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## Assessment of the triple reuptake inhibitor diclofensine: effort-based decision-making in a rodent model of motivational dysfunction

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**Assessment of the triple reuptake inhibitor diclofensine: effort-based decision-making in a rodent model of motivational dysfunction**

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**Abstract**

Serotonin-selective reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressant medications. Despite their popularity, they remain relatively ineffective at treating effort-related motivational symptoms of depression such as fatigue and anergia. Increasing research on triple reuptake inhibitors (TRIs) that target three neurotransmitters—dopamine, serotonin, and norepinephrine—has suggested that TRIs could have efficacy in targeting motivational dysfunction due to their dopaminergic effects. Previous research has shown that the dopamine depleting agent tetrabenazine can reliably induce motivational deficits in rats, as evidenced by a shift towards low-effort behavior in effort-based choice tasks, and provide a validated approach to creating a model of motivational dysfunction. This is consistent with human studies showing that people with major depression exhibit a bias toward low-effort activities. Diclofensine is a TRI with a relatively high affinity for the dopamine transporter and, therefore, it was hypothesized that this drug could improve motivational symptoms. The present study analyzed the ability of diclofensine to treat motivational deficits of depression through a rodent model of effort-based choice, the fixed ratio 5/chow feeding choice task. Diclofensine demonstrated the ability to partially reverse the effort-related effects of tetrabenazine; it

increased selection of high-effort FR5 lever pressing in rats at the 10.0 mg/kg dose and decreased chow intake at the 5.0 mg/kg and 10.0 mg/kg doses. Given the devastating impact to society, families, and individuals of inadequately treated depressive disorders, it is imperative that there is continued investment in the discovery of highly efficacious and tolerable antidepressants. This study contributes to the understanding and possible utility of TRIs as a treatment of motivational dysfunctions involved in depression in humans.

## **Introduction**

Major depressive disorder (MDD) is characterized by multiple episodes of depressed mood that persist for at least two weeks (Sharma et al., [2015](#); Kose & Cetin, [2018](#)). MDD is a severely debilitating disorder; it causes the largest amount of non-fatal disease burden, accounting for approximately 12% of total years lived with disability on a global scale (Lane, [2014](#)). The World Health Organization suggests that mental disorders account for five of the top ten causes of disability in industrialized countries, and of these disabling disorders, MDD ranks first. (Shelton & Tomarken, [2001](#)). Despite the prevalence and severity of depression, many antidepressant treatments do not provide adequate relief to patients, often resulting in severe residual symptoms and chronic functional impairment (Shelton & Tomarken, [2001](#)). Moreover, most antidepressants fail to reverse the core symptoms of depression involving motivation and effort-related symptoms (Salamone et al., [2016](#)). These symptoms can include anhedonia (the reduced ability to experience pleasure (Gorwood, [2008](#))), fatigue and motivational dysfunction, lassitude (a state of physical or mental weariness), loss of energy and reduced exertion of effort (Sharma et al., [2015](#); Yohn et al., [2016a](#); Yohn et al., [2016b](#)). These motivational deficits have significant

impacts on various aspects of individuals' lives, including their ability to maintain productivity or effective time-management at work, maintain social relationships leading to potential social withdrawal and isolation, engage in self-care activities, or maintain physical health by exercising and eating healthy (National Institute of Mental Health, [2016](#)). Previous research indicates that effort-related motivational function (i.e., exertion of effort in goal directed activity, and selection of high-effort actions) is modulated by dopamine in the brain. Therefore, it is imperative that the search for effective antidepressants involves a drug that acts via dopaminergic mechanisms and can improve the motivational aspects of depression (Shelton & Tomarken, [2001](#)).

The prominent hypothesis surrounding the development of MDD, known as the “monoamine deficiency” hypothesis, asserts that the pathophysiology of depression can be attributed to reduced levels of monoamines (Subbaiah, [2018](#); Sharma et al., [2015](#); Ferguson, [2001](#)). Monoamines include serotonin (5-HT), norepinephrine (NE), and dopamine (DA); monoaminergic neurons are present in the midbrain and project to almost all areas of the brain, which is why they are essential in numerous brain functions including mood, cognition, attention, appetite, sleep, motivation, and reward processing (Subbaiah, [2018](#)). The development of this hypothesis came from two observations: one that pharmacological depletion of these monoamines led to the development of depressive-like symptoms, and the other being that pharmacological agents that were later found to increase monoamine levels exhibited antidepressant effects (Schildkraut, [1965](#)). This “monoamine deficiency” hypothesis gained credibility due to the observed effectiveness of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), both of which enhance the neurotransmission of 5-HT and NE (Subbaiah, [2018](#)). Due to poor tolerability of TCAs and MAOIs, a new class of second-generation antidepressants, known as selective serotonin reuptake inhibitors (SSRIs),

emerged (Sharma et al., [2015](#); Ferguson, [2001](#)). SSRIs block inactivation of 5-HT by inhibiting its transport from the extracellular space back into the presynaptic cell. SSRIs have been shown to be effective for treating mood and anxiety-related symptoms, they remain relatively ineffective at treating effort-related motivational symptoms such as anergia and fatigue (Lane, [2014](#); Goodnick & Goldstein, [1998](#); Yohn et al., [2016b](#); Ferguson, [2001](#)). In fact, SSRIs may even induce or exacerbate these symptoms (Subbaiah, [2018](#); Salamone et al., 2016; Yohn et al., [2016a](#); Yohn et al., [2016b](#)). SSRIs also exhibit unwanted side effects such as gastrointestinal disturbances, sexual dysfunction, weight gain, and abnormal sleep patterns (Ferguson, [2001](#)).

Further research of psychopharmacologic treatment for depression led to the emergence of another class of second-generation antidepressants known as dual reuptake inhibitors, which includes 5-HT-NE reuptake inhibitors (SNRIs). It was shown that the SNRI venlafaxine exhibited greater response and remission rates than SSRIs (Sharma et al., [2015](#)). However, while they are effective at treating the mood-related symptoms of MDD, the motivational, effort-related, and psychomotor symptoms of MDD are not significantly improved by SNRIs (McLauchlan et al., [2002](#)). There is another subset of dual reuptake inhibitors known as DA-NE reuptake inhibitors (DNRI). Bupropion is a DNRI that increases DA and NE concentrations by enhancing their synaptic availability through its inhibitory effect on their respective transporters, and clinical reports indicate it can be effective at treating motivational dysfunction (Cooper et al., [2014](#); Lane, [2014](#)). Nomifensine is another DNRI that was originally tested for the treatment of ADHD (Lane, [2014](#)). Although studies showed that nomifensine was equally as effective at treating MDD as the tricyclic antidepressant imipramine, which primarily inhibits the reuptake of serotonin and norepinephrine, and it was more effective at treating effort-based symptoms related to work and interest in activities (Lane, [2014](#); Bremner et al., 1984).

The relative effectiveness of DNRI and ineffectiveness of SSRI and SNRI at treating the motivational symptoms of depression may be attributed to their inability to increase DA neurotransmission. DA neurons innervate the neocortex, basal ganglia, and limbic system, which are regions that are implicated in cognition, motivation, and reinforcement learning (Sharma et al., [2015](#); Subbaiah, [2018](#)). Research suggests that nucleus accumbens dopamine, which is part of the mesolimbic DA system, is involved in regulating behavioral activation and exertion of effort, which is why it is influential in depression pathogenesis (Dunlop & Numeroff, [2007](#); Lane, [2014](#); Salamone et al., [2016](#); Salamone et al., [2002](#)). For example, in behavioral models involving the regulation of work output in instrumental behavior, interfering with accumbens DA transmission in rats can decrease the ability to lever press for reinforcement when the work requirement is high (Salamone et al., [2016](#); Salamone et al., [2002](#)). Nucleus accumbens DA is associated with activational aspects of motivation, and therefore targeting DA should improve exertion of effort and selection of high-effort activities (Sharma et al., [2015](#)). Thus, the DAergic component of the action of a novel antidepressant could be able to address a broad range of depressive symptoms, including effort-related motivational dysfunctions.

Triple reuptake inhibitors (TRIs) have emerged as a promising new class of antidepressants that target all three MAs: DA, 5-HT, and NE (Sharma et al., [2015](#); Kose & Cetin, [2018](#)). TRIs have gained significant attention because of the potential benefits of their dopaminergic mechanisms; the addition of dopamine reuptake inhibition to NET and SERT blockade through treatment with a TRI may reduce side effects, improve response and remission rates, and speed the onset of antidepressant effect (Lane, [2014](#)). In addition, the dopaminergic component of a TRI may prevent against the typical hypodopaminergic effects exhibited with SSRIs and SNRIs, such as weight gain, sexual dysfunction, and lack of motivational effects. Moreover, TRI

monotherapy could solve many of the issues surrounding treatment by combining different SSRIs, SNRIs, and DA agonists, including poor compliance, risk of drug-drug interactions, lack of efficacy data, and possibility of cumulative toxicity (Subbaiah, [2018](#)). Most importantly, due to their dopaminergic mechanisms, TRIs may effectively activate mesolimbic DA transmission and improve the largely untreated motivational symptoms of depression. Although the ideal pharmacology of a TRI is still relatively unknown, it is hypothesized that compounds with a higher affinity for DAT may be required to act on motivational dysfunction, particularly if there is high SERT inhibition (Lane, [2014](#)). Although increases in extracellular DA due to high DAT inhibition raises concerns about abuse liability, TRI's may be the least abusable way to deliver high DAT inhibition to patients.

Animal models of effort-related decision making provide a valid model of the motivational impairment and low effort bias seen in humans with MDD. These models involve procedures that provide rats the choice to perform high-effort activities to receive more preferred reward options or low-effort activities for less preferred reward options (Salamone et al., [1999](#)). One type of effort-based procedure is the fixed ratio 5 (FR5) chow-choice feeding task. This procedure provides rats the option to press a lever five times to receive Bio-Serv high carbohydrate pellets or approach and consume a freely available but less preferred laboratory chow (Salamone et al., [2016](#); Yohn et al., [2016a](#); Yohn et al., [2016b](#); Salamone et al., [1999](#)). Under control conditions, rats will choose the high-effort, high-reward option; therefore, they will work to press the lever for the preferred food, resulting in high lever pressing and low chow consumption (Salamone et al., [2016](#); Yohn et al., [2016a](#); Yohn et al., [2016b](#)). However, DA antagonism or reduced DA concentration in the nucleus accumbens typically results in decreased selection of high-effort, high- reward choices and increased selection of low-effort, low-reward

options, resulting in lower lever pressing and high chow intake (Salamone et al., [2016](#)). Previous studies have accomplished dopamine depletion through the administration of DA-depleting agents like tetrabenazine (TBZ), a vesicular monoamine transporter-2 (VMAT-2) inhibitor. Even at low doses, TBZ blocks the storage of monoamines in presynaptic vesicles, thereby depleting levels of these neurotransmitters and preventing their transport between neurons and has its greatest effects in the nucleus accumbens. TBZ is used to treat symptoms of Huntington's Disease, and individuals prescribed TBZ have reported depressive-like symptoms (including fatigue and apathy), which validates the use of TBZ in these animal models of effort-related symptoms of MDD. However, drugs that facilitate DA transmission (e.g., bupropion) have been shown to reverse the low-effort bias induced by TBZ increasing lever pressing and decreasing show consumption, due to increase in extracellular levels of DA in the nucleus accumbens (Nunes et al., [2013](#); Randall et al., [2015](#)).

One TRI that exhibits potential antidepressant actions is an isoquinoline derivative named diclofensine, which has roughly equipotent effects on the neural transport of DA, 5-HT, and NE [9] (Keller et al., 1982; Burkard et al., [1983](#); Gasic et al., [1986](#)). Diclofensine was previously shown to successfully treat MDD in clinical trials, but the drug did not progress to development because the link between DA and motivational symptoms was still unknown years ago. Diclofensine's rank order of transporter affinity is DA > NE > 5-HT (in the range of 0.027–0.096  $\mu$ M) (Luethi et al., [2018](#)), and it increases extracellular levels of dopamine 4.8-fold over baseline level (Nakachi et al., [1995](#)). Diclofensine inhibits DAT and SERT in a 1.1 ratio, respectively. This ratio is significant as it exhibits diclofensine's DAT occupancy is sufficient to combat the hypodopaminergic effects that are often associated with serotonin reuptake inhibition (Luethi et al., [2018](#)). Furthermore, due to diclofensine's ability to increase dopamine neurotransmission



while also acting on serotonergic and norepinephrinergic mechanisms, it can be hypothesized to be a favorable candidate for effective treatment of effort-related motivational symptoms of depression. The present study aimed to investigate the effects of the TRI diclofenine by testing its ability to reverse the TBZ-induced motivational impairments on the FR5/chow-choice behavioral task. Based on its mechanism of action, it was hypothesized that diclofenine would reverse the effects of TBZ.

## **Materials and Methods**

### *Animals*

Adult male, Sprague-Dawley rats (Envigo, Indianapolis, IN, USA) were pair housed with 12-hour light/dark cycles at 23°C (lights on at 07:00 hours). Rats (n=11) weighed 274-324g at the beginning of the study, and were initially food restricted to 85% of their free-feeding body weight for operant training. Rats were fed supplemental chow to maintain weight throughout the study and modest growth was permitted. Home cages had water available *ad libitum*. Animal protocols were approved by the University of Connecticut Institutional Animal Care and Use Committee, and followed the National Institutes of Health (NIH) guidelines.

### *Pharmacological Agents and Dose Selection*

Diclofenine was obtained from AdooQ Bioscience (Irvine, CA) and dissolved in 10% dimethyl sulfoxide (DMSO), 15% Tween80, and 75% 0.9% saline. Diclofenine was dissolved in double volume. The DMSO/Tween 80/saline solution was administered as the vehicle control. Rats were administered 1.25, 2.5, 5.0, and 10.0 mg/kg of diclofenine or vehicle intraperitoneally (IP). The doses of diclofenine were based on piloting and previous studies. The VMAT-2

inhibitor, tetrabenazine (TBZ) (9,10-dimethoxy-3-(2-methylpropyl)-1,3,4,6,7, 11b hexahydro benzo[a]quinolin-2-one), was obtained from Tocris Bioscience (Ellisville, MO) and was dissolved in 20% DMSO, 80% 0.9% saline, and titrated with microliter quantities of 1N HCl until TBZ was completely dissolved (pH remained above 3.5-4.0). The DMSO/saline solution was administered as the vehicle control. Rats were administered a 1.0mg/kg dose of TBZ or vehicle IP. The dose of 1.0-mg/kg TBZ was based on extensive piloting studying as well as previous studies completed in the Salamone Lab (Rotolo et al., [2019](#); Rotolo et al., [2020](#); Rotolo et al., [2021](#)).

*Behavioral Procedure: The concurrent FR5/chow-choice procedure*

Behavioral sessions were conducted in operant conditioning chambers (28 x 23 x 23 cm; Med Associates). During initial training, a fixed interval schedule of reinforcement, Magazine Training, was utilized for two days wherein rats received a reinforcer (Bio-serv high carbohydrate 45 mg pellet) every 30 seconds during 30-minute sessions. For the following three days, rats were trained to lever press on a continuous reinforcement schedule using Fixed ratio (FR) 1. Rats were then shifted to the FR5 schedule (30-minute sessions 5 days/week) and trained for 5 additional weeks. After those 5 weeks, rats were then introduced to having concurrently available lab chow during the training session for an additional 5 weeks (Salamone et al., [2002](#)). Weighed amounts of laboratory chow (5P00 Laboratory Diet; Prolab or RHM 3000; Purina Mills; typically, 18-23 g) were concurrently available on the floor of the chamber during the FR5 sessions. Following the conclusion of the 30-minute session, rats were immediately removed from the operant chambers. Number of lever presses were recorded and chow intake was determined by weighing the remaining food (including spillage from a tray beneath the floor of

the chamber). Rats were trained until they attained stable levels of baseline lever pressing and chow intake (>1200 lever presses per 30 min). Of the 16 animals originally included in the study, 4 rats did not reach the required baseline number of lever presses, and were therefore excluded from the final statistical analysis. Initial lever pressing training occurred before the timeline of the current project, which is when drug testing began. Four days per week were baseline (no drugs) FR5/chow-choice days and one day per week was drug treatment. Drug treatment spanned six weeks.

### *Experimental Procedures*

#### General design features for behavioral pharmacology experiments

The effort-related choice experiments used a repeated measures design, with each rat receiving each drug treatment in a randomly varied order, once per week over the course of six weeks (no sequence repeated). Rats were tested 5 days per week, with four no-drug baseline days and one drug treatment day, and the weekend to give supplemental feeding and check body weights.

#### The ability of diclofenac to reverse TBZ-induced motivational impairments on the concurrent FR5/chow-choice behavioral procedure

Trained rats (n = 15) were administered either TBZ (1.0 mg/kg) or vehicle, and diclofenac (1.25, 2.5, 5.0, 10.0 mg/kg) or vehicle, via a series of two intraperitoneal injections on drug testing days. Rats received TBZ or vehicle 120 minutes prior to testing and diclofenac or vehicle 30 minutes before testing. The follow treatment combinations were given: TBZ vehicle + diclofenac vehicle; 1.0-mg/kg TBZ + diclofenac vehicle, 1.0 mg/kg TBZ + 1.25-mg/kg

diclofenac; 1.0-mg/kg TBZ + 2.5-mg/kg diclofenac; 1.0-mg/kg TBZ + 5.0-mg/kg diclofenac; 1.0-mg/kg TBZ + 10.0-mg/kg diclofenac. Drug treatments were administered once per week for a total of six weeks.

### *Statistical Analyses*

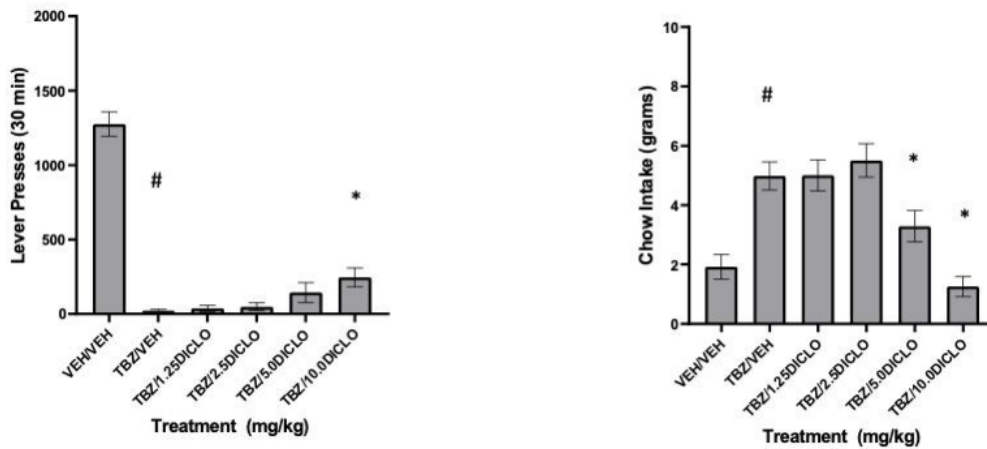
Repeated measures Analysis of Variance (ANOVA) was used to determine the effect of drug treatment on lever pressing and chow intake in the behavioral pharmacology experiments. ANOVA was completed by use of the Statistical Package for the Social Sciences (SPSS, version 28) computer software. Since there were significant overall  $F$  values for the two behavioral measures being used, non-orthogonal planned comparisons were performed, using the overall error term to assess differences between each treatment and the control condition (TBZ vehicle + diclofenac vehicle). The number of comparisons was restricted to the number of treatments minus one (Keppel, [1991](#)).

## **Results**

A repeated measures ANOVA revealed that there was an overall significant effect of drug treatment on lever pressing [ $F(5,50) = 90.693$ ,  $p < 0.05$ , effect size  $\eta^2 = 0.901$ ]. Planned comparisons showed that TBZ significantly decreased lever pressing compared to vehicle treatment [ $F(1,50) = 299.773$ ,  $p < 0.05$ ] and that co-administration of the dose of 10.0-mg/kg diclofenac with TBZ partially attenuated the effects of TBZ on lever pressing [ $F(1,50) = 9.532$ ,  $p < 0.05$ ], increasing lever pressing in TBZ-treated rats.

There was also a significant overall effect of drug treatment on chow intake [ $F(5, 50) = 13.509$ ,  $p < 0.05$ , effect size  $\eta^2 = 0.575$ ]. Additional planned comparisons revealed that TBZ

alone significantly increased chow intake relative to vehicle treatment [ $F(1,50) = 19.913, p < 0.05$ ] and that co-administration of 5.0- and 10.0-mg/kg diclofenac with TBZ significantly reduced chow intake compared with the TBZ plus vehicle condition [ $F(1,50) = 6.066, p < 0.05$ ;  $F(1,50) = 29.475, p < 0.05$ ], respectively.



**Figure 1. The ability of diclofenac to reverse TBZ-induced motivational impairments on the concurrent FR5/chow-choice behavioral procedure. a.** Mean ( $\pm$ SEM) of lever presses in 30-minute operant sessions across treatments with TBZ or vehicle and varying doses of diclofenac (or vehicle). **b.** Mean ( $\pm$ SEM) of chow consumption (grams) in 30-minute operant sessions across treatment conditions. VEH/VEH (vehicle + vehicle), TBZ/VEH (1.0-mg/kg tetrabenazine + vehicle), TBZ/1.25 (1.0-mg/kg tetrabenazine + 1.25-mg/kg diclofenac), TBZ/2.5 (1.0-mg/kg tetrabenazine + 2.5-mg/kg diclofenac), TBZ/5.0 (1.0-mg/kg tetrabenazine + 5.0-mg/kg diclofenac), and TBZ/10.0 (1.0-mg/kg tetrabenazine + 10.0-mg/kg diclofenac). (#  $p < 0.05$ , TBZ/VEH vs. VEH/VEH; \*  $p < 0.05$  diclofenac different from TBZ/VEH).

## Discussion

The present study examined the effects of the TRI diclofenine on effort-based choice behavior in rats. More specifically, the present study assessed the ability of diclofenine to reverse the low-effort bias induced by administration of TBZ on the FR5/chow-choice behavioral procedure. Consistent with previous findings (Nunes et al., [2013](#); Randall et al., [2015](#), Yohn et al., [2015a](#); Yohn et al., [2015b](#); Rotolo et al., [2019](#)), administration of 1.0-mg/kg TBZ shifted the choice behavior, decreasing high-effort lever pressing and increasing low-effort chow intake. TBZ was used to induce a low-effort bias because this drug has been shown to induce depressive-like symptoms, such as fatigue, in humans (Chen et al., [2012](#); Frank, [2009](#), [2010](#); Guay, [2010](#)). The low-effort bias induced by TBZ can be attributed to its ability to reduce DA levels in the nucleus accumbens, specifically since NaC DA is a main component in effort-based aspects of motivated behavior.

In partial support of the original hypothesis, co-administration of diclofenine was able to partially reverse the effects of TBZ on lever pressing for the Bio-Serve high-carbohydrate pellets at the highest dose and on chow intake at the two highest doses. These findings are consistent with diclofenine's high potency at DAT compared to SERT and NET. Previous studies employing the effort-based FR5/choice task illuminate the necessity of high DAT inhibition for reversing the motivational deficit induced by TBZ administration. Studies have shown that the SERT inhibitor fluoxetine failed to reverse TBZ-induced motivational deficits, and even promoted additional suppression in lever pressing (Yohn et. al., [2016a](#)). Additionally, the NET inhibitor desipramine failed to attenuate the TBZ-induced low effort bias in the FR5 chow feeding choice task. In fact, coadministration of TBZ and desipramine led to a further reduction in lever presses at higher doses (when administered alone or with TBZ) (Yohn et. al., [2016a](#)). In

contrast, DAT inhibitors such as bupropion, lisdexamfetamine, methylphenidate, and modafinil have shown to significantly reverse the effects of TBZ low-effort bias and re-induce high-effort bias in rats (Salamone et al., [2018](#); Nunes et al., [2013](#); Yohn et al., [2016a](#)). Diclofensine's ability to attenuate the TBZ-induced low effort bias is consistent with these findings. However, because diclofensine was only able to do so at the 10.0-mg/kg dose, future studies should evaluate the ability of diclofensine to attenuate the low-effort bias induced by tetrabenazine with a higher range of doses, specifically those greater than 10-mg/kg.

An additional potential future study should evaluate diclofensine's efficacy on the progressive ratio (PROG) chow feeding task, which involves an increase in the number of responses (e.g., lever presses) required to obtain a reward, such as a high carbohydrate pellet. In a PR schedule, the highest or last schedule value completed is referred to as the breakpoint; this breakpoint value serves as a measure of the maximum effort a rodent is willing to exert to obtain a desired reward. Therefore, the PROG chow feeding task provides a measure of how motivation changes as a function of effort (Glover et al., [2008](#)). Gaining a broad understanding of how enhanced DA transmission can alter distinct elements of motivation and effort would further validate the findings of the present study, and support the hypothesis that DAT inhibitors, or compounds that enhance DA transmission, could serve as a potential treatment for the motivational deficits associated with MDD.

The results of the current that show a decrease in chow intake at the 5.0-mg/kg dose could reflect potential appetite suppressant properties of diclofensine. This pattern of reduced lever pressing and chow consumption is very typical of a compound that exerts appetite suppressant effects, and it is known that compounds that inhibit the monoamine transporters can have these effects (Randall et. al., [2012](#); Axel et. al., [2010](#)). Other triple reuptake inhibitors have also

exhibited similar appetite suppressant properties. For example, the TRIs DOV 21, 947 (also known as amitifadine), and tesofensine have shown weight reducing effects in clinical trials; in fact, the weight reducing effects of tesofensine appeared greater than any current anti-obesity drug (Subbaiah, [2018](#); Astrup et al., [2008](#); DOV 21,947 Demonstrates Significant Body Weight and BMI Reductions, [2007](#)). These results, as well as the results from the present study, suggest that TRIs, such as diclofensine, could be useful to treat obesity or depression that is comorbid with obesity. However, it is important to consider that binge eating tendencies are influenced by general cortical DA, rather than subcortical DA (i.e. nucleus accumbens DA). The link between general cortical structures and motivation are not as prevalent, which should be taken into account if animal-models of motivation are used to determine the effectiveness of TRIs in treating obesity or binge eating. Moreover, TRIs like diclofensine may have therapeutic potential for other disease states, especially those that involve the hypofunction of all three monoamines, such as pain, addiction, ADHD, Parkinson's disease, and schizophrenia (Subbaiah, [2018](#)).

In summary, this experiment contributed to the characterization of TRIs by demonstrating the ability of diclofensine to partially reverse the effort-related effects of TBZ and increase high-effort responding in a task measuring effort-based choice. Behavioral assessment of diclofensine has shown that it lacks the stimulant-like properties of other DAT inhibitors, such as nomifensine (Keller et al., 2012). These results suggest that it is possible that TRIs with a high affinity for DAT may be effective at reducing motivational impairments with minimal induction of major psychomotor and other adverse side effects such as abuse liability, and overall be an effective antidepressant. Furthermore, the current research will provide insight into the ideal clinical profile of future pharmacological treatments for motivational dysfunction. These and other similar findings could lead to the development of TRIs that could potentially reverse the



long untreated motivational symptoms of depression and provide patients a safe, tolerable, and comprehensive remedy for their disorder, altogether improving their overall function.

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