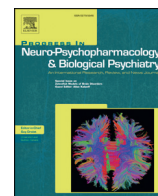




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## Lipoic acid and haloperidol-induced vacuous chewing movements: Implications for prophylactic antioxidant use in tardive dyskinesia

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### ABSTRACT

Tardive dyskinesia (TD), a potentially irreversible antipsychotic (AP)-related movement disorder, is a risk with all currently available antipsychotics. AP-induced vacuous chewing movements (VCMs) in rats, a preclinical model of TD, can be attenuated by antioxidant-based treatments although there is a shortage of well-designed studies. Lipoic acid (LA) represents a candidate antioxidant for the treatment of oxidative stress-related nervous system disorders; accordingly, its effects on AP-induced VCMs and striatal oxidative stress were examined. Rats treated with haloperidol decanoate (HAL; 21 mg/kg every 3 weeks, IM) for 12 weeks were concurrently treated with LA (10 or 20 mg/kg, PO). VCMs were assessed weekly by a blinded rater, and locomotor activity was evaluated as were striatal lipid peroxidation markers and serum HAL levels. VCMs were decreased by the lower dose (nonsignificant), whereas a significant increase was recorded with the higher dose of LA. HAL decreased locomotor activity and this was unaffected by LA. Striatal malondialdehyde (MDA) levels in HAL-treated rats were reduced by both LA doses, while 4-hydroxynonenal (4-HNE) levels were predictive of final VCM scores (averaged across weeks 10–12). Study limitations include differences between antipsychotics in terms of oxidative stress, LA dosing, choice of biomarkers for lipid peroxidation, and generalizability to TD in humans. Collectively, current preclinical evidence does not support a “protective” role for antioxidants in preventing TD or its progression, although clinical evidence offers limited evidence supporting such an approach.

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### 1. Introduction

Tardive dyskinesia (TD) represents a late onset, potentially irreversible movement disorder associated with ongoing antipsychotic exposure (Lerner et al., 2015). The average prevalence associated with the older conventional antipsychotics was in the range of 20% (Kane and Smith, 1982), with the risk even higher in certain populations (e.g., geriatric patients) (Jeste et al., 1995). While numerous theories have been posited regarding its underlying pathophysiology, the precise mechanisms remain unclear. This is evident when one looks at treatment – an array of different compounds have been investigated, although the

evidence is equivocal for most and to date only one agent, tetrabenazine (a vesicular monoamine transporter inhibitor [VMATI]), has been approved in Canada for hyperkinetic movement disorders, including TD (Lockwood and Remington, 2015). In a review of 11 studies where tetrabenazine was used, reported rates of moderate or greater improvement were in the range of 50–100%; however, tetrabenazine is also burdened with a number of side effects (Fasano and Bentivoglio, 2009). While the newer ‘atypical’ antipsychotics initially laid claim to marked reductions in risk of TD, there is debate as to how much better they are in this regard and it remains that no currently available antipsychotic, clozapine included, is without risk of TD (Achalia et al., 2014; Adam et al., 2014; Correll et al., 2004; Li et al., 2009; Remington, 2007; Tarsy et al., 2011). Moreover, the off-label use of these compounds has grown rapidly with the advent of the newer agents; for example, in Canada the use of antipsychotics in children and adolescents increased 114% between 2005 and 2009 (Pringsheim et al., 2011). Accordingly, TD remains a topic of interest and ongoing research as we seek to prevent its occurrence or, at the very least, develop effective, well-tolerated treatments.

*Abbreviations:* ANOVA, analysis of variance; D2, dopamine receptor 2; HAL, haloperidol; 4-HNE, 4-hydroxynonenal; I.M., intramuscular; 8-ISO, 8-isoprostane; LA, lipoic acid; MDA, malondialdehyde; TD, tardive dyskinesia; VCM, vacuous chewing movement; VEH, vehicle; VMATI, vesicular monoamine transporter inhibitor.

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One popular theory suggests that free radical production/oxidative stress plays a role in TD, and among putative treatments a number of compounds with antioxidant properties have been investigated, again with equivocal results (Bhidayasiri et al., 2013; Lockwood and Remington, 2015; van Harten and Tenback, 2011). As a rule, these trials have taken the form of treatment for existing TD, as compared to concomitant use as a preventive strategy when antipsychotics are initiated. However, it has been suggested that such trials be undertaken in humans (van Harten and Tenback, 2011), and other areas of medicine have embraced such a strategy (Conti et al., 2016).

A rodent model for antipsychotic-induced TD, involving the induction of vacuous chewing movements (VCMs), dates back almost four decades now (Waddington et al., 1983) and has been used extensively in efforts to better understand and treat TD (Casey, 2000). We recently reviewed preclinical evidence related to antioxidant-based treatment strategies, concluding that while results suggest benefits, there is insufficient evidence at present to advocate their use as an effective preventive strategy (Lister et al., 2014). This relates in part to trial design and methodology; as noted in the review, shorter study duration as well as choice of antipsychotic formulation and administration schedule compromise the interpretation of findings for a number of reports. Trial duration is important since acute and tardive VCMs are pharmacologically and neurochemically distinct (Egan et al., 1996), while formulation and administration schedule (e.g., daily injections vs. depot formulations or minipumps) are important since antipsychotics are metabolized rapidly in rodents (Cheng and Paalzow, 1992; Kapur et al., 2003).

Only five studies were identified in this review that used long acting injectable formulations and continued 12 weeks or longer (Andreassen et al., 1999; Fachinnetto et al., 2005, 2007a, b; Sachdev et al., 1999). Results were divided, with three reporting no benefits (Andreassen et al., 1999; Fachinnetto et al., 2007a; Sachdev et al., 1999). In terms of the two other reports, only one involved an intervention to prevent TD, diphenyl diselenide (Fachinnetto et al., 2007b); the second study indicated increased VCMs in haloperidol-treated animals exposed to a high fat diet in the 6 months before antipsychotic treatment was initiated (Fachinnetto et al., 2005).

Using these studies as a 'gold standard', the existing literature remains quite limited and results equivocal at best with regard to the preventative benefits of antioxidants in combination with antipsychotic treatment. Interestingly, the human literature has suggested a signal. In recently published guidelines focused on treatment of TD, it was concluded that for agents such as Vitamin E there is insufficient evidence to either support or refute use in the treatment of tardive movements (Bhidayasiri et al., 2013). An earlier Cochrane meta-analysis, however, concluded that individuals with antipsychotic-induced TD showed less deterioration in their symptoms if allocated to Vitamin E (Soares-Weiser et al., 2011).

Summarizing, the preventive benefit of antioxidants in TD's evolution and/or course remains an open question. Using the recommendations arising from our earlier review regarding study design, which also included in vivo measures of oxidative stress and/or antioxidant levels (Lister et al., 2014), the present study set out to further investigate the preventative benefits of antioxidants. We chose to look at lipoic acid (LA), a mitochondrial cofactor with antioxidant properties that has been identified as a particularly promising candidate agent for the prevention of brain disorders involving free radical processes (Packer et al., 1995, 1997). After ingestion and absorption this thiol has been shown to cross the blood-brain barrier and protect the brain from oxidative stress by scavenging radicals, regenerating other antioxidants like vitamin C and E, and increasing intracellular glutathione levels (Packer et al., 1997). Further, in vitro work suggests LA may prevent HAL-induced oxidative stress and dopamine D<sub>2</sub> receptor upregulation (Deslauriers et al., 2011). A single study has examined the effects of LA on antipsychotic-induced VCMs in rats but the aforementioned limitations hinder its interpretation; furthermore,

LA was only administered acutely on the final day of this study (Thaakur and Himabindhu, 2009).

Thus, the present study evaluated the preventive value of LA in reducing antipsychotic-induced VCMs and measures of oxidative stress. It was hypothesized that (i) LA co-treatment would attenuate VCMs and oxidative stress induced by haloperidol decanoate (HAL), with the higher dose having the greatest effect; (ii) the locomotor activity suppressing effect of HAL and serum HAL levels would be unaffected by LA; and, (iii) VCMs and measures of striatal lipid peroxidation, proposed biomarkers of oxidative stress, would be positively correlated.

## 2. Experimental procedures

### 2.1. Animals

Male Sprague-Dawley rats ( $N = 40$ , weight upon arrival: 225–250 g) obtained from Charles River (QC, Canada) were singly housed in a climate-controlled colony room ( $22 \pm 2$  °C; humidity 45–65%) on a 12-h light cycle (lights on at 0700) with free access to food and water. The Centre for Addiction and Mental Health's Animal Care Committee approved the experimental protocol, and animal treatment was consistent with the mandate of Ontario's Animals for Research Act as well as the guidelines of the Canadian Council on Animal Care.

### 2.2. Treatments

Haloperidol decanoate (HAL; Sandoz Canada Inc., QC, Canada), suspended in sesame oil, was administered via intramuscular (i.m.) injection at a concentration of 100 mg/mL. HAL dose was calculated by multiplying the desired daily dose of 1 mg/kg/d by 21, such that HAL rats received 21 mg/kg every three weeks. This dose was selected because it produces robust VCM behaviour in rats (Turrone et al., 2002, 2003b). Racemic  $\alpha$ -lipoic acid (LA; Toronto Research Chemicals Inc., ON, Canada) was suspended in a sweetened wet mash (powdered rat chow and water with 0.5% saccharin; Sigma-Aldrich, MO, USA) and fed to rats.

Upon arrival, rats were randomly assigned to the control group (VEH/VEH;  $n = 10$ ) or one of three experimental groups (HAL/VEH, HAL/LA10, HAL/LA20;  $n = 10$  each) and allowed to acclimatize to the facility for one week. A power analysis confirmed that this sample size would allow us to detect treatment changes  $> 50\%$  at a value of 0.80 ( $\alpha = 0.05$ , 2-sided). Rats were then fed 2 g of untreated or LA wet mash (10 or 20 mg/kg) for two days prior to the first injection of sesame oil vehicle or HAL (21 mg/kg, i.m.). Rats continued to receive untreated or LA wet mash Monday–Friday at approximately 1600 h for the following 12 weeks. Rats' access to dry chow was restricted overnight to ensure complete ingestion of the wet mash, and this was confirmed daily by observation.

### 2.3. Behavioural testing

Rats were individually placed on a flat, raised surface (diameter: 26 cm; height: 50 cm) for weekly assessment of VCMs by a single rater blind to experimental treatment. After a 2-min habituation period the number of VCMs occurring during a 2-min test period were recorded. Jaw movements were recorded as VCMs when they appeared to be purposeless, and consecutive "burst" movements were counted individually. Testing occurred immediately before Saturday afternoon injections of HAL on weeks 0, 3, 6, and 9.

Activity testing took place at the end of week 12 in a 0.49 m<sup>2</sup> chamber (Med Associates Inc., VT, USA) outfitted with infrared photo beams. Rats were individually tested for novelty-induced activity during a single 30-min test session with photocell interruptions quantified in 5-min time bins.

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