Supplementary materials: A systematic review of the cognitive effects of the COMT inhibitor, tolcapone, in adult humans

Our scoring system consisted of 11 items based on a mix of standard quality assessments as well as more specifically tailored questions for our systematic review. The papers scored a point for including each of the 1) a report of co-morbidities using an appropriate method including mood and anxiety disorders 2) a report of substance misuse co-morbidities assessed using an appropriate method 3) a report of the dosage of tolcapone used 4) an IQ measure 5) a report of level of education or equivalent 6) a report of appropriate cognitive performance measures 7) a numerical report of cognitive performance measures 8) a report of the demographics 9) controls selected or recruited from the same population that gave rise to the cases 10) the measures of exposure/ risk clearly defined, valid, reliable and implemented consistently 11) the assessors of exposure/ risk blinded to the case or control status of the participants.

TABLE S1 – Quality measures of studies

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author | Paper | Co-morbidities | Substance misuse co-morbidities | Tolcapone dosage | IQ measure | Education | Appropriate cognitive performance measures  | Numerical cognitive performance measures | Demographics well reported | Controls | Exposure/ risk | Assessors blinded? | Total |
| Cameron et al. | Effects of tolcapone and bromocriptine on cognitive stability and flexibility | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| Fremont et al. | Tolcapone Treatment for Cognitive and Behavioral Symptoms in Behavioral Variant Frontotemporal Dementia: A Placebo-Controlled Crossover Study | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Bhakta et al.  | Tolcapone-Enhanced Neurocognition in Healthy Adults: Neural Basis and Predictors | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Furman et al. | Augmenting Frontal Dopamine Tone Enhances Maintenance over Gating Processes in Working Memory | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| Peters et al. | Dopamine and Risky Decision-Making in Gambling Disorder | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 10 |
| Valomon et al.  | Effects of COMT genotype and tolcapone on lapses of sustained attention after sleep deprivation in healthy young men | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Martens et al. | Catechol-O-methyltransferase activity does not influence emotional processing in men | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 10 |
| Westphal et al. | Working memory, cortical dopamine tone, and frontoparietal brain recruitment in post-traumatic stress disorder: a randomized controlled trial | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| Kayser et al.  | Dopamine, locus of control, and the exploration-exploitation tradeoff | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Farrell et al.  | COMT Val(158)Met genotype determines the direction of cognitive effects produced by catechol-O-methyltransferase inhibition | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 11 |
| Scholz et al.  | Cortical dopamine reduces the impact of motivational biases governing automated behaviour | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 11 |
| Giakoumaki et al.  | Improvement of prepulse inhibition and executive function by the COMT inhibitor tolcapone depends on COMT Val158Met polymorphism | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 8 |
| Apud et al.  | Tolcapone improves cognition and cortical information processing in normal human subjects | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 11 |

TABLE S2 – Identified studies from the literature search and status (included, or excluded and reasons for this)

|  |  |  |  |
| --- | --- | --- | --- |
| Title | Author | Included? | Reason for exclusion  |
| Effects of tolcapone and bromocriptine on cognitive stability and flexibility | Cameron et al | Yes |  |
| Tolcapone Treatment for Cognitive and Behavioral Symptoms in Behavioral Variant Frontotemporal Dementia: A Placebo-Controlled Crossover Study | Fremont et al | Yes |  |
| Bad guys' among the antiparkinsonian drugs | Pirosek et al | No | Not in scope (a review) |
| Tolcapone-Enhanced Neurocognition in Healthy Adults: Neural Basis and Predictors | Bhakta et al | Yes |  |
| Augmenting Frontal Dopamine Tone Enhances Maintenance over Gating Processes in Working Memory | Furman et al | Yes |  |
| Effects of Dopaminergic Drugs on Cognitive Control Processes Vary by Genotype | Furman et al | No | Not in scope (not randomised trial- stratified) |
| Catechol-o-methyltransferase inhibitor tolcapone improves learning and memory in naïve but not in haloperidol challenged rats | Mihaylova et al | No | Not in scope (pre-clinical) |
| Dopamine and Risky Decision-Making in Gambling Disorder | Peters et al | Yes |  |
| Innovative mechanisms of action for pharmaceutical cognitive enhancement: A systematic review | Fond et al | No | Not in scope (systematic review) |
| Advances in the pharmacological management of Parkinson disease | Tolosa et al | No | Not in scope (a review) |
| The efficacy of homemade tolcapone in the treatment of patients with Parkinsons disease | Zhang et al | No | Not in scope (homemade tolcapone) |
| Effects of COMT genotype and tolcapone on lapses of sustained attention after sleep deprivation in healthy young men | Valomon et al | Yes |  |
| Current management of the cognitive dysfunction in Parkinson's disease: how far have we come? | Vale et al | No | Not in scope (not randomised trial- a review) |
| Catechol-O-methyltransferase activity does not influence emotional processing in men | Martens et al | Yes |  |
| Working memory, cortical dopamine tone, and frontoparietal brain recruitment in post-traumatic stress disorder: a randomized controlled trial | Westphal et al | Yes |  |
| [The usefulness of dopaminergic drugs in traumatic brain injury] | Orient-López et al | No | Not in scope (a review) |
| Treatment of Gambling Disorders | Yip et al | No | Not in scope (a review) |
| Enhancing dopamine tone modulates global and local cortical perfusion as a function of COMT val158met genotype | Furman et al | No | Not in scope (not randomised) |
| Diverse facets of COMT: from a plausible predictive marker to a potential drug target for schizophrenia | Gupta et al | No | Not in scope (a review) |
| Tolcapone Derivative (Tol-D) Inhibits Aβ42 Fibrillogenesis and Ameliorates Aβ42-Induced Cytotoxicity and Cognitive Impairment | Chen et al | No | Not in scope (tolcapone derivative) |
| Tolcapone, COMT polymorphisms and pharmacogenomic treatment of schizophrenia | Bitsios et al | No | Not in scope (article) |
| Treatment of cognitive deficits associated with schizophrenia: potential role of catechol-O-methyltransferase inhibitors | Apud et al | No | Not in scope (a review) |
| Effects of tolcapone on working memory and brain activity in abstinent smokers: a proof-of-concept study | Ashare et al | No | Not in scope (not randomised) |
| Dopamine, locus of control, and the exploration-exploitation tradeoff | Kayser et al | Yes |  |
| Highs and lows of cannabinoid-dopamine interactions: effects of genetic variability and pharmacological modulation of catechol-O-methyl transferase on the acute response to delta-9-tetrahydrocannabinol in humans | Ranganathan et al | No | Not in scope (not randomised) |
| General Aggregation-Induced Emission Probes for Amyloid Inhibitors with Dual Inhibition Capacity against Amyloid β-Protein and α-Synuclein | Jia et al | No | Not in scope (pre-clinical) |
| Tolcapone enhances food-evoked dopamine efflux and executive memory processes mediated by the rat prefrontal cortex | Lapish et al | No | Not in scope (pre-clinical) |
| COMT Val(158)Met genotype determines the direction of cognitive effects produced by catechol-O-methyltransferase inhibition | Farrell et al | Yes  |  |
| Optimization and pharmacological validation of a set-shifting procedure for assessing executive function in rats | Troudet et al | No | Not in scope (pre-clinical) |
| Membrane bound catechol-O-methytransferase is the dominant isoform for dopamine metabolism in PC12 cells and rat brain | Su et al | No  | Not in scope (pre-clinical) |
| Synthesis and Evaluation of Heterocyclic Catechol Mimics as Inhibitors of Catechol-O-methyltransferase (COMT) | Harrison et al | No | Not in scope (not RCT) |
| Orientation and cellular distribution of membrane-bound catechol-O-methyltransferase in cortical neurons: implications for drug development | Chen et al | No | Not in scope (pre-clinical) |
| Cortical dopamine reduces the impact of motivational biases governing automated behaviour | Scholz et al | Yes |  |
| Novel, non-nitrocatechol catechol-O-methyltransferase inhibitors modulate dopamine neurotransmission in the frontal cortex and improve cognitive flexibility | Byers et al | No | Not in scope (pre-clinical) |
| Anterior cingulate dopamine turnover and behavior change in Parkinson's disease | Gallagher et al | No | Not in scope (not randomised - convience sampling) |
| Improvement of prepulse inhibition and executive function by the COMT inhibitor tolcapone depends on COMT Val158Met polymorphism | Giakoumaki et al | Yes |  |
| Modulation of hippocampal dopamine metabolism and hippocampal-dependent cognitive function by catechol-O-methyltransferase inhibition | Laatikainen et al | No | Not in scope (pre-clinical) |
| Effects of catechol-O-methyltransferase inhibitors and L-3,4-dihydroxyphenylalanine with or without carbidopa on extracellular dopamine in rat striatum | Kaakkola et al | No | Not in scope (pre-clinical) |
| Brain catechol-O-methyltransferase (COMT) inhibition by tolcapone counteracts recognition memory deficits in normal and chronic phencyclidine-treated rats and in COMT-Val transgenic mice | Detrait et al | No | Not in scope (pre-clinical) |
| [A prospect of treatment for Parkinson's disease in the 21st century] | Yanagisawa et al | No | Not in scope (a review) |
| Tolcapone improves cognition and cortical information processing in normal human subjects | Apud et al | Yes |  |
| Generation and characterization of humanized mice carrying COMT158 Met/Val alleles | Risbrough et al | No | Not in scope (pre-clinical) |
| A proof of concept study of tolcapone for pathological gambling: relationships with COMT genotype and brain activation | Grant et al | No | Not in scope (no alternative control group) |
| Putative therapeutic targets for symptom subtypes of adult ADHD: D4 receptor agonism and COMT inhibition improve attention and response inhibition in a novel translational animal model | Tomlinson et al | No | Not in scope (pre-clinical) |
| Effects of COMT inhibitors on striatal dopamine metabolism: a microdialysis study | Kaakkola et al | No | Not in scope (pre-clinical) |
| Cognitive improvement during Tolcapone treatment in Parkinson's disease | Gasparini et al | No | Not in scope (no alternative control group) |
| Effects of selective catechol-O-methyltransferase inhibitors on single-trial passive avoidance retention in male rats | Khromova et al | No | Not in scope (pre-clinical) |
| Characterization of non-nitrocatechol pan and isoform specific catechol-O-methyltransferase inhibitors and substrates | Robinson et al | No | Not in scope (pre-clinical) |
| Sub-optimal performance in the 5-choice serial reaction time task in rats was sensitive to methylphenidate, atomoxetine and d-amphetamine, but unaffected by the COMT inhibitor tolcapone | Paterson et al | No | Not in scope (pre-clinical) |
| Telescoping phenomenon in pathological gambling: association with gender and comorbidities | Grant et al | No | Not in scope (does not look at effects of tolcapone- 'subjects enrolled in clinical research trials investigating the effectiveness of …, tolcapone etc') |
| Highlights from the Biennial International Congress on Schizophrenia Research (ICOSR), March 24-March 28, 2017 | Heimer et al | No | Not in scope (highlights from congress) |
| Clinical insights into pharmacogenetics and schizophrenia, part 2 | Kane et al | No | Not in scope (academic highlights) |
| Genotype-Dependent Effects of COMT Inhibition on Cognitive Function in a Highly Specific, Novel Mouse Model of Altered COMT Activity | Barkus et al | No | Not in scope (pre-clinical) |
| Release and elimination of dopamine in vivo in mice lacking the dopamine transporter: functional consequences | Benoit-Marand et al | No | Not in scope (pre-clinical) |
| Pharmacological Modulation of Temporal Discounting: A Systematic Review | Sarmiento et al | No | Not in scope (systematic review) |