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# Eltoprazine counteracts L-DOPA-induced dyskinesias in Parkinson's disease: a dose-finding study

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See Bezard and Carta for a scientific commentary on this article (doi:10.1093/brain/awu407).

In advanced stages of Parkinson's disease, serotonergic terminals take up L-DOPA and convert it to dopamine. Abnormally released dopamine may participate in the development of L-DOPA-induced dyskinesias. Simultaneous activation of 5-HT1A and 5-HT1B receptors effectively blocks L-DOPA-induced dyskinesias in animal models of dopamine depletion, justifying a clinical study with eltoprazine, a 5-HT1A/B receptor agonist, against L-DOPA-induced dyskinesias in patients with Parkinson's disease. A double-blind, randomized, placebo-controlled and dose-finding phase I/IIa study was conducted. Single oral treatment with placebo or eltoprazine, at 2.5, 5 and 7.5 mg, was tested in combination with a suprathreshold dose of L-DOPA (Sinemet®) in 22 patients with Parkinson's disease (16 male/six female; 66.6 ± 8.8 years old) with L-DOPA-induced dyskinesias. A Wilcoxon Signed Ranked Test was used to compare each eltoprazine dose level to paired randomized placebo on the prespecified primary efficacy variables; area under the curve scores on Clinical Dyskinesia Rating Scale for 3 h post-dose and maximum change of Unified Parkinson's Disease Rating Scale part III for 3 h post-dose. Secondary objectives included effects on maximum Clinical Dyskinesia Rating Scale score, area under the curve of Rush Dyskinesia Rating Scale score for 3h post-dose, mood parameters measured by Hospital Anxiety Depression Scale and Montgomery Asberg Depression Rating Scale along with the pharmacokinetics, safety and tolerability profile of eltoprazine. A mixed model repeated measures was used for post hoc analyses of the area under the curve and peak Clinical Dyskinesia Rating Scale scores. It was found that serum concentrations of eltoprazine increased in a dose-proportional manner. Following levodopa challenge, 5 mg eltoprazine caused a significant reduction of L-DOPA-induced dyskinesias on area under the curves of Clinical Dyskinesia Rating Scale [-1.02(1.49); P = 0.004] and Rush Dyskinesia Rating Scale [-0.15(0.23); P = 0.003]; and maximum Clinical Dyskinesia Rating Scale score [-1.14(1.59); P = 0.005]. The post hoc analysis confirmed these results and also showed an antidyskinetic effect of 7.5 mg eltoprazine. Unified Parkinson's Disease Rating Scale part III scores did not differ between the placebo and eltoprazine treatments. The most frequent adverse effects after eltoprazine were nausea and dizziness. It can be concluded that a single dose, oral treatment with eltoprazine has beneficial antidyskinetic effects without altering normal motor responses to L-DOPA. All doses of eltoprazine were well tolerated, with no major adverse effects. Eltoprazine has a favourable risk-benefit and pharmacokinetic profile in patients with Parkinson's disease. The data support further clinical studies with chronic oral eltoprazine to treat L-DOPAinduced-dyskinesias.

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**Abbreviations:** AUC $_{0-3}$  = area under curve 3 h post-dose; CDRS = Clinical Dyskinesia Rating Scale; C<sub>max</sub> = maximum concentration; HADS = Hospital Anxiety and Depression Scale; LIDs = L-DOPA-induced dyskinesias; RDRS = Rush Dyskinesia Rating Scale; TEAE = treatment-emergent adverse events; T<sub>max</sub> = time to maximum concentration; UPDRS = Unified Parkinson's Disease Rating Scale

# Introduction

Parkinson's disease is characterized by bradykinesia, rigidity, tremor and gait disturbances largely due to the progressive loss of midbrain dopaminergic innervating the striatum (Lees et al., 2009). Dopamine replacement strategies are effective for many motor symptoms and throughout the disease course essentially all patients with Parkinson's disease will receive treatment with L-DOPA. In a healthy individual, L-DOPA is converted by amino acid decarboxylase to dopamine within dopaminergic neurons and is released via normal synaptic and nonsynaptic mechanisms. In Parkinson's disease, conversion sites for L-DOPA to dopamine diminish progressively. A series of abnormal compensatory cellular and receptor complex alterations develop to counteract the dopamine deficiency. These alterations, together with L-DOPA treatment, result in wearing-off of medication effects and development of abnormally regulated movements, known as L-DOPA-induced dyskinesias (LIDs) (Obeso et al., 2000; Lees et al., 2009).

Several cellular and molecular mechanisms have been proposed to explain the development and onset of LIDs in Parkinson's disease (Obeso et al., 2000; Cenci et al., 2011; Huot et al., 2013). One possibility is that in advanced stage of dopaminergic cell loss, the remaining serotonergic neurons in the basal ganglia complex can specifically take up L-DOPA and convert it to dopamine (Ng et al., 1970, 1971; Hollister et al., 1979). In contrast to the normal situation, release of dopamine occurs in this setting when the serotonergic neurons are activated and dopamine functions as a false transmitter. This abnormally released dopamine stimulates postsynaptic dopamine receptors in an uncontrolled manner (Tanaka et al., 1999; Carta et al., 2007). In particular, uncontrolled stimulation of supersensitized dopamine D1 receptors in the direct striatonigral pathway are thought to mediate LIDs (Obeso et al., 2000; Cenci et al., 2011; Huot et al., 2013). Accordingly, LIDs in rats and monkeys can be reduced by pharmacological autoinhibition or lesioning of serotonin neurons (Bibbiani et al., 2001; Carta et al., 2007; Bezard et al., 2013). Serotonin release is regulated by somatodendritic 5-HT1A receptors and nerve terminal

5-HT1B receptors. In animal models of Parkinson's disease, 5-HT1A and 5-HT1B receptor agonists act synergistically and can completely eliminate LIDs (Carta *et al.*, 2007). Of particular interest are recent animal data using eltoprazine, a selective partial agonist at the 5-HT1A and 5-HT1B receptors. Acute administration of eltoprazine reduced LIDs at a low dose (0.3 mg/kg) in 6-hydroxydopamine (6-OHDA) lesioned rats treated with L-DOPA (Bezard *et al.*, 2013). In chronic studies, eltoprazine provided protection against the development of LIDs and suppressed already developed LIDs at doses of 0.3 mg/kg and 0.6 mg/kg. In a non-human primate model of LIDs [1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkeys treated with L-DOPA], an acute dose of eltoprazine at 0.75 mg/kg showed suppression of dyskinesias (Bezard *et al.*, 2013).

Oral or intravenous eltoprazine has previously been administered to > 600 male and female subjects in single and multiple dose safety and efficacy studies (Raghoebar et al., 1990; Verhoeven et al., 1992; Kohen, 1993; Tiihonen et al., 1993; de Koning et al., 1994; Wigal and Doung, 2011). Doses, ranging between 0.25 and 30 mg, were given to  $\sim$ 300 healthy subjects (Raghoebar et al., 1990; Wigal and Duong, 2011) and > 300 patients suffering from mental handicap and aggression (Verhoeven et al., 1992; Kohen et al., 1993; Tiihonen et al., 1993; de Koning et al., 1994) or attention deficit hyperactivity (ADHD; ClinicalTrials.gov disorder Identifier: NCT01266174). Overall the drug has been safe and well-tolerated. Eltoprazine has uncomplicated absorption, distribution, metabolism, and excretion parameters. The dose-limiting adverse events with single doses were nausea and somnolence/sedation, which were present at 5 mg, but reduced upon repeated dosing. Eltoprazine was originally developed to treat aggressive behaviour in psychiatric disorders (Raghoebar et al., 1990; Kohen, 1993; Tiihonen et al., 1993; de Koning et al., 1994) and was recently tested as a procognitive agent in a clinical trial in patients with ADHD (ClinicalTrials.gov Identifier: NCT01266174).

The positive effects of eltoprazine against LIDs in animal models and its beneficial safety profile in humans led us to evaluate eltoprazine as a potential novel therapy against LIDs in patients with Parkinson's disease. Placebo has a strong effect on LIDs (Goetz *et al.*, 2008), so it is critical

Table | Demographics of study participants.

Variable	Intention to treat population (n = 22)
Age (years)	66.6 (8.8)
Male/female	16 (72.7%)/6 (27.3%)
Height (cm)	172.6 (10.1)
Weight (kg)	69.9 (12.0)
Caucasian	22 (100%)
Disease duration (years)	11.6 (3.1)
LIDs (years)	3.41 (1.40)
Hoehn and Yahr stage	2.86 (0.44)
UPDRS-I	2.09 (1.41)
UPDRS-II	10.1 (4.7)
UPDRS-III	29.8 (10.0)
UPDRS-IV	8.23 (2.58)
UPDRS-IV-32	1.86 (0.83)
UPDRS-IV-33	1.68 (0.95)
UPDRS-IV-34	0.91 (1.11)
Dystonia	7 (31.8%)
Peak-dose dyskinesias	22 (100%)
L-DOPA	22 (100%)
DA agonist	17 (77%)
MAOB inhibitor	9 (41%)
COMT inhibitor	15 (68%)
LED (mg)	1191 (495)

The measures are taken from the intention to treat study population on the day of screening. For categorical variables; n (%) is presented. For continuous variables; mean (standard deviation). LID severity is indicated by results from questions 32–34 of UPDRS-IV, indicating duration, disability and painfulness of LIDs. L-DOPA equivalent (LED) was calculated according to Tomlinson et al. (2010). DA = dopamine.

to perform placebo-controlled trials when evaluating treatment effects on LIDs. We therefore undertook a phase I/IIA, double-blind, randomized, placebo-controlled, dose finding study with single oral eltoprazine treatment in an L-DOPA challenge-dose setting.

# Materials and methods

### **Patients**

The study population was planned to consist of 24 Parkinson's disease patients with LIDs, recruited at Karolinska Hospital and Skåne University Hospital in Sweden. The demographics of the intention to treat group (n=22) are presented in Table 1. Among these patients, 12 (equally divided over the two sites) were selected to be part of a pharmacokinetic population and subjected to blood sampling for the assessment of serum concentrations of eltoprazine.

### **Ethics**

In this double-blind, placebo-controlled, phase I/IIa first time in PD patients study, male and female patients with a diagnosis of idiopathic moderate Parkinson's disease and LIDs were

included. Exclusion criteria were atypical or secondary parkinsonism, signs of dementia or depression, a history of structural brain disease or ongoing treatment with amantadine and/or serotonergic compounds. Further details of inclusion and exclusion criteria are available in the Supplementary material.

As this study was the first exposure of eltoprazine to patients with Parkinson's disease, it was conducted as a single-dose, dose-finding study. Dose selection for this trial was based on previous clinical experience with eltoprazine demonstrating 'neuroactivity' (Raghoebar et al., 1990; Verhoeven et al., 1992; Kohen et al., 1993; Tiihonen et al., 1993; de Koning et al., 1994; Wigal and Duong, 2011; ClinicalTrials.gov Identifier: NCT01266174) as well as conventional scaling calculations based on pharmacokinetic exposures in various animal model studies demonstrating neuroactivity. Doses ranging between 0.25 and 30 mg have been administered to healthy subjects or patients in the aforementioned clinical trials. The doses (2.5, 5 and 7.5 mg) administered in this study were lower than those given to most of the healthy volunteers (Raghoebar et al., 1990; Wigal and Duong, 2011) and patients in other populations (Verhoeven et al., 1992; Kohen et al., 1993; Tiihonen et al., 1993; de Koning et al., 1994; ClinicalTrials.gov Identifier: NCT01266174). It was therefore believed that the benefit that could be obtained from this study would outweigh any risks. The study was approved by The Swedish Medical Product Agency, the local Ethics Committee, and performed in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. All patients provided informed written consent before enrolment. The study was registered with the Eudra CT number 2009-015928-28 and conducted between 15 December 2010 and 11 January 2012.

# Randomization and masking

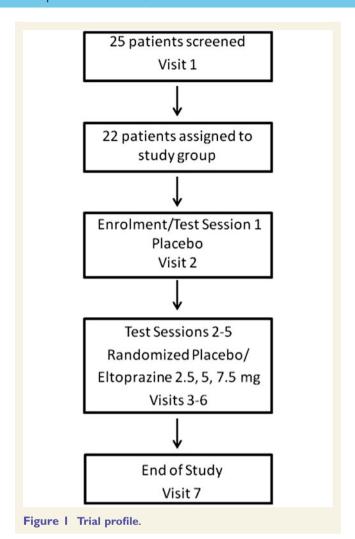
The investigational medicinal product was eltoprazine hydrochloride 2.5 mg capsules or matching placebo, labelled at the manufacturer. Patients were randomized to one of four sequence groups to receive three single doses of oral eltoprazine (2.5, 5 and 7.5 mg). An additional study treatment of 'randomized placebo' was administered in one of Visits 3 to 6 and 'run-in placebo' was administered at Visit 2. For details on randomization, see the Supplementary material.

### **Procedures**

As outlined in Fig. 1, patients first made a screening visit (Visit 1). Included patients then made five dosing visits and were exposed to placebo (twice) and all three eltoprazine (2.5, 5 and 7.5 mg) dosages, before making a final end-of-study visit (Visit 7). The investigator obtained a patient's written informed consent form before any study-related activity began. After signing the informed consent form, patients were screened for inclusion/exclusion criteria and safety assessments (for further details see Supplementary material). All concomitant medications were to be registered in the case report form.

At screening, symptoms of parkinsonism, depression, anxiety and vital signs were assessed as indicated in the study flow chart (Supplementary Table 1). Electrocardiography and blood draws for haematology and clinical chemistry were also performed, as well as screening for significant LIDs conducted by a suprathreshold challenge dose of L-DOPA

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(calculated as 150% of his/her regular dose up to a maximum of 250 mg). L-DOPA was given as Sinemet<sup>®</sup> (L-DOPA combined with carbidopa in a fixed ratio of 4:1). The patients fasted 2 h prior to dosing and allowed to eat 1 h post-dosing. Patients were observed for a period of 3 h after dosing.

Following the initial screening procedure (Visit 1), patients who met inclusion/exclusion criteria were scheduled to visit the clinic six times (during a period of 32 days after enrolment), where five visits were dosing visits and and one visit was a follow-up visit (final visit/early termination visit). Planned study visits and all study activities that were performed at the visits are described by the study flow chart (Supplementary Table 1). All study visits should have occurred within  $\pm 5$ -day window of the time points, except for Visit 2, which could have occurred within 30 days after screening. During each of the dosing visits (Visits 3 to 6), patients received suprathreshold dosage of L-DOPA. In addition, they received either placebo or one of three doses (2.5, 5, or 7.5 mg) of eltoprazine. The patients were rated with the Unified Parkinson's Disease Rating Scale part III (UPDRS-III), Clinical Dyskinesia Rating Scale (CDRS) (Hagell et al., 1999) and Rush Dyskinesia Rating Scale (RDRS) (Goetz et al., 1994) and observed (video filmed) just before dosing with L-DOPA and study medication (i.e. t = 0) and at 30-min

intervals up to 180 min after the challenge test of L-DOPA and study medication (~5 min of filming each time). The order of film sequences was blinded to the assessors. Separate code lists were generated for each site (and kept at the respective site). Each film sequence file was copied and renamed with an allocated code before distribution to the independent assessors. Each sequence was then rated by two independent, blinded raters, who had never met the patients. Scorings of the videos were made for UPDRS-III (except for rigidity which was scored on site during the visit), CDRS and RDRS.

A 2-day diary with three symptom lines—off, on (normal), on with dyskinesia (Reimer *et al.*, 2004)—were filled out by the patients between the screening and enrolment visits, and in between Visits 2 to 6 (1 day before dosing and one day after dosing) to evaluate any changes in perceived dyskinesia by the patients.

Assessment of psychiatric symptoms with the Hospital Anxiety and Depression Scale (HADS) was performed at each visit of the study. All adverse events were recorded in the case report form.

Twelve patients (equally divided over the two sites) were also subjected to additional blood sampling for the measurement of serum concentrations of eltoprazine for pharmacokinetic analysis. Eltoprazine serum concentrations were assessed pre-dose and 1, 2 and 4h post-dose at all dosing occasions. Serum was analysed for eltoprazine by a validated liquid chromatography/mass spectroscopy/mass spectroscopy assay (Biopharmaceutical Research Inc).

The study site was visited periodically by a monitor contracted by the sponsor. The monitor had direct access to case report forms, clinical records, original laboratory reports and other source data. All information recorded in case report forms was verified against source data. All discovered deviations from the procedures that could have affected observational data were recorded.

### **Outcome** measures

The prespecified primary objective of this study was to determine the effective dose of eltoprazine on the suppression of LIDs in Parkinson's disease patients treated with L-DOPA while maintaining the normal treatment effect of L-DOPA using the following efficacy measures: (i) dyskinesia ratings calculated as CDRS AUC<sub>0-3</sub> (area under curve 3 h post-dose) after L-DOPA and study medication intake; and (ii) the highest observed change in UPDRS III score up to 3 h after study medication was used to detect any deterioration of the normal treatment effect of L-DOPA. The highest observed change being defined as the difference between the maximum UPDRS III score 3 h post-dosing and the UPDRS III prior to any study medication.

The prespecified secondary objectives of this study were:

- (i) Number, frequency and severity of any adverse event recorded during the five test episodes that differ between eltoprazine and placebo;
- (ii) Dyskinesia ratings calculated as RDRS AUC<sub>0-3</sub> after L-DOPA and study medication intake;
- (iii) Dyskinesia ratings scored as the maximum score for CDRS ratings over 3 h after L-DOPA and study medication intake;
- (iv) Changes in the diary data between baseline and placebo at any of the three study medication dosages;

- (v) Change of the HADS score after study medication compared with placebo; and
- (vi) Development of depression over the course of the study period determined by the Montgomery Åsberg Depression Rating Scale and clinical judgement.

# Statistical analyses

The number of patients recruited to the study was based on a previous antidyskinetic study (Memdy04; Wictorin, Widner et al. unpublished data), in which memantine was given to Parkinson's disease patients with LIDs. Significant antidyskinetic effects of memantine were found in a crossover study of two consecutive 4-week treatment periods with 17 patients in the per protocol population and 19 patients in the intention to treat population. Based on comparative animal studies (Bezard et al., 2013), the effect size of eltoprazine is in the same range as memantine. The target number for inclusion was therefore set to 24. For the single L-DOPA challenge dosages, no similar data exist, but all recruited patients were included.

Unless otherwise stated, data are presented as mean  $\pm$  standard deviation (SD). The statistical analysis planned *a priori* was the Wilcoxon Signed-Rank test with paired comparisons between each dosing of eltoprazine and the randomized placebo. Both intention to treat and per protocol populations were analysed.

A post hoc analysis, using a SAS v9.3 and mixed model, repeated measures, of the CDRS AUC<sub>0-3</sub> and peak dose CDRS (defined as the measurement 90 min post-dosing with L-DOPA) was performed, to obtain measures of within- and between-subject variability and understand better the magnitude of effect of eltoprazine. A post hoc of CDRS at each time point post L-DOPA dosing was performed, to better understand the dose response over the 3h post-dosing. The post hoc analyses also allowed for the inclusion of baseline data collected at Visits 1 and 2. All available data on the intention to treat population were used in the post hoc analyses. The CDRS AUC<sub>0-3</sub> was analysed on a log scale so that the estimate of difference could be presented as a ratio (or equivalent percentage). In addition, analyses of untransformed peak CDRS were performed and repeated measures analyses were of untransformed data. Baseline covariates were included on a log scale where the endpoint was analysed on a log scale; otherwise baseline covariates were untransformed. All statistical comparisons were made relative to randomized placebo. Covariates included baseline placebo treatment and visit (or visit x time in the mixed model, repeated measures model).

# **Results**

Twenty-five patients were screened and of these, 22 patients met the inclusion/exclusion criteria. They were randomized and included in the intention to treat population and exposed to placebo (twice) and all three eltoprazine dosages (2.5, 5, or 7.5 mg) (Fig. 1). During each of the five dosing visits, patients concomitantly received suprathreshold dosages of L-DOPA. Two patients taking mirtazepin as concomitant medication were randomized even though they did not meet the eligibility criteria. The data from these two patients were included in the intention to

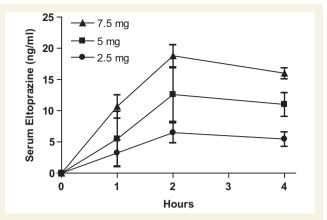


Figure 2 Serum concentration of eltoprazine. Eltoprazine concentration in serum was measured in 12 patients at 2.5 mg, 5 mg and 7.5 mg. Data are presented as mean  $\pm$  SD.

treat analysis, but were excluded in the per protocol analysis. Two patients were given the study medication in the wrong order per the randomization code. Consequently, 18 patients were included in the per protocol population.

# Pharmacokinetics of eltoprazine

A subgroup of 12 patients provided blood samples for serum measurements of eltoprazine. Figure 2 shows serum concentrations at 0, 1, 2 and 4 h after administration of eltoprazine. The maximum concentration ( $C_{\rm max}$ ) was 6.7 (0.2), 13.5 (2.3), and 19.8 (3.5) ng/ml following a single oral dose of 2.5, 5 and 7.5 mg eltoprazine, respectively. Likewise the AUC<sub>0-4</sub> after 2.5, 5, and 7.5 mg eltoprazine increased in a dose-proportional manner 18.3, 35.5, and 55.3 ng h/ml, respectively. At all concentrations, the time to maximum concentration of eltoprazine ( $T_{\rm max}$ ) was between 2 and 4 h.

# **Efficacy of eltoprazine**

### **Dyskinesia ratings**

The data and results for the primary (CDRS AUC<sub>0-3</sub>) and secondary (peak CDRS, RDRS AUC<sub>0-3</sub>) LID outcome measures are shown in Tables 2 and 3 (for the intention to treat population). The individual CDRS data are also presented in Supplementary Fig. 1. Compared to randomized placebo, there was a significant reduction of LIDs as measured by CDRS AUC<sub>0-3</sub> in the intention to treat [Table 2; -1.02 (1.49); P = 0.004] and per protocol [-1.16 (1.61); P = 0.016] populations treated with 5 mg of eltoprazine. At 2.5 mg [intention to treat: -0.64 (1.62); P = 0.065; per protocol: -0.65 (1.71); P = 0.084] as well as 7.5 mg [intention to treat: -0.43 (1.33); P = 0.103; per protocol: -0.538 (1.375); P = 0.082] eltoprazine tended to be antidyskinetic on CDRS AUC<sub>0-3</sub>. Results of the post hoc analysis supported these findings and provided additional information on the dose-response relationship. As shown in Table 4, there was an estimated 15% decrease (P = 0.003)

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in CDRS AUC<sub>0-3</sub> at 5 mg of eltoprazine, a 9% decrease with 7.5 mg (P = 0.083), and a 6% decrease with 2.5 mgof eltoprazine (P = 0.271). Importantly, the repeated measures of the change in CDRS, least squares means, at each time point demonstrate more clearly the dose effect of eltoprazine and show that the greatest effect appeared to be in the latter part of the time course, consistent with the  $T_{\text{max}}$  of eltoprazine (Fig. 3).

With 5 mg eltoprazine, there was a significant reduction in the maximum LID severity in the 3-h post-dose period [Table 3; -1.14 (1.59); P = 0.005]. There was a trend to a reduction in maximum LID severity, post-dose with 2.5 mg [-0.82 (1.89); P = 0.069] as well as 7.5 mg [-0.61](1.53); P = 0.077]. The post hoc analysis evaluated peak dose dyskinesia, i.e. that seen at the T<sub>max</sub> peak following L-DOPA dosing (90 min post L-DOPA). As shown in Table 4 and Fig. 3, the post hoc analysis demonstrated significant decreases in peak dose CDRS at both 5 mg (P = 0.034) and 7.5 mg (P = 0.0427).

Another rating scale for LIDs, RDRS AUC<sub>0-3</sub>, difference from placebo was used as a secondary outcome. In accordance with the data obtained using CDRS, 5 mg of eltoprazine [-0.15 (0.23); P = 0.003], but not 2.5 mg [-0.021 (0.188); P = 0.615] or  $7.5 \,\text{mg} [-0.026 (0.211);$ P = 0.555] of eltoprazine significantly suppressed LIDs (Table 3). Thus, it has been demonstrated with two independent dyskinesia scales, CDRS and RDRS, that eltoprazine at 5 mg reduces LIDs.

### Parkinsonian ratings

Another primary outcome measure related to the effect of eltoprazine on the highest observed change in UPDRS-III score up to 3h after study medication. The highest observed change being defined as the difference between the maximum UPDRS-III score 3h post-dosing and the UPDRS-III prior to any study medication. UPDRS-III scores did not differ between the placebo and eltoprazine treatments at 2.5, 5 or 7.5 mg [change of -2.52 (9.11), P = 0.053; -1.17 (6.62), P = 0.156; 0.49 (8.60), P = 0.375, respectively] (Table 2). No significant differences were found in UPDRS-III AUC<sub>0-3</sub> or maximum UPDRS-III scores 3 h post-dosing (Table 3). No changes were found in a diary administered the day before and after each treatment session (data not shown). Taken together, these data demonstrate that there is no deterioration of the normal anti-parkinsonian treatment effect of L-DOPA by eltoprazine co-treatment.

### Ratings of mood

Effects of eltoprazine on mood were other secondary outcomes in the study. HADS-D showed no significant alterations after eltoprazine administration at any of the studied dosages (Table 3). Likewise, eltoprazine caused no development of depression over the course of the study period, as measured by the Montgomery Asberg Depression Rating Scale [Screening: intention to treat: 5.23 (3.78) and Final visit: 5.14 (4.37)] or clinical

Table 2 Effects of eltoprazine on primary outcomes.

Variable	Test Session I Placebo	Randomized Placebo	Eltoprazine 2.5 mg	Eltoprazine 5 mg	Eltoprazine 7.5 mg	Difference Randomized Placebo -Test Session I Placebo	Difference Eltoprazine 2.5 mg – Randomized Placebo	Difference Eltoprazine 5 mg – Randomized	Difference Eltoprazine 7.5 mg – Randomized Placebo
CDRS AUC <sub>0-3</sub> Change in UPDRS within test session	7.53 (2.90)	7.48 (2.71) 3.46 (5.76)	6.84 (2.63) 0.93 (8.08)	6.47 (2.20) 2.29 (6.04)	7.06 (2.35) 3.95 (5.84)	0.04 (1.66) P = 0.975 1.05 (4.04) P = 0.272	-0.64 (1.63) $P = 0.065$ $-2.52 (9.11)$ $P = 0.053$	-0.102 (1.49) P = 0.004** -1.17 (6.62) P = 0.156	-0.043 (1.33) $P = 0.103$ $0.49 (8.60)$ $P = 0.375$

Dyskinesias assessed as mean CDRS AUC<sub>0.3</sub> and change within test session of UPDRS-III. At each visit, the change in UPDRS-III was determined as the difference between the UPDRS-III score prior to any study medication and the highest compared to randomized placebo are also presented. All data are from the intention to treat UPDRS-III score post-dosing for 3 h. Differences in randomized placebo response to the test session Placebo I and the dosages of eltoprazine when 

using paired Wilcoxon Signed Rank

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Table 3 Effects of eltoprazine on secondary outcome measures.

Variable	Test Session I Placebo	Randomized Placebo	Eltoprazine 2.5 mg	Eltoprazine 5 mg	Eltoprazine 7.5 mg	Difference Randomized Placebo –Test Session I Placebo	Difference Eltoprazine 2.5 mg – Randomized Placebo	Difference Eltoprazine 5 mg – Randomized Placebo	Difference Eltoprazine 7.5 mg – Randomized Placebo
Maximum CDRS after study medication	9.02 (3.37)	9.73 (3.87)	8.91 (3.55)	8.59 (3.36)	9.11 (3.70)	0.71 (2.06) P = 0.145	-0.82 (1.89) P = 0.069	-1.14 (1.59) P = 0.005 ***	-0.61 (1.53) P = 0.077
RDRS AUC <sub>0-3</sub>	1.73 (0.51)	1.67 (0.52)	1.65 (0.54)	1.53 (0.50)	1.65 (0.53)	-0.05 (0.29) P = 0.521	-0.02 (0.19) P = 0.615	-0.15 (0.23) P = 0.003***	-0.03 (0.21) P = 0.555
UPDRS-III AUC <sub>0-3</sub>	22.7 (6.3)	22.2 (6.2)	22.7 (6.2)	22.5 (6.8)	22.6 (6.4)	-0.57 (3.41) P = 0.826	0.49 (2.84) P = 0.814	0.35 (3.14) P = 0.988	0.45 (1.97) P = 0.766
Highest UPDRS after study medication	26.5 (6.9)	25.0 (7.2)	26.3 (8.8)	27.8 (10.5)	26.4 (8.1)	-1.50 (5.34) $P = 0.342$	1.30 (6.40) P = 0.639	2.80 (8.51) P = 0.388	1.35 (4.92) P = 0.150
Difference in HADS-A before and 3 h after study medication	- 0.86 (0.94)	-0.50 (1.14)	-0.27 (1.39)	0.18 (1.30)	-0.14 (0.77)	0.36 (1.43) P = 0.283	-0.14 (0.77) $P = 0.303$	0.58 (1.91) P = 0.044*	0.36 (1.36) P = 0.282
Difference in HADS-D before and 3 h after study medication	-0.18 (1.10)	-0.05 (0.58)	-0.27 (0.99)	-0.18 (0.96)	0.09 (0.87)	0.14 (1.17) P = 0.716	-0.23 (1.34) P = 0.672	-0.14 (0.99) $P = 0.617$	0.14 (1.17) P = 0.716

Dyskinesia measures on maximum observed CDRS post-dosing for 3 h and mean RDRS AUC<sub>0.3</sub>. Parkinsonian motor scores on UPDRS-III AUC<sub>0.3</sub> as well as highest UPDRS part III post-dosing for 3 h. The differences in randomized placebo response to the test session placebo 1 and the dosages of eltoprazine when compared to randomized placebo are also presented. All measures are from the intention to treat population (n = 22). Data are presented as mean  $\pm$  5D. \*\*\*P < 0.01; \*\*P < 0.05 using paired Wil coxon Signed Rank Test.

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Table 4 Post h	oc analyses	of AUC <sub>0-3</sub>	and peak d	lose d	yskinesia scores.
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Dose of eltoprazine		st square geometr e/randomized place		JC <sub>0-3</sub>	Difference in least square means peak dose CDRS (eltoprazine – randomized placebo)			
	Estimate	Lower 95% CI	Upper 95% CI	P-value	Estimate	Lower 95% CI	Upper 95% CI	P-value
2.5 mg	0.94	0.84	1.05	0.2709	-0.8127	-I.8872	0.2517	0.1314
5 mg	0.85	0.77	0.94	0.0027*	-1.0186	-1.9601	-0.0770	0.0345*
7.5 mg	0.91	0.81	1.01	0.0827	-1.0533	-2.0707	-0.0358	0.0427*

Left: Ratio of Least Squares Geometric Means (Eltoprazine/Randomized Placebo) in CDRS AUC<sub>0-3</sub>, Right: Differences of Least Squares Means in peak dose CDRS (90 min post L-DOPA) from Randomized Placebo. All measures are from the intention to treat population (n = 22). \*P < 0.05.

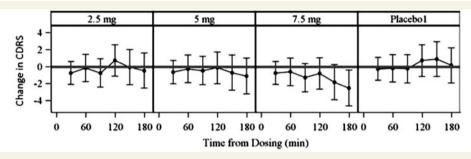


Figure 3 Post hoc analyses of CDRS scores. Mixed model repeated measures analysis of change in CDRS (compared to T = 0) at each time point over the 3 h session, with data representing least squares means differences from randomized placebo (set as 0 line) with 95% CI (Placebo I is baseline placebo, test session I). Measures are from the intention to treat population (n = 22).

judgement. However, it was found that HADS-A scores were significantly higher than placebo after 5 mg eltoprazine [0.68 (1.91), P = 0.044], but not for 2.5 mg [0.227 (1.72), P = 0.303] or 7.5 mg [0.364 (1.364), P = 0.282] (Table 3).

### Safety and reported adverse events

There were no discontinuations from the study. There were no deaths, serious adverse events, or other significant adverse events. As summarized and detailed in Table 5, six patients reported treatment-emergent adverse events (TEAEs) following placebo (Test Session 1), six patients reported nine TEAEs following placebo (Randomized Placebo), seven patients reported 10 TEAEs, following 2.5 mg eltoprazine, 12 patients reported 17 TEAEs following 5 mg eltoprazine, and 10 patients reported 20 TEAEs following 7.5 mg eltoprazine. The most frequent TEAEs following eltoprazine were fatigue, nausea and dizziness.

The only TEAEs that were reported in a treatment group (i.e. either following 2.5, 5 or 7.5 mg eltoprazine) and not in the placebo group (either Test Session 1 or Randomized Placebo) were vaginal haemorrhage (one patient following 2.5 mg), fatigue (three patients following 2.5 mg and two patients following 5 mg), abdominal pain upper (one patient following 5 mg), dysgeusia (one patient following 5 mg and one patient following 7.5 mg), and conjunctivitis, joint dislocation, muscle rigidity, and headache (each in one patient following 7.5 mg).

The haematology and serum chemistry results at screening and at the final visit showed that no clinically significant changes in mean laboratory parameter values occurred in the study (data not shown). There were eight protocol deviations. Most deviations were missed assessments or visits outside the protocol window. These were considered to be minor and should not affect the overall outcome of the study.

# **Discussion**

This study evaluated eltoprazine as a potential novel therapy of LIDs in patients with Parkinson's disease. This study was the first exposure of this drug in Parkinson's disease and was therefore designed as a single-dose, dosefinding study to obtain preliminary efficacy and safety data in Parkinson's disease patients with LIDs. The chosen doses are similar to or lower than those given to patients in other populations. The double-blind, randomized, placebo-controlled crossover design allowed for intraindividual comparisons of placebo effects as well as comparisons between the different doses and placebo in an unbiased manner. Several different rating scales, UPDRS-III, CDRS and RDRS, were used to address motor symptoms and dyskinesias. The CDRS is similar to the Abnormal Involuntary Movement Scale for dyskinesias (Guy, 1976), allowing for rating of individual limbs. CDRS has a high response level and limited ceiling effects

Table 5 Treatment-emergent adverse events by treatment arm and preferred term.

System Organ Class - Preferred Term	Test Session I (Placebo)	Randomized Placebo	Eltoprazine 2.5 mg	Eltoprazine 5 mg	Eltoprazine 7.5 mg
Eye disorders					ı
Conjuntivitis					1
Gastrointestinal	2	1	2	4	7
disorders					
Abdominal pain				1	
Dry mouth	1				1
Nausea	1	1	2	4	7
Vomiting		1		1	1
General disorders		1	3	3	
Fatigue			3	2	
Pyrexia		1		1	
Infections		1			
Nasopharyngitis		1			
Injury, poisoning and complications					1
Joint dislocation					1
Musculoskeletal and	1			2	1
connective tissue					
disorders					
Arthralgia	1			2	
Muscle rigidity					1
Neurological disorders	1		2	4	6
Dizziness	1		2	3	5
Dysgeusia				1	1
Headache					1
Psychiatric disorders		2	I	1	
Anxiety		1		1	
Low mood		1			
Nightmare		1	1		
Sleep disorder			1		
Reproductive system			1		
Vaginal haemorrhage			1		
Respiratory, thoracic and mediastinal disorders		I			
Epistaxis		1			
Skin and subcutaneous tissue disorders	2			1	1
Hyperhidrosis					1
Night sweats					1
Rash papular					
Vascular disorders	ı	1		ı	
Hypertension		ı			

Number of adverse events from the intention to treat population (n = 22).

The indicated number for each system organ class represent the number of patients affected. Some patients had more than one AE in a system organ class.

(Reimer *et al.*, 2004). The difference is that the original AIMS scale was developed for neuroleptic-induced tardive dysinesias and includes several ratings of the oral/facial components of this type of dyskinesias that is omitted in the CDRS. The CDRS can also be used for simultaneous dystonia rating if present. The RDRS is functional scale and complements the CDRS well. As neither the RDRS

nor CDRS assessed patient perception, the patients were also asked to put scores in a diary the day after the treatment. However, as the main effects of both L-DOPA and eltoprazine had gone within a few hours, the diary data turned out to be less useful compared to what they could become in a study with chronic L-DOPA and eltoprazine administration.

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The major finding of this study was that eltoprazine at 5 mg caused a significant reduction of LIDs measured by either CDRS or RDRS. The post hoc analysis revealed that the antidyskinetic effect of eltoprazine was most prominent, and indicated a dose-response, during the last hour of the test sessions. In accordance with these results, the pharmacokinetic analyses demonstrated a T<sub>max</sub> of eltoprazine between 2 and 4h post-dosing. In the present study, eltoprazine and L-DOPA were given at the same time, but since the  $T_{max}$  of L-DOPA preceds that of eltoprazine by  $\sim 1$  h, it is likely that pretreatment with eltoprazine prior to L-DOPA would result in a stronger antidyskinetic effect. It is, thus, probable that the antidyskinetic effects of eltoprazine are underestimated in this study and it will be important to evaluate the antidyskinetic effects of eltoprazine in a chronic study with an improved pharmacokinetic/pharmacodynamic profile of eltoprazine dosing.

It has previously been shown in open-label trials that the 5-HT1A receptor agonists buspirone (Kleedorfer et al., 1991; Bonifati et al., 1994; Politis et al., 2014) and sarizotan (Bara-Jimenez et al., 2005) have antidyskinetic properties. L-DOPA induces higher striatal synaptic dopamine concentrations in Parkinson's disease patients with LIDs compared with Parkinson's disease patients without LIDs (de la Fuente-Fernández et al., 2004) and buspirone prior to L-DOPA reduced L-DOPA-evoked striatal synaptic dopamine release, particularly in Parkinson's disease patients with mild LIDs (Politis et al., 2014). However, since placebo has a strong effect on LIDs (Goetz et al., 2008), it is critical to perform placebo-controlled trials with putative antidyskinetic agents. In a large placebo-controlled trial, sarizotan failed to convincingly counteract LIDs (Goetz et al., 2007) and, at higher doses, actually worsened parkinsonism. The later effect may partly depend upon its antagonistic actions at dopamine D2-like receptors. No placebo-controlled trials with buspirone have been reported.

There is no licensed treatment against LIDs. However, in addition to targeting the serotonin system, there are other pharmacological targets, including cholinergic, opiodergic and glutamatergic ones that have been reported to offer benefits for LID (Cenci et al., 2011; Huot et al., 2013). In particular, antagonism of metabotropic glutamate type 5 receptors (Berg et al., 2011) or NMDA receptors have antidyskinetic properties (Luginger et al., 2000; Del Dotto et al., 2001; da Silva-Júnior et al., 2005). Amantadine, a NMDA receptor antagonist (Greenamyre and O'Brien, 1991), is indeed, recommended for this indication by the Movement Disorder Society, but many patients with LIDs do not respond, or show only marginal response to amantadine (Sawada et al., 2010). There is no study that has used CDRS to assess L-DOPA-induced dyskinesias after acute administration of amantadine so no direct comparison can be made with our data on eltoprazine. However, following 3 weeks of treatment with amantadine, a 23% reduction of CDRS scores has been

reported (da Silva-Júnior et al., 2005). This reduction is somewhat higher than observed here after acute eltoprazine, but it will be more meaningful to make such comparisons when chronic eltoprazine has been investigated. Based on their pharmacological profile, it is anticipated that eltoprazine and amantadine inhibit LIDs via distinct mechanism(s) (Cenci et al., 2011; Huot et al., 2013). Eltoprazine is exerting antidyskinetic actions by stimulating 5-HT1A and 5-HT1B autoreceptors and thereby reducing the 'false' release of dopamine from serotonin terminals (Carta et al., 2007; Bezard et al., 2013). Moreover, 5-HT1B receptors are upregulated in dopamine D1 receptor containing striatonigral neurons following repeated L-DOPA in animal models of parkinsonism (Zhang et al., 2008). Stimulation of these postsynaptic 5-HT1B receptors by eltoprazine may counteract LIDs, as has previously been showed with another 5-HT1B receptor agonist, CP94253 (Carta et al., 2007; Zhang et al., 2008). Interestingly, a recent study has shown that eltoprazine and amantadine have additive antidyskinetic actions in animal models of LIDs (Bezard et al., 2013). Therefore, in the future clinical development of eltoprazine, in addition to trials aimed at establishing its antidyskinetic efficacy as a standalone treatment, it would be of interest to examine whether such additive effects can be obtained also in Parkinson's disease patients with LIDs treated with amantadine. It will also be important to examine whether eltoprazine has antidyskinetic properties in patients who have not responded to amantadine.

UPDRS-III scores did not differ between the placebo and eltoprazine treatments demonstrating that there is no deterioration of the normal treatment effect of L-DOPA by eltoprazine co-treatment. To study mood changes, HADS scores before and after study medication were compared with placebo at each study visit. A statistical observation was that HADS-A scores were higher after 5 mg eltoprazine, but as fewer patients complained about anxiousness after eltoprazine than placebo, the clinical significance is doubtful. The most frequent adverse events reported by the patients in this study were nausea and dizziness. Previous studies have shown that adverse events tend to tolerate out after 2–3 days of dosing and do not emerge if eltoprazine is dose titrated up from lower doses (de Koning *et al.*, 1994).

In conclusion, it appears that eltoprazine has beneficial antidyskinetic effects without altering normal motor responses to L-DOPA or inducing clinically significant adverse-effects. The most frequent adverse events reported by the patients in this study were nausea and dizziness, which is consistent with the adverse events reported in previous clinical studies with eltoprazine at similar doses. Moreover, based on preclinical experiments in Parkinson models and studies with eltoprazine in other disease conditions, it is anticipated that chronic eltoprazine administration could provide a more prominent antidyskinetic effect.

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# Supplementary material

Supplementary material is available at Brain online.

# References

- Bara-Jimenez W, Bibbiani F, Morris MJ, Dimitrova T, Sherzai A, Mouradian MM, et al. Effects of serotonin 5-HT1A agonist in advanced Parkinson's disease. Mov Disord 2005; 20: 932–36.
- Berg D, Godau J, Trenkwalder C, Eggert K, Csoti I, Storch A, et al. AFQ056 treatment of levodopa-induced dyskinesias: results of 2 randomized controlled trials. Mov Disord 2011; 26: 1243–50.
- Bezard E, Tronci E, Pioli EY, Li Q, Porras G, Björklund A, et al. Study of the antidyskinetic effect of eltoprazine in animal models of levodopa-induced dyskinesia. Mov Disord 2013; 28: 1088–96.
- Bibbiani F, Oh JD, Chase TN. Serotonin 5-HT1A agonist improves motor complications in rodent and primate parkinsonian models. Neurology 2001; 57: 1829–34.
- Bonifati V, Fabrizio E, Cipriani R, Vanacore N, Meco G. Buspirone in levodopa-induced dyskinesias. Clin Neuropharmacol 1994; 17: 73–82.
- Carta M, Carlsson T, Kirik D, Björklund A. Dopamine released from 5-HT terminals is the cause of L-DOPA-induced dyskinesia in parkinsonian rats. Brain 2007; 130: 1819–33.
- Cenci MA, Ohlin KE, Odin P. Current options and future possibilities for the treatment of dyskinesia and motor fluctuations in Parkinson's disease. CNS Neurol Disord Drug Targets 2011; 10: 670–84.
- da Silva-Júnior FP, Braga-Neto P, Sueli Monte F, de Bruin VM. Amantadine reduces the duration of levodopa-induced dyskinesia: a randomized, double-blind, placebo-controlled study. Parkinsonism Relat Disord 2005; 11: 449–52.
- Del Dotto P, Pavese N, Gambaccini G, Bernardini S, Metman LV, Chase TN, et al. Intravenous amantadine improves levadopainduced dyskinesias: an acute double-blind placebo-controlled study. Mov Disord 2001; 16: 515–20.
- de la Fuente-Fernández R, Sossi V, Huang Z, Furtado S, Lu JQ, Calne DB, et al. Levodopa-induced changes in synaptic dopamine levels increase with progression of Parkinson's disease: implications for dyskinesias. Brain 2004; 127: 2747–54.
- de Koning P, Mak M, de Vries MH, Allsopp LF, Stevens RB, Verbruggen R, et al. Eltoprazine in aggressive mentally handicapped patients: a double-blind, placebo- and baseline-controlled multicentre study. The Eltoprazine Aggression Research Group. Int Clin Psychopharmacol 1994; 9: 187–94.
- Goetz CG, Stebbins GT, Shale HM, Lang AE, Chernik DA, Chmura TA, et al. Utility of an objective dyskinesia rating scale for Parkinson's disease: inter- and intrarater reliability assessment. Mov Disord 1994; 9: 390–4.

- Goetz CG, Damier P, Hicking C, Laska E, Müller T, Olanow CW, et al. Sarizotan as a treatment for dyskinesias in Parkinson's disease: a double-blind placebo-controlled trial. Mov Disord 2007; 22: 179–86.
- Goetz CG, Laska E, Hicking C, Damier P, Müller T, Nutt J, et al. Placebo influences on dyskinesia in Parkinson's disease. Mov Disord 2008: 23: 700–7.
- Greenamyre JT, O'Brien CF. N-methyl-D-aspartate antagonists in the treatment of Parkinson's disease. Arch Neurol 1991; 48: 977–81.
- Guy W. Abnormal involuntary movement scale. ECDEU assessment manual for psychopharmacology. Washington, DC: US Government Printing Office; 1976. p. 534–37.
- Hagell P, Widner H. Clinical rating of dyskinesias in Parkinson's disease: use and reliability of a new rating scale. Mov Disord 1999; 14: 448–55.
- Hollister AS, Breese GR, Mueller RA. Role of monoamine neural systems in L-dihydroxyphenylalanine-stimulated activity. J Pharmacol Exp Ther 1979; 208: 37–43.
- Huot P, Johnston TH, Koprich JB, Fox SH, Brotchie JM. The pharmacology of L-DOPA-induced dyskinesia in Parkinson's disease. Pharmacol Rev 2013; 65: 171–222.
- Kleedorfer B, Lees AJ, Stern GM. Buspirone in the treatment of levodopa induced dyskinesias. J Neurol Neurosurg Psychiatry 1991; 54: 376–77.
- Kohen D. Eltoprazine for aggression in mental handicap. Lancet 1993; 341: 628–9.
- Lees AJ, Hardy J, Revesz T. Parkinson's Disease. Lancet 2009; 373: 2055-66.
- Luginger E, Wenning GK, Bösch S, Poewe W. Beneficial effects of amantadine on L-dopa-induced dyskinesias in Parkinson's disease. Mov Disord 2000; 15: 873–8.
- Ng KY, Chase TN, Colburn RW, Kopin IJ. L-Dopainduced release of cerebral monoamines. Science 1970; 170: 76–7.
- Ng KY, Colburn RW, Kopin IJ. Effects of L-dopa on efflux of cerebral monoamines from synaptosomes. Nature 1971; 230: 331–2.
- Obeso JA, Olanow CW, Nutt JG. Levodopa motor complications in Parkinson's disease. Trends Neurosci 2000; 23: S2–7.
- Politis M, Wu K, Loane C, Brooks DJ, Kiferle L, Turkheimer FE, et al. Serotonergic mechanisms responsible for levodopa-induced dyskinesias in Parkinson's disease patients. J Clin Invest 2014; 124: 1340–9.
- Raghoebar M, Mak M, Cournot A, Pistorius MC, Van Harten J, Roseboom H. Pharmacokinetics of eltoprazine in healthy male subjects after single dose oral and intravenous administration. Br J Clin Pharmacol 1990; 30: 879–83.
- Reimer J, Grabowski M, Lindvall O, Hagell P. Use and interpretation of on/off diaries in parkinson's disease. J Neurol Neurosurg Psychiatry 2004; 75: 396–400.
- Sawada H, Oeda T, Kuno S, Nomoto M, Yamamoto K, Yamamoto M, et al. Amantadine study group. Amantadine for dyskinesias in Parkinson's disease: a randomized controlled trial. PLoS One 2010; 5: e15298.
- Tanaka H, Kannari K, Maeda T, Tomiyama M, Suda T, Matsunaga M. Role of serotonergic neurons in L-DOPA-derived extracellular dopamine in the striatum of 6-OHDA-lesioned rats. Neuroreport 1999; 10: 631–34.
- Tiihonen J, Hakola P, Paanila J, Turtiainen M. Eltoprazine for aggression in schizophrenia and mental retardation. Lancet 1993; 341: 307.
- Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010; 25: 2649–53.
- Verhoeven WM, Tuinier S, Sijben NA, van den Berg YW, de Wittevan der Schoot EP, Pepplinkhuizen L, et al. Eltoprazine in mentally retarded self-injuring patients. Lancet 1992; 340: 1037–8.
- Wigal SB, Duong S. Pharmacokinetic evaluation of eltoprazine. Expert Opin Drug Metab Toxicol 2011; 7: 775–81.
- Zhang X, Andren PE, Greengard P, Svenningsson P. Evidence for a role of the 5-HT1B receptor and its adaptor protein, p11, in L-DOPA treatment of an animal model of Parkinsonism. Proc Natl Acad Sci USA 2008; 105: 2163–8.