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Cognitive, behavioural and sleep-related adverse effects on introduction of levetiracetam versus oxcarbazepine for epilepsy

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ABSTRACT

Objective: There is limited literature on cognitive, behaviour and sleep-related adverse effects of levetiracetam and oxcarbazepine among adult epilepsy patients, except for what is available from the initial efficacy trials. This study was initiated with the aim to evaluate the incidence and prevalence of various cognitive, behaviour and sleep-related adverse effects of levetiracetam versus oxcarbazepine among people with epilepsy.

Methods: The study was conducted in two parts: part A was a cross-sectional study, and part B was a longitudinal study. Trail making test A & B, digit symbol substitution test, Stroop colour and word test, controlled oral word association test and PGI memory scale, Neuropsychiatric Inventory, sleep log and ESS-I were used for assessment of cognitive, behaviour and sleep-related adverse effects.

Results: In the cross-sectional as well as prospective study, no significant difference was observed in the cognitive performance of patients in levetiracetam and oxcarbazepine group in any of the cognitive assessment. Among 120 patients enrolled in the cross-sectional study, significantly higher number of patients in the levetiracetam group compared to the oxcarbazepine group,had agitation/aggression (20% vs10%, $p = 0.047$) and irritability (26.7% vs 3.3%, $p = 0.007$).Among 132 patients enrolled in the prospective study, significantly higher increase in the domain score of agitation/aggression (14.5% vs 1.6%, $p = 0.028$) and irritability (17.7% vs 1.6%, $p = 0.018$) was observed in the levetiracetam group compared to oxcarbazepine group. A significantly higher proportion of patients in the oxcarbazepine group had hypersomnolence (11.3% vs 1.6%, $p = 0.026$), as compared to the levetiracetam group.

Significance: On cross-sectional as well as on longitudinal assessment, nearly one-fifth of patients on levetiracetam have behaviour related adverse effects, with dose modification required for half among these. Nearly 11% of patients on oxcarbazepine reported sleep-related adverse effects (higher total sleep duration per 24 h).

1. Introduction

Many factors can add to the poor quality of life in patients with epilepsy, including the etiology of epilepsy; seizure type, frequency, and duration; localization of the epileptic focus; age at onset of epilepsy; physiological and structural changes in the brain secondary to seizures; and adverse effects of antiepileptic drugs (AEDs).(Berto, 2002; Shetty et al., 2011; Taylor et al., 2011) In addition, a number of comorbidities related to cognition, behaviour, mood and sleep play an important role in determining the quality of life among people with epilepsy.(Meneses et al., 2009; Kwan et al., 2009; Viteva, 2014; Tracy et al., 2007) Adverse effects of AEDs are a modifiable factor in determining the quality of life in this population, and the adverse effects pertaining to the domains mentioned above are often difficult to attribute to epilepsy or its etiology versus medications. Second generation AEDs have a better risk-benefit ratio by achieving maximal seizure control with minimal adverse effects.(French and Gazzola, 2011) However, each of these may have highly specific adverse effects. (French and Gazzola, 2013) Among the second-generation AEDs, levetiracetam and oxcarbazepine are commonly used as monotherapy and polytherapy. There is limited literature on cognitive, behaviour and sleep-related adverse effects of levetiracetam and oxcarbazepine among adult epilepsy patients, except for what is available from the initial efficacy trials.

Some studies have shown levetiracetam to have a good impact on cognition.(Cramer Joyce et al., 2005; Helmstaedter and Witt, 2008; Koo

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et al., 2013; Piazzini et al., 2006) Oxcarbazepine is not known to have any detrimental effect on cognition in adults.(Äikiä et al., 1992; Salinsky et al., 2004) There are no studies on the effect of oxcarbazepine on behaviour. While there are several retrospective and prospective studies, on the behavioural adverse effects of levetiracetam, the majority of the studies have not used any behaviour assessment scale. Among people treated using levetiracetam, the occurrence of behavioural adverse effects has been reported to be anywhere between 16%–49%. There are two studies on the impact of levetiracetam on sleep over a short study period, with small sample size.(Cho et al., 2011; Zhou et al., 2012) A study with ten patients on levetiracetam showed that short-course treatment affected subjective daytime sleepiness.(Zhou et al., 2012) In a retrospective chart review-based study, 10% of patients on oxcarbazepine had daytime somnolence.(Shukla et al., 2016)In a surveillance study, about 14.2% of patients complained of sedation/drowsiness with oxcarbazepine.(Buggy et al., 2010)

This study was initiated with the aim to evaluate the prevalence of various cognitive, behaviour and sleep-related adverse effects of commonly used second-generation AEDs, levetiracetam and oxcarbazepine among people with epilepsy.

2. Materials and methods

This study was conducted over 18 months period starting from January 2017, among persons diagnosed with epilepsy at the Neurology services at an apex academic referral centre in India. The study was approved by the institutional ethics committee in January 2017.

2.1. Study design

The study was conducted in two parts: part A was a cross-sectional study in which, consecutive patients with epilepsy receiving anti-epileptic monotherapy with either levetiracetam (LEV) or oxcarbazepine (OXC) for at least past six months, were recruited and part B, the longitudinal study in which, consecutive patients with epilepsy in whom levetiracetam or oxcarbazepine add-on/monotherapy was about to be started, were recruited.

2.2. Sample size

The sample size was determined to find a difference between the proportion of each type of adverse effects (cognitive, behaviour and sleep-related) in two treatment groups (LEV and OXC) separately. (Bootsma et al., 2008; Kim et al., 2006; Shukla et al., 2016) The maximum sample size of the three (cognitive, behaviour and sleep-related) was taken as the sample size for the both cross-sectional and prospective study. With 60 patients in each treatment group, the study had a power of 80% and a significance level of 0.05.

2.3. Inclusion criteria

Adult patients (age ≥ 18 years), diagnosed to be suffering from epilepsy were recruited from the out-patients epilepsy clinic. The medication criteria are described above.

2.4. Exclusion criteria

Patients who did not give consent, patients with gross baseline mental subnormality, severe internal organ diseases, history of alcohol addiction or drug abuse, major co-morbid neurological or mental illness like autistic disorder, cerebral palsy, severe depression, encephalopathy or any associated speech disorder, as well as those with a pre-existing diagnosis of a primary sleep disorder like sleep apnea or restless legs syndrome,were excluded.

2.5. Methodology

Following informed consent, a detailed history, including age, sex, duration of epilepsy, frequency and semiology of seizures, and medication history were obtained through a pre-structured questionnaire. Assessment of cognition, behaviour and sleep-related adverse effects was carried out, as follows:

Patients in part A, the cross-sectional study group were evaluated only once at recruitment. Patients in part B, the prospective study group, were assessed at baseline, and six months follow-up. Presence of temporal relationship between the initiation of levetiracetam/ oxcarbazepine and cognition, behavioural and sleep-related adverse effects were recorded. Details about the duration of adverse effects, duration after the initiation of AED, dosage at which the adverse effect appeared, whether the dose was changed or the drug was stopped, and alleviation/ disappearance of adverse drug effect after dose decrease/ stoppage of the drug, were tabulated for all subjects enrolled in both parts. Adherence was measured by Morisky, Green and Levine Adherence Scale (MGL). Scores range from 0 to 4. A score of ≥ three was considered low adherence. (Morisky et al., 1986) Patients with low adherence were considered to be non-compliant.

2.5.1. Assessment of cognition

The PGI Memory Scale was used for memory assessment (Pershad and Wig, 2011). This scale consists of ten subtests including remote memory, recent memory, mental balance, attention and concentration, immediate recall, delayed recall, verbal retention for similar and dissimilar words, visual retention and recognition. Saying the alphabets from A to Z, counting backwards (20-1) and counting by minus three from 40 to 1 are the three items in mental balance subset in the PGI memory scale. Raw scores obtained for each subtest were converted according to the educational level. The converted scores were allotted 'dysfunction score' in the grade of increasing severity of impairment. Memory assessment was considered normal if the total dysfunction score was 0. The executive functions cognitive domain was assessed by using five tests: trail making test A (TMT-A), trail making test B (TMT-B) (Reitan, 1992), digit symbol substitution test (DSST) (Wechsler, 1981), Stroop colour and word test (ST) (Golden, 1978) and controlled oral word association test (COWA) (Borkowski et al., 1967).

2.5.2. Assessment of behaviour

Behaviour-related adverse effects were evaluated using the Neuropsychiatric Inventory (NPI).(Cummings et al., 1994) The domains assessed, include delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability and aberrant motor behaviour. Frequency, severity, and distress scores were obtained for each domain. Overall domain scores were calculated by multiplying frequency and severity scores. Prevalence of neuropsychiatric symptoms was determined by calculating the number and percentages of patients with NPI subscale domain score greater than 0. Presence of clinically relevant neuropsychiatric symptoms was determined by calculating the number and percentages of patients with NPI subscale score greater than 3. An increase of 30% or more from baseline NPI subscale domain score was considered as a significant change.

2.5.3. Assessment of sleep-related effects

Self-reported sleep-related effects were entered. Epworth sleepiness scale modified for north Indian population (ESS -I) was administered and scores tabulated.(Bajpai et al., 2016) In the cross-sectional study, details about self-reported sleep characteristics over one-week preceding evaluation were collected and tabulated. For the prospective longitudinal part, patients maintained a six-month sleep log immediately after recruitment.

2.6. Statistical analysis

Analyses were conducted in Stata version 13 (StataCorp LP, College Station, TX, USA). Non-parametric measures were used for analysis because of skewed distribution. In the prospective study, the intra-group comparison was analysed by McNemar'stest (nominal data) and Wilcoxon signed-rank test (continuous data). The inter-group comparison was analysed through logistic regression. In the cross-sectional study, the inter-group comparison was analysed by Mann-Whitney *U* test Binomial data was assessed by logistic regression to assess treatment group differences in cognitive, behaviour and sleep-related outcome measures after adjustment for reasonable covariates (age, duration of epilepsy, standardised dose, college educated and seizure frequency/month). Additional covariates were seizure frequency (> 1 /month), number of AEDs, duration of treatment, refractoriness to AEDs and gender. Univariate analyses were run for additional covariates and were included in the regression model if they were found to be significant (P < 0.15). Doses of the AED being received by the included patients were standardised relative to the ranges observed within each group. The formula used was 100 × (observed dose – minimum dose) / range of doses.(Meador et al., 2013, 2009) Results were considered to be statistically significant if the P value was < 0.05.

3. Results

This study was conducted over a period of two years in two parts, A and B, as detailed above.

3.1. Part A (cross-sectional study)

3.1.1. Patient demographics and clinical characteristics

A total of 120 patients were included (60 in the LEV group and 60 in the OXC group). The demographic and clinical characteristics of the patients in both groups are described in Table 1. Both the groups were well-balanced for the demographic and clinical characteristics. Patients in LEV group had a higher proportion of male patients [LEV - 39 (65%) vs. OXC - 29 (48.3%)]. The mean duration of treatment in the LEV group was 26.5 ± 21.8 months and 20.4 ± 18 months in the OXC group. The mean standardised dose in the LEV group was 47.5 ± 21.6 and 42.7 ± 24 in the OXC group. However, none of these differences was statistically significant.

Table 1
Patient characteristics of the Levetiracetam group and Oxcarbazepine groups (Cross-Sectional arm).

Clinical variable	Levetiracetam group	Oxcarbazepine group
Age Mean(SD)	25.5(11.1)	24.9(9.6)
Male n (%)	39 (65)	29 (48.3)
College educated n (%)	54 (90)	50 (83.3)
Duration of epilepsy, months Median (IQR)	30 (12.2-36.5)	24.3 (12.2-121.7)
Age at onset of epilepsy, years Mean(SD)	19.5 (11.4)	22.4 (11.7)
Generalised epilepsy n (%)	20(33.3)	NA
Focal epilepsy n (%)	40 (66.6)	60 (100)
Average dose (Last 6 months), mg/day Mean(SD)	1212.5 (324.1)	684.5 (215.9)
Standardised dose Mean(SD)	47.5 (21.6)	42.7 (24)
Duration of treatment, months Mean(SD)	26.5 (21.8)	20.4 (18.0)
Seizure frequency / month Median (IQR)	0.1 (0.1-0.46)	0.16 (0.16-0.47)
Seizure frequency (> 1 /month) n (%)	7 (11.6)	6 (10)
Presence of aura n (%)	18 (30)	21 (35)

SD, standard deviation; IQR inter quartilerange.

3.1.2. Cognitive measures

At least one domain was abnormal in 21(35%) patients in the LEV group, and in 23(38.3%) patients in the OXC group. No statistically significant differences were found, between the LEV and the OXC group on the Trail A ($p = 0.138$), Trail B ($p = 0.060$), DSST ($p = 0.522$), Stroop colour word score ($p = 0.197$) and COWA ($p = 0.743$) tests. In memory assessment, none of the patients in either group showed any abnormality in remote memory, recent memory, immediate recall and verbal retention for similar pairs. Eleven (18.3%) patients in the LEV group and 9(15%) patients in the OXC group had abnormal mental balance. Nine (15%) patients in the LEV group and 12 (20%) patients in the OXC group had abnormal attention and concentration. On logistic regression analysis with adjustment for baseline characteristics, there was no statistically significant difference in the performance of patients in both groups in any domain of the PGI-MS. Detailed observations are listed in supporting Table 1.

3.1.3. Behavioural adverse effects

Behavioural abnormality in at least one domain was seen in 21(35%) patients in the LEV group and 10(16.7%) patients in the OXC group ($p = 0.024$). The clinically significant score in at least one domain (Domain score > 3) was seen in 11(18.3%) patients in the LEV group and 1(1.7%) patients in OXC group ($p = 0.019$). Behavioural adverse effect attributable to the drug was present in 15(25%) in the LEV group and none in the OXC group. Agitation/aggression was observed more frequently in the LEV group [12(20%) patients] than in the OXC group [6(10%) patients]($p = 0.047$). Irritability was seen in 16(26.7%) patients in the LEV group and in 2(3.3%) patients in the OXC group, which was statistically significant ($p = 0.007$). Detailed observations are listed in Table 3 and supporting Table 1.

3.1.4. Sleep-related adverse effects

Patients with total sleep duration > 10 h per 24 h, as well as sleep duration in daytime > 1 h per day, were significantly higher in the OXC group (Table 3). Total sleep duration > 10 h per 24 h was seen in 1(1.7%) patients in LEV group and in 8(13.3%) patients in OXC group (p = 0.025). Sleep duration in daytime > 1 h per day was seen in 2(3.3%) patients in the LEV group and 11(18.3%) patients in the OXC group ($p = 0.029$). ESS –I score > 10 was seen in 1(1.7%) patients in the LEV group and 5(8.3%) patients in the OXC group. Detailed observations are listed in Table 3 and supporting Table 1.

3.2. Part B (Prospective study)

In the prospective study, 66 patients were enrolled in each group following adjustment to the sample size estimate for an anticipated drop-out of 10%.

3.2.1. Patient demographics and clinical characteristics

A total of 132 patients were recruited, of which five patients did not follow up, and three patients were non-compliant. Hence, 124 patients could be included for analysis (62 in the LEV group and 62 in the OXC group). The demographic and clinical characteristics of the patients in the LEV and OXC group are described in Table 2. Both the groups were well-balanced for the demographic and clinical characteristics (age, college education, age at onset of epilepsy, seizure frequency and drug-refractory epilepsy). While, the proportion of male patients were higher in the OXC group (77.4%) compared to the LEV group (58.1%), the median duration of epilepsy in the LEV group (54.7 months) was higher than in the OXC group (48.7 months) and the mean standardised dose in the LEV group (58.4 ± 26.9) was higher than in the OXC group (44.2

Table 2
Patient characteristics of the Levetiracetam group and Oxcarbazepine groups (Prospective arm).

Clinical variable	Levetiracetam group	Oxcarbazepine group
Age, years Mean(SD)	26.8 (9.4)	27.2 (10.2)
Male, n (%)	36 (58.1)	47 (77.4)
College educated, n (%)	54 (87)	54 (87)
Duration of epilepsy, months Median (IQR)	54.7 (12.2-121.7)	48.7 (12.2-97.3)
Age at onset of epilepsy, years Mean(SD)	20.3 (11.2)	21.6 (9.9)
Generalised epilepsy, n (%)	30 (48.3)	NA
Focal epilepsy, n (%)	32 (51.7)	62 (100)
Average dose in 6 months, mg/day Mean(SD)	1279.2 (359.6)	620.9 (247.3)
Standardised dose, Mean(SD)	58.4 (26.9)	44.2 (34.1)
Seizure frequency / month, Median (IQR)	0.4 (0.1-1.1)	0.4 (0.1-2)
Seizure frequency (> 1 /month), n (%)	15 (24.1)	21 (33.8)
Drug refractory epilepsy, n (%)	12 (19.3)	13 (20.9)
Other AED, n (%)	40 (64.5)	42 (67.7)
Nil	10 (16.1)	1 (0.02)
Phenytoin	3 (0.05)	0 (0)
Carbamazepine	0 (0)	1(0.02)
Topiramate	3(0.05)	2 (0.03)
Lacosamide	12 (19.3)	15 (24.1)
Clobazam	1(0.02)	2(0.03)
Phenobarbitone	5 0.08	6 (0.09)
Valporate	0 (0)	1(0.02)
Lamotrigine		

SD, standard deviation; IQR inter quartile range; AED antiepileptic drug.

±34.1); none of these differences was statistically significant.

3.2.2. Cognitive measures

In both LEV as well as OXC groups, no statistically significant difference was observed between baseline and six months, on the trail A time, Trail B time, DSST time, Stroop colour word score and COWA or on assessment of their memory (see Table 4). In the LEV group, 23(37.1%) patients had at least one domain in PGI-MS abnormal at baseline and 21(33.9%) patients at six months. There was no statistically significant difference in paired proportions. In the OXC group, 25(40.3%) patients had at least one domain in PGI-MS abnormal at baseline and 24(38.7%) patients at six months. In this group also, there was no statistically significant difference in the paired proportions. None of the patents in the LEV and OXC group had cognitive adverse effects attributable to the drug (see Table 6).

3.2.3. Behavioural adverse effects

In both the groups none of the patients had a clinically significant increase in domain score of delusions, hallucinations, depression/dysphoria, anxiety and elation/euphoria. Significantly higher proportion of patients had clinically significant increase in domain score of agitation/aggression (14.5% vs. 1.6%, p = 0.028) and irritability/lability in LEV group (17.7% vs. 1.6%, p = 0.018) compared to OXC group. There was no significant difference in the proportion of patients with a clinically significant increase in domain score of aberrant motor behaviour between the two groups (p = 0.737). The proportion of patients with a clinically significant increase in at least one domain score was significantly high in LEV group compared to the OXC group (p = 0.009). Behavioural adverse effects were observed to occur in a total of 13(20.9%) patients in the LEV group and 1(1.6%) patient in the OXC group, (p = 0.009). Mean duration of onset of behavioural adverse effects after initiation of LEV was 1.72 weeks (SD 0.47). Mean dosage at which the behavioural adverse effects appeared was 1681.8±252.3 mg. Dose reduction due to the behavioural adverse effects was made in 7(11.3%) patients, and the medication tapered off in 4 (6.5%) in the LEV group. Detailed observations are given in Table 5 and 6.

3.2.4. Sleep-related adverse effects

There was no significant difference between baseline and six months, nightly sleep duration and sleep onset latency in both LEV and OXC groups. There was a significant difference in the total sleep duration per 24 h between baseline and six months, in the OXC group, but not in the LEV group. The proportion of patients with ESS –I score > 10 at baseline and six months was not different in either group. The proportion of patients with total sleep duration > 10 h per 24 h, sleep duration in daytime > 1 h per day and having daily nap were significantly higher at six months compared to baseline in OXC group, but not in LEV group. There was no statistically significant difference in the paired proportions. Sleep-related was adverse effects were present in 7(11.3%) patients in the OXC group and 1 (1.6%) patient in the LEV group. Mean duration of onset of Sleep-related ADR after initiation of OXC was 1.2 weeks (SD 0.4). Mean dosage at which ADR appeared was 850 mg ± 350.7 mg. Dose reduction due to ADR was made in 6(9.7%) patients, and medication was tapered off in 1 (1.6%) patient in the OXC group. Detailed observations are given in Table 5 and 6.

4. Discussion

This is a well-powered study, conducted in two (cross-sectional and longitudinal) parts, evaluating cognitive, behavioural and sleep-related adverse effects of LEV versus OXC, among patients with epilepsy. One of the main observations is that nearly one-fifth of patients initiated on treatment with LEV experience behavioural adverse effects and half among these may require dose modification or withdrawal of the medication, in comparison with just about 1% among those initiated on OXC. In addition, nearly 11% patients initiated on treatment with OXC experience sleep-related adverse effects, mainly increase in the total time spent per 24 h, sleeping; compared to just 1% among those initiated on LEV. Cognitive performance was observed to be similar among patients on LEV and those on OXC, and there was no change in the same, after six months of continuation of treatment with these medications.

Studies evaluating cognitive, behavioural and sleep-related ADR due to oxcarbazepine and levetiracetam for adult epilepsy, assessed using specific measures are listed in supporting Table 2. There are no studies on the direct comparison of the cognitive adverse effects of LEV versus OXC. Similar to our observations, adverse effect on cognition, was not observed in previous studies on LEV or OXC. (Gomer et al., 2007; Huang et al., 2008; McKee et al., 1994; Zhou et al., 2008) Only one study had reported that 20% of the patients on OXC had subjective cognitive complaints. (Kim et al., 2006) But in cognitive assessment tests, such a deficit was not found, in fact, the OXC group performed better on attention and memory tests compared to topiramate group.

Although there are several studies on the behavioural adverse effects of LEV, only two have used behaviour-specific detailed assessment measures. In a randomised controlled trial, changes in behaviour scores over 20 weeks were compared between patients receiving LEV versus those receiving Lamotrigine. (Labiner et al., 2019) Lamotrigine was found to improve mood significantly. The incidence of behavioural adverse effects was not assessed. Data on the mean change in scores were compared between LEV and lamotrigine group, but intragroup analysis of whether behavioural measures changed significantly was not conducted. Another study, which used specific behaviour evaluation measures reported that LEV improves psychiatric symptoms. (Lee et al., 2011) Several studies and systematic reviews which did not use

Table 3
Cognitive, behaviour & sleep related adverse effects in the LEV vs OXC groups (cross-sectional arm).

Clinical outcomes	LEV	OXC	OR	CI	P value[1]
NPI - Domain score > 0, n (%)					
Delusions	0(0)	0(0)	–	–	–
Hallucinations	0(0)	0(0)	–	–	–
Agitation/Aggression	12(20)	6(10)	4.1	1.0 - 16.8	0.047
Depression/Dysphoria	2(3.3)	3(5.0)	10.8	0.1-1727.8	0.358
Anxiety	6(10)	2(3.3)	1.5	0.2 - 10.2	0.705
Elation/Euphoria	0(0)	0(0)	–	–	–
Apathy/Indifference	0(0)	0(0)	–	–	–
Disinhibition	6(10)	1(1.7)	6.1	0.6 - 63.1	0.130
Irritability/Lability	16(26.7)	2(3.3)	9.3	1.83 - 46.7	0.007
Aberrant motor behaviour	9(15)	1(1.7)	86.2	2.8 - 2640.8	0.011
NPI- At least one domain score > 0, n (%)	21(35)	10(16.7)	3.3	1.17 -9.4	0.024
NPI- At least one domain score > 3, n (%)	11(18.3)	1(1.7)	72.4	2.02 -2588.2	0.019
PGI- Memory scale (Abnormal) n (%)					
Remote memory	0(0)	0(0)	–	–	–
Recent memory	0(0)	0(0)	–	–	–
Mental balance	11(18.3)	9(15)	0.8	0.3 -2.4	0.740
Attention Concentration	9(15)	12(20)	0.4	0.1-1.3	0.136
Delayed recall	6(10)	8(13.3)	0.5	0.1 -1.5	0.206
Immediate recall	0(0)	0(0)	–	–	–
Verbal retention for similar pairs	0(0)	0(0)	–	–	–
Retention for dissimilar pairs	12(20)	13(21.7)	0.5	0.2 -1.3	0.165
Visual retention	3(5)	2(3.3)	0.8	0.1 - 8.0	0.856
Recognition	1(1.7)	1(1.7)	0.4	0.01 -12.0	0.620
PGI-MS (At least one domain abnormal), n (%)	21(35)	23(38.3)	0.5	0.2 -1.2	0.130
Cognition					
ADR attributable to drug present	Nil	Nil			
Behaviour					
ADR attributable to drug present, n (%)	15(25)	Nil			
Onset after initiation of AED, weeks, Mean (SD)	5.3(3.3)				
Dosage at which ADR appeared, Mean (SD)	1633.3(333.9)				
Dose reduction due to ADR, n (%)	11(18.3)				
Hyper somnolence					
ADR attributable to drug present, n (%)	Nil	10(16.6)			
Onset after initiation of AED, weeks, Mean (SD)		2.3(0.94)			
Dosage at which ADR appeared, Mean (SD)		825(162)			
Dose reduction due to ADR, n (%)		5(8.3)			

NPI, neuropsychiatric inventory; PGI-MS, PGI memory scale; ADR adverse drug reaction; AED, antiepileptic drug.
[1] Logistic regression after adjustment for covariates age, duration of epilepsy, standardised dose, college educated and seizure frequency/month.

behaviour specific assessment tools have reported the incidence of behavioural adverse effects ranging from 16%–49% with levetiracetam. (Cramer, 2003; Mbizvo et al., 2014; Mula et al., 2004; Verrotti et al., 2015; Weintraub et al., 2007; Wieshmann and Baker, 2013) This wide range could possibly be due to non-utilisation of behaviour specific assessment tools. The current study is the first to systematically evaluate behaviour related adverse effects using a detailed specific tool, and evaluating patients both cross-sectionally as well as longitudinally. The incidence and prevalence of behaviour related adverse effects were found to be similar, based on the two different parts of the current study; and also similar to the average of that reported in the previously published literature.

There are no prospective studies comparing sleep-related adverse effects of LEV versus OXC. A randomized controlled trial of 16 patients

Table 4
Cognition and sleep-related outcomes among epilepsy patients initiated on LEV vs OXC (Prospective arm).

Clinical Outcomes	LEV Pre test	LEV Post test	P value[1]	OXC Pre test	OXC Post test	P value[1]
Trail A, seconds, Mean (SD)	63.4 (34.0)	63.0 (33.1)	0.469	63.2 (32.2)	62.8 (31.9)	0.456
Trail B, seconds Mean (SD)	171.5 (116.8)	171.3 (117.9)	0.596	174.6 (110.9)	174.5 (111.3)	0.880
DSST, seconds Mean (SD)	237.5 (110.1)	236.7 (109.6)	0.455	230.9 (101.2)	231.1 (102.2)	0.681
Stroop colour word score Mean (SD)	38.1 (11.5)	38 (11.6)	0.857	39.6 (9.7)	39.5 (10.1)	0.893
COWA Mean (SD)	11.9 (5.1)	12.1 (5.1)	0.957	13.6 (4.9)	13.7 (5.5)	0.879
Sleep duration in night time per day, hrs, Mean(SD)	8(0.6)	8(0.7)	0.620	8.1(0.6)	8.2(0.7)	0.095
Total sleep duration per day, Mean (SD)	8.1(0.80	8.1(0.8)	0.655	8.3(1.0)	8.6(1.4)	0.022
Sleep onset latency per day, minutes Mean (SD)	17.7(3.7)	17.5(4)	0.545	18.6(3.7)	18(4.7)	0.841

DSST, digit symbol substitution test; COWA, controlled oral word association test.
[1] Wilcoxon signed-rank test.

Table 5
Behaviour and sleep-related outcomes among epilepsy patients initiated on LEV vs OXC (Prospective arm).

Clinical outcomes	LEV Pretest n (%)	LEV Post test n (%)	McNemar's test	OXC Pretest n (%)	OXC Post test n (%)	McNemar's test
NPI- At least one domain score > 3			0.01			1
Absent	41(66.1)	30 (48.4)		45(72.6)	44(71)	
Present	21(33.9)	32(51.6)		17(27.4)	18(29)	
PGI-MS (At least one domain abnormal)			0.5			1
Absent	39(62.9)	41(66.1)		37(59.7)	38(61.3)	
Present	23(37.1)	21(33.9)		25(40.3)	24(38.7)	
ESS –I score > 10			1			0.063
Absent	59(95.2)	59(95.2)		59(95.2)	54.(87.1)	
Present	3(4.8)	3(4.8)		3.0(4.8)	8(12.9)	
Total sleep duration > 10 hrs per day			1			0.031
Absent	58(93.5)	58(93.5)		58(93.5)	52(83.9)	
Present	4(6.5)	4(6.5)		4(6.5)	10(16.1)	
Sleep duration in daytime > 1 hr per day			1			0.016
Absent	61(98.4)	61(98.4)		58(93.5)	51(82.3)	
Present	1(1.6)	1(1.6)		4 (6.5)	11(17.7)	
Daily nap, yes			1			0.016
Absent	56(90.3)	57(91.9)		59(95.2)	52 (83.9)	
Present	6(9.7)	5(8.1)		3(4.8)	10(16.1)	

NPI, neuropsychiatric inventory; PGI-MS, PGI memory scale; ESS –I, Epworth sleepiness scale modified for north Indian population.

Table 6
Cognition, behavioural and sleep-related outcomes among epilepsy patients initiated on LEV vs OXC (Prospective arm).

Clinical outcomes	LEV	OXC	OR	CI	*P* value[1]
Significant increase in NPI - Domain score, n (%)					
Delusions	0(0)	0(0)			
Hallucinations	0(0)	0(0)			
Agitation/Aggression	9(14.5)	1(1.6)	15.9	1.3 - 188	0.028
Depression/Dysphoria	0(0)	0(0)			
Anxiety	0(0)	0(0)			
Elation/Euphoria	0(0)	0(0)			
Apathy/Indifference	0(0)	0(0)			
Disinhibition	0(0)	0(0)			
Irritability/Lability	11(17.7)	1(1.6)	15.8	1.6 – 157.5	0.018
Aberrant motor behavior	3(4.8)	1(1.6)	1.5	0.1- 19.7	0.737
Significant increase in NPI - At least one domain score > 0, n (%)	13(20.9)	1(1.6)	26.3	2.27 - 305.3	0.009
PGI-MS (Increase in dysfunction rating Score > 0 in at least one domain), n (%)	0(0)	0(0)			
Cognition – related ADR, n (%)	0(0)	0(0)			
Behaviour – related ADR, n (%)	13(20.9)	1(1.6)	26.3	2.27 - 305.3	0.009
Onset after initiation of AED (weeks)	1.72(0.47)	4(0)			
Dosage at which ADR appeared, Mean (SD)	1681.8(252.3)	1200(0)			
Dose change due to ADR, n (%)	7(11.3)	1(1.6)			
AED stopped due to ADR, n (%)	4(6.5)	0(0)			
Hypersomnolence, n (%)	1(1.6)	7(11.3)	13.7	1.4 - 135.4	0.026
Onset after initiation of AED (weeks), Mean(SD)	1(0)	1.2(0.4)			
Dosage at which ADR appeared, Mean(SD)	2000(0)	850(350.7)			
Dose change due to ADR, n (%)	1(1.6)	6(9.7)			
AED stopped due to ADR, n (%)	0(0)	1(1.6)			

NPI, neuropsychiatric inventory; PGI-MS, PGI memory scale; ADR adverse drug reaction; AED, antiepileptic drug.
[1] Logistic regression after adjustment for covariates age, duration of epilepsy, standardised dose, college educated and seizure frequency /month.

on LEV (1000 mg/day) and 15 patients on CBZ-CR (400 mg/day) reported sleep efficiency to increase in LEV group without any increase in daytime sleepiness. (Cho et al., 2011) Two other small uncontrolled studies also did not find any sleep-related adverse effect of LEV. (Cicolin et al., 2019; Zhou et al., 2012) In a retrospective chart review-based study, comparing OXC vs LEV found the OXC group to have a higher proportion of patients (10% vs 1%) complaining of daytime somnolence. (Shukla et al., 2016) Ours is a much larger, well-powered study; and our observations are similar to those reported in these studies, cited above.

Re-emphasizing the strengths of the current study, it has both cross-sectional as well as prospective longitudinal components, to assess the prevalence and incidence of adverse effects as well as intervention modifications due to these adverse effects. The use of standardised, sensitive and specific evaluation tools, especially for behaviour related adverse effects, is also a major strength of our study. Regression analysis adjusting for baseline characteristics further strengthened the observations of this study.

The main limitation of the study is that the follow-up duration is relatively short. The long-term impact of the drugs on cognition, behaviour and sleep-related parameters would be very interesting to study and utilize for planning long-term strategies for the treatment of patients with epilepsy, using these agents. Supporting sleep evaluation through polysomnography would have been ideal, however, was not feasible for this study.

Other limitations are; LEV group has concomitant medications that are significantly different than the OXC group. Specifically, 13 patients in the LEV group are also taking phenytoin or carbamazepine versus one patient in the OXC group. The results show similar cognitive function in the LEV and OXC group. Concomitant medications may have an impact on cognitive outcomes in both groups. There is a possibility that the LEV group would have had better cognitive outcomes if there is no difference in concomitant medication use. There is a significant difference in the seizure types in the two study groups. OXC was not used for any patient with generalized epilepsy for obvious reasons. The incidence of cognitive adverse effect could be different in focal and generalised epilepsy. The inclusion of only one type of seizure patients in the study would have reduced this confounding.

5. Conclusions

In conclusion, neither levetiracetam nor oxcarbazepine was found to have any adverse effect on cognition, among patients with epilepsy. More importantly, nearly one-fifth of patients on levetiracetam were found to have behaviour related adverse effects, with dose modification required for half among these. Nearly 11% of patients on oxcarbazepine reported sleep-related adverse effects (higher total sleep duration per 24 h). These observations remained consistent on cross-sectional as well as longitudinal assessment.

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Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2019.01.004.

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