

# Effect of lamotrigine on dopamine dependent behaviours in rats

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## Abstract

Lamotrigine is an antiepileptic drug which by inhibiting voltage dependent sodium channels inhibits release of glutamate. Thus Dopaminergic system is removed from inhibitory influence of glutamate, causing increase in levels of dopamine in striatum resulting in stereotyped behavior (SB) or abolition of catalepsy in animals. Objectives of our study were to study the effect of Lamotrigine (LTG) on dopamine dependent behaviours in rats and compare its intensity with effects produced by Dexamphetamine (DAM) and Apomorphine (APO), to study the effect of pretreatment of HAL on SB induced by LTG. and to study effect of LTG on catalepsy induced by HAL. We also did similar pretreatments with APO and DAM which we have used as reference drugs. We used albino rats of either sex (120-180 g) by random distribution in group of 10 animals each. Intensity of SB and catalepsy is assessed by Costall and Naylor scoring system. Our results indicate that, LTG produced (SB) at 5, 10, 20 and 40 mg/kg. Which is less in intensity than 1.5, 3 mg/kg of APO and 5, 10 mg/kg of DAM. This SB was abolished by HAL at 0.25 and 0.50 mg/kg, therefore we state that Lamotrigine produces SB by releasing dopamine and on weight basis LTG is less potent in antagonizing haloperidol induced catalepsy as compared to DAM and APO.

**Keywords:** Apomorphine, catalepsy, Dexamphetamine, Haloperidol, Lamotrigine, stereotype.

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## INTRODUCTION

Lamotrigine, a phenyltriazine derivative, has been demonstrated to possess multiple mechanisms of actions these include the selective blockade of the N- and P-type calcium channels in focal brain regions, blockade of voltage-dependent sodium channels, when sodium channels are over-activated<sup>1</sup>. Lamotrigine has also been shown to inhibit the release of excitatory amino acids such as glutamate and aspartate, and may have some agonistic effects on  $\gamma$ -aminobutyric acid<sup>1</sup>. It selectively

suppresses supranormal neuronal activities without affecting the basal neurophysiological state, which has clear implications in neuronal stabilization in seizure disorders and in bipolar disorder<sup>1</sup>. The corpus striatum and the substantia nigra pars compacta (SNc) receive glutamatergic innervation from the cerebral cortex via the corticostriatal and corticonigral projections respectively<sup>2</sup>. In vitro and in vivo biochemical studies have shown that glutamate, via activation of the N-methyl-D-aspartate (NMDA) type of glutamate receptors, regulates the synthesis and release of dopamine (DA) from the nigrostriatal DAergic neurons<sup>3-5</sup>. studies have demonstrated that NMDA receptor antagonist MK-801<sup>6</sup>, blocks NMDA receptors in the striatum and SNc and causes activation of the nigrostriatal DAergic neurons which increase in the synthesis and release of DA in the striatum<sup>2-4</sup>. Lesions of the frontal cortex, leading to a decrease in striatal glutamate levels<sup>7</sup>, were reported to enhance behavioural responses to amphetamine<sup>8,9</sup> and to decrease haloperidol catalepsy<sup>10</sup>. Haloperidol induced catalepsy was potentiated by subconvulsant doses of NMDA administered intraperitoneally (ip) and was

antagonised by MK-801 and other NMDA receptor antagonists<sup>11-13</sup>. Lamotrigine, by blocking the voltage-dependent Na<sup>+</sup> channels, inhibits the release of glutamate from the corticostriatal and corticonigral glutamatergic neurons. Consequently it decreases the concentration of glutamate in the striatum and SNc and thereby produce a functional lack of glutamate at the NMDA receptors in the striatum and SNc.. MK-801 which is a glutamate receptor antagonist is reported to cause activation of the nigrostriatal DAergic neurons with resultant increase in the synthesis and release of DA in the striatum<sup>2-4</sup> and occurrence of nigrostriatal DA-dependent behaviours in the rat<sup>14</sup>. Since lamotrigine reduces glutamate levels at the NMDA receptors in the striatum and SNc, we thought to study the effect of lamotrigine on nigrostriatal DA-dependent behaviours in the rats neurotransmission. Hyperfunctioning of the nigrostriatal DAergic system in the rat is responsible for the occurrence of stereotyped behaviour (SB). The SB manifests as sniffing behaviour and of the oral movement variety (OMV) characterised by gnawing, biting and licking behaviour. High doses of the directly acting DA agonist apomorphine induces SB by directly stimulating the postsynaptic striatal D2 and D1 DA receptors and indirectly acting DA agonists like amphetamines, in high doses, induces SB by releasing DA from the nigrostriatal DAergic neurons with resultant activation of the postsynaptic striatal D2 and D1 DA receptors by the released DA<sup>15</sup>. Hypofunctioning of the nigrostriatal DAergic system in the rat, with resultant functional lack of DA at the postsynaptic striatal D2 and D1 DA receptors, is responsible for induction of catalepsy, a state defined as a failure to correct the externally imposed postures by the animal. The neuroleptic haloperidol induces catalepsy by blocking the postsynaptic striatal D2 and D1 DA receptors<sup>16</sup>.

## MATERIALS AND METHODS

### ANIMALS

Albino rats of either sex (weighing 100-180 g), bred in Central Animal House Facility of the Institute, were used. The animals were maintained on a 12 hr light/dark cycle and had free access to food and water up to the time of experimentation. Atleast 1 hr before the experiments the animals were brought to the laboratory for acclimatization.. Each group consisted of 10 animals. Each animal was used only once. All observations were made between 10 and 17 hrs at 27°-30°C. The experimental protocols were approved by the Institutional Animal Ethics Committee and conducted according to the Indian National Science Academy Guidelines for the use and care of experimental animals.

### DRUGS

Drugs used were lamotrigine (Kopalle Ltd.), dexamphetamine sulphate (Koch-Light), apomorphine hydrochloride (Sigma), and haloperidol (Senorm injection, Sun Pharmaceuticals). Lamotrigine was dissolved in 2% solution of Tween 80 in distilled water. Dexamphetamine was dissolved in distilled water while apomorphine was dissolved in distilled water containing 0.2 mg/ml ascorbic acid. Haloperidol injection solution was diluted to required strength with distilled water. All drug solutions were prepared immediately before use and were injected intraperitoneally. The volume of injection was 5 ml/kg body weight for 2.5 to 40 mg/kg dose range of lamotrigine and 10 ml/kg body weight for 80 and 160 mg/kg doses of lamotrigine, while for the remaining drugs it was 2 ml/kg body weight. Doses refer to the forms mentioned. Drug doses, routes of administration and the testing time intervals were selected based on previous studies conducted in our laboratory and those reported in literature.

### Observation of SB

For observation of SB, the rats were placed in individual cages made of wire netting, measuring 30×20×20 cm, 30 min before drug treatment to allow adaptation to the new environment. The intensity of SB was assessed over a 30 sec observation period at 10 min intervals throughout its duration, using the scoring system of Costall and Naylor<sup>17</sup>, where periodic sniffing=score1, continuous sniffing=2, periodic biting, gnawing or licking =3, continuous biting, gnawing or licking =4. The maximum intensity of SB scored by each rat in the group was taken to compute the mean value of the group.

### Observation of catalepsy

For observation and measurement of catalepsy the animals were placed in individual perspex cages (30×20×20 cm), 30 min before drug treatment to allow adaptation to the new environment. Animals were tested for catalepsy according to the method of Costall and Naylor<sup>17</sup> by placing both front limbs of the animal over an 8 cm high wooden block and measuring the time for which the animal maintained the imposed posture. Scoring, modified from that of Costall and Naylor (1974), was as follows : maintaining the imposed posture 0-10 sec (0); 11-30 sec (1); 31-60 sec (2); 61-120 sec (3); 121 sec and more (4).

### Statistical Analysis

The results were statistically analysed by the Student's unpaired t-test with differences considered significant at P< 0.05.

## OBSERVATIONS AND RESULTS

Initially we confirmed by our findings that Tween 80 did not produce motor incoordination, ataxia, stereotyped behaviour or catalepsy in rats. It did not have significant

effect on behaviours induced by the DA agonists and on haloperidol induced catalepsy. During preliminary studies it was observed that animals treated with 2.5 to 40 mg/kg LTG appeared sedated between 10 to 30 min period after injection but did not exhibit catalepsy when tested at 30 min time interval after LTG injection. After 30 min interval animals receiving 2.5 mg/kg LTG returned to normal state and appeared the same as control animals treated with 5 ml/kg distilled water or Tween 80. After 30 min interval animals receiving 5 and 10 mg/kg LTG exhibited only stereotyped sniffing behaviour whereas animals treated with 20 and 40 mg/kg LTG also exhibited OMV of SB. The stereotyped behaviours usually manifested about 30 min after administration of LTG, reached maximum intensity about 60 min after LTG injection, and depending on the dose used, lasted for about 90 to 110 min, after which the animals became quiet and appeared the same as distilled water or Tween 80 treated control animals. LTG, at 80 and 160 mg/kg doses, had produced ataxia, motor incoordination and muscular hypotonia which interfered with the proper expression of OMV of SB in rats. These doses were therefore not used for subsequent studies. In case of apomorphine (1.5 and 3 mg/kg) the sniffing behaviour and OMV of SB manifested about 5 min after the injection and reached maximum intensity about 20 min. It lasted for about 40 to 50 min, depending on the dose used. With dexamphetamine (5 and 10 mg/kg) the sniffing behaviour and OMV of SB manifested about 10 min after the injection and reached maximum intensity about 60 min and lasted for about 2 to 2.5 hrs depending on the dose used.

#### Comparison of the intensity of SB induced by lamotrigine, apomorphine and dexamphetamine in rats.

The results are given in Table 1. The intensity of SB induced by 5 and 10 mg/kg lamotrigine was significantly lower than the intensity of SB induced by 1.5 and 3 mg/kg apomorphine and that induced by 5 and 10 mg/kg dexamphetamine ( $P < 0.001$ ). The intensity of SB induced by 20 mg/kg lamotrigine was significantly lower than the intensity of SB induced by 1.5 mg/kg apomorphine and 5 mg/kg dexamphetamine ( $P < 0.05$ ) and that induced by 3 mg/kg apomorphine and 10 mg/kg dexamphetamine ( $P < 0.001$ ). There was no significant difference between the intensity of SB induced by 40 mg/kg lamotrigine, 1.5 mg/kg apomorphine and 5 mg/kg dexamphetamine ( $P > 0.05$ ). However, the intensity of SB induced by 40 mg/kg lamotrigine was significantly lower than that induced by 3 mg/kg apomorphine and 10 mg/kg dexamphetamine ( $P < 0.01$ ).

**Table 1:** Comparison of the intensity of SB induced by lamotrigine (LTG), apomorphine (APO) and dexamphetamine (DAM) in rats.

Treatment (dose mg/kg ip)	Intensity Score (Mean $\pm$ S.E.M.)
LTG 5	1.2 $\pm$ 0.13 <sup>a</sup>
LTG 10	1.7 $\pm$ 0.15 <sup>a</sup>
LTG 20	2.3 $\pm$ 0.15 <sup>b,c</sup>
LTG 40	2.8 $\pm$ 0.13 <sup>d,e</sup>
APO 1.5	2.9 $\pm$ 0.10
APO 3	3.8 $\pm$ 0.13
DAM 5	2.9 $\pm$ 0.10
DAM 10	3.7 $\pm$ 0.15

<sup>a</sup> $P < 0.001$  as compared to groups receiving 1.5 and 3 mg/kg APO and 5 and 10 mg/kg DAM.

<sup>b</sup> $P < 0.05$  as compared to groups receiving 1.5 mg/kg APO and 5 mg/kg DAM.

<sup>c</sup> $P < 0.001$  as compared to groups receiving 3 mg/kg APO and 10 mg/kg DAM.

<sup>d</sup> $P < 0.01$  as compared to groups receiving 3 mg/kg APO and 10 mg/kg DAM.

<sup>e</sup>There was no significant difference between groups receiving 40 mg/kg LTG, 1.5 mg/kg APO and 5 mg/kg DAM.

#### Effect of haloperidol pretreatment on lamotrigine induced SB in rats

The results are given in Table 2. Haloperidol (0.25 and 0.5 mg/kg) did not induce SB in rats in any of the studies wherein it was used. Lamotrigine (5 to 40 mg/kg) induced dose-dependent SB in rats. Pretreatment with 0.25 mg/kg haloperidol abolished the SB induced by 5 mg/kg lamotrigine and significantly antagonised the SB induced by 10, 20 and 40 mg/kg lamotrigine. Pretreatment with 0.5 mg/kg haloperidol abolished the SB induced by 10, 20 and 40 mg/kg lamotrigine.

**Table 2:** Effect of haloperidol (HAL) pretreatment on lamotrigine (LTG) induced SB in rats.

NO. 2	Treatment (dose mg/kg ip)	Intensity Score Mean $\pm$ S.E.M.)
A	DW + LTG 5	1.3 $\pm$ 0.15
	HAL 0.2 + LTG 5	0.0
B	DW + LTG 10	1.6 $\pm$ 0.16
	HAL 0.25 + LTG 10	0.4 $\pm$ 0.16*
	HAL 0.5 + LTG 10	0.0
C	DW + LTG 20	2.3 $\pm$ 0.15
	HAL 0.25 + LTG 20	1.1 $\pm$ 0.10*
	HAL 0.5 + LTG 20	0.0
D	DW + LTG 40	2.7 $\pm$ 0.15
	HAL 0.25 + LTG 40	1.5 $\pm$ 0.16*
	HAL 0.5 + LTG 40	0.0

\* $P < 0.001$  as compared to respective distilled water pretreated control lamotrigine group by Student's unpaired t-test. DW = Distilled Water (2 ml/kg)

#### Effect of haloperidol pretreatment on dexamphetamine induced SB in rats:

The results are given in Table 3. Dexamphetamine (5 and 10 mg/kg) induced dose-dependent SB in rats. Pretreatment with 0.25 mg/kg haloperidol significantly antagonised the SB induced by 5 and 10 mg/kg dexamphetamine. Pretreatment with 0.5 mg/kg haloperidol abolished the SB induced by 5 and 10 mg/kg dexamphetamine.

**Table 3:** Effect of haloperidol (HAL) pretreatment on dexamphetamine (DAM) induced SB in rats.

No. 3	Treatment (dose mg/kg ip)	Intensity Score (Mean $\pm$ S.E.M.)
A	DW + DAM 5	2.8 $\pm$ 0.13
	HAL 0.25 + DAM 5	1.5 $\pm$ 0.16*
	HAL 0.5 + DAM 5	0.0
B	DW + DAM 10	3.6 $\pm$ 0.16
	HAL 0.25 + DAM 10	2.3 $\pm$ 0.15*
	HAL 0.5 + DAM 10	0.0

\*P<0.001 as compared to respective distilled water pretreated control dexamphetamine group by Student's unpaired t-test. DW = Distilled Water (2 ml/kg ip)

#### Effect of haloperidol pretreatment on SB induced by high doses of apomorphine in rats

The results are given in Table 4. Apomorphine (1.5 and 3 mg/kg) induced dose dependent SB in rats. Pretreatment with 0.25 mg/kg haloperidol significantly antagonised the SB induced by 1.5 and 3 mg/kg apomorphine. Pretreatment with 0.5 mg/kg haloperidol abolished the SB induced by 1.5 and 3 mg/kg apomorphine

**Table 4:** Effect of haloperidol (HAL) pretreatment on SB induced by high doses of apomorphine (APO) in rats.

No. 3	Treatment (dose mg/kg ip)	Intensity Score (Mean $\pm$ S.E.M.)
A	DW + APO 1.5	2.9 $\pm$ 0.10
	HAL 0.25 + APO 1.5	1.6 $\pm$ 0.16*
	HAL 0.5 + APO 1.5	0.0
B	DW + APO 3	3.8 $\pm$ 0.13
	HAL 0.25 + APO 3	2.5 $\pm$ 0.16*
	HAL 0.5 + APO 3	0.0

\*P<0.001 as compared to respective distilled water pretreated control apomorphine group by Student's unpaired t-test. DW = Distilled Water (2ml/kg ip).

#### Comparison of the effects of pretreatment with haloperidol on the SB induced by LTG, high doses of APO and DAM

Pretreatment with haloperidol, significantly antagonised the SB induced by LTG indirectly acting DA releaser DAM, directly acting D2 and D1 DA receptor agonist APO.(refer table2,table3.table4)

#### Effect of lamotrigine treatment on the cataleptic effect of haloperidol in rats.

The results are given in Table 5. Haloperidol (1 and 1.5 mg/kg) induced dose-dependent degree of catalepsy in the rats. Treatment with 5, 10 and 20 mg/kg lamotrigine significantly reduced the cataleptic effect of 1 mg/kg haloperidol while treatment with 40 mg/kg lamotrigine abolished the cataleptic effect of 1 mg/kg haloperidol. Treatment with 5, 10, 20 and 40 mg/kg lamotrigine significantly reduced the cataleptic effect of 1.5 mg/kg haloperidol.

#### Comparison of the effects of treatment with lamotrigine (LTG), apomorphine (APO) and dexamphetamine (DAM) on the cataleptic effect of haloperidol (HAL) in rats.

The results are given in Table 5. Treatment with 5,10 and 20 mg/kg LTG significantly reduced the cataleptic effect of 1 mg/kg HAL while treatment with 40 mg/kg LTG abolished the cataleptic effect of 1 mg/kg HAL. Treatment with 5,10, 20 and 40 mg/kg LTG significantly reduced the cataleptic effect of 1.5 mg/kg HAL. Treatment with 1.5 mg/kg APO abolished the cataleptic effect of 1 mg/kg HAL and significantly reduced the cataleptic effect of 1.5 mg/kg HAL. Treatment with 3 mg/kg APO abolished the cataleptic effect of 1.5 mg/kg HAL. Treatment with 5 mg/kg DAM abolished the cataleptic effect of 1 mg/kg HAL and significantly reduced the cataleptic effect of 1.5 mg/kg HAL. Treatment with 10 mg/kg DAM abolished the cataleptic effect of 1.5 mg/kg HAL. The results of comparison of the anticataleptic effects of LTG with the anticataleptic effects of APO and DAM are as follows: LTG (5, 10 and 20 mg/kg) was significantly less effective than 1.5 mg/kg APO and 5 mg/kg DAM in reducing the cataleptic effect of 1 mg/kg HAL. However, 40 mg/kg LTG, like 1.5 mg/kg APO and 5 mg/kg DAM abolished the cataleptic effect of 1 mg/kg HAL, indicating thereby that it was equieffective to 1.5 mg/kg APO and 5 mg/kg DAM in exerting the anticataleptic effect. Similarly, 5,10 and 20 mg/kg doses of LTG were significantly less effective than 1.5 mg/kg APO and 5 mg/kg DAM in reducing the cataleptic effect of 1.5 mg/kg HAL while 40 mg/kg LTG was equieffective to 1.5 mg/kg APO and 5 mg/kg DAM in reducing the cataleptic effect of 1.5 mg/kg HAL. LTG 40 mg/kg was however, significantly less effective than 3 mg/kg APO and 10 mg/kg DAM in exerting the anticataleptic effect since treatment with 3 mg/kg APO and 10 mg/kg DAM had abolished the cataleptic effect of 1.5 mg/kg HAL.



**Table 5:** Comparison of the effects of treatment with lamotrigine (LTG), apomorphine (APO) and dexamphetamine (DAM) on the cataleptic effect of haloperidol (HAL) in rats

Sr No	Treatment (dose mg/kg ip)	Catalepsy Score (Mean $\pm$ S.E.M.)
<b>A</b>	HAL 1 + VEH/DW	2.7 $\pm$ 0.15
	HAL 1 + LTG 5	2.1 $\pm$ 0.10 <sup>*a</sup>
	HAL 1 + LTG 10	1.8 $\pm$ 0.13 <sup>**a</sup>
	HAL 1 + LTG 20	0.9 $\pm$ 0.10 <sup>***b</sup>
	HAL 1 + LTG 40	0.0 <sup>d</sup>
<b>B</b>	HAL 1 + APO 1.5	0.0
	HAL 1 + DAM 5	0.0
<b>C</b>	HAL 1.5 + VEH/DW	2.7 $\pm$ 0.15
	HAL 1.5 + LTG 5	2.1 $\pm$ 0.10 <sup>*a</sup>
	HAL 1.5 + LTG 10	1.8 $\pm$ 0.13 <sup>**a</sup>
	HAL 1.5 + LTG 20	0.9 $\pm$ 0.10 <sup>***b</sup>
	HAL 1.5 + LTG 40	0.0 <sup>d</sup>
<b>D</b>	HAL 1.5 + APO 1.5	1.0 $\pm$ 0.00 <sup>***</sup>
	HAL 1.5 + APO 3	0.0
	HAL 1.5 + DAM 5	1.0 $\pm$ 0.00 <sup>***</sup>
	HAL 1.5 + DAM 10	0.0
	HAL 1.5 + APO 1.5	1.0 $\pm$ 0.00 <sup>***</sup>

\*P< 0.05; \*\*P< 0.01; \*\*\*P< 0.001 as compared to respective control groups treated with haloperidol and vehicle (VEH) or distilled water (DW). <sup>a</sup>P<0.001 as compared to respective groups treated with 1.5 mg/kg APO and 5 mg/kg DAM. <sup>b</sup>P< 0.01 as compared to respective groups treated with 1.5 mg/kg APO and 5 mg/kg DAM. <sup>c</sup>P< 0.001 as compared to groups treated with 3 mg/kg APO and 10 mg/kg DAM. <sup>d</sup>The difference between groups treated with 40 mg/kg LTG, 1.5 mg/kg APO and 5 mg/kg DAM was not significant.

## DISCUSSION

In the present study treatment with 5 and 10 mg/kg ip lamotrigine was found to induce sniffing type of SB only, while treatment with 20 and 40 mg/kg ip lamotrigine also induced OMV of SB in rats. After comparing it with apomorphine and dexamphetamine we found that on weight basis LTG is less potent in inducing SB. Pretreatment with haloperidol antagonised the SB induced by lamotrigine. This indicates that DAergic mechanisms are involved in the induction of SB by lamotrigine in rats. Lamotrigine might be inducing the SB either by directly stimulating the postsynaptic striatal D2 and D1 DA receptors or indirectly by releasing DA from the nigrostriatal DAergic neurons with resultant stimulation of the postsynaptic striatal D2 and D1 DA receptors by the released DA. The effects produced by pretreatment with haloperidol, on LTG induced SB and DAM-induced SB are resembling. This indicates that LTG induces SB by releasing DA with resultant stimulation of the postsynaptic striatal D2 and D1 DA receptors by the released DA similar to DAM. Therefore

we conclude that lamotrigine induces the SB by releasing DA from the nigrostriatal DAergic neurons with resultant stimulation of the postsynaptic striatal D2 and D1 DA receptors by the released DA, concurs with the observation that lamotrigine lacks appreciable in vitro affinity for the D2 and D1 DA receptors<sup>18</sup>. Our finding also indicates that lamotrigine, compared to dexamphetamine, is a weak DA releaser. Results from our study state that 5,10 and 20 mg/kg LTG are significantly less effective than 1.5 and 3 mg/kg APO, and 5 and 10 mg/kg DAM in antagonising the cataleptic effect of 1 and 1.5 mg/kg HAL. LTG at 40 mg/kg dose is however, significantly less effective than 3 mg/kg APO and 10 mg/kg DAM in antagonizing the cataleptic effect of 1.5 mg/kg HAL. Therefore lamotrigine, on weight basis, is significantly less effective than apomorphine and dexamphetamine in exerting the anticataleptic effect. It is possible that lamotrigine might also be releasing DA from the mesolimbic DAergic neurons and facilitating DA function in the mesolimbic region thereby counteracting depression as suggested by Botts and Raskind<sup>19</sup>. Further, since hallucinations are associated with excessive DA function in the mesolimbic region<sup>20</sup> our contention that lamotrigine might be releasing DA in the mesolimbic region is supported by the observations of Shinotoh *et al*<sup>21</sup>. DA releasers, which antagonises haloperidol catalepsy, is being clinically evaluated in patients of Parkinson's disease (PD), due consideration to the age of the patients, duration and severity of the illness should be given while selecting the patients for the study. The DA releasers should be evaluated in early cases with mild symptoms of PD but not in advanced severe cases, they might prove to be ineffective in relieving the signs and symptoms.. This might be the reason why lamotrigine, though effective in antagonising haloperidol catalepsy, was not effective in producing clinical improvement in patients of PD<sup>21-22</sup>. Similar was the observation with the NMDA antagonist dextromethorphan<sup>6</sup>. Dextromethorphan, though it antagonised haloperidol catalepsy<sup>13</sup>, failed to produce symptomatic improvement in patients of PD<sup>23</sup>. But as LTG is having antilutamatergic and dopamine enhancing activity, It can be tried in the treatment of bipolar disorders, alcohol dependence where those mechanisms are involved<sup>24</sup>.

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