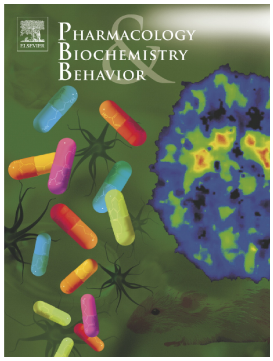


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# Partial Reversal of the effort-related motivational effects of tetrabenazine with the MAO-B inhibitor deprenyl (selegiline): implications for treating motivational dysfunctions

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Abbreviated title: deprenyl enhances effortful responding

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Research Highlights:

- Rats were assessed using tests of effort-related decision making.
- The VMAT-2 inhibitor tetrabenazine produced a low-effort bias in rats.
- The MAO-B inhibitor deprenyl partially reversed the effects of tetrabenazine.
- The MAO-A blocker moclobemide and the nonselective drug pargyline were ineffective.

Keywords: fatigue; anergia; depression; Parkinsonism; dopamine; animal models

**Abstract**

People with depression and Parkinsonism frequently show effort-related motivational symptoms, such as anergia, psychomotor retardation, and fatigue. Tasks that assess effort-related choice are being used as animal models of these motivational symptoms. The present studies characterized the ability of monoamine oxidase (MAO) inhibitors with varying selectivity profiles to reverse the low effort bias induced by the monoamine storage inhibitor tetrabenazine. Tetrabenazine produces depressive symptoms in humans, and because of its selective inhibition of VMAT-2, it preferentially depletes DA at low doses. Effort-based decision making is studied with tasks offering choices between high effort options leading to highly valued reinforcers vs. low effort/low reward options. Tetrabenazine shifted choice behavior, reducing selection of fixed ratio 5 lever pressing, but increasing intake of the concurrently available but less preferred lab chow. These effects of 0.75 mg/kg tetrabenazine were attenuated by co-administration of the MAO-B inhibitor deprenyl (selegiline). The ability of deprenyl to reverse the effects of tetrabenazine was marked by an inverted-U shaped dose response curve, with the middle dose (2.5 mg/kg) being effective. In contrast, neither the MAO-A selective antagonist moclobemide nor the nonselective drug pargyline reversed the effects of tetrabenazine, and moclobemide decreased lever pressing when administered alone. Deprenyl was originally developed as an antiparkinsonian drug, but it also has been shown to have antidepressant effects in humans and induce antidepressant-like effects in classical rodent models of depression. These studies have implications for the potential use of MAO-B inhibitors as treatments for the motivational symptoms of depression and Parkinsonism.

## 1. Introduction

Motivational symptoms such as psychomotor slowing, apathy, anergia and fatigue are often seen in major depression, Parkinsonism, multiple sclerosis and other disorders (Tylee et al. 1999; Stahl 2002; Demyttenaere et al. 2005; Salamone et al. 2006; Friedman et al., 2007; Tellez et al., 2008; Treadway and Zald 2011). In depression, the severity of motivational dysfunction is correlated with problems involving social functioning, employment, treatment outcomes and overall severity (Gullion and Rush, 1998; Tylee et al., 1999; Stahl 2002; Demyttenaere et al., 2005). In controlled laboratory studies, depressed patients show reduced selection of high effort options in tasks that measure effort-related decision making (Treadway et al., 2012; Yang et al. 2014, 2015). Patients with Parkinson's disease also show motivational dysfunctions such as fatigue and apathy (Friedman et al., 2007), as well as a low effort bias in tests of effort-based choice (Chong et al., 2015). In view of the debilitating nature of motivational dysfunction in people, and the relative resistance of these symptoms to common drug treatment such as serotonin uptake blockers (Stahl, 2002; Fava et al., 2014), it is important to develop animal models that assess effort-related motivational dysfunction.

Rodent tests of effort-related processes are being used as models of motivational symptoms (Salamone et al., 2007, 2015, 2016a,b,c; Yohn et al., 2016a,b,c,d). Effort-related choice behavior is studied with tasks that offer animals the option of choosing between a relatively valued reinforcer that can only be obtained by a high degree of effort vs. a lower effort/lower value option. In studies with rodents, such procedures include a T-maze barrier task (Salamone et al., 1991; Cousins et al., 1996; Mott et al., 2009, Pardo et al., 2012, Yohn et al., 2015b), effort discounting (Floresco et al., 2008; Bardgett et al., 2009; Hosking et al., 2015), and operant behavior tasks offering choices between responding on ratio schedules for highly

preferred reinforcers vs. approach and consumption of less preferred ones (Salamone et al., 1991; Cagniard et al., 2006; Randall et al., 2012, 2014, 2015; Sommer et al., 2015). Low systemic doses of DA antagonists, nucleus accumbens DA antagonism, and depletion of accumbens DA have been shown to shift choice behavior, decreasing selection of the high effort option (e.g. lever pressing or barrier climbing) and increasing selection of the lower effort alternative (Bardgett et al., 2009; Floresco et al., 2008; Salamone et al. 1991, 1994, 2002; Mai et al., 2012; Hosking et al., 2015). These effects are not due to changes in food preference, food intake, or reference memory (Salamone et al., 1991, 2002, Sink et al., 2008, Nunes et al., 2013b, Randall et al., 2012, 2014; Pardo et al., 2015; Yohn et al., 2015). In recent studies, the vesicular monoamine transport (VMAT-2) inhibitor tetrabenazine (TBZ) has been used to develop formal models of effort-related motivational impairments. TBZ reversibly inhibits monoamine storage and preferentially depletes DA at low doses (Pettibone et al., 1984; Tanra et al., 1995). TBZ induces depressive symptoms including fatigue and apathy in people (Frank 2009, 2014; Guay, 2010; Chen et al., 2012), and this drug also has been used in classical animal models of depression (Tadano et al., 2000; Wang et al., 2010). In studies of effort-related choice, TBZ produces a low-effort bias, decreasing selection of the high-barrier arm in rats tested on the T-maze choice task (Yohn et al., 2015a,b), and decreasing food reinforced FR5 or progressive ratio lever pressing while producing a concomitant increase in the intake of the concurrently available lab chow (Nunes et al., 2013, 2014; Randall et al., 2014; Yohn et al., 2016a,b). The reallocation of behavior from high to low effort options that is produced by TBZ is not due to alterations in food preference, hedonic taste reactivity, reduced appetite, or impairments in reference memory, but instead appears to be dependent on the work requirements of the task (Nunes et al., 2013; Pardo et al., 2012, 2015; Randall et al., 2012, 2014; Correa et al., 2015; Yohn et al., 2015a).

One important use of animal models is to assess the effects of potential drug treatments. Recent studies have shown that the ability of drugs that act on monoamines to reverse the effort-related effects of TBZ depends upon their pharmacological profile. The serotonin transport inhibitors (SSRIs) fluoxetine and S-citalopram did not reverse the effort-related effects of TBZ, and in fact tended to produce further impairments in lever pressing (Yohn et al., 2016a,b), as did the norepinephrine uptake inhibitor desipramine (Yohn et al., 2016a). In contrast, drugs that block DA uptake, including bupropion, GBR12909, PRX-14040, methylphenidate, and lisdexamfetamine, have all been shown to reverse the effects of TBZ in rats tested on the concurrent FR5 lever pressing/chow feeding concurrent choice task (Nunes et al., 2013; Yohn et al., 2016a,b,c; Salamone et al., 2016b).

Because MAO inhibitors are used to treat depression, Parkinsonism and other disorders (Cryan et al., 2005; Youdim and Bakhle, 2009), the present studies focused on the ability of MAO inhibitors with different patterns of selectivity to ameliorate the effort-related impairments induced by TBZ in rats, using the concurrent FR5/chow feeding choice task. Experiment 1 investigated the ability of moclobemide, which is a reversible MAO-A inhibitor that is used as an antidepressant in Europe and Canada, to attenuate the effects of TBZ. Experiment 2 explored the effects of deprenyl (selegiline), an irreversible MAO-B inhibitor. Although it was originally developed as an antiparkinsonian drug (Birkmayer et al., 1984), deprenyl has been shown to have antidepressant effects in humans (Jang et al., 2013; Sclar et al., 2013). Experiment 3 examined the effects of pargyline (PAR), which is a relatively nonselective irreversible MAO inhibitor. Based on previous results (Randall et al., 2014; Yohn et al., submitted) we hypothesized that deprenyl whould be able to partially attenuate the shift in response allocation induced by TBZ in rats tested on the FR5 choice procedure. In view of the positive findings with

deprenyl, the fourth experiment was a control study that focused on the actions of the effective dose of deprenyl (2.5 mg/kg) when administered in the absence of TBZ, as well as the highest doses of the other two drugs.

## 2. Materials and methods

### *2.1 Animals*

Adult male, drug-naïve, Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN, USA) were housed in a colony maintained at 23°C with 12-h light/dark cycles (lights on at 0700 hours). The rats (n=24) weighed 300-350 grams at the beginning of the study and were food-deprived to 85% of their free-feeding body weight for the experiments. Rats were fed supplemental chow to maintain the 85% free-feeding body weight throughout the course of the study with ad libitum water available in their home cages. Animal protocols were approved by the University of Connecticut Institutional Animal Care and Use Committee and followed NIH guidelines.

### *2.2 Behavioral Procedures*

*Concurrent FR5/chow-choice procedure:*

Behavioral sessions were conducted in operant conditioning chambers (28x23x23 cm3, Med Associates, Georgia, VT, USA) during the light period. Rats were initially trained to lever press on a continuous reinforcement schedule (30 minute sessions, during 5 days) to obtain 45mg high carbohydrate pellets, (Bio-serv, Frenchtown, NJ, USA), and then were shifted to the FR5 schedule (30 minute sessions, 5 days/week) and trained for several additional weeks until reaching a predetermined baseline number of lever presses (i.e., consistent responding ≥ 1,200

lever presses). Animals needed to consistently reach baseline criteria for approximately one week before being introduced to the concurrent FR5/chow-feeding choice procedure. With this task, weighed amounts of laboratory chow (Laboratory Diet, 5P00 Prolab RHM 3000, Purina Mills, St. Louis, MO, USA; typically 20-25 grams, four-five large pieces) were concurrently available in the chamber during the 30 min FR5 session. At the end of the session, rats were immediately removed from the chambers, lever pressing totals were recorded, and amount of chow consumed was determined by weighing the remaining food and spillage. Rats were trained until reaching and maintaining stable levels of baseline lever pressing and chow intake. Once animals achieved stable baseline rates experimental testing began. For most baseline days, rats did not receive supplemental feeding. However, over weekends and after drug tests, animals received supplemental chow in the home cage. On baseline days, rats mainly consumed pellets that were delivered from lever pressing during the 30 min session.

*2.3 Pharmacological agents and dose selection*

The reversible MAO-A inhibitor moclobemide; (4-chloro-N-(2-morpholin-4-ylethyl)benzamide) was obtained from Selleck Chemicals, (Houston, TX, USA), and was dissolved in de-ionized water heated at medium temperature on a hot-plate until it went into solution. De-ionized water was also used as the vehicle control. Doses (2.5, 5.0 and 10.0 mg/kg) were selected based on previous studies (Cryan et al., 2005; Eroğlu & Güven, 1988). The MAO-B inhibitor selegeline (deprenyl) ((R)-(-)-N-α-Dimethyl-N-2-propynylbenzeneethanamine hydrochloride) was obtained from Tocris, (Minneapolis, MN, USA), and was dissolved in 0.9% saline at room temperature; saline was also used as the vehicle control. Doses (1.25, 2.5 and 5.0 mg/kg) were selected based on reversal studies (Randall et al., 2014) and unpublished

preliminary studies from our laboratory. Pargyline, which is a relatively non-selective MAO inhibitor (N-methyl-N-2-propynyl-benzenemethanamine, monohydrochloride), was obtained from Cayman Chemical Company (Ann Arbor, MI, USA) and was dissolved in 0.9% room temperature saline until it went into solution. Saline was also used as the vehicle control. Previous studies using mice and rats in vivo have used a wide range of doses ranging from 5.0 mg/kg to 256 mg/kg. Thus, an initial pilot study using 6.25, 12.5 and 25.0 mg/kg doses of pargyline was done using rats in the FR5/ chow-choice procedure. Pargyline doses of 25.0 and 12.5 mg/kg PAR produced adverse effects resulting in a suppression of both lever pressing and chow intake (data not shown). Based on these results, it was decided that a dose progression of 1.56, 3.12 and 6.25 mg/kg was a better fit for the study. Tetrabenazine (TBZ; 9,10-dimethoxy-3-(2-methylpropyl)-1,3,4,6,7, 11b hexahydrobenzo[a]quinolizin-2-one), the VMAT-2 inhibitor, was purchased from Tocris Bioscience (Bristol, UK). TBZ was dissolved in a vehicle solution of 0.9% saline (80%) and DMSO (20%). 1N HCl /mL volume was then added to adjust the pH and get the drug completely into solution. The final pH of the TBZ solution was 3.5-4.0. The saline with 20% DMSO vehicle solution was administered as the vehicle control. The dose of 0.75 mg/kg was used based on previous studies (Nunes et al., 2013; Randall et al, 2014; Yohn et al., 2015a,b,c) and extensive unpublished pilot studies.

*2.4 Experimental Procedures*

For each experiment a different group of rats was used. All rats were trained on the concurrent FR5/chow feeding task as described above, and all experiments employed a within-subject design, in which each rat received all doses or vehicle treatments in their particular

experiment in a randomly varied order (acute intraperitoneal (IP) administration; one treatment per week). Baseline training sessions (i.e; non-drug) were conducted four days per week.

*2.4.1 Experiment 1: The MAO-A inhibitor moclobemide failed to attenuate the effects of TBZ on the concurrent FR5/chow-choice procedure.*

Trained rats (n=8) received the following treatments: TBZ vehicle plus moclobemide (MCL) vehicle; 0.75 mg/kg TBZ plus 2.5 mg/kg MCL; 0.75 mg/kg TBZ plus 5.0 mg/kg MCL; or 0.75 mg/kg TBZ plus 10.0 mg/kg MCL, and were tested for 30 minutes on the concurrent FR5/chow-choice procedure. IP injections of TBZ or vehicle were done 90 minutes before testing and MCL or vehicle injections were done 60 minutes prior to testing. Immediately after the session, rats were removed from the chambers, total lever presses were recorded, and chow consumed was calculated.

*2.4.2 Experiment 2: The MAO-B inhibitor deprenyl partially attenuated the effects of TBZ on the concurrent FR5/chow-choice procedure.*

Trained rats (n=9) received the following treatments: TBZ vehicle plus deprenyl (DEP) vehicle; 0.75 mg/kg TBZ plus 1.25 mg/kg DEP; 0.75 mg/kg TBZ plus 2.5 mg/kg DEP; or 0.75 mg/kg TBZ plus 5.0 mg/kg DEP, and were tested for 30 minutes on the concurrent FR5/chow-choice procedure. IP injections of TBZ or vehicle were done 90 minutes before testing and DEP or vehicle injections were done 30 minutes prior to testing. Immediately after the session, rats were removed from the chambers, total lever presses were recorded, and chow consumed was calculated.

*2.4.3. Experiment 3: The nonselective MAO inhibitor pargyline failed to attenuate the effects of TBZ on the concurrent FR5/chow-choice procedure*

Trained rats (n=8) received the following treatments: TBZ vehicle plus pargyline (PAR) vehicle; 0.75 mg/kg TBZ plus 1.56 mg/kg PAR; 0.75 mg/kg TBZ plus 3.125 mg/kg PAR; or 0.75 mg/kg TBZ plus 6.25 mg/kg PAR, and were tested for 30 minutes on the concurrent FR5/chow-choice procedure. IP injections of TBZ or vehicle were done 90 minutes before testing and PAR or vehicle injections were done 30 minutes prior to testing. Immediately after the session, rats were removed from the chambers, total lever presses were recorded, and chow consumed was calculated.

*2.4.4. Experiment 4: Effects of MAO inhibitors administered alone.*

Trained rats (n=8) received the following treatments: IP injection of saline 30 min prior to testing, PAR (6.25 mg/kg) 30 minutes prior testing, MCL (10.0 mg/kg ) 60 minutes prior testing and DEP (2.5mg/kg) 30 minutes prior testing. Animals were tested on the FR5/chow feeding choice task for 30 minutes. Once the session was over, rats were removed from the chambers, total lever presses were recorded, and chow consumed was calculated.

*2.5 Statistical Analyses*

For all experiments, total number of lever presses and gram quantity of chow intake from the 30 min session were analyzed using repeated measures ANOVA. A computerized statistical program (SPSS 14.0 for Windows) was used to perform all analyses. When there was a significant repeated measures ANOVA, non-orthogonal planned comparisons using the overall error term were used to assess the differences between each treatment and the control condition

(TBZ plus vehicle in experiments 1-3, saline vehicle in experiment 4), in which the number of comparisons was restricted to the number of treatments minus one (Keppel, 1973; pp 89-103).

**3. Results**

*Experiment 1: Moclobemide failed to attenuate the effects of TBZ on the concurrent FR5/chow-choice procedure*

In the dose range tested, MCL failed to produce a reversal of the effects of TBZ on effort-related choice behavior in animals tested on the concurrent FR5/chow-choice procedure. There was an overall significant effect of drug treatment on lever pressing [$F(4,28)=57.25$, $p<0.01$]. TBZ significantly decreased lever pressing compared to vehicle-vehicle control (planned comparisons, $p<0.01$). Moreover, co-administration of TBZ plus MCL 10.0 mg/kg further decreased lever pressing compared to TBZ plus vehicle (planned comparisons, $p<0.01$). An overall significant effect of drug treatment was also found on chow intake [$F(4,28)=119.80$, $p<0.01$]. TBZ significantly increased chow intake (planned comparisons, $p<0.01$). Furthermore, non-orthogonal planned comparisons revealed that co-administration of TBZ plus MCL 2.5, 5.0, and 10.0 mg/kg ($p<0.01$) significantly reduced chow intake compared to TBZ plus vehicle.

*Experiment 2: Deprenyl partially attenuated the effects of TBZ on the concurrent FR5/chow-choice procedure*

DEP produced a partial reversal of the effects of TBZ on effort-related choice behavior in animals tested on the concurrent FR5/chow-choice procedure. There was an overall significant effect of drug treatment on lever pressing [$F(4,32)=15.31$, $p<0.01$]. Planned comparisons showed that TBZ produced a significant reduction on lever pressing compared to vehicle-vehicle control

($p<0.01$). Moreover, co-administration of TBZ plus 2.5 mg/kg DEP significantly increased lever pressing compared to TBZ plus vehicle (planned comparisons, $p<0.01$). An overall significant effect of drug treatment was also found on chow intake [$F(4,32)=14.32$, $p<0.01$]. TBZ significantly increased chow intake (planned comparisons, $p<0.01$). Furthermore, non-orthogonal planned comparisons revealed that co-administration of TBZ plus 1.25 mg/kg DEP ($p <0.05$) and 2.5-5.0 mg/kg ($p<0.01$) significantly reduced chow intake compared to TBZ plus vehicle. Therefore, co-administration of TBZ and DEP (2.5 mg/kg) significantly increased lever pressing relative to TBZ alone, while chow consumption was significantly reduced at 1.25, 2.5 and 5.0 mg/kg compared to TBZ-vehicle treated animals.

*Experiment 3: Pargyline failed to attenuate the effects of TBZ on the concurrent FR5/chow-choice procedure*

In the dose range tested, PAR failed to produce a reversal of the effects of TBZ on effort-related choice behavior in animals tested on the concurrent FR5/chow-choice procedure. There was an overall significant effect of drug treatment on lever pressing [$F(4,28)=43.70$, $p<0.01$]. TBZ significantly decreased lever pressing compared to vehicle-vehicle control (planned comparisons, $p<0.01$). However, co-administration of PAR (1.56, 3.125 and 6.25 mg/kg) failed to reverse the effects of TBZ on lever pressing compared to TBZ-vehicle (planned comparisons). An overall significant effect of drug treatment also was found on chow consumption [$F(4,28)=12.22$, $p<0.01$]. TBZ significantly increased chow consumption compared to vehicle-vehicle control (planned comparisons, $p<0.01$). Moreover, co-administration of TBZ plus 6.25 mg/kg PAR significantly decreased chow consumption relative to TBZ-vehicle (planned

comparisons, $p<0.05$). Thus, co-administration of TBZ and PAR (6.25 mg/kg) significantly reduces chow consumption while having no effect on lever pressing compared to TBZ-vehicle.

*Experiment 4: Effects of MAO inhibitors administered alone*

There was an overall significant effect of drug treatment on lever pressing [$F(3,21)=25.85$, $p<0.01$]. Planned comparisons revealed that MCL (10.0 mg/kg) significantly reduced level pressing when compared to saline vehicle ($p< 0.002$), while DEP and PAR did not. However, there were no significant effects on chow consumption [$F(3,21)=2.203$, p = n.s.]

**4. Discussion**

Consistent with previous studies (Nunes et al., 2013; Randall et al., 2014; Yohn et al., 2015a,b, 2016a,b,c; Salamone et al., 2017), TBZ shifted effort-based choice in experiments 1-3, decreasing lever pressing and increasing chow intake. The use of TBZ as a pharmacological agent to induce effects related to depression in rodents is in part based upon reports indicating that side effects such as fatigue, apathy, anergia and other depressive symptoms can occur TBZ when is used to treat Huntington Disease (Frank 2009, 2014; Guay 2010; Chen et al., 2012). However, it should be emphasized that tests of effort-based decision making are not intended to provide broad or general models of depression, but rather to focus on a specific behavioral phenotype that is related to a particular set of symptoms seen across multiple psychiatric and neurological disorders (Salamone et al., 2016b). Modeling and studying specific symptoms is consistent with the initiative proposed by NIMH Research Domain Criterion (RDoC), which emphasizes specific psychiatric symptoms and their underlying neurobiology, rather than the traditional diagnostic categories or disorders (Cuthbert and Insel, 2013).

The selective MAO-A inhibitor MCL and the nonselective MAO inhibitor PAR failed to reverse the effects of 0.75mg/kg TBZ on effort-related choice in rats tested on the concurrent FR5/chow-choice procedure. MCL (10.0 mg/kg) in combination with TBZ further impaired performance by reducing lever pressing and chow intake compared to TBZ/vehicle. In addition, experiment 4 revealed that injection of MCL in the absence of TBZ significantly reduced lever pressing. Taken together, these results indicate that MCL does not increase exertion of effort in rats assessed by the FR5/chow feeding task. Although there is substantial evidence demonstrating that MCL is an effective antidepressant (Cryan et al., 2005), this drug is relatively selective for MAO-A, which is critical for the metabolism of serotonin (5-HT; Finberg 2014; Finberg and Rabey, 2016). Thus, inhibition of MAO-A should substantially increase extracellular levels of 5-HT (Stanley et al., 2007), potentially having negative effects on motivated behavior similar to those seen with serotonin uptake blockers SSRIs such as fluoxetine and citalopram (Yohn et al. 2016a,b,d). This idea is consistent with a recent paper reporting that fluoxetine impaired psychomotor functions in people (Mendhe et al., 2017), and with several clinical studies reporting the relative ineffectiveness of fluoxetine and several other SSRIs for treating effort-related dysfunctions (Katz et al., 2004; Nutt et al., 2007; Fava et al., 2014; Padala et al., 2012; Stenman and Lilja, 2013; Rothschild et al., 2014). Although MAO-A inhibitors and SSRIs have different mechanisms of action through which they influence 5-HT transmission, MAO-A inhibitors such as MCL do increase extracellular levels of 5-HT (Freezer et al., 2005; Stanley et al., 2007), which could potentially lead to downstream effects such as alterations in DA transmission (Di Mascio et al. 1998; Ichikawa and Meltzer, 1995; Yohn et al., 2016d), which could result in effort-related dysfunctions. Although the precise mechanisms underlying this effect are not clear, evidence indicates that it could be due to increased stimulation of $5\text{-HT}_{2C}$

receptors in nucleus accumbens and/or ventral tegmental area (Di Giovanni et al. 2000; Di Matteo et al. 2008). Thus, because of its selective effects on MAO-A, it is reasonable to suggest that the actions of MCL on 5-HT transmission would lead to alterations in effort-related decision making in rats. Furthermore, MAO-A is also known to metabolize norepinephrine, and recent studies have shown that the norepinephrine uptake inhibitor desipramine failed to reverse the effort-related effects of TBZ, and that desipramine and atomoxetine reduce operant responding when administered alone (Yohn et al. 2016a,d). Human studies have yielded mixed results in terms of the anergic or fatigue-related effects of MCL. Papakostas and Fava (2006) reported that MCL produced rates of fatigue as a side effect that were comparable to those produced by SSRIs. However, it is generally reported that there is little in the way of psychomotor retardation that is produced by MCL at clinical doses (Bonnet 2003), and some patients with chronic fatigue syndrome treated with MCL seem to benefit from an increase in vigor and overall energy (Hickie et al., 2000). Because MCL is typically given chronically in clinical settings, future studies should examine the effects of repeated MCL on performance of tasks measuring effort-based decision making.

In experiment 2, the results showed that the MAO-B inhibitor DEP (2.5 mg/kg) produced a partial reversal of the effect of TBZ on effort-related choice behavior in animals tested on the concurrent FR5/chow-choice procedure (figure 2). In experiment 4, DEP by itself did not have any effect on effort-related behavior (figure 4). The ability of MAO-B inhibitors such as DEP to improve motivational function is consistent with studies from the clinical literature. Although MAO-B inhibitors were originally developed as antiparkinsonian drugs (Schapira et al., 2011, Fabbrini et al., 2012), recent studies show that DEP is effective at reducing depressive symptoms in people with major depression, and in producing antidepressant-like effects in traditional

animal models (Varga and Tringer, 1967, Birkmayer et al., 1984; Jang et al. 2013; Sclar et al. 2013; Shimazu et al., 2005; Kasai et al., 2017). A case study reported that DEP improved depressive symptoms in a treatment-resistant patient at doses that also increased DA transmission as measured by PET imaging (Kitaichi et al. 2013). Krishna et al. (2014) found that administration of MAO-B inhibitors to Parkinson's disease patients reduced apathy symptoms. The development of fatigue in early Parkinson's disease patients was reduced by the MAO-B inhibitor rasagiline (Stocchi 2014). Smith et al. (2015) reported that when rasagiline was given in combination with antidepressants to Parkinsonian patients with motivational symptoms, there was significant improvement in fatigue and a trend towards reduction in apathy compared to patients that received antidepressants plus placebo.

In the present study, the 2.5 mg/kg dose of DEP was the only effective dose, and overall the actions of DEP on lever pressing in TBZ-treated rats was characterized by an inverted-U shaped dose response curve. This appears to be a consistent finding for the effects of DEP in tests of effort-based choice. Randall et al. (2014) observed that DEP could reverse the effects of TBZ on progressive ratio responding, and Yohn et al. (submitted) found that systemic and intra-accumbens DEP increased progressive ratio output in rats tested on a progressive ratio/chow feeding choice task. In all cases, the effect of DEP was characterized by a narrow inverted-U shaped dose response curve. It is possible that at higher doses DEP is blocking both MAO-A and MAO-B, and as a result the possible positive effects of MAO-B inhibition where overshadowed by adverse effects related to MAO-A that were similar to those seen in the MCL experiment. Evidence indicates that the selectivity of MAO inhibitors is concentration dependent, and DEP is selective for MAO-B only at lower doses but it is non-selective at high doses (Magyar 2011).

In summary, the present studies offer novel information about the motivational effects of a range of MAO inhibitors with different selectivity profiles. It was found that not every MAO inhibitor used in these experiments was effective in reversing the low-effort bias induced by TBZ in rats tested on the FR-5/choice procedure. The MAO-B inhibitor DEP was able to reverse, albeit partially, lever pressing impairment in rats treated with TBZ. In contrast, the MAO-A inhibitor MCL failed to reverse the effects of TBZ, and further impaired the animals when co-administered with TBZ. Biochemical research indicates that 5-HT and norepinephrine are both substrates for MAO-A, while DA is a substrate for both isozymes (Finberg 2014; Finberg and Rabey, 2016), although when expressed in yeast cells, recombinant human MAO-B showed a higher $K_{cat}$ and a lower $K_m$ for deamination of DA than human MAO-A (Edmondson et al., 2009). Moreover, there is evidence that DEP is relatively selective for MAO-B at low doses, while it blocks both isozymes at higher doses (Magyar 2011). Taking these results together, it is reasonable to suggest that the pattern of effects seen with MCL were due to blockade of 5-HT and/or norepinephrine metabolism induced by MAO-A inhibition (Yohn et al., 2016a,d). It is possible that the ability of a low dose of DEP to partially reverse the effects of TBZ is due in part to increases in DA transmission due to inhibition of MAO-B. DEP-induced inhibition of MAO-B could be affecting DA metabolism, and could also be elevating endogenous phenylethylamine, which acts to stimulate DA release and block uptake (Miklya 2017). DEP could also be augmenting DA transmission because l-amphetamine is a metabolite of deprenyl (Bundgaard et al., 2016), and it is possible this could have contributed to the effects seen in the present studies. In contrast, the descending limb of the inverted-U shaped dose response curve for DEP could be due to actions of higher doses of DEP on 5-HT and/or norepinephrine. Future research in humans (e.g. Wardle et al., 2011; Treadway et al., 2012; Chong et al., 2015) and animal models

should be conducted to determine which MAO-inhibitors could be useful as treatments for effort-related neuropsychiatric dysfunctions such as fatigue, anergia, and psychomotor slowing, and also should characterize the neurochemical mechanisms that underlie these effects.

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Figure Captions.

Figure 1: Effects of MAO-A inhibitor moclobemide (MCL) on FR5/chow-choice procedure. On measures of lever pressing, mean (+SEM) total lever presses (A) and chow consumption (B) after 30 minutes of testing. TBZ/VEH significantly decreased lever pressing compared to VEH/ VEH (## $p < 0.01$). Co-administration of MCL (10.0 mg/kg) plus TBZ further decreases lever presses compared to TBZ/VEH alone (** $p < 0.05$). TBZ/VEH significantly increased chow consumption compared to VEH/VEH (##). Co-administration of TBZ plus 2.5, 5.0, and 10.0 mg/kg MCL significantly decreased chow consumption relative to TBZ/VEH (** $p < 0.05$).

Figure 2: Effects of MAO-B inhibitor deprenyl (DEP) on FR5/chow-choice procedure. On measures of lever pressing, mean (+SEM) total lever presses (A) and chow consumption (B) after 30 minutes of testing. TBZ/VEH significantly decreased lever pressing compared to VEH/ VEH (## $p < 0.01$). Co-administration of TBZ plus 2.5 mg/kg DEP significantly increased lever pressing compared to TBZ plus vehicle (** $p < 0.05$). TBZ/VEH significantly increased chow consumption compared to VEH/VEH (## $p < 0.01$). Co-administration of TBZ plus 1.25, 2.5 and 5.0 mg/kg DEP significantly decreased chow consumption relative to TBZ/VEH (** $p < 0.05$).

Figure 3: Effects of non-selective MAO inhibitor pargyline (PAR) on FR5/chow-choice procedure. On measures of lever pressing, mean (+SEM) total lever presses (A) and chow consumption (B) after 30 minutes of testing. TBZ/VEH significantly decreased lever pressing compared to VEH/ VEH(## $p < 0.01$). Co-administration of PAR (1.56, 3.125 and 6.25 mg/kg) plus TBZ failed to reverse the effects of TBZ/VEH on lever pressing. TBZ/VEH significantly increased chow consumption compared to VEH/VEH (## $p < 0.01$). Co-administration of TBZ plus 6.25mg/kg PAR significantly decreased chow consumption relative to TBZ/VEH (** $p < 0.05$).

Figure 4: Effects of MAO inhibitors on the concurrent FR5/chow-choice procedure when administered in the absence of TBZ. On measures of lever pressing, mean (+SEM) total lever

presses (A) and chow consumption (B) after 30 minutes of testing. MCL (10.0 mg/kg) significantly reduced lever pressing compared to VEH (** $p < 0.05$), while PAR 6.25 mg/kg and 2.5 mg/kg DEP did not. There was no effect in chow consumption.

Research Highlights:

- Rats were assessed using tests of effort-related decision making.
- The VMAT-2 inhibitor tetrabenazine produced a low-effort bias in rats.
- The MAO-B inhibitor deprenyl partially reversed the effects of tetrabenazine.
- The MAO-A blocker moclobemide and the nonselective drug pargyline were ineffective.

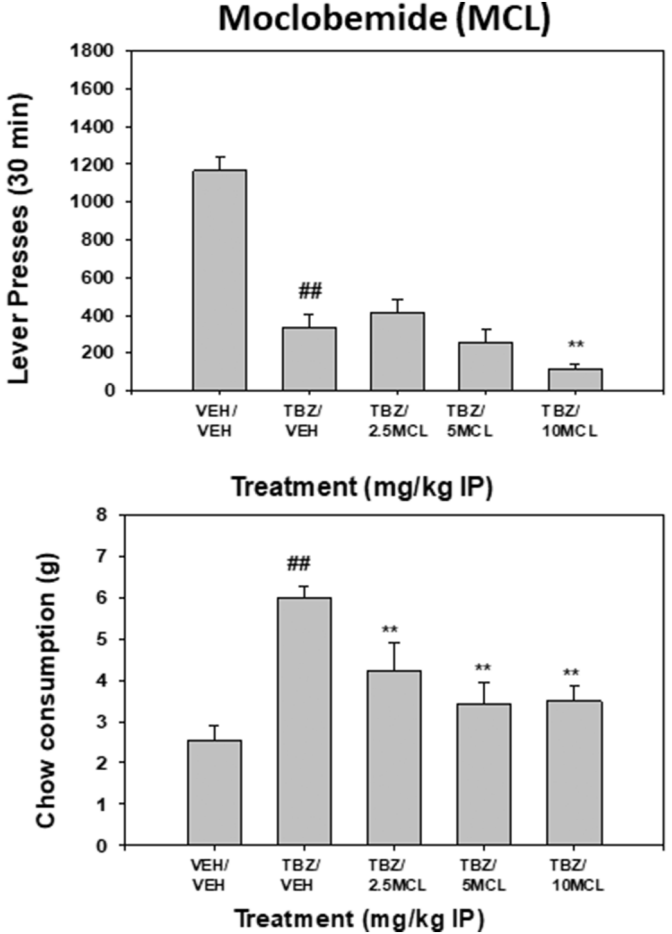
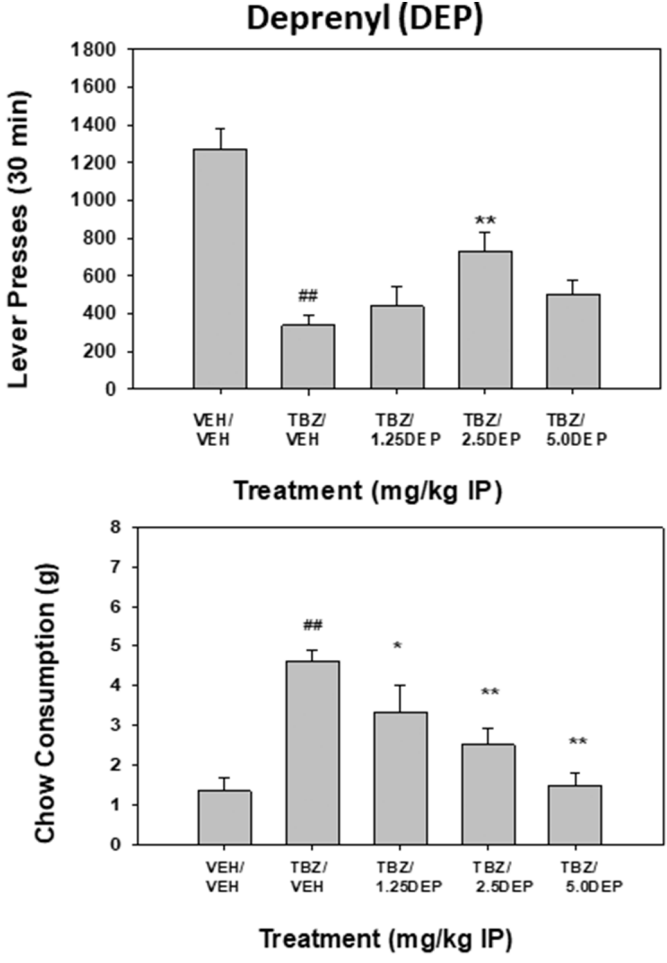

Moclobemide (MCL)
Lever Presses (30 min)
1800
1600
1400
1200
1000
800
600
400
200
0
##
**
VEH/ VEH
TBZ/ VEH
TBZ/ 2.5MCL
TBZ/ 5MCL
TBZ/ 10MCL
Treatment (mg/kg IP)
Chow consumption (g)
8
7
6
5
4
3
2
1
0
##
**
**
**
VEH/ VEH
TBZ/ VEH
TBZ/ 2.5MCL
TBZ/ 5MCL
TBZ/ 10MCL
Treatment (mg/kg IP)

Figure 1


Deprenyl (DEP)
Lever Presses (30 min)
1800
1600
1400
1200
1000
800
600
400
200
0
##
**
VEH/ VEH
TBZ/ VEH
TBZ/ 1.25DEP
TBZ/ 2.5DEP
TBZ/ 5.0DEP
Treatment (mg/kg IP)
Chow Consumption (g)
8
7
6
5
4
3
2
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*
**
**
VEH/ VEH
TBZ/ VEH
TBZ/ 1.25DEP
TBZ/ 2.5DEP
TBZ/ 5.0DEP
Treatment (mg/kg IP)

Figure 2

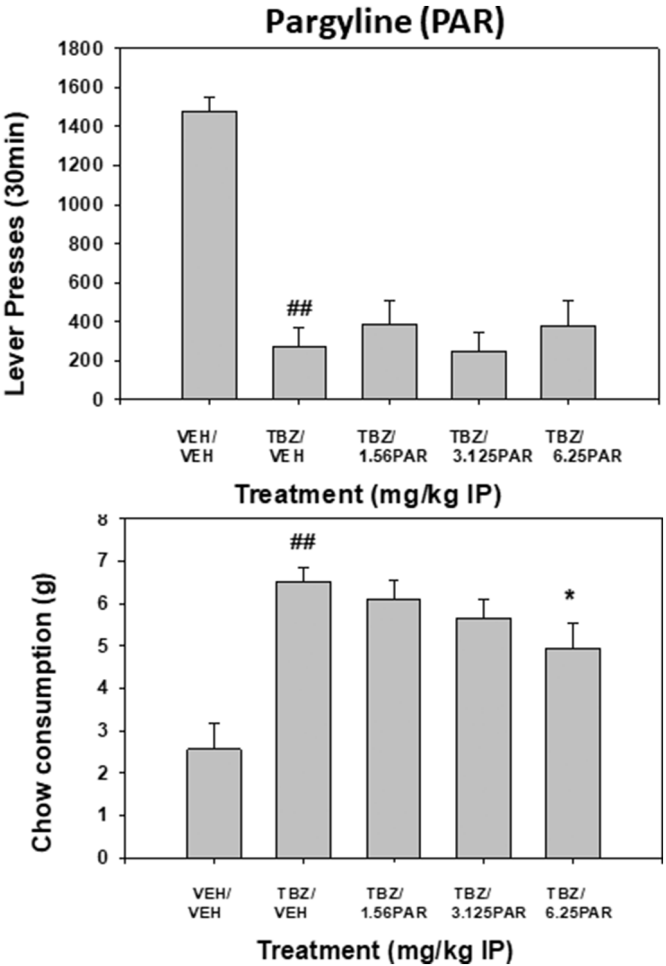
Pargyline (PAR)
Lever Presses (30min)
1800
1600
1400
1200
1000
800
600
400
200
0
##
VEH/ VEH
TBZ/ VEH
TBZ/ 1.56PAR
TBZ/ 3.125PAR
TBZ/ 6.25PAR
Treatment (mg/kg IP)
Chow consumption (g)
8
7
6
5
4
3
2
1
0
##
*
VEH/ VEH
TBZ/ VEH
TBZ/ 1.56PAR
TBZ/ 3.125PAR
TBZ/ 6.25PAR
Treatment (mg/kg IP)

Figure 3

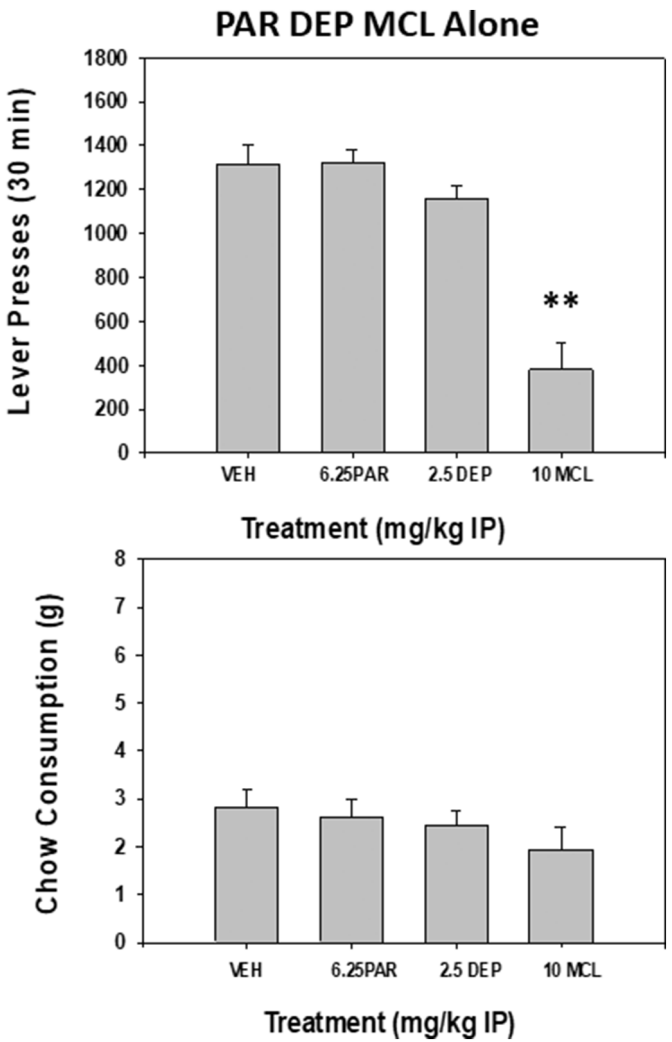
PAR DEP MCL Alone
Lever Presses (30 min)
1800
1600
1400
1200
1000
800
600
400
200
0
**
VEH
6.25PAR
2.5 DEP
10 MCL
Treatment (mg/kg IP)
Chow Consumption (g)
8
7
6
5
4
3
2
1
0
VEH
6.25PAR
2.5 DEP
10 MCL
Treatment (mg/kg IP)

Figure 4