·临床研究·

新型抗癫痫药物对老年癫痫患者骨密度、认知功能及睡眠呼吸参数的影响研究

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【摘 要】 目的 探讨新型抗癫痫药物左乙拉西坦(LEV)、拉莫三嗪(LTG)对老年癫痫患者骨密度、认知功能及睡眠呼吸的影响。**方法** 选择2024年1月至6月海南医学院第一附属医院收治的112例老年新发癫痫患者为研究对象,采用随机数表法将患者分为LEV组(38例)、LTG组(38例)和卡马西平(CBZ)组(36例),三组老年新发癫痫患者均采用单药治疗6个月。比较三组患者的临床疗效,治疗前及治疗6个月后骨密度(BMD)、血清指标[甲状旁腺激素(iPTH)、碱性磷酸酶(ALP)、脑源性神经营养因子(BDNF)]、认知功能[简易精神状态检查(MMSE)]及睡眠呼吸参数[呼吸紊乱指数(AHI)、平均动脉血氧饱和度($MSaO_2$)、最低动脉血氧饱和度($LSaO_2$)]情况,并评估治疗期间不良反应发生情况。采用SPSS 25.0统计软件进行数据分析。根据数据类型分别采用单因素方差分析或χ^2检验进行组间比较。**结果** LEV组、LTG组及CBZ组治疗有效率分别为89.47%、86.84%及86.11%,差异无统计学意义($P>0.05$)。三组患者治疗前后股骨颈与股骨大转子BMD、$MSaO_2$比较,差异无统计学意义($P>0.05$)。治疗6个月后,三组患者腰椎BMD、AHI均较治疗前降低,iPTH、ALP、BDNF、MMSE评分及$LSaO_2$均较治疗前显著升高;且LEV组及LTG组患者治疗后腰椎BMD、BDNF、MMSE评分及$LSaO_2$均高于CBZ组,LEV组及LTG组治疗后iPTH、ALP及AHI均明显低于CBZ组,差异均有统计学意义($P<0.05$)。LEV组、LTG组及CBZ组患者药物相关不良反应总发生率分别为7.89%、7.89%及11.11%,差异无统计学意义($P>0.05$)。**结论** 对于老年新发癫痫患者,LEV、LTG及CBZ单药治疗6个月均具有良好疗效,不良反应少,但新型抗癫痫药LEV及LTG在改善认知功能、缓解睡眠呼吸障碍、降低对骨代谢的影响方面更具优势。

【关键词】 老年人;癫痫;左乙拉西坦;拉莫三嗪;卡马西平;认知功能;骨代谢;睡眠呼吸障碍

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Effects of new antiepileptic drugs on bone mineral density, cognitive function and sleep breathing in elderly patients with epilepsy

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【Abstract】 Objective To explore the effects of new antiepileptic drugs levetiracetam (LEV) and lamotrigine (LTG) on bone mineral density, cognitive function, and sleep breathing in elderly patients with epilepsy. **Methods** A total of 112 elderly patients with new-onset epilepsy admitted to the First Affiliated Hospital of Hainan Medical University from January 2024 to June 2024 were selected as study subjects. They were divided into an LEV group ($n=38$), an LTG group ($n=38$), and a carbamazepine (CBZ) group ($n=36$) by a random number table method. All three groups of elderly patients with new-onset epilepsy were treated with monotherapy for 6 months. The three groups were compared in the clinical efficacy and bone mineral density (BMD), serum indicators [intact parathyroid hormone (iPTH), alkaline phosphatase (ALP), brain-derived neurotrophic factor (BDNF)], cognitive function [mini-mental state examination (MMSE)], and sleep breathing parameters [apnea hypopnea index (AHI), mean arterial oxygen saturation ($MSaO_2$), lowest arterial oxygen saturation ($LSaO_2$)] before treatment and after 6 months of treatment. The incidence of adverse reactions during treatment was assessed. SPSS 25.0 was used for data analysis. According to the data type, one-way analysis of variance or *Chi*-square test was used for comparison between groups. **Results** The effective rates of treatment in the LEV group, LTG group, and CBZ group were 89.47%, 86.84%, and 86.11%, respectively, with no statistically significant difference ($P>0.05$). There were no statistical differences in femoral neck and greater trochanter BMD and $MSaO_2$ among the three groups before and after treatment ($P>0.05$). After 6 months of treatment, lumbar spine BMD and AHI in the three groups decreased compared with those before treatment, while iPTH,

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ALP, BDNF, MMSE score and $LSaO_2$ significantly increased compared with before treatment. Furthermore, lumbar spine BMD, BDNF, MMSE scores, and $LSaO_2$ in the LEV group and LTG group after treatment were higher than those in the CBZ group, while iPTH, ALP, and AHI after treatment were significantly lower than those in the CBZ group, all differences being statistically significant ($P<0.05$). The total incidence rates of drug-related adverse reactions in LEV group, LTG group and CBZ group were 7.89%, 7.89%, and 11.11%, respectively, with no statistically significant difference ($P>0.05$). **Conclusion** For elderly patients with new-onset epilepsy, LEV, LTG and CBZ monotherapy for 6 months all demonstrate good efficacy with few adverse reactions. However, the new antiepileptic drugs LEV and LTG have greater advantages in improving cognitive function, alleviating sleep-disordered breathing, and reducing the impact on bone metabolism.

【**Key words**】 aged; epilepsy; levetiracetam; lamotrigine; carbamazepine; cognitive function; bone metabolism; sleep-disordered breathing

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癫痫是临床常见神经系统疾病,在老年人群中患病率仅次于卒中及痴呆,且老年癫痫患者共病发生率高,以基于年龄因素的退行性疾病及基础疾病诱发居多,诊疗难度大[1]。《中国老年癫痫患者管理专家共识》[2]中明确指出,老年癫痫患者基础疾病多,选择药物治疗时应充分考虑药物代谢特点、不良反应、患者耐受性等,且高龄患者器官功能衰退,对药物灵敏性更强,不良反应风险更高,保证用药安全性尤为重要。卡马西平(carbamazepine,CBZ)作为经典抗癫痫药,可降低神经元兴奋性的传导速度,减轻癫痫发作强度及频率,但血药峰值个体差异大,药代动力学有所欠缺,可影响骨代谢,并引起胃肠道反应、中枢神经系统反应等不良反应[3]。近年研究发现,新型抗癫痫药,如左乙拉西坦(levetiracetam,LEV)、拉莫三嗪(lamotrigine,LTG)等,酶诱导活性相对较小,对其他药物代谢影响较小,药物之间相互作用小,用于老年患者安全性较高[4,5]。LEV 或 LTG 等新型抗癫痫药的应用价值是否高于 CBZ,还需更多临床试验证据。基于此,本研究对 LEV、LTG 及 CBZ 治疗老年新发癫痫患者的临床效果及安全性进行评估,为老年癫痫的临床治疗提供参考数据。

1 对象与方法

1.1 研究对象

选择 2024 年 1 月至 6 月海南医学院第一附属医院收治的 112 例老年新发癫痫患者为研究对象,采用随机数表法将患者分为 LEV 组(38 例)、LTG 组(38 例)和 CBZ 组(36 例)。本研究获得海南医学院第一附属医院医学伦理委员会批准(批号:202312-HY-003)。患者及家属对研究内容知情并签署知情同意书。本研究符合《赫尔辛基宣言》。

纳入标准:(1)符合《国际抗癫痫联盟癫痫发作和癫痫综合征分类标准(2017)》[6]诊断标准;(2)首次诊断;(3)年龄≥65 岁;(4)入院前未接受抗癫痫治疗。排除标准:(1)合并脑肿瘤等器质性病变;(2)合并肝硬化等重要器官功能障碍;(3)酒精依赖或药物成瘾史;(4)对本研究药物过敏;(5)合并精神分裂症等精神疾病。剔除标准:(1)自行停药、减药等,遵医行为差;(2)研究期间失访。

1.2 方法

1.2.1 治疗方法 LEV 组给予左乙拉西坦片(华润赛科药业有限责任公司,H20217081,0.25 g)口服治疗,初始剂量为 0.5 g/次,2 次/d,随后根据治疗情况及耐受程度调整,可每 2 周增加给药剂量 0.25 g/次,2 次/d,最大剂量不超时 3 g/d。LTG 组给予拉莫三嗪片(三金集团湖南三金制药有限责任公司,H20050596,25 mg),初始剂量为 25 mg/次,1 次/d,随后根据病情调整,可每 2 周增加给药剂量 25 mg/次,1 次/d,最大剂量不超时 200 mg/d。CBZ 组给予卡马西平片(西南药业股份有限公司,H50020217,0.1 g)口服治疗,初始剂量为 0.1 g/次,1~2 次/d,随后根据病情调整,每 2 周增加或减少给药剂量,最大剂量不超过 0.4 g/次,3 次/d。3 组均连续治疗 6 个月,指导患者家属监督患者遵医嘱服药,并每周电话随访 1 次,每月上门随访 1 次,随访时询问用药情况,督促患者按时按量服药。

1.2.2 疗效评估 以治疗前及治疗 6 个月后发作频率变化评估疗效[7],分为完全控制(临床发作完全消失)、显著改善(发作频率减少>75%)、良好(50%<发作频率减少≤75%)、效果差(25%<发作频率减少≤50%)、无改善(发作频率减少≤25%或加重),其中完全控制、显著改善、良好被认为是治疗有效。

1.2.3 观察指标 分别于治疗前及治疗 6 个月后检测以下指标。(1)骨密度(bone mineral density,BMD):使用双能 X 线骨密度检测仪(美国 GE,型号:LUNAR DPX-IQ)检测,患者平卧位,髋部固定,分别测量腰椎(腰 2 至腰 4 节段)、股骨颈、股骨大转子的 BMD。(2)血清指标:采集空腹外周肘静脉血 3~4 ml,1 500 转/min,离心 10 min(离心半径 8 cm)得到血清标本。使用化学发光法(德国 Roche)检测甲状旁腺激素(intact parathyroid hormone,iPTH)水平;使用全自动生化分析仪(美国

BECKMAN COULTER,型号:AU5800)检测碱性磷酸酶(alkaline phosphatase,ALP)水平;使用双抗体夹心法(美国 Research and Development Systems)检测脑源性神经营养因子(brain-derived neurotrophic factor,BDNF)。(3)认知功能:使用简易精神状态检查(mini-mental state examination,MMSE)[8]评估,总分最高分为30分,得分越低,认知功能越差。(4)睡眠呼吸参数:使用多导睡眠监测系统(美国 REMBRANDT,型号:moonnet 26)在夜间22:00~次日7:00监测睡眠呼吸参数,记录夜间睡眠期间的呼吸紊乱指数(apnea hyponea index,AHI)、平均动脉血氧饱和度(mean arterial oxygen saturation,$MSaO_2$)及最低动脉血氧饱和度(lowest arterial oxygen saturation,$LSaO_2$)。

1.2.4 安全性评价 评估三组患者治疗期间药物相关不良反应发生情况。

1.3 统计学处理

采用 SPSS 25.0 统计软件进行数据分析。符合正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示,多组间比较采用单因素方差分析,组内两两比较采用 SNK-q 检验。计数资料以例数(百分率)表示,组间比较采用χ^2检验。$P<0.05$ 为差异有统计学意义。

2 结 果

2.1 三组患者基线资料

三组患者均未出现遵医行为差及失访病例,无剔除病例。三组患者基线资料比较,差异无统计学意义($P>0.05$;表1)。

2.2 三组患者临床疗效

三组患者治疗有效率比较,差异均无统计学意义($P>0.05$;表2)。

2.3 三组患者治疗前后 BMD

三组患者治疗前后股骨颈与股骨大转子 BMD 比较,差异均无统计学意义($P>0.05$)。治疗6个月后,三组患者腰椎 BMD 均较治疗前降低,且 LEV 组及 LTG 组治疗后腰椎 BMD 均高于 CBZ 组,差异均有统计学意义($P<0.05$;表3)。

2.4 三组患者治疗前后血清指标

治疗6个月后,3组患者 iPTH、ALP 及 BDNF 水平均较治疗前显著升高;治疗后 LEV 组与 LTG 组患者 iPTH、ALP 水平均明显低于 CBZ 组,BDNF 明显高于 CBZ 组,差异均有统计学意义($P<0.05$;表4)。

表1 三组患者基线资料比较

Table 1 Comparison of baseline data among three groups

Item	LEV group(n=38)	LTG group(n=38)	CBZ group(n=36)	χ^2/F	P value
Gender[n(%)]				0.416	0.812
Male	25(65.79)	27(71.05)	26(72.22)		
Female	13(34.21)	11(28.95)	10(27.78)		
Age(years, $\bar{x}\pm s$)	72.36±5.19	72.09±4.98	71.88±4.72	0.087	0.917
Disease course(months, $\bar{x}\pm s$)	12.52±2.39	13.09±2.42	12.89±2.31	0.563	0.571
Education level(years, $\bar{x}\pm s$)	9.03±1.98	9.22±1.87	9.15±1.90	0.095	0.909
Attack type[n(%)]				0.286	0.991
Focal	31(81.58)	30(78.95)	30(83.33)		
Generalized	6(15.79)	7(18.42)	5(13.89)		
Aphanogene	1(2.63)	1(2.63)	1(2.78)		
Etiology[n(%)]				1.425	0.994
Structural	29(76.32)	27(71.05)	28(77.78)		
Infectious	2(5.26)	3(7.90)	2(5.55)		
Metabolic	1(2.63)	2(5.26)	1(2.78)		
Immunogenic	2(5.26)	1(2.63)	1(2.78)		
Unknown	4(10.53)	5(13.16)	4(11.11)		

LEV: levetiracetam; LTG: lamotrigine; CBZ: carbamazepine.

表2 三组患者临床疗效比较

Table 2 Comparison of clinical efficacy among three groups [n(%)]

Group	n	Complete control	Significant improvement	Good effect	Poor effect	No improvement	Effective rate
LEV	38	14(36.84)	11(28.95)	9(23.68)	3(7.89)	1(2.63)	34(89.47)
LTG	38	12(31.58)	12(31.58)	9(23.68)	4(10.53)	1(2.63)	33(86.84)
CBZ	36	11(30.56)	10(27.78)	10(27.78)	4(11.11)	1(2.78)	31(86.11)

LEV: levetiracetam; LTG: lamotrigine; CBZ: carbamazepine.

表 3 三组患者治疗前后 BMD 比较

Table 3 Comparison of BMD before and after treatment among three groups (g/cm^3, $\bar{x}\pm s$)

Group	n	Lumbar spine BMD		Femoral neck BMD		Femoral greater trochanter BMD	
		Before treatment	After 6 months of treatment	Before treatment	After 6 months of treatment	Before treatment	After 6 months of treatment
LEV	38	0.769±0.112	0.747±0.092*#	0.764±0.114	0.751±0.098	0.652±0.103	0.639±0.097
LTG	38	0.766±0.108	0.746±0.098*#	0.761±0.105	0.749±0.101	0.650±0.098	0.637±0.096
CBZ	36	0.765±0.104	0.672±0.093*	0.760±0.112	0.742±0.103	0.649±0.101	0.631±0.093
F		0.014	7.609	0.013	0.081	0.009	0.070
P value		0.986	0.001	0.987	0.922	0.992	0.933

LEV: levetiracetam; LTG: lamotrigine; CBZ: carbamazepine; BMD: bone mineral density. Compared with before treatment, *$P<0.05$; compared with CBZ group, #$P<0.05$.

表 4 三组患者治疗前后血清指标比较

Table 4 Comparison of serum indicators before and after treatment among three groups ($\bar{x}\pm s$)

Group	n	iPTH(pmol/L)		ALP(μg/L)		BDNF(μg/L)	
		Before treatment	After 6 months of treatment	Before treatment	After 6 months of treatment	Before treatment	After 6 months of treatment
LEV	38	36.79±4.19	51.46±5.83*#	31.45±6.12	56.26±7.06*#	6.07±1.11	8.65±1.42*#
LTG	38	35.45±5.12	52.80±6.41*#	31.27±5.92	57.39±6.83*#	6.12±1.29	8.42±1.58*#
CBZ	36	35.08±4.83	59.16±5.67*	31.05±6.04	63.43±8.15*	6.19±1.30	7.35±1.23*
F		1.354	17.330	0.041	10.081	0.088	8.750
P value		0.262	<0.001	0.960	<0.001	0.916	<0.001

LEV: levetiracetam; LTG: lamotrigine; CBZ: carbamazepine; iPTH: intact parathyroid hormone; ALP: alkaline phosphatase; BDNF: brain-derived neurotrophic factor. Compared with before treatment, *$P<0.05$; compared with CBZ group, #$P<0.05$.

2.5 三组患者治疗前后认知功能

治疗 6 个月后,三组患者 MMSE 评分均显著升高,且 LEV 组及 LTG 组明显高于 CBZ 组,差异均有统计学意义($P<0.05$;表 5)。

表 5 三组患者治疗前后 MMSE 评分比较

Table 5 Comparison of MMSE score before and after treatment among three groups (points, $\bar{x}\pm s$)

Group	n	Before treatment	After 6 months of treatment
LEV	38	18.54±2.89	26.64±1.87*#
LTG	38	18.64±2.46	26.42±1.93*#
CBZ	36	18.73±2.57	23.59±2.26*
F		0.048	25.921
P value		0.953	<0.001

LEV: levetiracetam; LTG: lamotrigine; CBZ: carbamazepine; MMSE: mini-mental state examination.

2.6 三组患者治疗前后睡眠呼吸参数

三组患者治疗前后 $MSaO_2$ 比较,差异无统计学意义($P>0.05$)。治疗 6 个月后,三组患者 AHI 显著降低,$LSaO_2$ 显著升高;LEV 组与 LTG 组 AHI 低于 CBZ 组,$LSaO_2$ 高于 CBZ 组,差异均有统计学意义($P<0.05$;表 6)。

2.7 三组患者药物相关不良反应

三组患者药物相关不良反应发生率比较,差异无统计学意义($P>0.05$;表 7)。

3 讨 论

老年癫痫患者受身体机能衰退、合并症多等因素影响,维持药物血药浓度能力受限,临床给药剂量需考虑发作状态控制情况及肝肾功能状况[9]。CBZ 作为传统一线抗癫痫药,通过调控神经细胞膜上的钠离子通道发挥抗癫痫作用,但其钠通道阻滞作用也能引起心血管系统、泌尿系统等的不良反应,其用药安全性是临床关注的焦点[10]。LTG 作为新型抗

表 6 三组患者治疗前后 AHI、$MSaO_2$ 及 $LSaO_2$ 比较

Table 6 Comparison of AHI, $MSaO_2$ and $LSaO_2$ before and after treatment among three groups ($\bar{x}\pm s$)

Group	n	AHI(times/h)		$MSaO_2$(%)		$LSaO_2$	
		Before treatment	After 6 months of treatment	Before treatment	After 6 months of treatment	Before treatment	After 6 months of treatment
LEV	38	10.45±1.98	5.50±1.27*#	96.82±1.65	97.56±1.06	84.06±3.09	90.42±2.87*#
LTG	38	10.29±1.89	5.87±1.36*#	96.74±1.59	97.45±1.27	84.12±2.83	89.68±2.75*#
CBZ	36	10.34±1.93	6.97±1.30*	96.98±1.70	97.22±1.34	84.26±2.95	86.81±2.54*
F		0.068	12.501	0.203	0.735	0.044	17.950
P value		0.934	<0.001	0.817	0.482	0.957	<0.001

LEV: levetiracetam; LTG: lamotrigine; CBZ: carbamazepine; AHI: apnea hyponea index; $MSaO_2$: mean arterial oxygen saturation; $LSaO_2$: lowest arterial oxygen saturation. Compared with before treatment, *$P<0.05$; compared with CBZ group, #$P<0.05$.

表7 三组患者药物相关不良反应情况比较

Table 7 Comparison of drug-related adverse reactions among three groups [n(%)]

Group	n	Nausea and vomiting	Dizziness and headache	Drowsiness	Fatigue	Skin rash	Total
LEV	38	1(2.63)	1(2.63)	0(0.00)	1(2.63)	0(0.00)	3(7.89)
LTG	38	0(0.00)	1(2.63)	1(2.63)	1(2.63)	0(0.00)	3(7.89)
CBZ	36	1(2.78)	1(2.78)	1(2.78)	0(0.00)	1(2.78)	4(11.11)

LEV: levetiracetam; LTG: lamotrigine; CBZ: carbamazepine.

癫痫药,不仅是一种电压依赖性钠通道阻滞剂,还能抑制电压门控性钙通道,并稳定突出前膜,抑制兴奋性神经递质的释放,抗癫痫效果好,与其他药物的相互作用少,药代动力学特征良好[11]。LEV是一种具有全新作用机制的抗癫痫药,可阻断谷氨酸受体,使过度兴奋的突触传递减少,还能通过影响神经递质的合成及释放,促进神经细胞膜电生理活动稳定,抗癫痫疗效良好,且患者耐受性较好[12]。本研究结果显示,LEV组、LTG组及CBZ组治疗有效率均超过80%,且3组药物相关不良反应总发生率组间也无明显差异,提示LEV、LTG及CBZ单药治疗6个月的疗效及安全性均良好,临床实用性较高。

另据文献报道,抗癫痫药常通过抑制神经元兴奋性减少癫痫发作,但由于这种抑制作用缺乏特异性,可同时降低病变部位及正常部位神经元的兴奋性,可能造成患者认知功能下降[13]。本研究中,三组患者治疗6个月后MMSE评分均显著升高,且LEV组及LTG组治疗后高于CBZ组,提示经抗癫痫药治疗后,老年新发癫痫患者认知功能均有所提升,但新药LEV及LTG对认知功能的改善效果更佳。究其原因可能为抗癫痫药可使癫痫样异常放电引起的神经元损伤降低,促进患者认知功能改善,而LEV具有神经元保护作用,LTG可选择性抑制组蛋白脱乙酞基酶,优化神经元传递过程,因此LEV组及LTG组在改善认知功能方面更具优势[14,15]。本研究结果显示,三组患者治疗后BDNF均显著升高,LEV组及LTG组治疗后BDNF水平高于CBZ组,而BDNF作为神经元生长因子,具有促神经元修复、促神经元及突触增殖与分化等作用[16],表明新型抗癫痫药LEV及LTG在促神经元修复方面具有一定优势。

有报道指出,不同类型的抗癫痫药均能诱导患者骨代谢紊乱,增加老年癫痫患者骨质疏松风险[17]。本研究中,三组患者治疗6个月后腰椎BMD均较治疗前降低,而LEV组及LTG组治疗后高于CBZ组,提示3种抗癫痫药单药治疗6个月均造成一定骨流失,但LEV及LTG对骨代谢的影响小于CBZ,与Mann等[18]报道相似。本研究分析相关血清指标发现,三组患者治疗后iPTH、ALP均较治疗前显著升高,而LEV组及LTG组治疗后低于CBZ组,其中iPTH可间接影响破骨细胞活动,促骨钙转换,ALP则是骨代谢标志物之一,可反映成骨细胞活性[19]。因此,推测LEV及LTG对骨代谢不良影响更小的原因为二者对下丘脑-垂体-肾上腺轴的影响可能较CBZ更小,使iPTH等激素紊乱减轻,进而减少对骨代谢的影响[20]。

近年研究还发现,癫痫患者常伴睡眠呼吸障碍,且共病诱导交感神经系统异常激活、低氧血症等,加剧认知障碍及睡眠结构紊乱等不良事件,形成恶性循环[21]。本研究中,三组患者治疗后AHI均降低,$LSaO_2$升高,LEV组及LTG组治疗后AHI低于CBZ组,$LSaO_2$高于CBZ组,提示抗癫痫单药治疗对缓解老年先发癫痫患者睡眠呼吸障碍有利,且LEV及LTG对睡眠呼吸障碍的改善效果更佳。究其原因可能为抗癫痫治疗使癫痫放电对交感神经系统异常激活现象减少,LEV还能阻断谷氨酸受体,有利于脑干区域播散性去极化,进一步改善睡眠呼吸障碍[12];LTG则可能通过调控神经递质的释放,参与下丘脑Orexin神经元活性的调节,改善睡眠-觉醒、呼吸等功能[11]。此外,本研究作为单中心小样本量研究,代表性有所欠缺,未来还需联合其他医疗机构开展多中心、大样本量研究,对本研究结果加以验证。

综上,LEV、LTG及CBZ单药治疗老年新发癫痫患者效果良好,安全性较高,但新型抗癫痫药LEV、LTG能进一步改善患者认知功能及睡眠呼吸障碍,且对骨密度的不良影响更小,应用前景更好。

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