 11 was found to be 8.85 with a range of 5 (6–11) (see Supplementary Material for further details). The IRR between the two raters was 0.90. More detailed descriptions of the key findings are elaborated upon below. Excluded studies and reasons for exclusion are listed in Table S2 in the Supplementary Material.

After undertaking screening for all the studies, 13 met the criteria to be included in the systematic review.

Cameron et al. conducted a crossover study in which the effect of a single oral 200 mg dose of tolcapone on cognitive stability and flexibility was explored. They used a saccade task that involved showing the subjects different visual cues to either promote looking

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| Population | Adults |
|---|---|
| Intervention | Administration of at least one oral dose of tolcapone |
| Control | An appropriate control condition i.e. a placebo |
| Outcome | Cognitive performance on cognitive function tasks |

**Figure 1.** Table detailing selection criteria of review.

forward (pro-saccade) or looking away (anti-saccade) and recording the rapid eye movements. The results of the saccade task can allow the relationship between the subject maintaining a behavior (cognitive stability) despite distraction and changing their behavior in response to a stimulus (cognitive flexibility) to be analyzed. The authors found that tolcapone reduced performance efficiency and increased (ie worsened, delayed) reaction time compared to placebo implying a detrimental impact to cognitive aspects of performance that is, suggesting a reduced ability to flexibly adapt to the environment.

Fremont et al. used an *N*-back working memory task as well as a Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) to examine the effect of tolcapone on cognitive and behavioral symptoms in patients diagnosed with behavioral variant frontotemporal dementia (bvFTD) ($n$ = 28). The *N*-back task involves subjects using a response pad with numbered buttons while being shown a sequence of numbers. Subjects are then asked to remember and record the number shown *N*-times before (for the one-back, subjects are asked what the previous number was and for the two-back, the number shown two numbers ago). The RBANS is a tool used often in patients with dementia to assess multiple cognitive domains, for example, language, and immediate and delayed memory. A crossover design was used, with tolcapone being administered at 100 mg three times daily for the first day, with a following 200 mg daily for the next 6 days. During the pilot testing for this study, they found that the two-back and 3-back tests were too difficult for most bvFTD patients to do; therefore, they only included the 0-back and 1-back conditions in the study. They found a trend toward improvements in language, irritability, and apathy under tolcapone and a significant improvement in depression. Tolcapone did not have a significant effect on the *N*-back task, suggesting that working memory was not enhanced in individuals with bvFTD. However, as noted, the full *N*-back task version was not administered due to participants being unable to attempt the harder levels—therefore, it is hard to make firm conclusions about tolcapone's cognitive effects (of lack thereof) in this context.

Bhakta et al. used the MATRICS Consensus Cognitive Battery (MCCB) followed by a five-choice-continuous performance test (5C-CPT) in a crossover study to examine changes in cognitive performance and the distribution of electrical activity after 200 mg tolcapone administration. The MCCB uses several tests that are designed to measure seven cognitive domains, including speed of processing and visual and verbal learning. The 5C-CPT is designed to assess cognitive and attentional control processes by getting subjects to move a joystick in response to different target or inhibitory stimuli. The study found that the effects of tolcapone adopted an inverted-U relationship depending on baseline performance in healthy men and women ($n$ = 27); tolcapone enhanced 5C-CPT in low-baseline performers (in terms of attentional and inhibitory control), whereas it impaired those with a high baseline. They also found that tolcapone significantly improved verbal fluency for all levels of baseline performance.

Furman et al. conducted a crossover study using a hierarchical working memory task to determine the influence of cortical dopamine (with a single 200 mg dose of tolcapone) on memory maintenance and input and output gating in healthy participants ($n$ = 49). The hierarchical memory task involved subjects observing a sequence of visual stimuli (letters, numbers, and symbols). The order of stimuli in the sequence varied, creating a range of difficulty. The gating mechanisms mentioned in this study refer to systems that selectively modulate the input and output into memory stores, allowing for adaptations and updating of working memory. They found that tolcapone improved working memory maintenance rather than gating; specifically, this was shown in a task condition that maximizes maintenance and minimizes gating demands.

Peters et al. used a risky-choice task to look at impairments of decision-making and cognitive control in individuals with gambling disorder in a crossover study ($n$ = 14). The task presented subjects with a choice of either a smaller and more certain reward or a larger but riskier option over 112 trials of varying probabilities and amounts. After administration of a single dose of 200 mg tolcapone, risky decision-making was increased as there was a shift toward risk neutrality, that is, the individual being indifferent to risk when making a decision. Computational modeling using Bayesian analysis in this study did not reveal consistent reductions in risky decision-making under the tolcapone condition in gamblers, and if anything, tolcapone was associated with increased risky choice.

Valomon et al. used a psychomotor task to test sustained vigilant attention under tolcapone in healthy male subjects following a period of prolonged wakefulness ($n$ = 30). Two doses of 100 mg tolcapone were administered at 11 and 23 hours of prolonged wakefulness in a crossover study. The psychomotor vigilance test used consisted of a timer appearing at random intervals on a screen, with subjects asked to press the "space" bar as soon as they detected the stimulus. They found that tolcapone did not improve sustained attention but rather further impaired sleep loss-induced performance, particularly in Val/Met and Met/Met genotypes. Tolcapone was also found to increase attentional lapses after sleep deprivation.

Martens et al. used an emotional test battery consisting of a Facial Expression Recognition Task (FERT), an Emotional Recall Task, an Emotional Categorization Task, and a Faces Dot Probe Task to assess the impact of tolcapone, and the COMT genotype on emotional processing. Within this parallel study, healthy subjects ($n$ = 74; group size ranged between 17 and 19) were administered a single 200 mg dose of tolcapone or a placebo. They found that neither tolcapone nor the COMT genotype influenced emotional processing or mood ratings.

Westphal et al. investigated whether increasing cortical dopamine function in individuals with severe PTSD improved their working memory performance using an emotional working memory task. A 200 mg dose of tolcapone was administered to subjects

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**Table 1.** Summary of Eligible Studies

| Author | Year of publication | Study design | Cognitive test used (domain measured) | Dose of tolcapone | Number of participants | Condition of participants | Mean age | Gender of participants (male, female) | Summary of results |
|---|---|---|---|---|---|---|---|---|---|
| Cameron et al. | 2018 | Crossover | Saccade task (cognitive stability and flexibility) | 200 mg (one in morning–test 5 h postdrug administration) | 16 (provided data from all 3 sessions–19 started) | 21–36 y | 24.0 | 11, 5 | Tolcapone reduced overall performance efficiency.<br>Tolcapone increased reaction time (participants were slower).<br>Implied tolcapone had a detrimental impact to cognitive aspects of performance. |
| Fremont et al. | 2020 | Crossover | Performance on *N*–back working memory task (working memory)<br>Secondary outcome: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Measures of cognitive performance)<br>NPI–Q (neuropsychiatric/ behavioral symptoms)<br>Clinical Global Impressions scale (CGI) (general clinical status) | 100 mg three times daily for first day<br>200 mg three times daily for next 6 d | 28 | 40–85 y old<br>Matis Dementia Rating Scale–2 (MDRS2) rating score less than 136<br>Behavioral Variant Frontotemporal Dementia | 63.1 | 14, 14 | Tolcapone did not significantly enhance working memory in patients with bvFTD.<br>There were no significant differences in total RBANS, NPI–Q, or CGI scores between tolcapone and placebo. |
| Bhakta et al. | 2017 | Crossover | MATRICS Consensus Cognitive Battery (MCCB)<br>Electroencephalogram–based reverse–translated 5 Choice–Continuous Performance Test (5C–CPT)<br>MCCB tests cognitive domains relevant to cognitive deficits in schizophrenia | 200 mg (on each test day separated by 1 wk) | 27 (31 enrolled)<br>Val/Val = 17<br>Met/Met = 10 | Psychiatrically and medically healthy men and women<br>18–35 y | Subgroup means reported only:<br>Val/Val = 22.0<br>Met/Met = 24.0 | Val/Val = 14, 3<br>Met/Met = 5, 5 | Tolcapone enhanced neurocognition (cognitive and attentional control processes) in specific subgroups of healthy individuals. |
| Furman et al. | 2020 | Crossover | Hierarchical working memory task (working memory with varied maintenance and gating demands) | 200 mg | 49 (60 recruited) (45 for imaging analysis) | Healthy participants<br>No history of medical, psychiatric or neurological contraindications | 21.6 | 23, 26 | Tolcapone improves working memory maintenance without demonstrable effects of gating. |
| Peters et al. | 2020 | Crossover | 112 trials of risky–choice task (value–based | 200 mg (single dose) | 14 | South Oaks Gambling Screen (SOGS) scores >5 | 32.6 | 8, 6 | Tolcapone increased risky decision–making by shifting preference in |

**Table 1.** *Continued*

| Author | Year of publication | Study design | Cognitive test used (domain measured) | Dose of tolcapone | Number of participants | Condition of participants | Mean age | Gender of participants (male, female) | Summary of results |
|---|---|---|---|---|---|---|---|---|---|
| | | | decision–making and cognitive control) | | | 18–50 y old<br>Good health | | | gamblers more toward risk neutrality. |
| Valomon et al. | 2018 | Crossover | Questionnaires, cognitive and neurobehavioral tasks, and waking EEG recordings<br>Psychomotor vigilance test (sustained vigilant attention) | Two doses of 100 mg at 11 and 23 h of prolonged wakefulness | 30<br>Val/Val = 10<br>Val/Met = 10<br>Met/ Met = 10 | Healthy | Val/Val = 23.7<br>Val/Met = 23.3<br>Met/Met = 23.3 | Male | Tolcapone further deteriorated the sleep loss–induced impairment of vigilant attention.<br>Tolcapone does not improve sustained attention after prolonged wakefulness in any COMT genotype. |
| Martens et al. | 2022 | Parallel (Group sizes shown in number of participants column) | Emotional test battery: Facial Expression Recognition Task (FERT), Emotional Categorization Task (ECAT), Faces Dot Probe Task (FDOT), Emotional Recall Task (EREC) (tests multiple dimensions of emotional behaviors and emotional processing–sensitive to antidepressant actions)<br>Profile of Mood States questionnaire (POMS), visual analogue scales (VAS) | 200 mg | 74<br>Met placebo = 19<br>Val placebo = 19<br>Met tolcapone = 19<br>Val tolcapone = 17 | Nonsmoking Healthy | Met placebo = 23.3<br>Val placebo = 25.3<br>Met tolcapone = 24.8<br>Val tolcapone = 22.5 | Male | No effect of tolcapone or COMT Val158Met genotype on performance on an emotional test battery or any effects on subjective mood ratings. |
| Westphal et al. | 2021 | Crossover | fMRI working memory task (working memory) | 200 mg (single dose) | 30 | Military veterans from outpatient clinics within US department of Veteran Affairs exhibiting a range of PTSD severity<br>PTSD severity assessed with Clinician–Administered PTSD Scale for the DSM–5 (CAPS–5) | 35.5 | 25, 5 | Tolcapone increased cortical responses to fearful relative to neutral stimuli in higher severity PTSD subjects, and reduced cortical responses to fearful stimuli for lower severity PTSD subjects |
| Kayser et al. | 2014 | Crossover | Reward learning and exploitation clock–based task | 200 mg (single dose) | 67 completed task (70 enrolled) | Healthy subjects without history of neurological and | 30.0 | 34, 33 | Tolcapone significantly increased exploration. |

**Table 1.** *Continued*

| Author | Year of publication | Study design | Cognitive test used (domain measured) | Dose of tolcapone | Number of participants | Condition of participants | Mean age | Gender of participants (male, female) | Summary of results |
|---|---|---|---|---|---|---|---|---|---|
| | | | (exploration–exploitation trade–off, executive function) | | 64 for genotype–specific analyses | psychiatric illnesses | | | |
| Farrell et al. | 2012 | Parallel (Group sizes shown in number of participants column) | *N*–back task of working memory (working memory)<br>Gambling task | 200 mg | 67<br>16–18 per group[a] | Healthy men<br>18–50 y old<br>No history of psychiatric or neurologic disorder<br>None taking psychotropic medication | Across study 23.7[b] | Male | Tolcapone had opposite effects in the 2 genotype groups: worsened *N*–back performance (working memory) in Met–COMT subjects but enhanced it in Val–COMT subjects. |
| Scholz et al. | 2022 | Crossover | Motivational Go NoGo task (motivational biases vs. automated behaviors, executive function) | 200 mg | 35 (44 completed study) | Healthy | 31.3 | 26, 9 | Tolcapone decreased motivational bias. |
| Giakoumaki et al. | 2008 | Crossover | *N*–back and letter–number sequencing (LNS) tasks (working memory) | 200 mg | 23 (24 recruited)<br>Val/Val = 12<br>Met/Met = 11 | Healthy | Val/Val = 26.6<br>Met/Met = 24.6 | Male | Tolcapone improved performance in the *N*–back and LNS tasks only in Val/ Val group. |
| Apud et al. | 2006 | Crossover | Neuropsychological testing (NPT) and fMRI (working memory and prefrontal cognitive processing)<br>Neuropsychological battery[c] | 100 mg three times daily for 7 d from first day<br>200 mg three times daily for next 6 d | 47 (51 qualified for study)<br>34 included for fMRI, 39 for COMT enzyme assays | 18–55 y<br>Healthy<br>Off medication for 6 wk<br>Subjects with family history of schizophrenia, schizoaffective disorder or schizophrenia spectrum disorder were excluded | Val/Val = 35.5<br>Val/Met = 38.4<br>Met/Met = 33.8 | Val/Val = 6, 9<br>Val/Met = 14, 7<br>Met/Met = 4, 7 | Tolcapone enhances memory and executive cognition and the physiologic efficiency of prefrontal cortical information processing in normal human subjects. |

[a]Paper was not clear.
[b]Paper was not clear for the separate groups so overall average age across all groups was given.
[c]NPT included the following: N-back test of working memory and updating (dependent measure included accuracy and RT), verbal fluency (for categories), verbal episodic memory, continuous performance test of target detection and attention, CANTAB intradimensional/extradimensional componential test of set shifting, letter number span, Trail Making B Test of attention, visual scanning and rapid set switching, Wisconsin card sorting test of executive function.

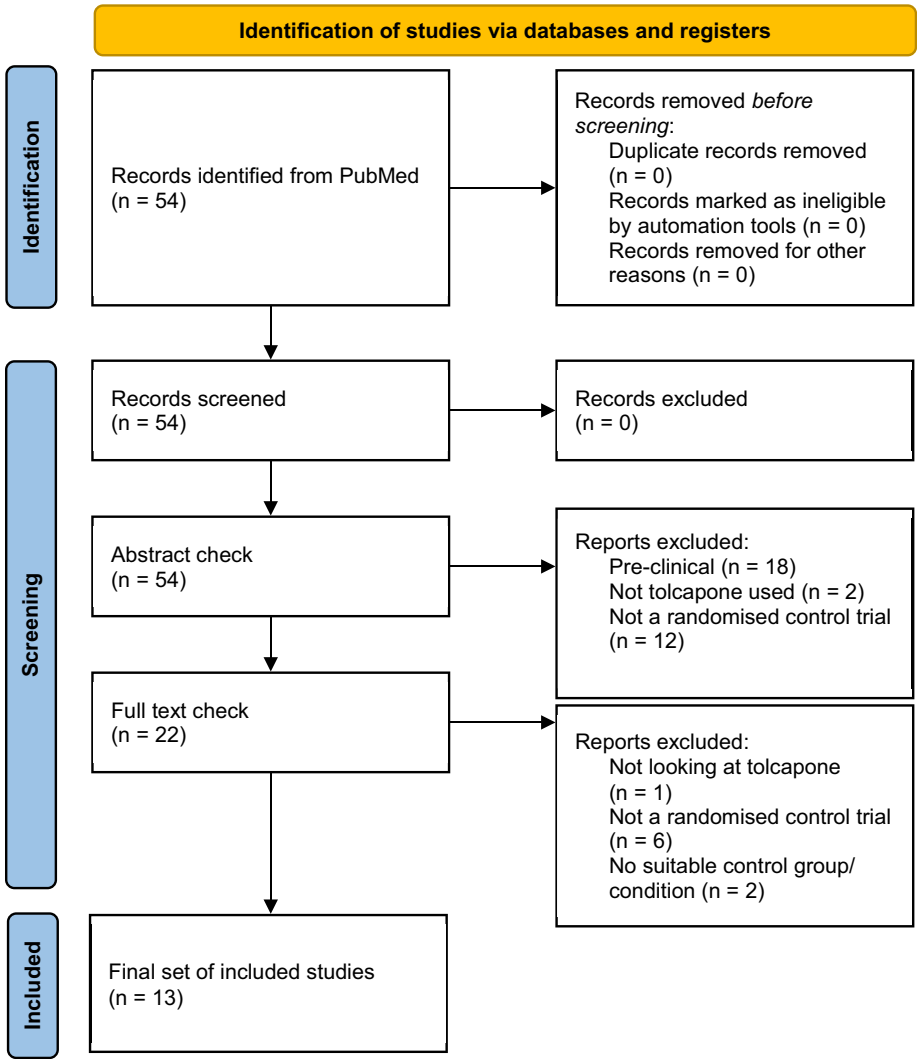


**Figure 2.** PRISMA flowchart.

with varying levels of PTSD severity ($n$ = 30) in a crossover study design. The study found that the results followed an inverted-U relationship as subjects with a lower PTSD severity, and subsequently, a potentially higher cortical dopamine tone, saw a worsening of performance under tolcapone; however, those with a higher PTSD severity and subsequently, a relatively lower cortical dopamine tone, showed improvements in working memory compared to placebo.

Another study conducted by Kayser et al. used a clock-based task to assess reward learning and the exploration–exploitation trade-off (the decision between seeking out a potentially greater value reward or keeping within the known environment). During the task, participants observed a clock face with a 5-second rotation and were required to press a key to stop the clock. Rewards were assigned based on the varying interaction between probability, magnitude, and response time. They used a crossover study to look at the effects of a single 200 mg dose of tolcapone on healthy male and female participants ($n$ = 67). They found that tolcapone significantly increased exploration, in particular in Met/Met, subjects compared to placebo.

Farrell et al. used the $N$-back working memory task to explore the inverted-U model of COMT inhibition. They used a parallel study testing 200 mg tolcapone versus placebo in healthy men in COMT Met158Met and COMT Val158Val polymorphisms ($n$ = 67; the sample size was not clear in the paper but appeared to be between 16 and 18 per group). They found that in Val-COMT subjects, working memory improved under tolcapone but was impaired in the Met-COMT subjects compared to placebo. They also found that reaction time decreased under tolcapone (ie improved) in Val-COMT subjects but not in Met-COMT subjects.

Scholz et al. explored the influence of frontal dopamine on the relationship between motivational biases and automated behavior using healthy men and women ($n$ = 35). They did this by using a motivational Go NoGo task in a crossover study. The task involved showing participants different cues that required either a response (Go) or not (NoGo) to win rewards or to avoid punishment. The ability to control the motivational bias depends on choosing between action-valence congruent (choosing a Go response to win a task or a NoGo response to avoid a punishment) and incongruent cues (choosing a Go response to avoid a punishment). They found that tolcapone globally reduced motivational biases across both bias-congruent and incongruent Pavlovian-instrumental trials.

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Giakoumaki et al. used *N*-back and letter-number sequencing tasks to assess working memory. Using a crossover study, they assessed 23 healthy males following the administration of 200 mg tolcapone compared to a placebo. The letter-number sequencing task required the participants to remember and reorder chains of mixed-up letters and numbers with varying difficulty. It is designed to assess participants' working memory and information processing with the accuracy of the task referring to the number of correct strings identified. Val/Val subjects had improved working memory and higher accuracy in the letter-number sequencing responses under tolcapone compared to placebo.

Apud et al. used neuropsychological testing including an *N*-back test of working memory, verbal fluency and verbal episodic memory tasks to investigate the effect of tolcapone on prefrontal cortical information processing. They used a crossover study to test a mix of healthy males and females ($n = 47$). Tolcapone was taken for 7 days before testing commenced; 100 mg was administered three times on the first day and then 200 mg was taken three times daily for the remaining 6 days. They found that tolcapone improves memory as well as enhances prefrontal cortical information processing within the subjects. They also found that under tolcapone, executive cognition is improved; this refers to functions involved in control and direction, for example, information processing, decision-making, and planning.

Having described the above studies, we then considered conducting a meta-analysis from the data in some of the studies. The studies include a wide range of tasks resulting in an array of domains being explored. The most common task used was the *N*-back task designed to assess working memory; this was used in four of the studies. Several of the results from the studies were presented graphically, which could not directly be used in the meta-analysis (ie actual numbers were not presented in a way through which they could be reliably extracted). Therefore, we contacted the authors of the papers where this was the case, requesting access to the necessary variables (eg mean and standard deviation of performance in each condition). Unfortunately, the data were unavailable due to the authors no longer having access to it. We then attempted to extract the data from the graphs; however, one of the papers was unclear about the nature of the error bars and another was presented in a format that was unable to be interpreted accurately by hand. After being able to source three sets of results for the reaction time of the *N*-back task, it was discovered that two of the papers had been split into the COMT genotypes, however, the third had not. Therefore, there were insufficient data to conduct a meta-analysis.

## Discussion

This systematic review focused on the effects of tolcapone, a COMT inhibitor that predominantly increases dopamine in the PFC, on cognition in adults compared to an appropriate control condition (ie placebo). Dopamine within the PFC plays a key role in the efficiency of many cognitive functions.[28,29] Below, we synthesize key findings as a function of DSM-5 listed cognitive domains.

### *Executive function*

#### Working memory

Generally, the effect of tolcapone on working memory was found to be contingent on the COMT genotype polymorphism, such that cognitive enhancing effects were most consistently found in Val–Val polymorphism status[19,20,30] (ie in those with putatively lower cortical dopamine levels pre-treatment). This is consistent with inverted-U models of cortical function.[31,32] The inverted-U theory here describes the potential effect of the modulation of dopamine on an individual based on their level of baseline dopamine (or performance on a cognitive task in some cases). These levels seen before administration can impact the direction and magnitude of effect of tolcapone. In participants with the Val-COMT variant, working memory was improved under tolcapone compared to placebo.[19,20] Tolcapone was also found to improve accuracy in a letter-number sequencing task in those homozygous with the Val allele, further suggesting improvements in working memory as well as information processing. However, subjects with the Met-COMT genotype showed a relative decrement in working memory after administration of tolcapone. It should be noted that these findings were from studies that involved only healthy males. Another study that did not break down groups into their COMT genotypes, found that tolcapone enhanced prefrontal cortical processing overall.[13] In patients with bvFTD, however, tolcapone was found not to have any effect on working memory.[33] This could reflect an inability of tolcapone to significantly modulate a cognitive function whose neurobiological underpinnings have been affected by organic pathology.

#### Decision-making

Tolcapone was reported to have increased risky decision-making in patients with gambling disorder.[18] The study did not separate participants based on their COMT polymorphism, however, reporting this with their small sample size ($n = 14$) would have been problematic.

Tolcapone was shown to increase exploration[34] during research of the exploration–exploitation trade-off, which is linked to decision-making. This suggests that after administration of tolcapone, subjects were more likely to leave the familiar environment, in search of potentially more value in an unknown stimulus. This supports the notion that tolcapone can have an effect on that aspect of decision-making but further research would be required to understand exploration and its contextual significance.

#### Cognitive stability and flexibility

During a task that the authors felt to measure cognitive stability and flexibility, tolcapone was found to decrease performance efficiency and increased reaction time, both implying a detrimental impact to cognitive aspects of performance.[35] This was found particularly in Met/Met subjects compared to placebo. However, the study used a saccade task tracking eye movements, which is challenging to interpret within a cognitive flexibility framework—more conventionally, this domain would be measured using, for example, a set-shifting task.

#### Motivational biases versus automated behaviors

Tolcapone decreased motivational biases across both bias-congruent and incongruent Pavlovian-instrumental trials,[36] suggesting an increase in cortical dopamine reduces the impact of motivational biases governing automated behavior. This study had a large ratio of male to female participants which should be taken into consideration; the results might not generalize similarly well to non-males.

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### Complex attention

#### Sustained vigilant attention

During a period of 40 hours of extended wakefulness, administration of tolcapone was shown to impair sleep loss-induced performance, particularly in subjects with Val/Met and Met/Met variants compared to Val/Val variants.[37] It was also seen to increase the frequency of attentional lapses after sleep deprivation. Overall, tolcapone seemed to have a detrimental effect on sustained vigilant attention in adult healthy males, in this study.

#### Cognitive and attentional control processes

When studying cognitive and attentional control processes, the effects of tolcapone generally adopted an inverted-U relationship depending on the baseline performance on the task.[38] Subjects with a low baseline performance saw an improvement in cognitive and attentional control processes under tolcapone compared to placebo. However, tolcapone was found to impair participants with a high baseline performance. Within this study, it should be highlighted that a small sample size was used, specifically, only three women were tested with the Val/Val variant.

### Emotional processing

Neither tolcapone, nor COMT genotype, were found to influence emotional processing or mood rating in healthy male subjects.[39]

### Limitations

Several potential limitations should be considered in relation to this systematic review. First, while we considered conducting a meta-analysis (as noted in our preregistration), an insufficient nature and number of studies was found to do this—studies were few in number and often adopted diverse methods, including variable reporting approaches and different neurocognitive testing procedures, prohibiting a meaningful pooling of effect estimates. This disallowed any meta-analysis at this stage. Second, there were not many overlaps of cognitive domains being tested across studies, which presented problems when trying to group data and draw strong conclusions. The majority of the studies used different methods to assess cognitive performance, for example, although there were multiple studies testing working memory, a variety of tasks were used such as an *N*-back task, a hierarchical working memory task and an fMRI working memory task. Third, we limited the literature search to English Language articles on PubMed and as such grey literature or articles in other languages may have been overlooked. At the same time, this approach does mean that all papers considered herein were peer-reviewed and could be readily interpreted by the study team. A limitation of much of the existing literature is that some potential confounding variables for the baseline level of dopamine were not measured such as whether participants had any degree of sleep deprivation or different levels of caffeine or nicotine consumption prior to study participation. With a lack of mention of these factors, it is uncertain as to whether they had a role to play within the results, and therefore conclusions drawn from the studies.

Due to the variation in dosing amounts and dosing duration, for example, a one-off, versus a daily dose, across the literature, it is not clear if cognitive effects of tolcapone differ markedly as a function of dosage regimens. This was a limitation of the literature and should be addressed in future work.

When looking at the quality of the studies included, some of the studies did not score highly within our criteria, which could potentially hinder the conclusions drawn from the studies, suggesting further research in this area is necessary.

## Conclusions

Our first hypothesis was only partially supported: while some studies found cognitive enhancing effects of tolcapone (irrespective of COMT polymorphism) this was not a universal finding either within or across cognitive domains. Our second hypothesis was also only partly supported: particularly for working memory tasks,[13,19,20] there was evidence that effects of tolcapone operated according to an inverted "U" model of human cognition. Specifically, tolcapone tended to enhance performance in people with putatively lower baseline cortical dopamine (Val–Val status) and to have no effect (or impair performance) in those with putatively higher baseline cortical dopamine (Met-Met status). It was unclear if this might generalize across other cognitive domains and this was challenging to consider, due to the relative poverty of studies.

Most of the studies examined the effects of tolcapone in healthy subjects but there was a limited number looking at the effect of tolcapone in clinical groups. One study showed there was no effect of tolcapone on working memory in patients with bvFTD which could be due to the deficiencies in the dopamine systems linked to the disease,[40] and another examined gambling disorder with unclear or potentially detrimental cognitive effects for tolcapone.[18]

Given that tolcapone can impact cognition, as shown in many but not all of the studies considered in this systematic review, it would be valuable to further examine its effects in larger sample sizes and a greater diversity of populations. For example, future work could examine effects across genders and also in different clinical cohorts, such as patients with impulsive or compulsive disorders. Evaluation of cognitive effects of tolcapone may shed further light on the role of cortical dopamine in human cognition but also the mechanisms by which tolcapone may show efficacy in the treatment of certain disorders linked to executive dysfunction, such as OCD.[11]

**Supplementary material.** The supplementary material for this article can be found at http://doi.org/10.1017/S1092852924000130.

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