An update of the Hong Kong Epilepsy Guideline: consensus statement on the use of antiepileptic drugs in Hong Kong

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ABSTRACT

Objective: New information about antiepileptic drugs has arisen since the publication of the Hong Kong Epilepsy Guideline in 2009. This article set out to fill the knowledge gap between 2007 and 2016 on the use of antiepileptic drugs in Hong Kong.

Participants: Between May 2014 and April 2016, four consensus meetings were held in Hong Kong, where a group comprising 15 professionals (neurologists, paediatricians, neurosurgeons, radiologists, and clinical psychologists) from both public and private sectors aimed to review the best available evidence and update all practising physicians on a range of clinical issues including drug-related matters. All participants were council members of The Hong Kong Epilepsy Society.

Evidence: A literature review of the clinical use of antiepileptic drugs as monotherapy suggested Level A evidence for levetiracetam and Level B evidence for lacosamide. No change in the level of evidence was found for oxcarbazepine (Level A evidence) or pregabalin (undesignated), and no evidence was found for perampanel. A literature review on the clinical use of antiepileptic drugs as adjunctive therapy suggested Level A evidence for both lacosamide and perampanel. No change to the level of evidence was found for levetiracetam (Level A evidence), oxcarbazepine (Level A evidence), or pregabalin (Level A evidence). A literature search on the use of generic antiepileptic drugs suggested Level A evidence for the use of lamotrigine in generic substitution.

Consensus process: Three lead authors of the Subcommittee drafted the manuscript that consisted of two parts—part A: evidence on new antiepileptic drugs, and part B: generic drugs. The recommendations on monotherapy/adjunctive therapy were presented during the meetings. The pros and cons for our health care system of generic substitution were discussed. The recommendations represent the 'general consensus' of the participants in keeping with the evidence found in the literature.

Conclusions: Recommendations for the use of levetiracetam, lacosamide, oxcarbazepine, pregabalin, and perampanel were made. The consensus statements may provide a reference to physicians in their daily practice. Controversy exists over the use of generic products among patients who are currently taking brand medications. In this regard, approvals from prescriber and patient are pivotal. Good communication between doctors and patients is essential, as well as enlisting the assistance of doctors, nurses, and pharmacists, therapeutic blood monitoring if available, and the option of brand antiepileptic drug as a self-financed item. The physical appearance of generic drugs should be considered as it may hamper drug compliance. Support from medical services is recommended. In the longer term, the benefit of flexibility and the options to have a balance between the generic and brand drug market may need to be addressed by institutions and regulatory bodies.

Hong Kong Med J 2017;23:74–88
DOI: 10.12809/hkmj166027

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Introduction

Epilepsy is a chronic neurological condition that places a high economic burden on patients from childhood to senescence. In Hong Kong alone, more than 70 000 patients have seizures as a chronic condition and many more have developed seizures as a result of an acute symptomatic medical condition; both of which may require the use of antiepileptic drugs (AEDs). There are currently 155 registered pharmaceutical products in Hong Kong classed as AEDs and approved by the Department of Health, excluding drugs that are prescribed off-label. The general guiding principles for physicians in the selection of AEDs are derived from evidence-based medicine and the last version of The Hong Kong Epilepsy Guideline already provides ample advice.[1] As the number of published papers and meta-analysis is fast-growing, The Hong Kong Epilepsy Society (HKES) considers it important to review the best available evidence and to update all practising physicians with regard to their position on a range of clinical issues including drug-related matters. As such, HKES prepared a series of consensus statements to supplement The Hong Kong Epilepsy Guideline of 2009.

Four consensus meetings were convened between May 2014 and April 2016 during which time a group of 15 professionals consisting of neurologists, paediatricians, neurosurgeons, radiologists, and clinical psychologists participated in structured discussions in four major areas: AEDs, status epilepticus, refractory epilepsy, and women and epilepsy. The participants represented both the public and private sectors. They were all council members of HKES. The current paper addresses the topic of AEDs.

In part A of this consensus statement, we have compiled all the papers and studies published in 2007 or later, using the citation index from PubMed, Ovid and Google Scholar, that are concerned with the clinical use of AEDs as either monotherapy or adjunctive therapy. The research papers must be written in English with seizure outcome as their primary endpoint. Only AEDs licensed in Hong Kong after 2001 are included in this review. Studies pertaining to benzodiazepine and intravenous preparations only of any AED were not reviewed, nor were those that focused exclusively on subgroups of patients in which prognosis may be affected by parameters other than drug treatment (eg neurosurgical cohorts).

The research papers were rated as randomised controlled trial, cohort study (including retrospective study), meta-analysis or review, and where possible, graded as class I, II, or III level of evidence, in line with the previous version of The Hong Kong Epilepsy Guideline.[1] Level A evidence is defined as the availability of one Class I study or more, or meta-analysis suggesting a similar rating. Level B evidence is defined as the availability of one Class II study or more, or meta-analysis suggesting a similar rating. Level C evidence is defined as the presence of more than two Class III studies.

In part B of this consensus statement, we have compiled all the studies published in 2007 or later, using the citation index from PubMed, Ovid and Google Scholar, that are related to human studies of generic preparations of AEDs. The same classification of evidence is employed. The analyses in both parts A and B are of particular importance to local health care providers, because Hong Kong has a special health-financing situation in which the majority of patients are treated under the public hospital system. As a result, hospital-based practice

香港腦癇指引更新：香港使用腦癇藥物的共識聲明

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目的：自2009年香港腦癇學會發表腦癇指引後，不少新的腦癇藥物和相關資訊陸續出現。本文回顧2007年至2016年之間腦癇藥物的資訊。

參與者：2014年5月至2016年4月期間舉行了四次共識會議。成員由15位來自公營及私營醫療系統的專業人士組成，當中包括腦科、兒科、腦外科和放射科醫生，以及臨床心理專家。會議旨在討論根據最佳現有證據，為業界提供最新腦癇藥物的資訊。所有參與者均為香港腦癇學會的成員。

證據：單藥治療方面，開普蘭（levetiracetam）的臨床證據已經達到循證醫學甲級水平，拉科酰胺（lacosamide）也達到乙級水平。至於奧卡西平（oxcarbazepine）和普瑞巴林（pregabalin）的證據則沒有任何改變。癲控達膜衣錠（perampanel）還沒有足夠的循証證據。至於輔助治療的應用方面，拉科酰胺和癲控達膜衣錠也達到甲級水平。開普蘭、奧卡西平和普瑞巴林則並沒有改變（它們均達至甲級水平）。關於學名藥的文獻，目前拉莫三嗪（lamotrigine）鈉通道阻斷劑的循証證據已經達到甲級水平。

綜述過程：附屬委員會中三位主要成員負責編寫文章，當中包含兩個部份：第一部份為新藥的證據，第二部份則關於學名藥的使用。會議中發表了有關單藥治療和輔助療法的建議，亦廣泛討論學名藥的優點和缺點。專家建議提供整體性的共識，也大致接納臨床的證據。

結論：專家建議對開普蘭、拉科酰胺、奧卡西平、普瑞巴林和癲控達膜衣錠的使用提供了指引，亦可作為醫生臨床的參考。病人從品牌藥轉服學名藥是一具爭論性的議題。當中處方醫生以及病人的同意至關重要。我們亦應注意病人與醫生之間的溝通，醫生、護士和藥劑師的協助，血液濃度的幫助（如有），以及自費品牌藥選擇的提供。學名藥的外型跟品牌藥的差異也可以帶來服藥依從性的問題。醫護人員的支援也是非常重要的。長遠來說，可能須要由監管機構解決用藥的靈活性，以及學名藥和品牌藥市場之間取得平衡的選擇。

is likely to influence the standard of care delivered to the majority of chronic epilepsy patients and the health care costs of medical treatment.

Part A: evidence on new antiepileptic drugs

A total of 95 eligible papers were submitted for the purpose of writing this consensus statement. Articles that focused on zonisamide, eslicarbazepine, and brivaracetam were not reviewed because these agents were not registered with Department of Health at the time of writing. Papers pertaining to topiramate were not reviewed as the drug was registered in Hong Kong before 2001. Papers on retigabine were not reviewed as this drug has currently limited usage in Hong Kong following an alert from the Food and Drug Administration (FDA) of the United States. The remaining drugs of interest were collated based on their indications.

Monotherapy

Levetiracetam

Two Class I studies, 10 Class II studies, and 16 Class III studies were found under this indication for levetiracetam (LEV). One Class I study that randomised patients to LEV or carbamazepine found non-inferiority of LEV.[2] Another Class I study randomised paediatric patients with juvenile absence epilepsy to LEV or placebo and reported a non-significant superiority in terms of seizure response.[3] One Class II study compared LEV with lamotrigine (LTG) and another Class II study compared LEV with carbamazepine or sodium valproate. Both studies demonstrated that LEV was as efficacious as the other standard regimens.[4,5]

The evidence in the paediatric population was generally positive.[3,4,6,7] At the opposite end of the spectrum, geriatric patients were also shown in a Class II study to benefit from LEV monotherapy.[8] One Class II study detailed the conversion of treatment in patients with existing partial-onset epilepsy to extended-release LEV monotherapy.[9] In the Chinese population, one Class III study demonstrated the usefulness of LEV monotherapy.[10] The overall level of conclusion is supported by an expedited review from the International League Against Epilepsy (ILAE).[11]

Statement 1: The level of evidence for LEV monotherapy reaches Level A.

Oxcarbazepine

Four Class III studies and one meta-analysis were found under this indication for oxcarbazepine (OXC). Another three Class III studies recruited patients with mixed indications (Table 1[12-19]). The evidence in the paediatric subgroup suggested that OXC may be useful in children across a range of conditions, from idiopathic to symptomatic and cryptogenic epilepsy.[12] Of interest, one study that recruited Chinese patients for the purpose of both mono- and adjunctive therapy showed that OXC was as effective as LTG or topiramate.[13] Oxcarbazepine is already indicated as monotherapy in partial epilepsy. The recommendation for the use of OXC remains unchanged.

Statement 2: The level of evidence for OXC monotherapy remains unchanged (Level A).

Lacosamide

Lacosamide (LCS) produces slow inactivation of neuronal sodium channels. We found one Class

TABLE 1. A review of the use of oxcarbazepine as an antiepileptic drug[12-19]

Study	Class	Study population / outcome
Monotherapy. Level of evidence reached: A. Recommendation: unchanged from The Hong Kong Epilepsy Guideline 2009		
Koch and Polman,[15] 2009	Meta-analysis	CBZ and OXC were similarly effective and well-tolerated
Eun et al,[16] 2012	Class III	Paediatrics
Franzoni et al,[12] 2009	Class III	Paediatrics
Franzoni et al,[12] 2009	Class III	OXC was effective and well-tolerated in paediatric group
Dogan et al,[17] 2008	Class III	Adults, 62.6% were seizure-free; discontinuation rate: 8%
Adjunctive therapy. Level of evidence reached: A. Recommendation: unchanged from The Hong Kong Epilepsy Guideline 2009		
French et al,[14] 2014	Class I	Extended-release preparation
Mixed		
Kang et al,[13] 2012	Class III	Adult
Lee et al,[18] 2010	Class III	Adult
Seneviratne et al,[19] 2008	Class III	Adult

Abbreviations: CBZ = carbamazepine; OXC = oxcarbazepine

II study and two Class III studies on the use of LCS monotherapy and two Class III studies with mixed indications (Table 2[20-45]). One conversion study showed that 425 patients completed LCS maintenance with a favourable safety profile at a nominal dose of 400 mg per day.[20] In another study, the seizure-free rate was 72.3% at 1 year and the withdrawal rate was 15%.[21] In the study by Lattanzi et al,[22] 58 patients were converted from a background single AED to LCS with just over half (55.2%) becoming seizure-free. Only 20.8% of patients reported mild-to-moderate adverse events. The FDA has approved use of LCS as monotherapy in epilepsy since September 2014 and there was a plan to seek its approval for use with the same indication in Europe in 2016.

Statement 3: The level of evidence for LCS monotherapy reaches Level B.

Pregabalin

Pregabalin (PGB) has binding properties to the alpha-2-delta units of calcium channels. We found one Class I study, one Class II study, and one meta-analysis for PGB under this indication (Table 3[14,46-57]). Pregabalin was compared with LTG in a study of 330 patients using a double-blind, non-inferiority design with the primary efficacy endpoint being the proportion of patients to achieve seizure freedom for 6 months. In the study, however, PGB was inferior to LTG on both intention-to-treat and per-protocol analyses.[46] In the study by French et al,[14] conversion from a first or second AED to PGB was

TABLE 2. A review of the use of lacosamide as an antiepileptic drug[20-45]

Study	Class	Study population / outcome
Monotherapy. Level of evidence reached: B. Recommendation: changed from The Hong Kong Epilepsy Guideline 2009		
Wechsler et al,[20] 2014	Class II	Adult
Giráldez et al,[21] 2015	Class III	Adult
Lattanzi et al,[22] 2015	Class III	Adult (conversion)
Adjunctive therapy. Level of evidence reached: A. Recommendation: changed from The Hong Kong Epilepsy Guideline 2009		
Husain et al,[23] 2012	Class I	Adult
Runge et al,[24] 2015	Class III	Adult
Stephen et al,[25] 2014	Class III	Adult (21.9% seizure-free and 21.9% had >50% reduction)
Pasha et al,[26] 2014	Class III	Paediatric
Rosenfeld et al,[27] 2014	Class III	Adult (open-label extension)
Gulati et al,[28] 2015	Class III	Paediatric
Rosenow et al,[29] 2015	Class III	Adult (open-label extension)
Geffrey et al,[30] 2015	Class III	Tuberous sclerosis complex patients
Flores et al,[31] 2012	Class III	Adult (UK epilepsy clinic)
Kamel et al,[32] 2013	Class III	Adult
Verrotti et al,[33] 2013	Class III	Adult and paediatric
Toupin et al,[34] 2015	Class III	Paediatric
Zadeh et al,[35] 2015	Class III	Adult
Rastogi and Ng,[36] 2012	Class III	Paediatric
Grosso et al,[37] 2014	Class III	Paediatric
Grosso et al,[38] 2014	Class III	Lennox-Gastaut syndrome, paediatric (reduction 29%)
Lee et al,[39] 2016	Class III	Adjunctive LCS to LEV monotherapy
Buck and Goodkin,[40] 2012	Meta-analysis	Paediatric
Paquette et al,[41] 2015	Meta-analysis	14 Studies (38%-41% achieved 50% responder rate)
Biton et al,[42] 2015	Meta-analysis	-
Sawh et al,[43] 2013	Meta-analysis	-
Mixed		
Yorns et al,[44] 2014	Class III	Paediatric
Novy et al,[45] 2013	Class III	Adult

Abbreviations: LCS = lacosamide; LEV = levetiracetam

undertaken in 125 patients and the results showed that PGB monotherapy was safe and efficacious in partial epilepsy. No recommendation may be given at this stage regarding the use of PGB monotherapy in epilepsy.

Statement 4: The level of evidence for PGB monotherapy remains unchanged (not designated).

Perampanel

No study on the use of perampanel (PER) monotherapy could be found using the current search criteria. Other information pertaining to PER is shown in Table 4.[58-69]

Statement 5: The level of evidence for PER monotherapy remains unchanged (no recommendation).

TABLE 3. A review of the use of pregabalin as an antiepileptic drug[14,46-57]

Study	Class	Study population / outcome
Monotherapy. Level of evidence reached: undesignated. Recommendation: no recommendation at present		
Kwan et al,[46] 2011	Class I	Adult
French et al,[14] 2014	Class II	Historical controlled trial, positive for patients inadequately controlled
Zhou et al,[49] 2012	Meta-analysis	
Adjunctive therapy. Level of evidence reached: A. Recommendation: unchanged from The Hong Kong Epilepsy Guideline 2009		
French et al,[14] 2014	Class I	Adult, controlled release
Zaccara et al,[47] 2014*	Class I*	Non-inferiority comparison between PGB and LEV
Lee et al,[48] 2009	Class I	Adult
Valentin et al,[50] 2009	Class III	Adult
Tsounis et al,[51] 2011	Class III	Adult
Stephen et al,[52] 2011	Class III	Adult, high rate of withdrawal
Ryvlin et al,[53] 2010	Class III	Adult
Pulman et al,[54] 2014	Meta-analysis	-
Lozsadi et al,[55] 2008	Meta-analysis	-
Gil-Nagel et al,[56] 2009	Meta-analysis	-
Uthman et al,[57] 2010	Meta-analysis	30% Withdrawal rate

Abbreviations: LEV = levetiracetam; PGB = pregabalin

* This study differs from other Class I studies in that the comparison arm was an antiepileptic agent rather than placebo

TABLE 4. A review of the use of perampanel as an antiepileptic drug[58-69]

Study	Class	Study population / outcome
Monotherapy. Level of evidence reached: undesignated. Recommendation: no recommendation at present		
No study		
Adjunctive therapy. Level of evidence reached: A. Recommendation: changed from The Hong Kong Epilepsy Guideline 2009		
French et al,[60] 2012 (study 304)	Class I	>12 Years of age, 50% responder rate of 64.2%
French et al,[59] 2013 (study 305)	Class I	
French et al,[58] 2015	Class I	Idiopathic generalised epilepsy
Krauss et al,[61] 2012 (study 306, 307)	Class I	
Juhl and Rubboli,[63] 2016	Class III	Adult, 50% responder rate of 27.2%
Brodie and Stephen,[64] 2016	Class III	Adult, 50% responder rate of 14.8%
Shah et al,[65] 2016	Class III	Adult, 50% responder rate of 57.5%
Kwan et al,[62] 2015	Pooled results	Enzyme-inducing AED might affect PER
Steinhoff et al,[66] 2014	Class III	Retention rate of 69%
Kramer et al,[67] 2014	Pooled results	Increasing dose from 8 to 12 mg might provide additional benefits
Steinhoff et al,[68] 2014	Class III	50% Responder rate of 46%
Hsu et al,[69] 2013	Meta-analysis	-

Abbreviations: AED = antiepileptic drug; PER = perampanel

Adjunctive therapy

Levetiracetam

One Class I and two Class III studies were identified using the search criteria. In addition, two Class III studies reported mixed indications and two meta-analyses were published (Table 5[2-10,13,70-94]). In the only Class I study available for this indication, patients with idiopathic generalised epilepsy were randomised to receive LEV 3000 mg per day or placebo. The results suggested that a reduction by ≥50% of myoclonic seizures may be achieved in 58.3% of patients.[70] One Class III study reported the use of LEV among patients with rolandic epilepsy or variants: a >50% reduction in seizure frequency was achieved by 62.5% of patients.[71] There is no new recommended level of evidence for LEV under this indication.

A review of the behavioural side-effects of LEV revealed possible variation among paediatric and adult subjects. Nervousness, aggression, and hostile behaviour have been reported as putative behavioural adverse events. In paediatric cohorts, the proportion of such adverse events was 20% to 30%.[70-72,94] By comparison, the behavioural side-effects in adults were less prominent.[72-75,94]

Statement 6: The level of evidence for LEV adjunctive therapy remains unchanged (Level A).

Oxcarbazepine

One Class I study and three Class III studies (with mixed indications) were identified (Table 1[12-19]). In the study by the PROSPER Investigators Study Group, adjunctive OXC reduced seizure magnitude by 38.2% to 42.9%. Adverse event rates and safety profiles suggested improved tolerability.[95] Oxcarbazepine is currently licensed for adjunctive therapy in epilepsy and no change to the current recommended level of evidence was made.

Statement 7: The level of evidence for OXC adjunctive therapy remains unchanged (Level A).

Lacosamide

Three pivotal clinical studies outlined the clinical usefulness of LCS in patients with refractory epilepsy: one Phase II and two Phase III studies.[76,96,97] These 12-week, randomised, double-blind, placebo-controlled, multicentre trials enrolled subjects with partial-onset seizures with or without secondary generalisation who were not adequately controlled with one to three concomitant AEDs. Study 1 compared doses of LCS 200, 400, and 600 mg/day with placebo.[96] Study 2 compared doses of LCS 400 and 600 mg/day with placebo.[76] Study 3 compared doses of LCS 200 and 400 mg/day with placebo.[97] Following an 8-week phase to establish baseline seizure frequency, subjects were titrated to the randomised dose. During the titration phase in all three trials, treatment was initiated at 100 mg/day (50 mg given twice daily) and increased by weekly increments of 100 mg/day to the target dose. The titration phase lasted 6 weeks in Study 1 and Study 2 and 4 weeks in Study 3. In all three trials, the titration phase was followed by a maintenance phase for 12 weeks. The primary endpoint was reduction in 28-day seizure frequency (baseline to maintenance phase) compared with the placebo group. A statistically significant effect was observed with LCS treatment at doses of 200 mg/day (Study 3), 400 mg/day (Study 1, 2, and 3), and 600 mg/day (Study 1 and 2).

An observational phase IV open-label study to assess the efficacy, safety, tolerability, and additional outcomes of LCS in Hong Kong patients aged ≥18 years showed that LCS had efficacy and adverse effects similar to those described in the literature from other parts of the world. In a cohort of 105 patients, the proportion who achieved a 50% reduction in seizure frequency was 54.5 with a mean titration time of 6.75 weeks and a mean maintenance dose of 158.6 mg/day. The efficacy profile was satisfactory whether or not LCS was combined with concomitant sodium channel blockers (45.8% vs 46.5%). The side-effect profile included apprehension and aggression, drowsiness and tiredness, headache, memory problems, dizziness, numbness, and gait disturbance (local data).

Statement 8: The level of evidence for LCS as adjunctive therapy reaches Level A.

Pregabalin

Three Class I studies, four Class III studies, and four meta-analyses were found pertaining to PGB under this indication (Table 3[14,46-57]). One study evaluated the efficacy and tolerability of adjunctive PGB as a controlled-release formulation. The 50% responder rate (ie percentage of patients achieving 50% reduction in seizure frequency) was 45.9% for a daily dose of 330 mg.[98] Another randomised study tested PGB versus LEV in a head-to-head comparison in 409 patients. The drug PGB was non-inferior to LEV with a similar tolerability to LEV as adjunctive therapy.[47] In a multicentre, randomised study of PGB versus placebo, PGB was effective and tolerable as adjunctive therapy in the Asian population.[48] This drug is currently licensed for adjunctive therapy in epilepsy and there is no change to the level of evidence regarding its recommended use.

Statement 9: The level of evidence for PGB as adjunctive therapy remains unchanged (Level A).

Perampanel

A total of four Class I clinical studies demonstrated the efficacy of PER among patients with refractory epilepsy.[58-61] These were all double-blind studies and all evaluated the 50% responder rate as a seizure

TABLE 5. A review of the use of levetiracetam as an antiepileptic drug[2-10,13,70-94]

Study	Class	Study population	Outcome
Monotherapy. Level of evidence reached: A. Recommendation: changed from The Hong Kong Epilepsy Guideline 2009			
Brodie et al,[2] 2007	Class I	Adult	58.5% Achieved seizure freedom with LEV. Withdrawal rate of 19.2% with LEV
Fattore et al,[3] 2011	Class I	Paediatric	23.7% Responders in LEV vs 4.8% of placebo
Coppola et al,[6] 2007	Class II	Paediatric, BECTS	LEV vs OXC
Rosenow et al,[4] 2012	Class II	Adult/paediatric	LEV = LTG
Trinka et al,[5] 2013	Class II	Adult	-
Werhahn et al,[8] 2015	Class II	Elderly	-
Borggraefe et al,[7] 2013	Class II	Paediatric	LEV vs sulthiamine. Sample size not reached due to limited recruitment
Suresh et al,[77] 2015	Class II	Adult	-
Jung et al,[78] 2015	Class II	Adult	-
Chung et al,[9] 2012	Class II	Adult	-
Consoli et al,[79] 2012	Class II	Post-stroke patients	-
Hakami et al,[80] 2012	Class II	Patients with substitution monotherapy	-
Chung et al,[76] 2016	Class III	Adult	-
Zhu et al,[10] 2015	Class III	Adult	-
Xiao et al,[81] 2014	Class III	Paediatric	-
Kang et al,[13] 2012	Class III	Paediatric	-
Bertsche et al,[82] 2014	Class III	Paediatric	-
Stephen et al,[83] 2011	Class III	Adult	-
Verrotti et al,[84] 2009	Class III	Paediatric	Effective for childhood occipital Gastaut type
Belcastro et al,[85] 2008	Class III	Patients with late-onset post-stroke seizures	77.1% Achieved seizure freedom
Verrotti et al,[86] 2008	Class III	Paediatric (absence)	~50% Achieved seizure freedom
Kutlu et al,[87] 2008	Class III	Patients with late post-stroke seizures	82.4% Seizure-free
Perry et al,[88] 2008	Class III	Paediatric	LEV and CBZ had similar efficacy and well tolerated
Verrotti et al,[89] 2008	Class III	Paediatric/JME	~50% Achieved seizure freedom
Belcastro et al,[90] 2007	Class III	Patients having Alzheimer's with late-onset seizures	16% Discontinuation rate
Sharpe et al,[91] 2008	Class III	JME	8% Seizure-free
Khurana et al,[92] 2007	Class III	Paediatric	61% Achieved seizure freedom
Verrotti et al,[93] 2007	Class III	BECTS	All patients were seizure-free or with reduction of >50%
Adjunctive therapy. Level of evidence reached: A. Recommendation: unchanged from The Hong Kong Epilepsy Guideline 2009			
Noachtar et al,[70] 2008	Class I	Patients with idiopathic generalised epilepsy	50% Responder rate recorded in 58.3%
Werhahn et al,[73] 2011	Class III	Elderly	-
Droz-Perroteau et al,[74] 2011	Class III	Adult	-
Mixed			
von Stulpnagel et al,[71] 2010	Class III	Patients with rolandic epilepsy and variants	62.5% Responded well
Kuba et al,[75] 2010	Class III	Adult	11% Seizure-free and retention rate was 69.3%
Lo et al,[94] 2011	Meta-analysis	-	-
Mbizvo et al,[72] 2012	Meta-analysis	-	-

Abbreviations: BECTS = benign epilepsy of childhood with centrotemporal spikes; CBZ = carbamazepine; JME = juvenile myoclonic epilepsy; LEV = levetiracetam; LTG = lamotrigine; OXC =oxcarbazepine

outcome. The corresponding risk ratio for 50% responder rate for 4 mg, 8 mg, and 12 mg were 1.54, 1.8, and 1.72. The most common treatment-emergent adverse effects were dizziness, drowsiness, headache, fatigue, and nasopharyngitis. The pooled results suggested that a higher dose was more efficacious if the side-effects could be tolerated.[62] There was one ongoing study on the use of PER among patients with secondary generalised seizures.

Statement 10: The level of evidence for PER as adjunctive therapy reaches Level A.

Part B: Generic drugs

The last version of the The Hong Kong Epilepsy Guideline gave advice on the use of generic drugs, details of which can be revisited in the original guideline of 2009.[1] There might be a perceived difference between pharmaceutical equivalence, which is the requirement of the exact product, and bioequivalence, which is the concept of assigning no difference among products in terms of drug absorption. There have been positional statements that outline the possible risks involved when switching antiepileptic agents from a brand to a generic preparation.[99] Clinicians are understandably perturbed by the prospect of inadvertent seizures and loss of quality of life for their patients. The criteria applied by authorities to license generic products give rise to various issues. For instance, the concept of bioequivalence does not require the generic product to demonstrate clinical efficacy among patients. Most bioequivalence studies are performed among healthy subjects rather than individual patients. Antiepileptic drugs are placed in the same category as immunosuppressants and psychotropic drugs, in which generic substitution is necessarily given consideration before implementation. The benefit of generic AEDs is clear in countries where health care financing is either state-run or public-funded, but may still be important in terms of patient choice in countries where private health care or an insurance-based system is practised because patients may want to lower their premium by using generic products. It may be argued that the use of generic products will increase the potential availability of drugs to a broader population of patients including those who are underprivileged or resident in communities where the drug budget is restricted.

There is a growing need for review and update of recommended guidelines on issues related to generic products as the evidence for newer drugs has become more eminent. The prescription of and expenditure on newer agents has risen sharply over the last 5 to 10 years. Clinicians now have a far greater number of AEDs at their disposal compared with a decade ago. There is divided opinion in the professional community about the use of generic products and when it will be considered optimal and safe for epilepsy patients. In general, communities that rely on a state-financed or government-funded health care system are under greater pressure to consider generic product prescription, compared with private-funded or out-of-pocket payment health care financing systems.

Our literature search identified 13 studies published in or after 2007 that fulfilled the initial inclusion criteria. Four studies were of the Class I category, one of the Class II category, and eight of the Class III category (Table 6[100-116]). Six studies had LTG as the study AED.[100-105] Two studies had topiramate as the study focus[106,115] and the remaining studies adopted multiple drug regimens.[107-111] A good level of evidence came from a randomised controlled trial of 'generic-brittle' patients in a double-blind, multiple-dose, steady-state, fully replicated crossover bioequivalence study of LTG. The study demonstrated that the generic product was bioequivalent to the brand medication. Such observations were supported by the secondary outcomes of seizure control and tolerability—32 of 35 patients reported no deterioration of seizures, and dose-related adverse events were experienced by 14 patients while on the generic product and 15 patients while on the brand product. The study highlighted the use of the therapeutic level as a guide over a period of time while the patient is switched from brand to generic or vice versa.[100] Two Class I studies with preliminary results disseminated during the annual meeting of the American Epilepsy Society in 2015 showed no deviation from FDA's bioequivalence standards in C_{max} and area under the curve when comparing two most disparate generic products in a single dose and chronic disease model respectively (methodology given in Diaz et al in 2013[101]). One well-designed study of 35 patients randomised patients from six epilepsy centres to receive LTG as one of two treatment sequences that comprised four study periods of 14 days each, during which time balanced doses of an oral generic LTG product were given every 12 hours. Disparate generic LTG in patients with epilepsy demonstrated bioequivalence with no detectable difference in clinical effects.[102] A similar result was found from the only Class II study from our literature search.[103] The best level of evidence in epilepsy patients supported the switch of LTG (sodium channel blocker) from brand to generic preparation. It remains controversial whether these findings can be extrapolated to other AEDs because LTG is by far one of the most widely used first-line AEDs.

Most Class III studies indicated an opposite result compared with the Class I and II studies. These studies showed that generic substitution may result in increased acute seizure–related events and higher use of medical services. The switch-back rates for AEDs from generic to brand were higher in these

TABLE 6. Compilation of studies published in 2007 or after related to human studies of generic preparations of antiepileptic drugs[100-116]

Class	Type and No. of subjects	Results
Class I studies		
Piñeyro-López et al,[115] 2009	Class I, 28 subjects (TPM)	Pharmacokinetic sampling up to 6 days per formula Pharmacokinetic and clinical outcomes not significantly different
Privitera et al,[102] 2016	Class I, 35 patients (EQUIGEN chronic-dose study) [multiple regimens of LTG]	No loss of seizure control, no unexpected adverse effects, and standardised side-effect measure scores were not different between generics
Diaz et al,[101] 2013	Class I, 50 subjects (EQUIGEN single-dose study) [LTG]	Bioequivalence among brand to high generic, brand to low generic, and high to low generic shown. No outliers and no serious adverse effects
Ting et al,[100] 2015	Class I, 35 patients (LTG)	Selection of 'generic-brittle' patients. Pharmacokinetic profiles for brand and generic at the end of 2-week treatment period. Generic was bioequivalent to the brand. 32/35 in the ITT group reported no worsening of seizures. Dose-related adverse effects were similar between generic and brand
Class II studies		
Srichaiya et al,[103] 2008	Class II, 28 subjects (LTG)	Lamotrigine used. No significant change in pharmacokinetic and clinical parameters
Class III studies		
Andermann et al,[104] 2007	Class III, 1142 subjects (LTG)	More adverse effects with generic drug
LeLorier et al,[105] 2008	Class III, 671 subjects (LTG)	Higher use of medical services and longer hospital stay with generic drugs
Zachry et al,[107] 2009	Class III, 416 subjects (multiple drugs)	More epilepsy-related acute care required for generic drugs
Duh et al,[106] 2009	Class III, 948 subjects (TPM)	Additional AEDs required if generic drug was prescribed; length of hospital stay was longer
Rascati et al,[108] 2009	Class III, 991 subjects (multiple drugs)	Similar results to Zachry et al in 2009[107]
Labiner et al,[109] 2010	Class III, 33 625 subjects (multiple drugs)	High risk of using medical resources if generic preparation was used, longer hospital stay, and more out-patient visits
Gagne et al,[110] 2010	Class III, 1762 subjects (multiple drugs)	Higher risk of epilepsy-related outcomes
Chaluvadi et al,[111] 2011	Class III, 260 subjects	A higher proportion of patients had to switch back to brand preparations due to adverse effects
Other consensus statements		
Cañadillas-Hidalgo et al,[116] 2009	Not replacing innovative AED by its generic	
Position statement from American Epilepsy Society[114]	Acknowledged the bioequivalence of brand and FDA-approved generic products. Substitution might reduce cost without affecting efficacy	
Position statement from Italian League Against Epilepsy[112]	Automatic switching of brand to generic AED not recommended	
Position statement from French Chapter of International League Against Epilepsy[113]	Uniqueness of epilepsy as a class of disease in which generic substitution is problematic	

Abbreviations: AED = antiepileptic drug; FDA = Food and Drug Administration; ITT = intention-to-treat; LTG = lamotrigine; TPM = topiramate

studies. Of note, these studies had larger sample sizes but all the studies were retrospective in nature. These studies might also have involved a wide range of prescribing practices and some patient factors might not have been taken into account.

Overall, most studies suggested bioequivalence of brand and generic AEDs. This result was also in keeping with a meta-analysis which concluded that if only the highest level of evidence is considered, there is no significant difference in terms of seizure control, whether or not the patient is taking brand or generic products.[117] A UK pharmacovigilance body, the Medicine and Healthcare products Regulatory Agency, issued guidelines regarding the use of generic products in 2013 and specifically divided AEDs into three categories, each of which had specific recommendations regarding the switching of brand to generic products (Appendix).[118] Category 1 relates to products among which a specific manufacturer's product should be ensured (eg phenytoin, carbamazepine, phenobarbital, and primidone). Category 2 relates to products for which generic switching is considered neutral, but clinical judgement should be exercised in so doing

(eg sodium valproate, LTG, OXC, topiramate). Category 3 relates to products for which generic substitution is considered safe (eg LEV, gabapentin) [Table 6[100-116]]. The UK National Institute for Health and Care Excellence guideline[119] recommended that a consistent supply should be made available to the epilepsy patient unless the prescriber, in consultation with the patient, considers that this is not a concern.

We acknowledge the controversy about switching from a brand to a generic product. There appears to be a divide in the positional statements and guidelines between countries with public-funded health care and those with private health care. Many associations, including the Italian League Against Epilepsy,[112] American Academy of Neurology,[114] and the French Chapter of ILAE[113] have expressed concerns about generic substitution of AEDs, emphasising the uniqueness of epilepsy as a class of disease in which generic substitution is problematic when carried out for this indication. The latest position statement from the American Epilepsy Society acknowledges the bioequivalence of brand and FDA-approved generic products and the fact that substitution may reduce cost without compromising efficacy. The Society advises the importance of using either immediate-release or extended-release preparations uniformly throughout the switching process. They acknowledge that tablet or capsule colour or shape may impact drug compliance. They also state that the counselling of switching should include an indication of bioequivalence and not inferiority when the information is conveyed to the patient(s) and their family members.[114]

A pilot study pioneered by the Hospital Authority Head Office on the switching of phenytoin from a generic back to a brand product due to supplier issues suggested that proper counselling and follow-up logistics in conjunction with a pre- and post-drug level at 2 weeks may be adequate for the exercise. In 40 patients recruited from the Prince of Wales Hospital and Queen Mary Hospital, no patients developed a toxic level of plasma phenytoin during the switching process (four patients had a toxic-level pre-switching that remained post-switching). Plasma phenytoin concentration increased in 23 patients and decreased in 17. The conclusion was that there was no consistent trend in the change of plasma drug level (personal communication). Apart from isolated cases of reported dizziness, no serious adverse event occurred. The rate of hospitalisation as a result of the switch in that study was not available to us at the time of writing this review.

Statement 11: There is Level A evidence for generic substitution of LTG (a sodium channel blocker), taking into account the drug's pharmacodynamics and pharmacokinetics.

The HKES upholds the safety of patients above all else. Following a review of the current evidence, the HKES has made the following revisions for the reference of physicians. Doctors can initiate treatment in patients with epilepsy with either a brand or generic product. Switching from a brand to a generic product or between generic products requires great care by clinicians and health care administrators. Automatic substitution at a pharmacy level is not recommended. If switching takes place as a result of cost considerations, prescriber and patient approval must be sought, in liaison with the pharmacist. Prescriber approval is not equivalent to a medical decision. The course of treatment, including choice of drug and dosage, is determined by the doctor and forms part of a medical decision. When the use of generic drugs is based on cost-effective analyses, prescriber approval is a logistic and economic decision. Depending on the type of health care setting, a request for generic substitution may begin with the patient or the health administrator, in liaison with the attending doctor/pharmacist. Patient approval may not be equivalent to medical consent. This can be a requirement of the health care system to which the patient belongs or a self-initiated step from the patient who has subscribed to insurance plans with affordable premiums. The physician should discuss any switch with the patient from both a medical and layman's perspective. Good communication is considered fundamental to the provision of care.[120] Therefore, in a private health care system, the choice for generic drugs may begin with a patient's request, followed by prescriber approval. In a public health care system, the choice for generic drugs may begin with prescriber's request, followed by patient approval. Follow-up and monitoring logistics should be mutually agreed to ensure patient safety. A change in the physical appearance of medications may hinder compliance. This facet of the switch must be taken into account by all parties. In the special situation where switching from a brand to a generic product takes place among patients who have achieved remission while on antiepileptic therapy, clinicians must take into account the drug's pharmacokinetics and the support of medical services. Assistance from nursing staff, enlisting therapeutic blood monitoring, and the option to use the AED as a self-financed item (both public and private setting) should be made available.

Statement 12: Controversy exists over the use of generic products among patients who are currently taking brand medications. Prescriber and patient approval is pivotal. There should be good communication between doctors and patients; enlisting assistance from doctors, nurses, and pharmacists; therapeutic blood monitoring if available; and the option of brand AED as a self-financed item. The physical appearance of generic drugs may hamper drug compliance. Support from

medical services is recommended. In the longer term, the benefit of flexibility and the option to have balanced use of generic and brand drugs may need to be addressed by institutions and regulatory bodies.

Conclusions

New evidence on AEDs has arisen since the publication of the Hong Kong Epilepsy Guideline in 2009. There is Level A evidence for LEV monotherapy and Level B evidence for LCS monotherapy. There is Level A evidence for LCS and PER adjunctive therapy. No change to the level of evidence is evident for LEV, OXC, and PGB. The use of generic preparations of AEDs should be considered following prescriber and patient approval, with support from medical services (doctors, nurses, pharmacists). It is important to emphasise that a generic preparation is not inferior, that shape and colour of tablets may be different, there may be therapeutic blood monitoring (if available), and patients may have the option of self-financing items.

Appendix

Additional material related to this article can be found on the HKMJ website. Please go to <http://www.hkmj.org>, and search for the article.

Acknowledgement

This project was supported in part by an unrestricted grant from the Hong Kong Epilepsy Society.

Disclaimer

This consensus statement is designed to assist clinicians by providing an analytical framework for the drug treatment of epilepsy. It is not intended to establish a community standard of care, replace a clinician's medical judgement, or establish a protocol for all patients.

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