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**Assessing the effects of Pergolide on the motivational aspects of depression in rats using operant conditioning**

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Honors Thesis

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## **Abstract**

Pergolide is an ergot derivative dopamine agonist which acts on the dopamine D2 and D3, alpha2- and alpha1-adrenergic, and 5-hydroxytryptamine receptors. It was previously used as a treatment for the symptoms of Parkinson's disease, but was taken off of the market as a result of causing increased risk of heart disease. As a dopamine agonist, pergolide stimulates D2 receptors, which are associated with improvement of symptoms of movement disorders. This link exists because the highest concentration of D2 receptors in the brain is in the basal ganglia, which is involved in motor control. Given the connection between pergolide, dopamine, and motor function, this paper analyzes the effects of pergolide on motivation related to depression. Individuals who have been diagnosed with depression show decreased locomotion, which is correlated with the severity of the depression. The symptoms associated with depression of lethargy and low motivation can be modeled in rats using the vesicular monoamine transporter inhibitor tetrabenazine (TBZ), which depletes dopamine. It has been shown that dopamine transport blockers such as bupropion and GBR12909 can reverse the effects of TBZ in rats, but this study will investigate the effects of a dopamine receptor agonist on motivation. Using an FR-5 fixed- ratio/chow feeding choice task, laboratory rats are given the option of choosing to either press the lever and receive a preferred high carbohydrate pellet or approach and consume the less preferred lab chow provided concurrently in the operant conditioning box. TBZ reduces selection of lever pressing, and it was hypothesized that treatment with pergolide would reverse the effects of TBZ and increase lever pressing in the effort-related choice task.

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## Table of Contents

Pages 1-6.....	Introduction
Pages 6-8.....	Methods
Pages 8 & 9.....	Results
Pages 10-16.....	Discussion
Page 17.....	Conclusion
Pages 18-20.....	References

## **Introduction**

Motivation as a concept involves the basic need of organisms to access stimuli needed for survival, like food and water. Reinforcement and punishment are examples of the learning processes that organisms undergo, which teach them specific behaviors that regulate the probability, proximity, and availability of significant stimuli. There are many environmental factors that contribute to the selection of particular behaviors in a given context, even after the appropriate responses to stimuli are acquired (Salamone et al., 2012). According to one conceptualization, reward processing follows a sequence of six cognitive operations. First is option generation, when the options for possible rewarding behaviors are created. Next is decision making, when the options undergo cost-benefit analysis in order to balance potential rewards against associated costs, which results in the selection of one of the options. After the decision is made and an option is chosen, the preparatory phase occurs which is the physiological arousal before a reward is obtained. Step four is action and effort, when action is taken in order to obtain the reward, followed by consummation or the pleasurable effect that follows obtaining the reward. Lastly is reinforcement learning, where the subject learns how to behave in future interactions with similar stimuli (Halachakoon et al., 2020).

Motivational dysfunctions have been implicated in the psychopathology of a variety of psychiatric disorders including depression and schizophrenia. Disorders of diminished motivation are characterized by impairment in goal-directed behavior, thought and emotion (Spiegel et al., 2018). In people diagnosed with depression, there exists a low effort bias (i.e., a reduced tendency to select high-effort activities). People with depression and related disorders also show psychomotor or motivational

impairments in addition to changes in mood. Examples of these psychomotor damage can be anergia, fatigue, and psychomotor retardation (Randall et al., 2014). Other central features of depression include concentration and memory problems, which are associated with cognitive control deficits. Other cognitive impairments and negative biases can occur as a result of these deficits. Cognitive control is also integral in motivation and goal-directed behavior, because it constitutes the processes that allow changes in cognition and behavior to tailor both towards the present goal (Grahek et al., 2019).

It is known that one of the key factors involved in effort-based decision making is dopamine transmission. The dopamine system is important in reward prediction, motivational arousal, and responsiveness to conditioned stimuli. It has also been suggested that dopamine is needed in the process of attributing incentive to motivational stimuli. This modifies the view of an organism about the reward, to go from liking it to wanting it and treating it as an incentive (Belujon et al., 2017). Due to the connection between DA and motivation, much research has been done on the subject and it has been found that decreased DA transmission in animal models mimics the motivational effects associated with depression in humans. It is known that dopamine antagonists as well as nucleus accumbens dopamine depletions in rats negatively impact performance on motivated tasks that involve avoidance, punishment, and taste aversion (Salamone et al., 2003).

Extensive research has been conducted on the role of dopamine depletion in effort-related choice tasks in rats. In experiments using rats, effort-based decision making is studied by using tasks that offer the animal a choice. This choice is between a

higher effort action which leads to a more highly valued reinforcer, or a lower effort option which leads to a less valued reinforcer. (Randall et al., 2014). Using tetrabenazine (TBZ), which is a selective and reversible inhibitor of VMAT-2 (vesicular monoamine transporter- type 2), the effects of dopamine depletion can be simulated in rats. Tetrabenazine depletes monoamines like dopamine and blocks their storage. Its effects are greatest on striatal dopamine, and it is used to treat Huntington's disease. When used for treatment, common side effects are depressive symptoms like fatigue. Because it can produce the symptoms of depression, TBZ has been used often to study animal models of depression (Nunes et al., 2013). In a concurrent progressive ratio (PROG)/chow feeding choice task, where rats have the choice between lever pressing on a progressive schedule reinforced by preferred high-carbohydrate pellets or consuming a less preferred laboratory chow that is available in the chamber, TBZ significantly decreased total lever presses and there was significant effect of treatment on active lever time (Randall et al., 2014). In the same choice task, the dopamine D1 antagonist ecopipam also significantly decreased total lever presses (Randall et al., 2014), highlighting a clear connection between dopamine depletion and effort-related behavior in rats.

In a study researching the effects of bupropion, which inhibits both norepinephrine and dopamine reuptake, it elevated extracellular dopamine levels in the nucleus accumbens core and increased phosphorylated dopamine and cyclic-AMP related phosphoprotein immunoreactivity, which is consistent with the stimulation of D1 and D2 dopamine receptors (Randall et al., 2014). Dopamine transport blockers like bupropion enhance dopamine transmission by inhibiting dopamine transporters and



therefore increasing the amount of extracellular dopamine. Bupropion also significantly increased all measures of progressive ratio lever pressing (Randall et al., 2014), providing insight into pharmacological treatments for the motivational symptoms associated with depression. Clinical studies show that DAT inhibitors like bupropion, amphetamine, and methylphenidate can improve motivation in people. This matches the results seen in rats treated with DAT blockers to reverse effort-related impairments. DAT blockers in studies successfully increased selection of high-effort activities in rats. Additionally, modafinil, which inhibits DAT and acts as a wakefulness agent, has been shown to improve motivational function in people diagnosed with depression. Modafinil also elevates extracellular dopamine, which supports the fact that dopamine transmission is crucial to motivation (Rotolo et al., 2020).

In addition, it has been shown that D1 agonists are able to reverse the effects of D1 antagonists (Yohn et al., 2015). Dopamine agonists work by binding to the active site on the dopamine receptor and stimulating the same intrinsic biological activity as the neurotransmitter. In a study done to assess D1 agonist/antagonist interactions and the effect on effort-related decision making, the D1 antagonist ecopipam and the D1 agonists SKF38393, SKF81297 and A77636 were used to treat rats. Using an FR5/chow-feeding choice task, it was found that ecopipam decreased lever pressing and increased chow consumption. Each of the D1 agonists were able to reverse the effects of ecopipam on the effort-related task, and they increased lever pressing (Yohn, 2015).

Dopamine agonists have also been tested in mouse models of Parkinson's disease (Wakamatsu et al., 2007). Using transgenic mice (Syn130m) which expressed

truncated  $\alpha$ -synuclein in dopaminergic neurons, the researchers were able to create an animal model of Parkinson's disease with significant loss of dopaminergic neurons in the substantia nigra pars compacta and reduced spontaneous locomotor activity. These mice were then treated with L-DOPA (a precursor to dopamine) as well as D2 agonists quinpirole and talipexole, and the D1/D2 agonist pergolide. With administration of all four drugs, there was effective reversal of the dopamine reduction. In addition, pergolide was able to reverse reduction in exploratory behavior in the mice (Wakamatsu et al., 2007). The current study evaluates the effect of the ergotamine derivative dopamine agonist pergolide (8 $\beta$ [(methylthio)methyl]-6-propylergoline monomethanesulfonate) on an effort-related choice task in rats.

Pergolide is a potent, direct-acting dopamine agonist used in treating Parkinson's disease. It is an agonist found recently to have high affinity for D3 receptors. Pergolide has higher affinity for dopamine D2 receptors than for D1 receptors. There have also been reports that the in vivo dose required to activate D2 receptors may not be the appropriate dose for interaction with D1 receptors (Fuller et al., 1982). Pergolide acts on dopamine D2 and D3,  $\alpha$ 2- and  $\alpha$ 1-adrenergic, and 5-hydroxytryptamine (5-HT) receptors (*Pergolide*) Research has been done on the link between treatment with Pergolide and tardive dyskinesia in rats. In rats, low doses of pergolide (0.01mg/kg or less, intraperitoneally) decreased dopamine turnover, serum prolactin concentration, and decreased blood pressure in rats who were spontaneously hypertensive. At somewhat higher doses (0.05 mg/kg or more, intraperitoneally), pergolide caused contralateral turning in nigrostriatal-lesioned rats, elevation of serum corticosterone, and hypermotility with stereotyped behavior (Fuller et al., 1982). At low

doses, pergolide acts presynaptically on auto receptors modulating dopamine release, while at high doses it produces appetite suppression and atypical locomotion.

In Parkinson's disease, there is a degeneration of the nerve cells in the substantia nigra, which controls movement. These nerve cells either die or become impaired, losing the ability to produce dopamine, and studies have shown that symptoms of Parkinson's develop in patients with an 80 percent or greater loss of dopamine-producing cells in the substantia nigra (*Parkinson's disease*). In a study done assessing the effects of pergolide treatment in Parkinson's patients compared to levodopa, a precursor to dopamine which also stimulates dopamine transmission, both drugs showed significant increase in Activity of Daily Living (ADL) and motor examination subscores of the Unified Parkinson's Disease Rating Scale (UPDRS) compared to the baseline and this improvement was maintained throughout the study period (Bonuccelli et al., 2002). There is, therefore, evidence that suggests that treatment with pergolide may increase lever pressing on an effort-related choice task in rats, due to its motor effects in humans. The hypothesis of the current study was that pergolide would increase lever pressing in the effort-related choice task. However, what is uncertain is whether or not low doses may produce the opposite effect due to actions on presynaptic autoreceptors.

## **Methods**

### ***Subjects:***

Adult male Sprague Dawley rats (Envigo, Indianapolis, IN, USA) were housed in a colony maintained at 23°C with 12-h light/dark cycles. Rats (n=8) weighed 275-299g

at the beginning of the study, and were initially restricted to 85% of their free feeding body weight for operant training. Rats were fed supplemental lab chow to maintain body weight targets throughout the study, with water available ad libitum. Rats were allowed modest weight gain throughout the experiment based upon a growth curve approved by the animal care staff and attending veterinarian. Animal protocols were approved by the University of Connecticut animal care and use committee, which followed NIH guidelines.

***Apparatus:***

Behavioral sessions were conducted in operant chambers (28 x 23 x 23 cm; Med Associates, Fairfax, VT), with a single lever on the left side of the chamber, and a pellet dispenser in the middle of the wall containing the manipulandum. The sessions were controlled by Med PC software (version 5.0).

***Behavioral Procedures:***

Behavioral sessions were conducted in operant chambers and lasted 30 minutes a day for 5 days/week. After 3 days of magazine training rats were trained to lever press on a FR1 schedule to receive 45-mg high carbohydrate pellets for 3 days. This was followed by 5 weeks of training on a FR5 schedule, after which lab chow was introduced into the chamber. During each FR5/chow feeding choice session, 15-20g of lab chow was available on the floor of the chamber, and animals had a choice between the two sources of food. Rats were trained on this FR5/chow feeding choice procedure for 5 weeks, after which drug testing began. Sessions lasted 30 min a day for 5 days/week.

Rats were generally tested 5 days per week, with four baseline days and one drug treatment day.

### ***Drug Treatment:***

Pergolide (8 $\beta$ [(methylthio)methyl]-6-propylergoline monomethanesulfonate) intraperitoneal injections were administered to the rats in doses of 0.01mg/kg, 0.02 mg/kg, and 0.04 mg/kg or vehicle (0.9% saline) with a 15 minute lead time.

## **Results**

### ***Effects of Pergolide on Lever Pressing***

With respect to lever pressing, for the vehicle (M=1544, SEM= 85.15238). For the 0.01mg/kg dose, (M= 730.8571, SEM= 119.6345) . For 0.02mg/kg (M= 328.8571, SEM= 82.49446) and for the 0.04mg/kg dose (M=144.5714, SEM= 36.6732). For the

**Fig. 1**

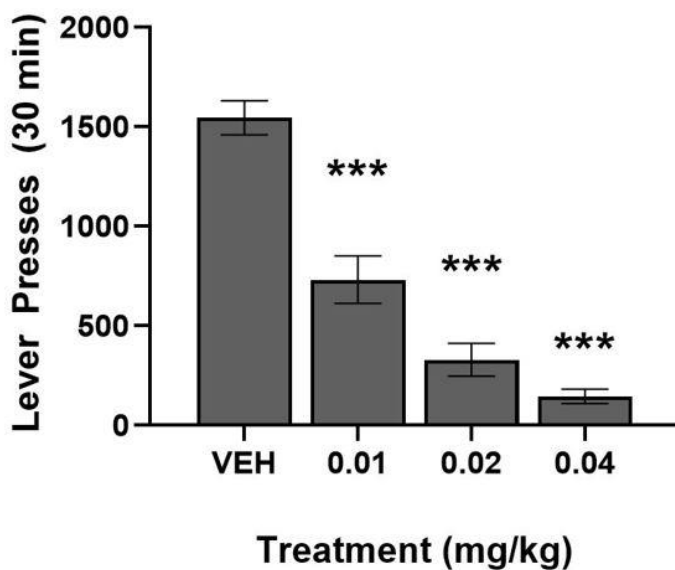


Chart showing the significant decrease in lever presses at 0.01mg/kg, 0.02mg/kg, and 0.04mg/kg compared to the vehicle.

chow intake, with the vehicle (M= 2.075g, SEM of 0.504279).

At the 0.01mg/kg dose, (M=3.025g, SEM=0.604605).

At the 0.02mg/kg dose, (M=3.3875g, SEM= 0.72466)

and at the 0.04 mg/kg dose (M=2.1g, SEM= 0.285044). A

repeated measures ANOVA was performed and for lever

pressing, there was a significant reduction ( $F(3,21) = 69.83, p < 0.001$ ), and planned comparisons revealed that each dose significantly differed from vehicle ( $p < 0.001$ ).

### ***Effects of Pergolide on Chow Consumption***

For chow, repeated measures ANOVA showed that there was no overall effect ( $F(3,21)=1.92, p=0.16$ ). There appeared to be an inverted-U shaped trend, with low doses tending to increase buy higher doses tended to decrease. This was supported by

**Fig. 2**

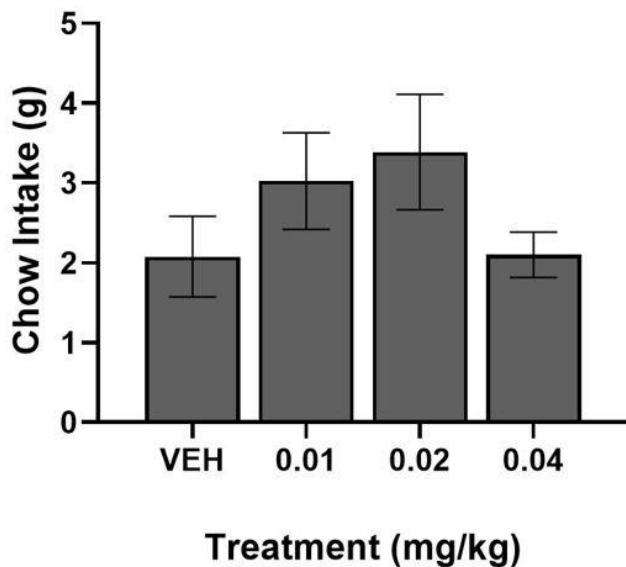


Chart showing the change in chow consumption after administration of the doses 0.01mg/kg, 0.02mg/kg, and 0.04mg/kg of pergolide. There was no significant trend seen in the results.

a quadratic trend ( $p < 0.05$ ) for chow consumption as shown by orthogonal analysis of trend. In pilot studies, a dose of 0.08mg/kg was given, but this dose was determined to be too high and therefore was not included in the final study.

## **Discussion**

The aim of this study was to assess the effects of the dopamine agonist pergolide in rats on performance of an effort-related choice task. It is known that rats exhibit initiation and maintenance of motivated behavior. They also make effort-related decisions by using behavioral resources appropriately according to the motivational value of stimuli and the amount of effort needed to obtain stimuli (Nunes et al., 2013). The present experiment evaluated effort-related choice behavior by using an FR5/chow-feeding task with intraperitoneal injections of pergolide.

The results did not support the hypothesis that pergolide would increase lever pressing as a dopamine agonist. There was a significant decrease in lever pressing associated with the 0.01 mg/kg, 0.02 mg/kg, and 0.04 mg/kg doses of pergolide compared to the vehicle. There was no significant effect on chow intake as a result of pergolide treatment, though there was a trend towards an increase in chow intake at lower doses. This suggests that pergolide had a complex mixture of effects, which could be due to a combination of pre- and postsynaptic actions.

The observed results may have occurred because of the level of intrinsic biological activity that is produced by pergolide. Because pergolide can be classified as a partial agonist, there is potential for antagonistic effects. As a partial agonist, it is possible that the level of intrinsic biological dopamine activity that it produces is still lower than that of dopamine. Therefore, when dopamine receptors are being occupied by pergolide, dopamine transmission is in fact inhibited compared to normal levels. At receptors, partial agonists have lower intrinsic activity compared to full agonists. This allows them to act as either functional antagonists or functional agonists, depending on

the levels of the biological neurotransmitter (full agonist) in a given environment.

Without the presence of a full agonist, partial agonists bind to the receptor and produce the same response as the biological neurotransmitter, therefore acting as functional agonists. When the full agonist is present, partial agonists reduce the response seen from full agonists due to occupation of the receptor, acting as functional antagonists. (Lieberman et al., 2004).

Alternatively, it is known that at high doses pergolide produces appetite suppression. Pergolide is currently FDA approved for use in horses to treat pituitary pars intermedia hyperplasia or equine Cushing's Syndrome (ECS) (Forney). In field trials of pergolide treatment in horses, decreased appetite occurred but was usually transient. Weight loss, anorexia, lethargy, and behavioral changes were also observed in some horses. Additionally, effects of the central nervous system were noted including ataxia and dyskinesia. It has been recommended that horses start with a lower dose for the first two days, then move to the full dose because of the potential for decreased appetite during pergolide treatment (Papich et al., 2021). While weight loss in horses may have been transient, this experiment used weekly injections and the rats were not being treated chronically with the drug. It is possible, therefore, that decreased lever pressing for the highest 0.04 mg/kg dose was the result of appetite suppression. This is supported by the lack of significant overall increase in chow consumption at low doses. High doses of pergolide can also produce locomotion and stereotyped behavior, which could also provide insight into the obtained results. Locomotion could have impacted the lever pressing behavior in the rats of this study because moving around the chamber is incompatible with staying near the lever and pressing it.



Another possible explanation of the suppression of lever pressing induced by pergolide is that it is decreasing release of dopamine by acting as an agonist at presynaptic DA receptors (Fuller et al., 1982). This action could have contributed to the decrease in lever pressing, as well as the slight tendency for chow intake to increase at low doses. Nevertheless, there was not a significant corresponding increase in chow consumption. If pergolide was only affecting the choice in rats to press the lever or eat the available chow, then it would be expected that their appetite would remain the same and decreased lever pressing would coincide with higher chow consumption to compensate for the lack of pellets. This, however, was not the case. There was a small increase in chow consumption at the 0.01 mg/kg and 0.02 mg/kg doses compared to the vehicle condition. In fact, the average highest amount of chow consumption was produced by the 0.02 mg/kg dose at 3.3875 g. It would follow that perhaps at the two lower doses, dopamine transmission was inhibited but appetite was not affected. At the 0.04 mg/kg dose, however, the mean chow consumption was almost the same as it was with the vehicle at 2.1 g and 2.075g, respectively. This suggests appetite suppression in addition to inhibition of dopamine transmission at that dose. At the 0.08 mg/kg dose, results were deemed unusable for the study. Both chow consumption and lever pressing were decreased with one rat in the pilot study that produced 1235 lever presses with the vehicle and only 2 lever presses with 0.08mg/kg pergolide. That same rat consumed 3.1g of chow with the vehicle and 0.9g with the 0.08mg/kg dose. This further suggests that appetite suppression may occur with high doses of pergolide in rats.

In comparison with the current literature on dopamine agonists, these results suggest that they may not all be equally effective in increasing effort-related motivation. While some D1 receptor dopamine agonists were able to effectively attenuate the motivational impairments caused by dopamine antagonists like ecopipam (Yohn et al., 2015), pergolide administration on its own did not increase effort-related behaviors in rats. This suggests that additional dopamine agonists should be tested for their effectiveness in increased effort-related behavior for the development of better targeted clinical treatment for the motivational aspects of depression.

Moving forward with research on dopamine agonists and effort-related behavior, it is possible that other partial agonists or other doses may be more effective. Pergolide has a higher affinity for D2 receptors than D1 receptors, and as mentioned above the doses at which D1 versus D2 receptors are activated may be different. In a study done comparing the effects of the drugs dihydrexidine hydrochloride (selective D1 agonist, 0.4-0.9 mg/kg) or sumanirole maleate (selective D2 agonist 0.05-0.3 mg/kg) in monkeys on a touch screen running tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB), it was found that at high dosages, the D2 agonist improved spatial working memory performance (Marino et al., 2019). Conversely, at high doses of the D2 agonist reversal learning was impaired and reach response latency was slowed. There were no consistent cognitive effects observed with the D1 agonist at any of the doses tested. There was, however, a significant decrease in trial completion rate at the high doses of both D1 and D2 agonists. This is consistent with decreased motivation. These results show the effects of D1 and D2 agonists on cognitive and motor behaviors in healthy monkeys, as well as dose specific

insensitivities of the D1 agonist (Marino et al., 2019). Doses selective for either D1 or D2 receptors may have contributed to the results seen in this experiment.

Perhaps the focus of this line of research should be focused on new dopamine partial agonist third-generation antipsychotics such as aripiprazole, brexpiprazole, and cariprazine. These drugs have been described as dopamine-serotonin system stabilizers. Aripiprazole (ARI) can reduce dopaminergic neurotransmission when dopamine activity is high and enhance neurotransmission when dopamine activity is low. ARI also maintains a balance in motor function and prolactin release, which are important areas of dopaminergic neurotransmission (Burda et al., 2011). In a study that assessed the effects of aripiprazole on progressive ratio responding in rats, it was found that ARI relieved motivational anhedonia in a stress-induced model. It was also shown that long-term aripiprazole administration reinstated the motivational drive to acquire the reward in the progressive ratio task (Scheggi et al., 2018). It is possible that these dopamine partial agonists are more effective in promoting effort-related behavior than pergolide. Additionally, the use of new atypical antipsychotics could produce fewer adverse side effects than typical antipsychotics. While typical antipsychotics bind tightly to the dopamine D2 receptor, atypical antipsychotics bind more loosely and have higher dissociation constants than dopamine itself (Seeman, 2002). It is thought that the tight binding of typical antipsychotics is what produces symptoms such as tardive dyskinesia (Cornett et al., 2017). Animal models of the motivational dysfunction associated with depression will continue to provide insight into the therapeutic effects of dopamine partial agonists, which is valuable for clinical treatment of depression.

The overall implications of this research suggest that pergolide could be used to treat other dopamine related disorders other than depression. Because pergolide successfully lowered lever pressing in the effort-related choice task, this supports the idea that it could be used in the treatment of schizophrenia or tardive dyskinesia at low doses (Fuller et al., 1982). Since the results show that pergolide at low doses reduces dopamine transmission by binding to presynaptic receptors, this could be important in the treatment of schizophrenia, which is characterized by hyperactive dopamine transmission in the mesolimbic areas and the prefrontal cortex (Brisch et al., 2014).

Because the symptoms of schizophrenia are associated with heightened dopamine transmission, treatment with pergolide at low doses could help alleviate cognitive symptoms. With respect to tardive dyskinesia, which involves involuntary movements and is associated with use of antipsychotic medication, treatment with pergolide could lower dopamine levels in the basal ganglia which controls motor function. The prevailing theory as to why antipsychotic medication causes tardive dyskinesia is that chronic downregulation of dopamine receptors by antagonists could cause upregulation in dopamine receptor responsiveness, resulting in hypersensitivity of the receptors in the basal ganglia (Cornett et al., 2017). There are three types of antipsychotics: first-generation, second-generation, and third generation. First-generation typical antipsychotics are competitive dopamine antagonists such as haloperidol. Competitive dopamine antagonists' function by binding to the active site of the dopamine receptor and blocking dopamine transmission. Typical antipsychotics are used to treat schizophrenia, but they are also the most likely to cause tardive dyskinesia (Cornett et al., 2017). With these results, there is potential for use of a dopamine

agonist at low doses in the treatment of schizophrenia instead of using an antagonist. Treatment with pergolide could potentially alleviate the side effect of tardive dyskinesia in people who are currently treated with typical antipsychotics, or it can be used to treat tardive dyskinesia in individuals who do not have the option to switch antipsychotic medications.

Other clinical implications of these results pertain to tics associated with Tourette Syndrome. In Tourette Syndrome, tics are associated with dysfunction of the basal ganglia pathways. It is thought that tics are produced because of excess dopamine in the striatum, which excites thalamo-cortical circuits (Leisman et al., 2022). In a randomized trial performed in children with Tourette Syndrome, treatment with pergolide was associated with lower tic severity scores as well as lower attention-deficit hyperactivity disorder symptom scores (Gilbert et al., 2003). The results from this experiment support the previous evidence that pergolide can be an effective treatment for tics in Tourette Syndrome. Because pergolide reduced lever pressing at low doses, the results from this study are in accordance with the previous evidence that pergolide reduces dopamine transmission by acting presynaptically on dopamine receptors. Therefore, this further supports the idea that pergolide can be used to treat tics in Tourette Syndrome by lowering dopamine transmission in the basal ganglia.

**Conclusion**

In conclusion, the dopamine partial agonist pergolide did not produce the expected results of increased lever pressing. The doses administered significantly lowered lever pressing and did not provide evidence that pergolide stimulates effort-related choices in operant conditioning tasks in rats. Moving forward, it is important to continue to study the motivational aspects of depression and the potential for treatment of these symptoms with third generation dopamine partial agonists.

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