HOW TO IMPLEMENT QUALITY USE OF MEDICINES IN DEVELOPING COUNTRIES—AN EXAMPLE FROM CHINA

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I hereby certify that this thesis is submitted in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a written statement from each co-author; and endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications.

Lan Gao

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CHAPTER 3

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CHAPTER 4

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CHAPTER 5

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GLOSSARY OF ABBREVIATIONS AND ACRONYMS

QUM	-	Quality use of Medicine
EBM	-	Evidence-based Medicine
CMA	-	Cost Minimisation Analysis
CEA	-	Cost Effectiveness Analysis
CUA	-	Cost Utility Analysis
CBA	-	Cost Benefit Analysis
HRQoL	-	Health-related Quality of Life
AEDs	-	Antiepileptic Drugs
RTG	-	Retigabine
LAC	-	Lacosamide
ESL	-	Eslicarbazepine
CAR	-	Carisbamate
BRI	-	Brivaracetam
PER	-	Perampanel
LEV	-	Levetiracetam
LTG	-	Lamotrigine
OXB	-	Oxcarbazepine
TPM	-	Topiramate
CBZ	-	Carbamazepine
WTP	-	Willingness to Pay
QALY	-	Quality-adjusted Life Year
ICER	-	Incremental Cost Effectiveness Ratio
GDP/Capita	-	Gross Domestic Production/Capita
CNY	-	Chinese Yuan
RCT	-	Randomised Controlled Trial
T_2DM	-	Type 2 Diabetes Mellitus
QWB-SA	-	Quality of Well-being Scale, Self-Administered

EQ-5D	-	EuroQol
MMSE	-	Mini Mental State Examination
TTO	-	Time-Trade-Off
SG	-	Standard Gamble
VAS	-	Visual Analogue Scale
CV	-	Contingent Valuation
COI	-	Cost of Illness
MLR	-	Multiple Linear Regression
SD	-	Standard Deviation
IGR	-	Interquartile Range
ANOVA	-	Analysis of Variance
ICC	-	Intra-class Correlation Coefficient

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Abstract

In this thesis, we aimed to evaluate the feasibility to apply the concept of quality use of medicine in developing country at the micro level using China as an example.

When evaluating the technical feasibility of applying quality use of medicine (QUM) principles in a developing country, firstly, we attempted to identify and summarise the clinical evidence on the efficacy and safety of different drugs, to provide the scientific data for formulation of clinical recommendation. Then considering the limitations of the decision making in chronic diseases based on efficacy and safety, we translated and validated a health utility measure (Quality of Well-Being Scale Self-Administered, QWB-SA) in Chinese epileptic patients. Furthermore, to prove the value for money, cost-effectiveness analysis (CEA) studies were performed to ascertain the clinical and economic consequences. Fourthly, for purpose of providing a more transparent CEA threshold to interpret Incremental Cost-effectiveness Ratio (ICER) from CEA studies, an empirical study was carried out to quantify the Willingness-to-Pay per Quality-adjusted Life Year (WTP/QALY) value in epileptic and general populations. Lastly, with the intention to aid the healthcare planning, disease prioritising, and benefit assessment, we undertook a holistic burden of disease study by gauging the economic burden of epilepsy in China.

In these studies, we made several useful findings. First, via the meta-analysis, we found that newer generation of antiepileptic drugs (AEDs) as the adjunctive treatment were more effective than placebo while with higher incidence of adverse effects. Second, we also found out that as a preference-based utility measure, QWB-SA outperformed EuroQol (EQ-5D) in terms of better sensitivity and fewer ceiling effects. Third, even with increased life expectance, QALYs, lower incidences in diabetes-related complications comparing with glimepiride, using the WTP/QALY threshold of CNY 100,000, administration of liraglutide was not cost-effectiveness in China. Fourth, we found that it is feasible to construct the CEA threshold by valuing the utility and WTP simultaneously, and the 1 to 3 times GDP/Capita could potentially serve as the CEA threshold

reference in the Asian region. Fifth, we found that epilepsy is a cost-intensive disease in China from a societal perspective.

In conclusions, this thesis has illustrated how to realise the quality use of medicine at the micro-level in a developing country. Our findings are useful in informing the clinicians and decision-makers to better understanding the importance of quality drug uses and strategies to realise it, particularly for developing countries.

Chapter 1. Introduction and Overview

1.1 National medicines policy

Policy is the set of principles and protocols that guide decision-making with the intent to achieve some pre-specified outcomes. In the area of health, pharmaceutical policy has developed into a specialised discipline whereby policymakers can watch and learn from the interventions and experience made in other countries and regions. During the past 20 years, health policy and more recently, pharmaceutical policy have been a major concern for governments, international organisations, politicians, and the public. Specifically, pharmaceutical policy debates concern issues such as access to medicines, health targets, evidence-based medicine, rationing, resource allocation, innovation and product quality have been encountered frequently worldwide (1).

Practically and theoretically speaking, a national drug policy is an irreplaceable part of national health policy. Nonetheless, not everyone agrees that drug policy should be separated and distinct from health policy. Someone argue that the drug policy is best left to the field of health policy studies, and that the difference between health policy and drug policy is only a question of policy on different levels (1). However, fundamental differences could be found between health and drug policies in terms of four aspects. Firstly, the actors involved are different; secondly, the power relations between professionals and management are different; thirdly, the business and political nature of the actors involved is different; and lastly, the focus of the pharmaceutical profession's work is different from the focus of the professionals providing health care. Generally speaking, the involved parties in these two policies are distinctive, regardless of many similarities (1). Hence, drug policy should be developed independently from but congruent with the overall objectives of health policy.

According to the World Health Organisation (WHO), a national drug policy is a commitment to a goal and a guide for action, and expresses and prioritises the medium- and long-term goals set by the government for the pharmaceutical sector, and identifies the main strategies for attaining them (2). It provides a framework within which the activities of the pharmaceutical sector can be coordinated. A national drug policy will cover both the

public and the private sectors, and involve all the main actors in the pharmaceutical field, and brings health educator, practitioner, other healthcare providers and suppliers, the medicine industry, healthcare consumers and even the media together for optimal healthcare outcomes by focusing especially on people's access to and wise use of medicines. The objectives of a national drug policy are to ensure the access to equitable, available and affordable essential drugs; to make sure the quality, safety and efficacy of all medicines; and also to promote the rational use of therapeutically sound and cost-effective drugs by health professional and consumers (2).

To achieve these objectives, a sound drug policy requires a thorough study and understanding of the problems of the specific context. Formulation of a drug policy requires an understanding of the institutional systems through which pharmacy services and programs are delivered, funded, and regulated, and through which drug policy is made and implemented. In particular, a number of different questions regarding the regulation of safety, efficacy, access, price and equity are addressed in a drug policy analysis and at various levels (1). Inevitably, emergence of new diseases and introduction of new medicines would challenge existing organisational and economic structures. Since the overall goal of a drug policy is to achieve rational drug use, this makes the issues and focus in policy analysis dynamic, and therefore constantly changing (1).

As mentioned above, a national drug policy is a comprehensive framework in which each component plays an important role in achieving one or more of the objectives of the policy (e.g. access to medicines, quality control and rational use of medicines)(1, 2). This policy has to balance the various goals and objectives, creating a complete and consistent entity. For instances, access to essential drugs can only be achieved through rational selection, affordable prices, sustainable financing and reliable health and supply systems. Each of the four components of the "access framework" is essential but not sufficient in itself to ensure access. Similarly, rational drug use depends on many factors, such as rational selection, regulatory measures, educational strategies and financial incentives (2).

Questions relating to drug financing have become increasingly crucial in the formulation and implement of

national drug policy as well (3). For maintenance of population health, cost should not constitute a substantial barrier to peoples' access to medicines they need. Obviously, drug financing secures equity access to drugs, especially for the financially disadvantaged groups in the population. However, to maintain sustainable drug financing in the long-term, it requires a balance between demand, the cost of meeting this demand, and available resources. In practice, all these factors can be manipulated and have to be managed properly. For example, the demand can be altered through improved use of drugs, education, barriers to care and user charges while the cost of meeting the demand can be reduced via improved efficiency and rational use of drugs (2). Available resources can be increased from patient co-payments, prepayment (insurance) schemes, government funding from general tax revenue etc. Thus, balancing these three components is vital for the sustainability of a national drug policy.

As a matter of fact, drug costs constitute an important share of the total health budget. Pharmaceutical's mean share of Gross Domestic Production (GDP) has been valued at 1.2% in OECD countries in recent decades (4). Pharmaceuticals accounted for 15.4% of total health cost, with public spending accounting for about half of this amount (4). Since 1970, the average share of GDP for pharmaceuticals in most countries has increased 1.5% more per year than GDP growth (5). Regardless of obvious medical and economic importance of drugs, there are still widespread problems with lack of access, poor quality, irrational use and wastage. Although for developed or some transitional countries, the quality control and availability of drugs might not be the primary concerns, problems can still exist due to irrational drug uses. Consequently, the illness and suffering are prolonged or even worsened, leading to substantial waste of limited resources. Using Netherlands, a country with low antibiotic uses as an example, overprescribing still occurs as shown in a national survey among GPs. In that survey, six diseases for which national guidelines advised against the use of antibiotics were studied. The percentage of consultations in which GPs prescribed an antibiotic for these diseases ranged from 6% (asthma in children under 12 years) to 67.2% (sinusitis) (6).

At present, quality use of medicines is a case of point in western countries (1). Policy issues initially focused on getting pharmaceutical manufacturers to ensure the quality, efficacy and safety of medicines. As result of the

increasing use of sophisticated medicines which are usually much more costly, the fiscal burden begins weighing on third party payers and patients. The concept of quality use of medicines became extremely attractive as governments and insurers became aware that suboptimal medicine use was one of the major causes of many unnecessary morbidity, mortality and a waste of resources (7).

When implemented properly, quality use of medicines can contribute to the realization of a national drug policy in several ways: promotes long-term drug financing viability, ensures the equity access to drug; boost the healthcare outcomes for patients by avoid unnecessary adverse effects or suffering or diseases; and curbs irrational health care expenditure. Therefore, the promotion of the quality use of medicines becomes one of the critical objectives for most healthcare systems worldwide in formulating a National Drug Policy.

1.2 Rational use of Medicine

Quality use of medicines, which integrates both rational and optimal use of medicines, has become a primary objective for most countries in formulating a national drug policy. For quality use, first and foremost, the drugs have to be used rationally. In addition, the drugs, whether prescribed, recommended, and/or self-selected should be used judiciously, with non-medicinal alternatives considered as needed, to achieve the goals of therapy by delivering beneficial changes in actual health outcomes (8). After all, delivering optimal changes in actual health outcomes for the user is the ultimate goal of quality use of medicines.

Unfortunately, published statistics indicate more than half of all medicines over the world were prescribed, dispensed or sold inappropriately (9). Examples of irrational use of medicines include use of too many medicines per patient, inappropriate use of antimicrobials and failure to prescribe in accordance with clinical guidance. In fact, all drugs, sometimes can be used irrationally by prescribers and patients. Consequently, many of the gains of efficient selection, procurement and distribution can be lost by irrational prescribing as well as by lack of adherence to treatment by the patient. Moreover, irrational drug use has both medical and economic

consequences. In clinical terms, inappropriate treatment may lead to unnecessary suffering and death, to iatrogenic disease and extra hospital admissions etc.(2). From the societal perspective, the consequences of irrational drug use also include a decrease of public confidence in the health care system and negatively impacting on attendance rates of curative and preventive services. Lastly, from the economic terms, an enormous waste of resources could be caused by irrational drug use, which is a large opportunity cost to the healthcare system (2).

The problems related to irrational drug use are complex. Hence, the WHO advocates that it is the government that should take a leading role in developing a clear policy on how to promote rational drug use. This policy should lead to a comprehensive national programme to promote rational drug use by both health workers and consumers, covering both public and private sectors. Due to the high economic cost of irrational drug use imposed on society and the healthcare system, a large public investment in budgetary and human resources would be justifiable (2).

There are two definitions regarding the rational use of medicines. According to the WHO, rational use of drugs refers to that patients receive medications appropriate to their clinical needs, in doses that meet their own requirements, for an adequate period of time, and at the lowest cost to them and their community (2). According to the World Bank, the rational use of medicines integrates two major principles: 1. Use of drugs according to scientific data on efficacy, safety and compliance; and 2. Cost-effective use of drugs within the constraints of a given health system (10). This definition differs from the WHO's in two aspects. Firstly, it explicitly indicates that scientific data needs to form the basis of decision about drug use. Secondly, the World Bank makes clear that drug use should be managed according to the financial capabilities of the society within which the decision is made, whereas the WHO definition states that the medicines chosen should have the lowest cost possible regardless of context (10). Regardless of definition adopted, it is doubtless that rational drug use promotes quality of care and cost-effective therapy.

To facilitate the implementation of quality use of medicine, all stakeholders need to be educated and encouraged to use drugs rationally; some managerial measures may help to ensure implementation; and regulations may be needed to enforce some implementations, especially for the private sector (10). Therefore, strategies to promote rational drug use can be educational, managerial or regulatory.

From a societal perspective, quality use of medicine also requires quality use of limited resources simultaneously. Because resources are scarce and limited, ensuring stable and adequate financing for health care is becoming increasingly difficult as a result of the combined effects of economic pressures, continued population growth and the growing burden of chronic diseases (2). Consequently, it is important to set priority for public funding. For countries with sufficient evidences, health care funding for diseases with greater burdens should be prioritised. For countries with paucity of such information, it would be the most helpful for local authorities to adopt evidence from other countries in an adapted and timely manner.

At the same time, quality use of healthcare resources can be realised by careful selection of essential drugs and reimbursement decision-making as well. Access to essential drugs is a prerequisite for realizing a national drug policy. If available, affordable, of good quality and properly used, drugs can offer a simple, cost-effective answer to many health problems. The essential drug concept is central to a national drug policy because it can promote equity for the health care system. Thus, the core in this concept is that the use of limited number of carefully selected drugs based on agreed clinical guidelines could lead to a better supply of drugs, to more rational prescribing and to lower costs (2). There are several explicit reasons underlying the importance of essential drugs concept. First, essential drugs, which are selected on the basis of safe and cost-effective clinical guidelines, give better quality of care and better value for money. The procurement of fewer items in larger quantities would result in economies of scale and more price competition among suppliers. At the same time, quality assurance, procurement, storage, distribution and dispensing are all easier with a reduced number of drugs. Training of health workers and drug information can be more focused, and prescribers also gain more experience quicker with fewer drugs and are more likely to recognised drug interactions and adverse reactions (2). According to the statistics of WHO, by the end of 1999, 156 developed and developing countries had

national or institutional lists of essential drugs for different levels of care; 127 of these lists had been updated in the previous five years, and 94 were divided into levels of care(2). There are substantial evidences that the use of national lists of essential drugs has contributed to an improvement in the quality of care and to a significant saving in drug cost. For example, one study performed in Korea, where a national drug policy was introduced in 2000, reported that prohibiting dispensing by General Practitioners (GPs) was associated with a reduction in antibiotic used (11). Another study from Chile, where a new regulation prohibiting the dispensing of antibiotics without prescription by private sectors was associated with a reduction in overall sales of antibiotics (12).

Similarly, reimbursement policy also has a direct effect on the control of the healthcare spending. Decision-makers must make funding choices between technologies competing for the same scarce resources during this process. In particular, decision-maker will need the scientific evidence on why to pay for a health technology and how to pay for it on the long-term and also account for equity of access. Obviously, affordable prices would certainly be a prerequisite for ensuring access to drugs either in public or private sector. Actually, due to the fundamental differences in nature between medicines and other consumer products, medicines are unavoidably expensive in both absolute and relative terms. Due to asymmetry in information, medicines are often selected by a physician for a specific patient and reimbursed wholly or partly by a third-party insurer or the government. This can decrease or eliminate price sensitivity for the patient. Moreover, insurance, especially when a state provides universal health insurance for its citizens can lead to strong and sometimes excessive demand (4). Both can create moral hazard. Thus, a well-balanced reimbursement policy significantly contributes to the quality and optimal use of healthcare resources.

Other than the essential drug list, clinical recommendation (or standard treatment guidelines) has probably the most potential to promote rational drug use (13). Ideally, clinical recommendation should cover the most common diseases and complaints for the specific context. It is now generally accepted that clinical recommendation, especially for developing countries, should be developed for each level of care, based on the prevalent morbidities and the competency of available prescribers. As such, it defines the desired prescribing

behavior and constitutes the core of all educational, regulatory and managerial interventions. Most importantly, it also defines the selection of essential drugs and reimbursement policy. As far as possible, the selection of treatment should be evidence-based and take into account local economic realities (14). At the same time, according to WHO, clinical recommendations should indicate the most cost-effectiveness therapeutic approach, on the basis of valid clinical evidence. It is even argued that clinical recommendations have the greatest impact on rational drug uses if the end-users (prescribers and, to a certain extent, patients) are closely involved in their developments. Promising results have been obtained from implementation of clinical recommendations. Compliance with recommended guidelines had been shown to significantly alter malaria and diarrhoea in terms of improvements in consultations and dispensing times (15). However, it is worth noting that the primary goal of clinical recommendations is to improve the quality of care, rather than simply reducing cost (16). Overall, establishing a sound, broad-based programme for quality drug use could lead to better quality of care and improved cost-effectiveness.

1.3 Evidence-based medicine

Since the national drug policy plays a significant role in realizing the goals of overall health, welfare and well-being of society, the evidence base for formulating a drug policy becomes a critical part. It has been widely accepted that applying the concept of Evidence-based medicine (EBM) can serve this purpose. EBM approaches can inform health policy making (17), day-to-day decisions in public health, and systems-level decision such as those facing hospital managers. EBM can also support the appropriate goal of gaining the greatest health benefit from limited resources, which is consistent with the aim of quality use of health resources.

EBM requires the integration of the best research evidence with clinical expertise and patient's unique values and circumstances. By best research evidence, it means valid and clinically relevant research, often from basic sciences of medicine, but especially from patient-centered clinical research into the accuracy of diagnostic tests (including the clinical examination), the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative, and preventive regimens. By clinical expertise, it refers to the ability to use clinical

skills and past experience to rapidly identify each patient's unique health state and diagnosis, their individual risks and benefits of potential interventions, and their personal circumstances and expectations. By patient values, it means the unique preferences, concerns and expectations each patient brings to a clinical encounter which must be integrated into clinical decisions. Lastly, by patient circumstances, it means their individual clinical state and the clinical setting (18).

The definition of evidence in EMB is as follows: any empirical observation about the apparent relation between events constitutes potential evidence. Thus, the unsystematic observations of individual clinician constitute one source of evidence and they are able to provide profound insight even though there are considerable limitations (19). Accordingly, EMB posits a hierarchy of evidence to guide clinical decision-making. The N of 1 randomized controlled trial (RCT) comes first as it can provide definitive evidence of treatment effectiveness in individual patient. The systematic review of RCTs ranks as the second if the methodologically strong RCTs with consistent results have been included, while single RCT may be somewhat weaker (19). On the other hand, observational studies may over-estimate treatment effects in an unpredictable fashion, hence the results are far less trustworthy than those from RCTs' (19). Physiologic studies and unsystematic clinical observations provide the weakest inferences about treatment effects. This hierarchy implies a clear course of action—always looking for the highest available evidence. Together, the highest ranked evidence with other incorporative values (e.g. local circumstances and patient values) can guide clinical experts to develop the recommendation for disease treatment (19).

Actually, the experimental study designs--RCTs are the cornerstones for evaluating the effectiveness and safety of drugs prior to marketing. Recently, investigators have applied standardised methods to the identification, selection and summarization of evidence and to the valuing of outcomes when results from RCTs are inconclusive. Previously, unsystematic approach was used to identify and collect evidence that could lead to biased ascertainment of treatment effect (20). In comparison, systematic review deals with this issue by explicitly stating inclusion and exclusion criteria for evidence to be considered, conducting a comprehensive search for the evidence, and summarizing the results according to explicit rules that include examining how

effects may vary in different patient subgroups (20). When a systematic review pools data across studies to provide a quantitative estimate of overall treatment effect, it is called a meta-analysis. Systematic review provides strong evidence when the quality of the included studies is sound and sample sizes are large. Because judgment is required in many steps of a systematic review (including specifying inclusion and exclusion criteria, applying these criteria to potentially eligible studies, evaluating the methodological quality of the individual studies, and selecting an approach to data analysis), systematic reviews are still subject to bias (20). Nevertheless, with a more rigorous approach to identifying and summarizing data, systematic reviews reduce the likelihood of bias in estimating the causal links between management options and patient outcomes (20). At the very least, a systematic review will restrict the included studies to those that meet minimal methodological standards. For example, systematic review address a question of therapy will often include only RCTs.

1.3.1 Development of clinical recommendations

To develop a clinical recommendation for quality use of medicines, it involves several steps along with the formal strategies for doing so. The first step in clinical decision-making is to define the decision, which involves specifying the alternative courses of action and the possible outcomes. The outcomes of a specific treatment such as to cure or delay or prevent an adverse outcome, are the targets when designing such treatment. However, treatments are associated with their own adverse outcomes—side effects, toxicity, and inconvenience. Ideally, the definition of the decision should be substantially comprehensive—all reasonable alternatives will be considered and all possible beneficial and adverse outcomes identified (20). After identifying the options and outcomes, decision makers must evaluate the links between the two; and ask two questions: "What will the alternative management strategies yield in terms of benefit and harm?" (21, 22) and "How are potential benefits and risks likely to vary in different groups of patients (21, 23)?" Once these questions are answered, making treatment recommendations involves value judgements about the relative desirability or undesirability of possible outcomes. Particularly, values or value judgments refer to the process of trading off positive and negative consequences of alternative management strategies.

Then, evidence should be used to determine the link between options and outcomes in all relevant patient subgroups. To achieve this, RCTs along with other evidence will be synthesized via meta-analysis if necessary. This is critical in determining the strength of the resultant recommendation. RCTs with consistent results can provide unbiased, and provide "Grade A" (strong) recommendation. RCTs with inconsistent result or with major methodological weakness would provide "Grade B" (less strong) recommendation, while "Grade C" (Intermediate-strength) recommendations come from observational studies and from generalizations from RCT in one group of patients to a different group of patients. In addition, the uncertainty associated with the trade-off between benefits and risks will determine the strength of the recommendation as well (24). If the benefits of a treatment outweigh risks obviously both in consequences and costs, experts will recommend this treatment to typical patients confidently, whereas if the balance between benefits and risk bears uncertainty, the recommendation will become weaker (24).

In the next step, the incorporated values are to be integrated to decide on optimal course of action. This process can be achieved via decision analysis or practice guideline (systematically developed statements to assist practitioner and patient about appropriate health care for specific clinical circumstances) (25). Decision analysis applies explicit, quantitative methods to analysing decisions under conditions of uncertainty; it allows clinicians to compare the expected consequences of pursuing different strategies. In other words, decision analysis provides a formal structure for integrating the evidence about the beneficial and harmful effects of treatment options with the values or preferences associated with those beneficial and harmful effects. Most clinical decision analyses are built as decision trees (or Markov models), which usually include one or more diagrams showing the structure of the decision tree used for the analysis (20). Additionally, when a decision analysis includes costs among the outcomes, it becomes an economic analysis and summarises trade-offs between health changes and resource expenditure (26, 27). Practice guidelines, on contrary, place less emphasis on precise quantification than decision analysis. Instead, it relies on the consensus of a group of decision makers, ideally including experts, front-line clinicians, and patients, who carefully consider the evidence and decide on its implications (20). Both decision analysis and practice guidelines can be

methodologically strong or weak and thus may yield either valid or invalid recommendations primarily depending on the strength of the evidence.

1.3.2 Utility

As mentioned above, in formulating a clinical recommendation for a treatment, RCTs serve as the primary evidence for the efficacy and safety outcomes of a specific medication. Meanwhile, assigning preferences to outcomes, especially the patient preferences have become increasingly important (20). Many guidelines are silent on the matter of patient preferences, hence, it may be assumed that these guidelines adequately represent patients' interests. Furthermore, although reported rarely, it also would be valuable to know which principles (e.g. patient preference, distributive justice) were given priority in guiding decisions about the value of alternative interventions (20). This is especially important for a decision analysis, which requires explicit and quantitative specification of values. The values, expressed as utilities, represent measurements of the value to the decision maker of the various outcomes of the decision. Treatment is administered to patients in order to increase longevity, prevent future morbidity, and make patients feel better (28). For feeling better, it encompasses avoiding discomfort, disability, and distress (29). The first two of these endpoints are relatively easy to measure, and clinicians are willing to substitute physiologic or laboratory test for the direct measurement of the third endpoint. However, during the last two decades, clinicians have recognised the importance of direct measurement of how people are feeling and the extent to which they are able to function in daily activities that are associated with health *per se,* which refers to Health-related Quality of Life (HRQoL) (28). We have to admit that under most circumstances, prolonging life expectancy is a sufficient reason to initiate a treatment, though there are exceptions to this rule. If treatment leads to deterioration in HRQoL, patients may be concerned that trivial gains in life expectancy come at too high a cost. This concern is vividly illustrated by patient decisions pertaining to whether to accept cancer chemotherapy that will provide marginal gains in longevity (28). When the goal of treatment is to improve how people are feeling (rather than to prolong their lives) and physiological correlates of patients' experience are lacking, HRQoL measurement is imperative. For example, it is meaningless for studies of antidepressant medication that failed to measure

patients' mood (28). Difficulty in adopting HRQoL outcome is the often uncertainty between physiological or laboratory measures and HRQoL outcome (28). As surrogate endpoints such as bone density for fractures, cholesterol level for coronary artery disease deaths, have often proven to be misleading, changes in conventional measures of clinical status show only weak to moderate correlations with changes in HRQoL (30, 31) and also failed to detect patient-important changes in HRQoL (32). RCTs that measure both physiological endpoints and HRQoL may show effect on one but not the other. For instance, trials in patients with chronic lung disease have shown treatment effect on peak flow rates—without improvements in HRQoL (33, 34). Hence, it is not secure to rely on surrogate clinical outcomes only. Without information about the effect on HRQoL, neither the clinician nor the patient can make a fully informed decision.

Although HRQoL (for the generic, non-preference based instrument, e.g. Short-form 36) allows the comparisons across conditions, it will become questionable for health care policy decisions that involve integrating costs (28). Such decisions require choices about resource allocation across diseases, condition, or medical problems and they inevitably mandate cost considerations. Choosing among health care programs requires standardised comparisons that allow relating the impact of very different treatment modalities on very different conditions. Inevitably, this involves putting a value on health states; and may thus require sophisticated weighting for patient preferences and may necessitate relating health states to anchors of death and full health. Most importantly, such utility measures (preference-weighted or value-weighted, to provide a single number that summarises all the HRQoL) may aid policy makers in making the right decisions about how public money is allocated (28). Since those instruments weigh the duration of life according to its quality, their output can be used to calculate the Quality-adjusted Life Year (QALY). QALY integrates quality and quantity of life into one score, enabling the comparisons across diseases and populations. Most importantly, QALY has become a standard measure of HRQoL in cost-effectiveness research in clinical medicine (35). Particularly, a QALY gained can be divided into two components. Component one is the amount gained due to quality improvement (the gain in HRQoL during the study time period) and component two is the amount gained due to quantity improvement (such as the amount of life extension etc.) (36). Thus, utilities are holistic measures that enable patients to express, in a single value, their preferences for a particular health state. To date, a

number of utility measures are available to quantify these values directly (e.g. Short Form-6D, EuroQol, Quality of Well-Being Scale) but the issue of which of these instruments is the best remains controversial.

1.4 Economic evaluation

In the course of practice, clinicians make considerable decisions about the care of individual patients at the micro level, primarily on the basis of their previous experiences and the results from EBM (as discussed in Section 1.3). At the same time, clinicians also participate in decisions for large groups of patients nationally or internationally at a more macro level (37). When making decisions, it is not enough to only weigh the benefits and risks of a health technology, but also need to prove whether these benefits are worth the health care resources consumed (37). Furthermore, by paying attention to rational use of medicines, the drugs should show cost-effectiveness within the constraints of a given health system (The World Bank) (10). This would contribute to ensuring long-term equality access to those drugs, as well as sustainability of the healthcare system. Evidence has to be convincing for health policymakers that the benefits of the health technologies justify the costs. To serve this purpose, economic evaluation is usually performed.

By definition, economic evaluation is a set of formal, quantitative methods used to compare two or more treatments, programs, or strategies with respect to their resource use and their expected outcomes (38, 39). When performing the economic analysis, if two strategies are analysed but only costs are compared, this comparison would inform the resource-use of the decision and is termed as cost analysis (37). Comparing two or more strategies only by their consequences (such as efficacy and safety endpoints in RCTs) inform only the outcomes proportion of the decision and is termed as cost-consequence analysis (40). A full economic comparison requires that both the costs and consequences be analysed for each of the strategies being compared. The cost estimates are calculated as the summation of the product of physical resources consumed (e.g. drugs) and their unit cost. While all types of economic evaluation measure costs almost in the same way, depending on way benefits are measured, the following four types of full economic evaluations are

distinguished (40). However, it is worth mentioning that for the reimbursement policy making, cost utility analysis (CUA) is usually adopted as the supporting evidence.

- Cost minimization analysis (CMA): the evaluation is based on the assumption that the outcomes of the compared health technologies are equivalent thereby resulting in an assessment based solely on comparative cost.
- Cost effectiveness analysis (CEA): the health benefits are measured in natural or physical units.
- Cost utility analysis (CUA): the benefits of an intervention are measured in a more comprehensive way than CEA by combining both effects on morbidity (quality) and mortality (quantity) in a single preference-weighted index using health utilities. This is usually expressed as QALY, disability adjusted life years (DALYs) or healthy years equivalents (HYEs).
- Cost benefit analysis (CBA): the benefits are valued in monetary term, which is the same units as costs, through techniques such as contingent valuation. CBA provides a broader comparison between alternative claims on limited societal resources, enabling such comparisons to be made between treatment options within healthcare and even with options in other public sectors (41).

In consistent with construction of treatment recommendations, economic evaluations typically take estimates of treatment effect from RCTs. Evidence on effectiveness may come from systematic reviews of clinical studies or from a single study (37). In the former case it is important that reasons for inclusion and exclusion of studies from the systematic review are given. In the latter case it is crucial to consider whether the estimated treatment effect from a particular trial is representative of the whole body of evidence for the treatments concerned.

Corresponding to the data sources of effectiveness, there are primarily two approaches to compute the costs—from patient-level data (which collects the data alongside RCTs) (42) or decision analytic modelling (43). For the patient-level data, it is subject to a number of limitations. Firstly, RCT, with the intention for product licensing, typically adopts placebo as a comparator. However, placebo would not be a relevant comparison for the economic question because they do not reveal the incremental impact of the new drug on population health

relative to existing therapeutic agents. In addition, the majority of RCTs are designed to detect differences in one or more intermediate biomedical markers (such as level of blood pressure, lipids) as substitutes for the final health outcomes. Knowing that an intervention has a positive impact on intermediate surrogate outcome marker is not sufficient to show cost-effectiveness and the impact on final health outcomes such as mortality and morbidity and these will have to be indirectly quantified. Thirdly, the normally inadequate follow-up time and the sometime small sample size of RCTs pose another issue. In comparison, decision analytic modelling, which provides a framework for bringing a range of data sources (e.g. RCT, clinical, cost and HRQoL data) together, offers a promising answer. It can provide a structure that approximately reflects the possible prognoses that individuals of interest may experience, and how the treatments being evaluated may impact on these prognoses. It can also offer a means of translating the relevant evidence into estimates of the cost and effects of the alternative options being compared; and facilitates an assessment of the various types of uncertainty relating to the evaluation.

Generally speaking, economic evaluation is concerned with the process of measurement through the collection of data relating to effectiveness, resource use, unit costs, and utilities. Ultimately, it is concerned with informing appropriate decisions in health care about resource allocation under condition of uncertainty.

1.4.1 Willingness-to-Pay (WTP)/QALY threshold

From the CUA/CEA studies, cost per unit of outcome ratios, that is incremental cost-effectiveness ratio (ICER), can be derived that depicts the costs required to obtain one QALY. There are a couple of approaches to interpret the ICER. In an ideal world of complete information, data indicating the forgone health (or other) outcomes from other interventions or programs, within and outside health care, would be readily available (37). Nonetheless, actually, such kind of data is very limited. Alternatively, investigators have proposed a variety of second-best interpretative strategies. One approach assumes that previous decisions to adopt new medical therapies of known cost-effectiveness reveal an underlying set of values with which to judge the acceptability of the current treatment candidate (37). However, CEA studies may differ in terms of methods, data and

assumption, which make the straightforward comparison of ICER problematic. The other approach is to use a WTP/QALY threshold. If the ICER of a particular treatment falls below a WTP/QALY threshold of a specific context, this treatment is considered cost-effectiveness. Nevertheless, countries varying in social, cultural, political and economic statuses may differ with respect to the value they place on health benefits vs. other commodities. There is no reason why $ 50000 per QALY as an acceptable cost-effectiveness threshold for the United States is applicable to a less-industrialized country, say, China, where the opportunity cost of such resources will be much lower. It has been well recognised that the governments of various countries vary in their WTP for health and health gains. Therefore, it is critical to choose an appropriate cost-effectiveness threshold that reflects the acceptable value of health gain within a specific decision-making context.

As discussed above, the advantage of QALY as a measure of health outcome is that it can simultaneously capture gains from reduced morbidity (quality gains) and reduced mortality (quantity gains), and combine them into a single measure. Moreover, the combination is based on the relative desirability of the different outcomes. This way the more desirable (more preferred) health states receive greater weight and will be favoured in the decision analysis.

To define the cost-effectiveness threshold, contingent valuation (CV)—WTP, is usually used. As the name suggested, contingent valuation studies use survey methods to present respondents with hypothetical scenarios about the program or problem under evaluation. Theoretically, in contingent valuation, respondent has to consider what he/she would be willing to pay, and thereby sacrifice in terms of other commodities, for the program benefits if they were in the market place (44). WTP is a measure of value based on the premise, central to economic theory, that the value of a good is simply what it is worth to those who consume it or benefit from it. The amount an individual is willing to pay for a particular good may be higher, or lower, than the cost of that good. In the case of market goods, the comparison between the price of the good and the individual's WTP for it determines whether or not he or she will buy the good.

WTP to avoid an illness contains several components. The benefits from a healthcare program may include intangible benefits (which are the value of improved health *per se*), future health care cost avoided and increased productive output due to improved health status (44). One restricted perspective on WTP is that it would be used only to value those components of benefit for which no money values existed from other market source. Therefore, in this scenario, WTP estimates are restricted to quantifying the money value of changes in health *per se*, with future health care cost savings and production gains being valued using market prices (e.g. human capital calculation). This type of WTP can also reflect the intangible cost due to a disease or disorder. Alternatively, a global perspective on WTP is to gauge the monetary value of anticipated health benefits, future out-of-pocket saving (cost offsets from other medications), and income effect (costs associated with work absence or early retirement). As such, the global WTP approach is able to value the health program from a societal perspective.

Despite the popularity of CV in valuing healthcare benefits, there are issues with the obtained WTP estimates. First, the estimates obtained can vary substantially by the elicitation method used (e.g. ex post and ex ante perspectives can create different WTP values). Second, it is important that the WTP estimates obtained are relevant to the decision-making context. Nevertheless, in spite of these issues, this approach is now firmly established within the research community (44), and WTP studies could provide valuable information to policy makers on the magnitude of individuals' preferences and may better reflect societal value (44).

1.5 Burden of disease

Even if a drug has outweighing benefit against risks stemmed from strong evidence along with an acceptable ICER for a specific context, for the health policy decision-making (e.g. whether include this drug into the essential drug list or reimburse it), the answer is not necessarily positive. Another important contributor of quality use of medicines cannot be neglected as well. Given the constraints within a health care system, either for selection of essential drugs or national drug financing, it is important to set priorities (2). The knowledge

on the burden of disease can serve this purpose. In addition to this, evidence on burden of disease can also help to ensure the equity access to health care technologies, which is an essential objective of national drug policy. By definition, equity means a desire to share benefit and cost fairly across the community as much as possible. Given the restrictions on health care resources, it is impossible to satisfy everyone in the health system (45), the general policy in either essential drug selection or reimbursement decision-making is technologies that target at more burdensome diseases are given priority, all other things being equal (46).

Burden of disease could be gauged in terms of three aspects: epidemiological level (morbidity, mortality), economic level (cost of illness study) and humanistic level (HRQoL). Public health specialists have monitored the burden of certain diseases for many decades with epidemiological parameters such as prevalence, incidence and mortality (47). Epidemiological data can answer the question "how big is the health problem?" in a specific country. However, it cannot always reflet accurately the magnitude of resource consumption and humanity loss, caused not only by fatal effect but also by non-fatal effect of disease. Meanwhile, HRQoL can give us an overview on the impact of the disease at the population level. But to aid the health care planning, resource allocation, regulatory development and benefits assessment, measuring the burden of disease in the economic level would be most helpful. Cost-of-Illness (COI) study is normally performed as an effective measure of burden of disease (48), which translates simple descriptive epidemiology parameters into a measure of resource use and productivity loss in monetary terms. It can provide an efficient lower-bound estimate of the benefits of avoiding an illness (49). The value of cost of illness studies can be seen via their frequent uses by policy-makers. For example, in response to a request from US Congress, the National Institute of Health (NIH) released a report on the updated costs of illness for numerous diseases in 2000 (49). Another study of the cost of injuries was used to motivate Centres for Disease Control and Prevention (CDC) requests for proposals for injury centres (50, 51).

In fact, numerous cost-of-illness studies have been conducted and instrumental in public health policy debates because they highlight the magnitude of the impact of an illness on society or a part of society (50). For specific stakeholders, such as government, such knowledge can show the financial impact a disease has on public

programs (52, 53). For employers, they can show which diseases have an especially large effect on their costs (54, 55). Knowledge of the burden of an illness can help policy makers to decide which diseases need to be addressed first by the health care system.

Theoretically speaking, a comprehensive COI study would include both direct and indirect costs, although the specific focus of a study may make one or the other unnecessary. Direct costs measure the opportunity cost of resources used for treating a particular illness, whereas indirect cost measure the value of resources lost due to a particular illness. By definition, opportunity cost is the value of the forgone opportunity to use in a different way those resources that are used or lost due to illness (56). In particular, direct cost includes direct medical cost (hospitalisation, outpatient care, medications, diagnostic test etc.) and direct none-medical cost (transportation, relocation etc.). Mortality cost, morbidity cost, and informal care cost are summarised for the estimation of indirect cost. Another cost component is the intangible cost, though it is rarely reported. Intangible cost includes pain, suffering, anxiety or fatigue because of an illness or the treatment of an illness. Intangible cost could be measured through the utility or WTP approach (44).

In summary, COI studies can demonstrate which disease may require increased allocation of prevention or treatment resource, but they are limited in determining how resources are to be allocated because they do not measure benefits. Thus, along with CEA, CUA or CBA studies, COI studies can represent an important analytic tool in public health policy formulation.

Thesis overview

It has been pointed out that the health system is in the midst of a long term and fundamental shift in balance from services to technologies, from personal services provided by doctors, nurses and hospitals to technology embodied in medicines, as well as equipment and procedures (57). Therefore, with the increasing use of medicine, the health outcomes would be better if we use the existing and new medicines wisely, rationally and optimally. In order to realise the quality use of medicine, according to the introduction, it is important to practice two principles: firstly, use of drugs according to scientific data on efficacy, safety and compliance; and secondly, cost-effective use of drugs within the constraints of a given health system. In another word, quality use of medicines helps to achieve both the cost-effectiveness use of medicines for specific indications and also ensure that everyone in the community gets and uses properly the best medicines for them and achieves the optimal changes in actual health outcomes. Clinical recommendation, essential drug list, and reimbursement policy are regarded as the important means to achieve the quality use of medicine. Among these three strategies, clinical recommendation plays the central role as it can define the scope for the other two. Hence, identifying the evidence to formulate a clinical recommendation becomes critical. It has been recognised that EBM can serve this purpose, by integrating the best evidence with the clinical expertise as well as patient's unique value. Stronger evidence can support the formulation of stronger recommendation to a large extent. Normally, the methodologically sound RCTs with consistent results can be rated as "Grade A" evidence. For individual jurisdiction, to formulate a clinical recommendation for a particular disease, it would be ideal to extract efficacy and safety outcomes from RCTs that recruited participants locally because the heterogeneity in characteristics may lead to variability in response to certain medicines. However, such kind of data is not always readily available for each jurisdiction, which hinders the timely access to the new drugs. Fortunately, at present, the efficacy of new drugs is usually tested through multinational clinical trials for many years, which provides the acceptable evidence for cross-country comparison. Thus, with this trend becoming more prominent overtime, it would be much easier and acceptable to adopt efficacy and safety data for local use. This is particularly important for developing countries.

Subsequently, how to identify and summarise the evidence from numerous RCTs becomes the first concern of this thesis (Chapter 2). Epilepsy, as the most common neurological disorders affecting people of all ages from infants to the elderly, has a prevalence rate ranging from 0.52% to 1.5% and incidence between 70 and 100 per 100,000 from younger adults to the elderly (58-60). The treatment modality for this population is mainly antiepileptic drugs (AEDs) (61), though Vagal Nerve Simulation (VNS) and surgery are sometimes applied as well. In terms of treatment effectiveness, about 50% of patients will achieve seizure remission on their initial monotherapy. This is followed by another 15 to 25% of patients who might obtain seizure remission after one or more treatment modalities have been made, and the remaining 20 to 30% patients would not achieve satisfactory seizure remission (60, 62). In the last two decades, a series of new generation AEDs has been marketed worldwide primarily targeted at patients with persistent seizures. But, no consensus has been reached as to whether to recommend them for routinely clinical use. Therefore, in this chapter, we aimed to identify and synthesise the efficacy (seizure free and responders' rates) and safety endpoints and perform a systematic review and meta-analysis of newer generation AEDs as adjunctive treatment for patients with refractory partial-onset seizures. By doing so, we intended to illustrate the first step in formulating a clinical recommendation in support of quality use of medicines by adopting published data for local use.

Nonetheless, in clinical decision-making, it is not enough to only consider the advantages and disadvantages when administer a medication as the evidence alone cannot determine the best course of action. Most would agree that the values and preferences that the clinician must use to balance the risks and benefits should be those of the patient. This is especially the case for treatment aimed at chronic diseases (e.g. epilepsy, diabetes, coronary artery disease etc.), as the vast majority of currently available medicines cannot cure the disease, but to delay the progression and improve the quality of life and reduce the chance of disability. Therefore, the patient value for the healthcare outcomes actually should be treated as equally important as efficacy and safety. This has been vividly illustrated by patient decision regarding whether to accept toxic cancer chemotherapy that will provide marginal gains in longevity (28). To assess the patient values, the HRQoL is usually measured. Most HRQoL questionnaires (e.g. disease-specific HRQoL tools) describe the resultant health states in a way that is sufficient to inform clinicians and patients, but they do not quantify how much individuals or society

value specific health states. Thus, utility measures that have the preferences or values anchored to death (0) and full health (1.0) are preferable not only because they summarise all the aspects of HRQoL, but also because the utilities can be compared across diseases, conditions, or medical problems. Last but not least, it can be used to calculate Quality-adjusted Life Year (QALY), which is widely adopted as the effectiveness outcome in the economic evaluation. Therefore, utility measures are holistic that ask patients to express, in a single value, their strength of preferences for particular health states, more specifically, the more preferable an outcome, the more utility associated with it. In lieu of this, to measure the patient's preferences using acceptable, valid and reliable instruments emerge as the primary concern in this thesis. Furthermore, even though different HRQoL instruments are designed to measure the same psychological construct, HRQoL have different descriptive systems and algorithms for utility score generation. Subsequently, comparisons between the performances of these instruments can at least provide evidence when integrating patient values into the clinical decision-making.

In order to address the aforementioned objectives, we recruited patients with epilepsy from two tertiary hospitals in China and applied two widely used health utility measures, QWB-SA and EQ-5D to assess the validity and comparability of these two instruments. The epileptic patients were chosen because as a chronic disease, the primary treatment goals for antiepileptic care are to reduce the seizure frequency and improve the quality of life. Hence, in choosing an AED for individual patients, the patient values should be incorporated. China, as the selected research field in our study, is a country with the fastest economic growth for nearly three decades. There is also the corresponding growth in the healthcare expenditures. According to the national statistics (National Health and Family Planning Commission of the People's Republic of China) in 2012, the total health care cost was CNY 2891.44 billion (USD 463.72 billion) (1 USD=6.2353 CNY, December 2012). However, it is not a common practice to take patient values into consideration either at individual or population level when making clinical recommendation in China. This can be seen through the small quantity of utility measures that are available in Chinese-language. So the translation and validation of health utility measure would help to fill this gap. Besides, as the growing awareness of the importance of HRQoL for patients, clinicians and policy-makers would require such information to aid with decision-making process at micro and macro levels in

China. Our study was hoping to offer such reference utility data source in this area. Hence, in Chapter 3, we aimed to translate, culturally adapt and validate a health utility measure in Chinese epilepsy patients, and compare the performances of QWB-SA and EQ-5D.

Given the constraints on healthcare budget, cost containment is always an important concern for the policy-makers. When considering whether to recommend a drug, it is not enough to weigh between benefits and risks only. The drug has to prove the benefits justify the increased cost, which is one of the objectives of quality use of medicine. To answer this question, an economic evaluation is then performed. As discussed in the Chapter 1, there are two approaches to conduct an economic evaluation, using patient-level data (collected data along with a clinical trial) and decision-analytic modelling (pooling data from different sources). In Chapter 4, we used the latter approach (decision-analytic modelling) to evaluate the treatment and economic consequences of liraglutide applied in patients with Type 2 Diabetes Mellitus (T_2DM) from Chinese health care system perspective. With the largest population size in the world, the health resource is stretched to the limit in China. Taking T_2DM as an example, to date, there are about 20 million diabetes sufferers in China, and the number is expected to reach 50 million in 2025 (63). However, the acquisition costs for liraglutide is high when compared to other available anti-diabetic treatments. Even it has been licensed for market use, it is does not mean the administration of liraglutide is cost-effective in the long-term. Therefore, it is imperative to ascertain the economic consequences of liraglutide and assist to decide the place of liraglutide in the clinical recommendation for T_2DM.

The primary outcome from economic evaluation, especially the CEA/CUA studies, as previously mentioned is an ICER. In order to interpret the ICER, each jurisdiction will need a stated threshold to serve as a transparent and consistent decision rationale when making a clinical recommendation or reimbursement policy. Generally, an explicit threshold of CEA can be proposed by individuals or institutions, estimated from WTP studies, or gleaned from retrospective analysis of previous resources allocation decisions (64). When it comes to Asian countries, which are at the starting point to apply health economic evaluation to the clinical recommendation

and reimbursement policy makings, there are insufficient cases and records that can be traced for retrospective analysis and few WTP research evaluating the monetary value of QALY performed to date (65, 66). An easy option of setting threshold of CEA in these countries would be to adopt GDP/Capita values proposed by WHO, which claimed to be based on the expected direct and indirect benefits to national economies. However, controversies still abound with this suggested threshold, with researchers arguing that it might be too arbitrary to apply to all settings (67). In addition to this, the relationship between WTP/QALY from empirical studies and GDP/Capita still remains the subject of debate (64, 67). The CEA threshold is critical in determining the cost-effectiveness of a health technology. Consequently, it will contribute substantially to the quality use of medicines as a cornerstone. As such, more empirical studies with the intention to ascertain the CEA threshold is urgently needed. In Chapter 5, an empirical study recruiting both epilepsy patients and general population was conducted to quantify the WTP/QALY threshold in China.

In the former chapters, to realise the quality use of medicine, we have demonstrated how to identify and summarise the evidence to formulate clinical recommendation and make reimbursement policy, to integrate patient values into this process via measuring utility, to evaluate the cost-effectiveness of medicines, to interpret the ICER, and to set CEA threshold via empirical research. However, they cannot inform how to prioritise the diseases to promote the equality access and maximise utility of available health resource. As discussed in the Chapter 1, COI study, which gauges the burden of disease at the economic level, is an important analytic tool for healthcare planning, benefit assessment, and formulation of prevention policy. Therefore, in Chapter 6, a COI study was performed to gauge the direct, indirect and intangible cost due to epilepsy in China with the intention to provide a reference point for decision-makers. According to a literature review (68), the estimated epilepsy population is approximately 4 million in China. Although the epilepsy is not ranked as the top ten chronic diseases in China (National Statistics), the notorious effect of epilepsy on psychological well-being and work capability may lead to substantial increase in indirect and intangible costs. In this case, our study was hoped to offer a comprehensive picture on the total economic burden of epilepsy in China, which can serve as the important evidence for the health policy planning.

In summary, in this thesis, firstly, we showed how to identify and synthesise the clinical evidence in order to formulate a clinical recommendation, which is the critical step in the quality use of medicine. The evidence plays a key role in clinical recommendation formulation, essential drug selection, and reimbursement policy making, whereas the clinical recommendation is the guidance for essential drug selection and reimbursement policy making. Then, beyond the efficacy and safety concerns, clinicians and policy-makers also need to integrate patient values into the clinical decision-making, as it has been increasingly realised that weighing between treatment benefits and risks alone cannot always lead to the best health outcome, especially for patients with incurable or chronic diseases. Thus, we translated and validated a health utility tool to provide a useful instrument for either clinical or policy-level use. An economic evaluation was then performed to ascertain the economic consequences of administration a drug, with the intention to justify the value for money. Consequently, we also attempted to set a transparent CEA threshold via empirical study for the interpretation of ICER from the economic evaluations. Finally, a COI study was conducted to reflect the economic burden of epilepsy in China. All these efforts aim to demonstrate the process of implementing quality use of medicines and help to accelerate the timely access to advanced treatment in a developing country. Details of individual studies designed to address these objectives would be presented in the subsequent chapters in the form of publications. Following is a list of the main research contents to be presented in this thesis:

Chapter No.	**Research Topic**
2	Developing clinical recommendations and selecting essential drugs--Identifying and summarising the efficacy and safety evidence (systematic review and meta-analysis)
3	Beyond the efficacy and safety outcomes, incorporating patient values into clinical decision-making -- Validation and comparison of health-related utility measures
4	Are the benefits worth the money? Providing the evidence by economic evaluation – example of Cost-effectiveness analysis
5	Interpreting the incremental cost-effectiveness ratio – Quantifying the WTP/QALY threshold –Epilepsy
6	Prioritising the diseases and promoting equality --a Cost-of-Illness analysis --Epilepsy
7	Conclusions

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Clinical efficacy and safety of the newer antiepileptic drugs as adjunctive treatment in adults with refractory partial-onset epilepsy: A meta-analysis of randomized placebo-controlled trials

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RCTs

Summary
Objective: To evaluate the clinical efficacy and safety of the newer antiepileptic drugs (AEDs), namely, Eslicarbazepine (ESL), Retigabine/Ezogabine (RTG), Carisbamate (CAR), Lacosamide (LAC), Brivaracetam (BRI) or Perampanel (PER) as adjunctive therapy for adults with partial-onset seizures (POS).
Methods: A systematic review of Randomized placebo-controlled Trials (RCTs) of newer AEDs was conducted. Electronic databases and identified bibliographies were searched to retrieve RCTs. The primary outcomes were responder rates and withdrawal rates, adverse effects. Pooled effects of Odds Ratio (OR), Risk Ratio (RR) and Risk Differences (RD) were derived from meta-analysis implemented in Revmen 5.1.
Results: In total, 15 RCTs were included. All the studies contained a baseline and treatment phase. The pooled OR of all newer AEDs vs placebo was 2.16 (95%CI: 1.82, 2.57) for responder rates, 1.54 (1.12, 2.10) for withdrawal rates, 1.67 (1.34, 2.08) for adverse effects. The indirect comparisons between individual newer AED and all other newer AEDs suggested the similar results in responder rates (ORs, BRI 1.79 [—1.50, 5.08], RTG 1.41 [0.49, 2.33]).
Conclusions: The pooled ORs suggested newer AEDs might be more effective than placebo while with higher incidence of adverse effects. The indirect comparisons suggested BRI, followed by RTG, might be more effective than all other newer AEDs, which could be confirmed by future clinical studies.

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Introduction

Epilepsy is typically characterized by recurrent and unprovoked seizures (without any immediate identified causes) (Costa et al., 2011) caused by abnormal transmission of electrical signals and neuronal activity in the brain. Antiepileptic drugs (AEDs) can usually provide satisfactory control of symptoms for most of patients. Generally, about 50% of patients will achieve seizure remission on their initial monotherapy, seizure remission in another 15—25% of patients might be obtained after altering/adding one or more treatment modalities, and the remaining 20—30% patients would not achieve satisfactory seizure remission. Thus, patients without satisfactory seizure remission on two or more different AED therapies are usually defined as having refractory epilepsy (Begley et al., 1994; Preux and Druet-Cabanac, 2005). During the last decade, a number of newer AEDs with more desirable safety profile have been introduced into the market in order to offer better seizure control for patients with epilepsy, especially for those with refractory epilepsy. Consequently, add-on therapy with newer AEDs is now considered standard care for patients with refractory epilepsy (French et al., 2004).

In seeking market approval for these newer AEDs, pharmaceutical companies have provided the results of many randomized controlled trials (RCTs) as supporting evidence. Hence, there are quite a number of RCTs comparing the newer AEDs with placebo as adjunctive treatment for patients with partial-onset seizure. Not surprisingly, almost all the RCTs showed the newer AEDs offer better seizure control and demonstrate acceptable safety and tolerability in this population (Castillo et al., 2000; Chaisewikul et al., 2001; Costa et al., 2011; Jette et al., 2008; Lozsadi et al., 2008; Pereira et al., 2002; Ramaratnam et al., 2001; Saconato et al., 2009). However, due to relatively small number of enrolled participants in individual study and the lack of head-to-head comparisons between these newer drugs, uncertainties about the claimed efficacy or safety of the newer AEDs over traditional ones still exist. Furthermore, doctors would need strong evidence to justify the price of prescribing these newer interventions. It would be difficult for physicians to choose from many newer AEDs with all confirmed to be more effective than placebo.

To provide this information, we have conducted a systematic review and meta-analysis to synthesize the evidence regarding the magnitude of efficacy, safety, and tolerability of add-on newer AEDs in treating the refractory partial-onset seizure patients when compared to placebo, and to ascertain whether the newer AEDs are more effective than existing AEDs.

Methods

Data sources

An electronic literature search was performed using terms as followed: seizure(s), epilepsy, partial-onset epilepsy/seizures, refractory, adults, adjunctive/add-on therapy/treatment, double-blind, placebo-controlled, randomized trials, RCT (controlled) clinical trial, with one of following newer AEDs: Eslicarbazepine (ESL), Retigabine/Ezogabine (RTG), Carisbamate (CAR), Lacosamide (LAC), Brivaracetam (BRI) or Perampanel (PER) as an extension in Embase, Medline, Cochrane database from inception to the 30th January, 2012. These six AEDs were selected as they were introduced or invented within the last four years, and represent the newest generation of antiepileptic medication.

Additionally, a manual search was also conducted to retrieve additional literature from the bibliography of the identified articles from the electronic search.

Inclusion criteria

There were predefined criteria for the inclusion of relevant studies:

(1) Written in English and full text available.
(2) Adult participants who have failed at least one to two kinds of AEDs were explicitly diagnosed with partial-onset epilepsy according to the guideline of International League Against Epilepsy (ILAE).
(3) Double-blinded studies with a matched placebo or at least included a double-blinded, placebo-controlled arm.
(4) Reported the responder rate (50% reduction in seizure frequency comparing to baseline) and number of total patients in each group.
(5) The treatment duration was more than 4-weeks with at least 30 patients in each arm.

Data extraction

Information to be extracted included: the study design, drug dosage(s), patients' characteristics, diagnosis criteria, number of Intention to Treat (ITT) population and safety population. Primary outcomes information included: responder and seizure free rates (both comparing to baseline), withdrawal rates and withdrawal due to adverse effects, and adverse effects rates. Secondary outcomes information included: predefined adverse effect rate for dizziness, somnolence, fatigue, headache, nausea, and ataxia.

Two reviewers (LG and FLZ) independently performed the data extraction process while resolving any discrepancies via discussion. Only mutually agreed data were included in the analyses.

Definition

There is no unanimously accepted diagnosis guideline for refractory partial-onset epilepsy. Empirically, in our study, refractory partial-onset epilepsy was referred to patients who failed to respond to at least one or two kinds of AEDs before enrolled in the studies while still suffered more than 4 seizures per 28 days prior to the baseline of each research.

Data analysis

The Revman 5.1 software was utilized to perform the meta-analysis. In order to compare the newer AEDs with placebo, we used the random-effect of weighted Mantel-Haenszel

method to estimate the pooled Odds Ratios (ORs) and 95% Confidence Intervals (CI). In addition to this, where applicable, the Risk Ratios (RR), Risk Difference (RD) or Number Needed to Treat (NNT) with 95%CI of primary variable were also presented for better understanding.

Subgroup analyses were also conducted to detect the difference in various drug doses. Heterogeneity was assessed via the I^2 test that measures the percentage of total variation across studies due to heterogeneity (Deeks et al., 2001). A percentage of 25%, 50%, 75% indicates low, medium, high heterogeneity (Deeks et al., 2001). Additionally, we performed adjusted indirect comparisons between each newer AED and the pooled effect of all other AEDs utilizing the Bucher frequentist method (Bucher et al., 1997).

Results

Included studies for the meta-analysis

At first, 151 studies were identified. After reading the title of retrieved studies, 75 studies were excluded due to irrelevance. Then a careful reading of abstracts eliminated a further 57 papers, leaving 19 studies meeting the predefined inclusion criteria. However, 4 studies just providing the abstracts (Hirsch et al., 2010; Porter et al., 2005; Sperling et al., 2008; van Paesschen and von Rosenstiel, 2007) without other available details were subsequently excluded. Finally, 15 RCTs compared the target newer AEDs with placebo were included in the meta-analysis (The culling process was shown in Fig. 1). The characteristics of the included studies were summarized in Table 1.

Primary outcomes

New AED vs placebo

Responder rates

Responder rates were higher in all newer AED groups when using placebo as comparator, regardless of dosage. The pooled ORs ranged from 1.49 (95%CI: 1.19, 1.88) (in the case of CAR) to 3.78 (95%CI: 1.73, 8.26) (in the case of BRI). Heterogeneity was low among those synthesized studies (between 0% and 3%) (Fig. 2) (RR, RD and NNT with 95% CI are presented in Table 2).

Seizure free rates

In terms of seizure free rates, the combined outcomes also favored the newer AEDs over placebo, with ORs ranged between 2.20 (95%CI: 0.72, 6.74) (in the case of LAC) and 4.48 (95%CI: 0.57, 35.29) (in the case of BRI). In consistency with responder rates, the seizure free rate enjoyed a low heterogeneity as well (0% in all synthesizes) (Fig. 4).

Safety outcomes

Excepted for BRI (ORs for withdrawal rates was 3.44 [95%CI: 1.01, 11.72], and AEs was 1.29 [95%CI: 0.69, 2.40]), the pooled effects of all the other newer AEDs reflected lower odds than placebo in safety outcomes. For instance, the ORs for withdrawal rates ranged from 0.36 (95%CI: 0.18, 0.72) (LAC) to 0.89 (95%CI: 0.56, 1.40) (ESL), accompanied with adverse effects varied between (ORs) 0.44 (95%CI: 0.26, 0.75) (LAC) and 0.84 (95%CI: 0.42, 1.70) (PER). Whereas, PER had a favorable profile over placebo in withdrawal rate with OR 1.17 (95%CI: 0.45, 3.05) (Figs. 3—5).

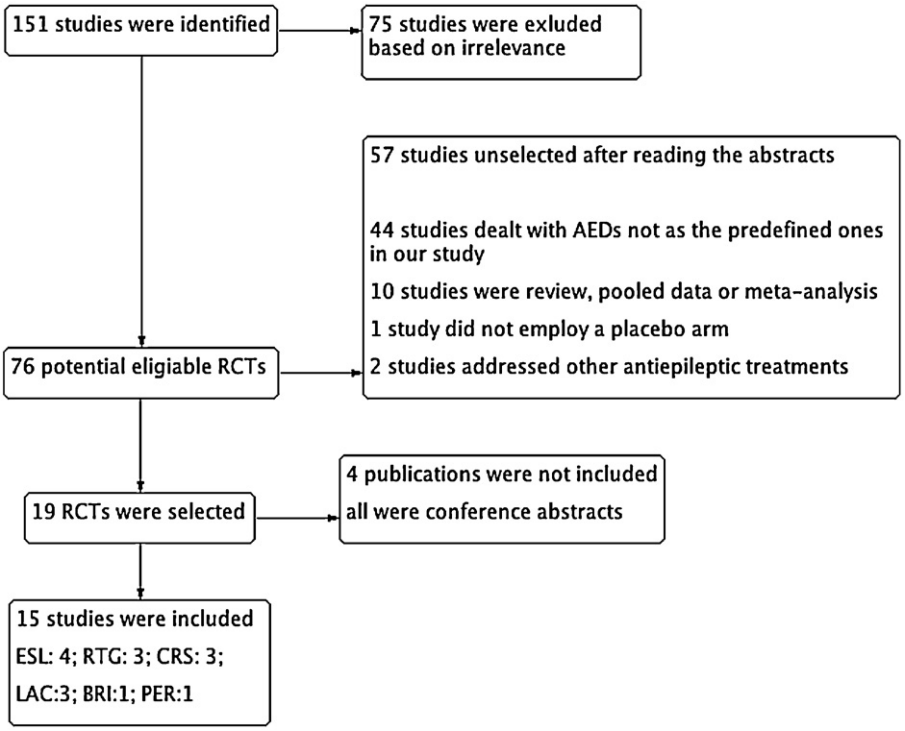

Figure 1 Study selection process.

Table 1 Characteristics of included studies.

Included studies	Number of patients (ITT)	Study design	Prior AEDs (median range)	Baseline AEDs, number and type	Duration of epilepsy (Mean ± SD or range)	Patient age (Mean ± SD or range)	Gender (%male)	Drug dosage	Seizure types subgroups (%)			
									Simple	Complex	PT-GN	UC
Eslicarbazepine												
Elger (2007)	143	8-week baseline	POS	1 or 2	16.7 ± 11.7	39.3 ± 11.4	44	1200 mg QD	34	72	80	NA
		12-week treatment		VPA, TPM, LTG,	19.5 ± 12.6	39.8 ± 11.9	35	600 mg BID	37	71.7	80	NA
				CNZ, PHT	20.0 ± 13.6	40.4 ± 10.8	43	Placebo	28	80.9	72	NA
Elger (2009)	397	8-week baseline	POS	1 or 2	19.4 ± 12.57	37.0 ± 11.93	48	Placebo	44	69.6	47	3.9
		2-week titration		CBZ, LTG, VPA,	21.0 ± 11.70	37.8 ± 11.43	50	400 mg QD	43	69	40	4
		12-week maintenance		LEV TPM, PHT	23.1 ± 13.50	41.3 ± 12.04	54	800 mg QD	44	71.4	40	5.1
					20.4 ± 11.85	38.4 ± 11.71	43	1200 mg QD	45	70.6	40	4.9
Gil-Nagel (2009)	245	8-week baseline	POS	1 or 2	23.8 ± 13.03	37.7 ± 12.07	43	Placebo	64	71.3	36	35
		2-week titration		CBZ, VPA, PHT,	22.5 ± 11.78	36.8 ± 10.65	35	800 mg QD	55	84.7	28	38
		12-week maintenance		LEV, TPM, LTG	23.0 ± 13.01	36.0 ± 11.43	35	1200 mg QD	58	80	36	31
Ben-Menachem (2010)	393	8-week baseline	POS	1–3	25.4 ± 13.06	36.7 ± 12.2	52	Placebo	59	84	34	28
		14-week treatment[a]		CBZ, VPA, LTG,	24.7 ± 11.52	37.6 ± 11.2	39	400 mg QD	53	80.2	30	27
				CLB, LEV, PHT	22.4 ± 11.63	36.4 ± 12.6	51	800 mg QD	57	76.2	32	27
					23.0 ± 12.90	36.9 ± 11.6	52	1200 mg QD	56	81.6	40	25
Retigabine (Ezogabine)												
Porter (2007)	396	8-week baseline	POS	1 or 2	20.8 ± 11.2	34.5 ± 10.3	52	Placebo	49	85.4	25	NA
		8-week titration		CBZ, LTG, VPA,	21.2 ± 12.0	36.8 ± 10.9	54	200 mg TID	67	82.8	23	NA
		8-week maintenance		TPM, GBP, PHT	19.7 ± 12.0	37.0 ± 10.2	53	300 mg TID	33	85.3	34	NA
					20.1 ± 11.4	38.3 ± 11.9	49	400 mg TID	55	93.4	25	NA
French (2011)	305	8-week baseline	POS	1–3	23.1 ± 12.8	36.7 ± 11.6	47	Placebo	NA			
		6-week titration		NA	23.7 ± 13.0	37.7 ± 12.6	44	400 mg TID				
		12-week maintenance										
Brodie (2010)	ITT-FDA 538	8-week baseline	POS	1–3	22.8 ± 11.8	37.7 ± 11.75	50	Placebo	NA			
		6-week titration		CBZ, LTG, VPA,	22.5 ± 13.0	37.5 ± 12.02	42	200 mg TID				
		12-week maintenance		LEV	22.5 ± 12.7	37.7 ± 12.77	52	300 mg TID				

Carisbamate												
Halford (2011)	540	8-week baseline 2-week titration 12-week maintenance	POS	1–3 CBZ, VPA, TPM, LTG, PHT, LEV	18.8 ± 12.33 19.8 ± 13.45 21.2 ± 13.20	37 ± 12.2 37 ± 12.0 37 ± 12.5	48 49 51	Placebo 400 mg BID 600 mg BID	NA			
Sperling (2010)	Study 1 561	8-week baseline 12-week treatment	POS	1–3 CBZ, VPA, LTG,	Study 1 19.0 (1–55)	36 ± 13.06	46	Placebo 100 mg BID	NA			
				TPM	20.0 (1–52) 18.0 (1–57)	35 ± 12.11 35 ± 12.87	49 55	200 mg BID				
	Study 2 555		POS		Study 2 16.0 (1–50) 15.0 (1–58) 16.0 (1–62)	36 ± 12.21 36 ± 11.70 35 ± 13.94	42 51 52					
Faught (2008)	533	8-week baseline 4-week titration 12-week maintenance	POS	1–3 CBZ, LTG, TPM	25 22 20	38 ± 9.9 37 ± 10.7 36 ± 13.1	45 48 45	Placebo 50 mg BID 150 mg BID	41 41 42	85 78 81	43 48 40	6 6 6
					21 19	38 ± 12.4 36 ± 11.5	49 51	400 mg BID 800 mg BID	35 37	81 84	41 34	6 9
Lacosamide												
Halász (2009)	415	8-week baseline 6-week titration 12-week maintenance	POS	1 or 2 NA	24.6 ± 11.77 25.1 ± 12.89 24.7 ± 13.08	38.9 ± 11.11 39.9 ± 11.71 41.2 ± 11.61	48 43 49	Placebo 100 mg BID 200 mg BID	34 45 38	86 94 87	75 74 71	NA NA NA
					23.6 ± 12.74	39.4 ± 10.53	42	300 mg BID	47	91	66	NA
Ben-Menachem (2007)	477	8-week baseline	POS	1–3	21.1 ± 12.23	38.5 ± 10.93	56	Placebo	37.4	85	80	NA
		4-week titration 12-week maintenance		CBZ, VPA, LTG, TPM, LEV	22.9 ± 12.30 22.8 ± 13.15	36.9 ± 11.70 37.9 ± 12.96	55 43	100 mg BID 200 mg BID	41.1 36.5	87 92	77 80	NA NA
Chung (2010)	402	8-week baseline 6-week titration 12-week maintenance	POS	1–3 LEV, LTG, CBZ, OXC, PHT, TPM	25.4 ± 13.34 24.5 ± 13.16 23.4 ± 13.28	38.1 ± 11.96 39.1 ± 12.37 36.8 ± 11.76	47 51 49	Placebo 200 mg BID 300 mg BID	NA			

Table 1 *Continued*

Included studies	Number of patients (ITT)	Study design	Prior AEDs (median range)	Baseline AEDs, number and type	Duration of epilepsy (Mean ± SD or range)	Patient age (Mean ± SD or range)	Gender (%male)	Drug dosage	Seizure types subgroups (%)			
									Simple	Complex	PT-GN	UC
Brivaracetam												
French (2010)	208	4-week baseline 7-week treatment	POS	1 or 2 CBZ, PHT, VPA, LTG, LEV, CLB	21.7 ± 13.0 16.0 ± 11.5 22.9 ± 13.5 19.1 ± 10.8	33.6 ± 11.3 32.7 ± 12.2 35.3 ± 13.7 30.9 ± 11.6	44 60 54 54	Placebo 2.5 mg BID 10 mg BID 25 mg BID	44.4 36 30.8 30.8	83 90 87 83	54 74 75 56	1.9 0 1.9 1.9
Perampanel												
Krauss (2012)	Study 206 152	4-week baseline 8-week titration 4-week maintenance	POS	1 or 2 NA	22.9 ± 13.69 25.1 ± 13.45 23.0 ± 12.99	38.1 ± 11.62 40.0 ± 11.38 42.5 ± 12.06	45 43 43	Placebo 2 mg BID 4 mg BID	51 45.1 52.9	96 100 94	59 59 63	NA NA NA
	Study 208 47	4-week baseline 12-week titration 4-week maintenance		1—3 NA	18.0 ± 9.27 22.3 ± 15.07	45.5 ± 12.05 40.7 ± 11.99	50 47	Placebo 12 mg QD	30 31.6	90 84	100 82	NA NA

ITT: intention-to-treat; Abbreviations of drugs: Carbamazepine, CBZ; Valproate, VPA; Gabapentin, GBP; Clonazepam, CNZ; Lamotrigine, LTG; Phenobarbital, PB; Phenytoin, PHT; Topiramate, TPM; Oxcarbazepine, OXC; Levetiracetam, LEV; Clobazam, CLB; Eslicarbazepine, ESL; Lacosamide, LAC/LCM; Retigabine (Ezogabine), RGB; Carisbamate, CAR; Brivaractam, BRI; Perampanel, PER. NA: Not available. SZ: seizures; PT: partial; GN: secondary generalized; UC: unclassified.

[a] 1200 mg group included 2-week of titration phase.

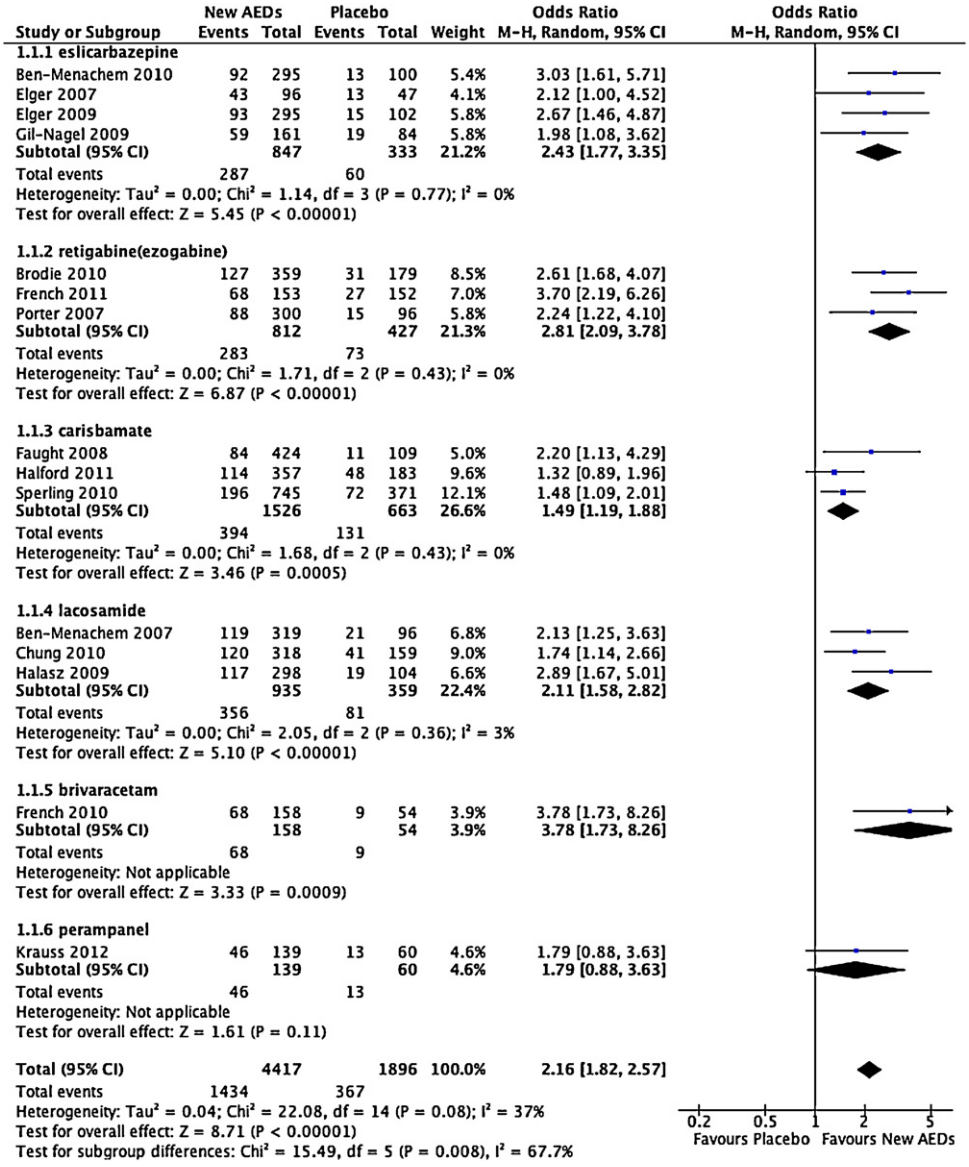

Figure 2 Pooled effects of responder rates (newer AED vs placebo).

Table 2 Newer AED vs placebo: responder rates (Mean and 95%CI).

New AED	Risk Ratio (RR)	Risk Difference (RD)	NNT (all doses)	NNT (dose with maximum responder rate)
ESL	1.89 (1.47, 2.42)	0.17 (0.12, 0.22)	5.88 (4.55, 8.33)	4.55 (3.45, 6.67)[a]
RTG	2.16 (1.71, 2.71)	0.19 (0.12, 0.26)	5.26 (3.85, 8.33)	4.34 (3.23, 6.67)[b]
CAR	1.35 (1.12, 1.61)	0.07 (0.04, 0.11)	14.29 (9.09, 25.00)	NA
LAC	1.68 (1.35, 2.08)	0.16 (0.11, 0.21)	6.25 (4.76, 9.09)	5.00 (3.58, 9.09)[c]
BRI	2.58 (1.39, 4.81)	0.26 (0.14, 0.39)	3.85 (2.56, 7.14)	NA
PER	1.53 (0.89, 2.61)	0.11 (−0.02, 0.24)	9.09 (4.17, 50.00)	NA

NA: not available.
[a] Eslicabazepine 1200 mg/day.
[b] Retigabine 1200 mg/day.
[c] Lacosamide 600 mg/day.

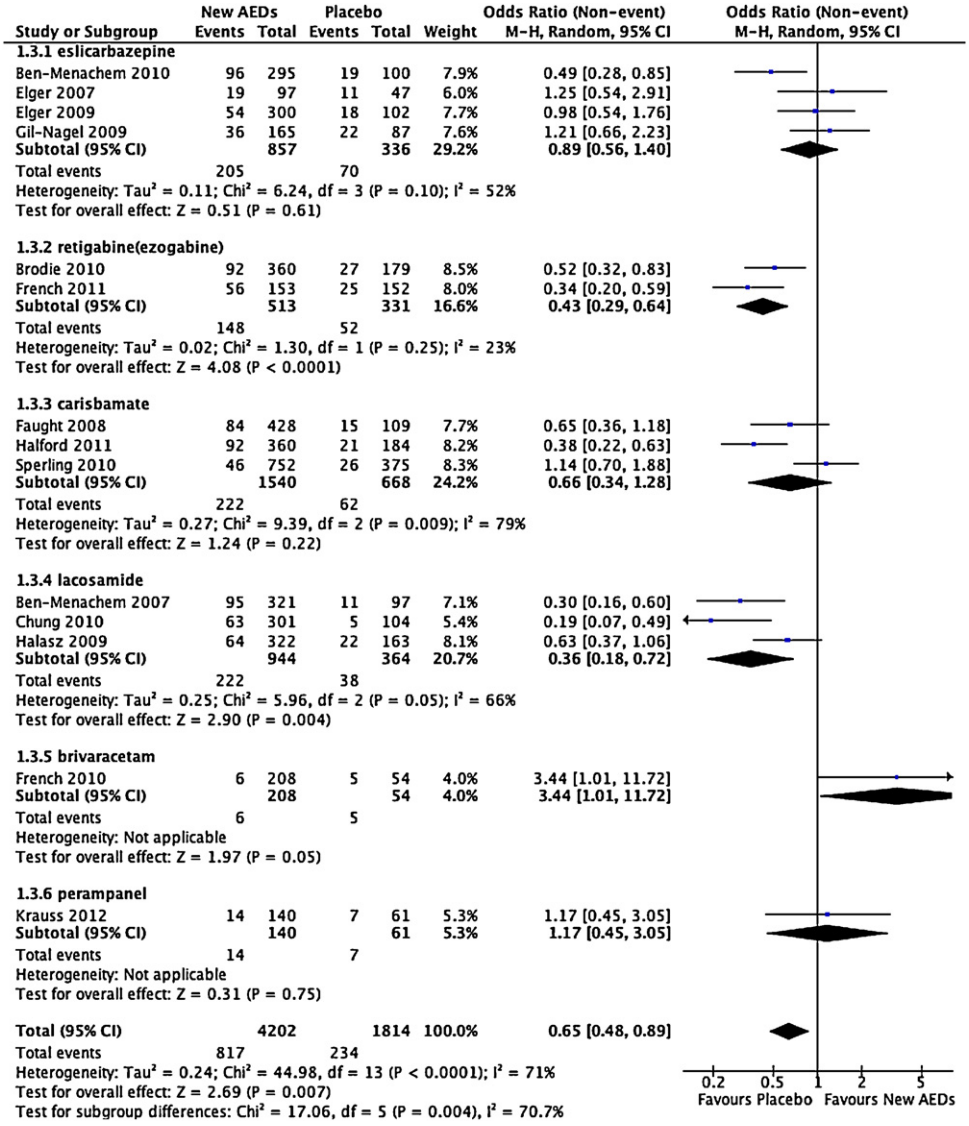

Figure 3 Pooled effects of withdrawal rates (newer AED vs placebo).

Nevertheless, a recognized potential adverse effect of RTG is prolonged QT-interval, this effect have been evaluated in the retrieved studies. According to the three RCTs pertaining to RTG, no major difference in EKG was detected for subjects receiving RTG treatment compared to placebo (Brodie et al., 2010; French et al., 2011; Porter et al., 2010); but only one RCT specified that no changes were observed in QT (Brodie et al., 2010).

Subgroup analyses

Subgroup analyses were performed based on the different dosages of AEDs. In terms of responder rates, ESL 1200 mg (OR 3.05 [95%CI: 2.12, 4.38]) was more effective than 800 mg (OR 2.81 [95%CI: 1.73, 4.57]) and 400 mg (OR 1.65 [95%CI: 0.97, 2.81]). Similarly, although three doses of LAC showed favorable results over placebo in the responder rates, there was an upward trend in seizure responder rates with increasing dose (200 mg OR 1.62 [95%CI: 1.10, 2.37] vs 600 mg OR 2.61 [95%CI: 1.67, 4.09]). Moreover, identical results could be observed in RTG studies as well. By contrast, the only subgroup analysis of two CAR studies investigated the lower dose of CAR, which detected that 800 mg was less effective than the combined effectiveness of all the doses (including 100, 400, 800, 1200, 1600 mg doses) in terms of responder rates. (800 mg OR 1.36 [95%CI: 0.76, 2.45] vs Combined OR 1.51 [95%CI: 1.20, 1.89]) (Supplementary Figures).

From the synthesized results of studies with dose-escalation arms, it was observed that ESL (1200 mg), RTG (1200 mg), and LAC (600 mg) enjoyed the most favorable profiles in 50% seizure frequency reduction compared to placebo. In the subgroup analysis of seizure free rates, ESL, LAC, RTG, and CAR also displayed an upward trend with dose-escalation in improvement of seizure controls. However, the TEAEs and withdrawal rates were positively related with dose-escalation as well (Supplementary Figures).

All newer AEDs vs placebo

In addition to the separate comparison between each newer AED and placebo, we combined all the RCTs to calculate the

Table 3 Secondary outcomes (OR, 95%CI).

Adverse effects	ESL	I^2	No. of RCTs and Pts	RTG	I^2	No. of RCTs and Pts	CAR	I^2	No. of RCTs and Pts	LAC	I^2	No. of RCTs and Pts	BRI	I^2	No. of RCTs and Pts	PER	I^2	No. of RCTs and Pts	All AEDs
Dizziness	0.26* (0.16, 0.42)	0	4/1193	0.25* (0.17, 0.37)	0	3/1251	0.49* (0.35, 0.70)	94	2/1671	0.21* (0.14, 0.31)	22	3/1308	1.16 (0.27, 5.07)	NA	1/158	1.17 (0.46, 3.00)	NA	1/153	0.33* (0.22, 0.49)
Headache	0.74 (0.47, 1.18)	18	4/1193	1.07 (0.76, 1.51)	29	3/1251	0.79 (0.50, 1.24)	NA	1/544	0.54* (0.36, 0.79)	56	3/1308	1.11 (0.31, 3.97)	NA	1/158	1.46 (0.52, 4.10)	NA	1/153	0.82* (0.63, 1.06)
Fatigue	0.92 (0.33, 2.57)	NA	1/395	0.26* (0.15, 0.46)	72	2/844	1.19 (0.57, 2.48)	NA	1/359	0.45* (0.23, 0.87)	0	2/903	0.76 (0.14, 4.06)	NA	1/158	1.00 (0.24, 4.17)	NA	1/153	0.49* (0.36, 0.68)
Somnolence	0.65 (0.41, 1.01)	26	4/1193	0.37* (0.23, 0.58)	0	2/946	0.55* (0.34, 0.87)	64	2/1486	0.73 (0.43, 1.24)	0	3/1308	1.11 (0.31, 3.97)	NA	1/158	1.28 (0.40, 4.12)	NA	1/153	0.60* (0.46, 0.79)
Nausea	0.31* (0.14, 0.70)	0	3/791	0.60 (0.25, 1.42)	NA	1/539	1.34 (0.60, 3.00)	NA	1/359	0.39* (0.23, 0.67)	27	3/1308	NA	NA	NA	7.95* (1.59, 39.83)	NA	1/153	0.59* (0.32, 1.10)
Ataxia	NA	NA	NA	0.31* (0.12, 0.80)	NA	1/305	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.31* (0.12, 0.80)

Pts: patients; NA: not applicable.
* $p < 0.05$, statistically significant.

pooled ORs of all newer AEDs vs placebo in the primary variables. It intended to provide an overall effect size of newer AEDs compared to placebo. Specifically, the result showed the pooled ORs of responder rates compared to placebo was 2.16 (95%CI: 1.82, 2.57), which was in favor of the newer AEDs. Similarly, seizure free rate of all newer AEDs was in line with responder rates (OR 3.07 [95%CI: 1.77, 5.34]). By contrast, in terms of safety outcomes (withdrawal rates, TEAEs rates, withdrawal due to AEs), the profile of placebo was more desirable, with pooled ORs of 0.65 (95%CI: 0.48, 0.89), 0.60 (95%CI: 0.48, 0.75), 0.43 (95%CI: 0.27, 0.70), respectively (Figs. 2—5 and Supplementary Figures).

Secondary outcomes

Newer AED vs placebo

The incidences of six AEs were higher with ESL, and LAC compared to placebo. The only RCT reporting incidences of ataxia was a RTG study (French et al., 2011) with OR 0.31 (95%CI: 0.12, 0.80) (Table 3). It should also be noted that AEs reported in all the studies were mild to moderate and mostly occurred during the titration phase. Lastly, almost all the studies observed the incidences of those six AEs increased with the escalation dosage of newer AEDs (Table 3) (Supplementary Figures).

All newer AEDs vs placebo

For the six predefined adverse effects of dizziness, headache, somnolence, fatigue, nausea, and ataxia, the pooled ORs of all the newer AEDs compared to placebo were as followed: dizziness OR 0.33 (95%CI: 0.22, 0.49), headache OR 0.82 (95%CI: 0.63, 1.06), somnolence OR 0.60 (95%CI: 0.46, 0.79), fatigue OR 0.49 (95%CI: 0.36, 0.68), nausea OR 0.59 (95%CI: 0.32, 1.10), and ataxia OR 0.31 (95%CI: 0.12, 0.80), indicating the six AEs were more frequently occurred in newer AEDs treated patients.

Individual newer AED vs all other newer AEDs

Due to lack of direct comparisons between the newer AEDs, it might be difficult for clinicians to choose among these competing medications. In this analysis, the effect of each newer AED (irrespectively of dose) was compared to the combined effects of all other newer ones.

In the indirect comparison, ESL (OR 1.16 [95%CI: 0.24, 2.08]), RTG (OR 1.41 [95%CI: 0.49, 2.33]), and BRI (OR 1.79 [95%CI: −1.50, 5.08]) were more effective than all other newer AEDs based on variable of responder rates. By contrast, CAR (OR 0.61 [95%CI: 0.08, 1.14]), LAC (OR 0.96 [95%CI: 0.18, 1.74]), and PER (OR 0.82 [95%CI: −0.61, 2.25]) were not superior to all other newer AEDs in reducing seizure frequency. Dissimilar with responder rates, seizure free outcomes favored LAC (OR 1.55 [95%CI: 0.90, 2.20]) over the same comparator. All the outcomes had the 95%CI of their pooled OR crossed one.

The withdrawal rates in ESL, CAR, BRI and PER were lower related to all other newer AEDs. In comparison, LAC and RTG showed significant higher withdrawal rates than all other newer AEDs, with OR 1.73 (95%CI: 0.71, 2.75) and OR 1.48 (95%CI: 0.59, 2.37), respectively. In respect to adverse effects rates, in line with higher withdrawal rates, LAC and

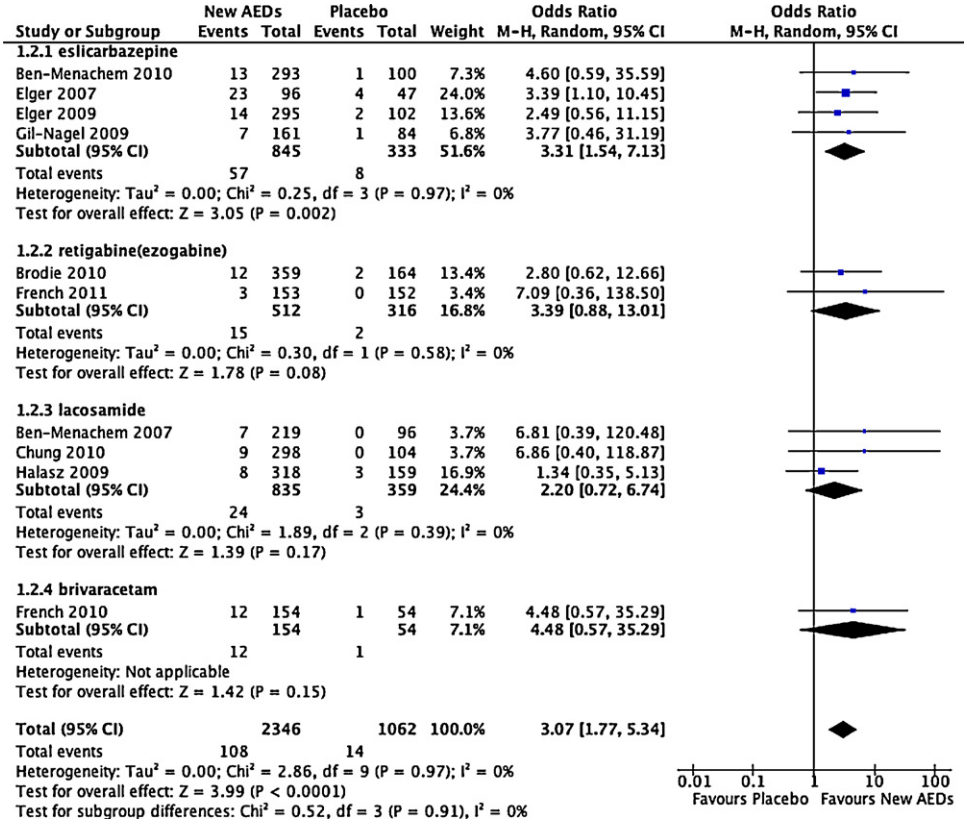

Figure 4 Pooled effects of seizure free rates (new AED vs placebo).

RTG treatments also had more AEs than all others combination (OR 1.35 [95%CI: 0.29, 2.41] and OR 1.28 [95%CI: 0.64, 1.92] respectively). It was noted that, though enjoyed a lower withdrawal rates, ESL showed an increased incidences in adverse effects (OR 1.10 [95%CI: 0.52, 1.68]). In general, BRI produced the highest OR in responder rates (OR 1.79 [95%CI: −1.50, 5.08]) while with the least incidences in withdrawal and AEs (Table 4).

Discussion

The first generation AEDs like carbamazepine, valproate, and phenytoin are still widely administered and offer ideal seizure control for a large amount of epilepsy patients. So it is imperative to figure out whether and when we should consider using the newer generation of AEDs.

Our study synthesized the existing literatures reporting the results of clinical trials about the newer AEDs that have been introduced or invented within the last 4 years (ESL [approved by European Medicines Agency (EMA) in 2009], LAC [approved in 2008] and RTG [approved by FDA and EMA in 2011]), or withdrawn from application (CAR [FDA and EMA application were withdrawn in 2010]) or still under phase 3 trials (PER and BRI) (Bialer, 2011). Furthermore, the approved indications for these newer AEDs (LAC, ESL, RTG) are all as adjunctive treatment for refractory partial-onset epilepsy. Only patients who failed two kinds of first line AEDs or cannot achieve seizure free under the maximum dosage of first line AEDs are eligible for these newer AEDs. Therefore, synthesis of RCTs would offer the best evidence for the newer generation of AEDs with respect to efficacy, safety and tolerability.

The findings from our study are:

Firstly, generally speaking, the newer AEDs demonstrate to be superior to placebo in terms of seizure control, as shown by pooled responder and seizure free rates, while the overall adverse effect and withdrawal rates are disappointingly higher than placebo. Secondly, BRI, RTG and probably ESL are more effective in reducing the seizure frequency as measured by responder rates. However, CAR may be less efficacious as evaluated by the same variable, all are compared to placebo. Thirdly, in terms of tolerability, which measured by withdrawal rates, LAC and RTG had poorer tolerability than other new AEDs, while BRI and PER are well tolerated in the included RCTs. Fourthly, while the newer AEDs produced more AEs than placebo, the incidence of predefined AEs were comparable among those newer AEDs. Fifthly, ESL (1200 mg), RTG (1200 mg), LAC (600 mg) produced better responder rates than other lower dosages of particular drug. Lastly, when the indirect comparisons were performed, BRI, followed by RTG, might be preferable AEDs over all other newer AEDs. However, CAR may be less efficacious than all other newer AEDs.

Meanwhile, there were meta-analyses reporting the effects of newer AEDs as add-on therapy to refractory partial-onset seizures patients (Beyenburg et al., 2012; Costa et al., 2011). Costa et al. (2011) synthesized 62 placebo-controlled and 8 head-to-head RCTs, they reported

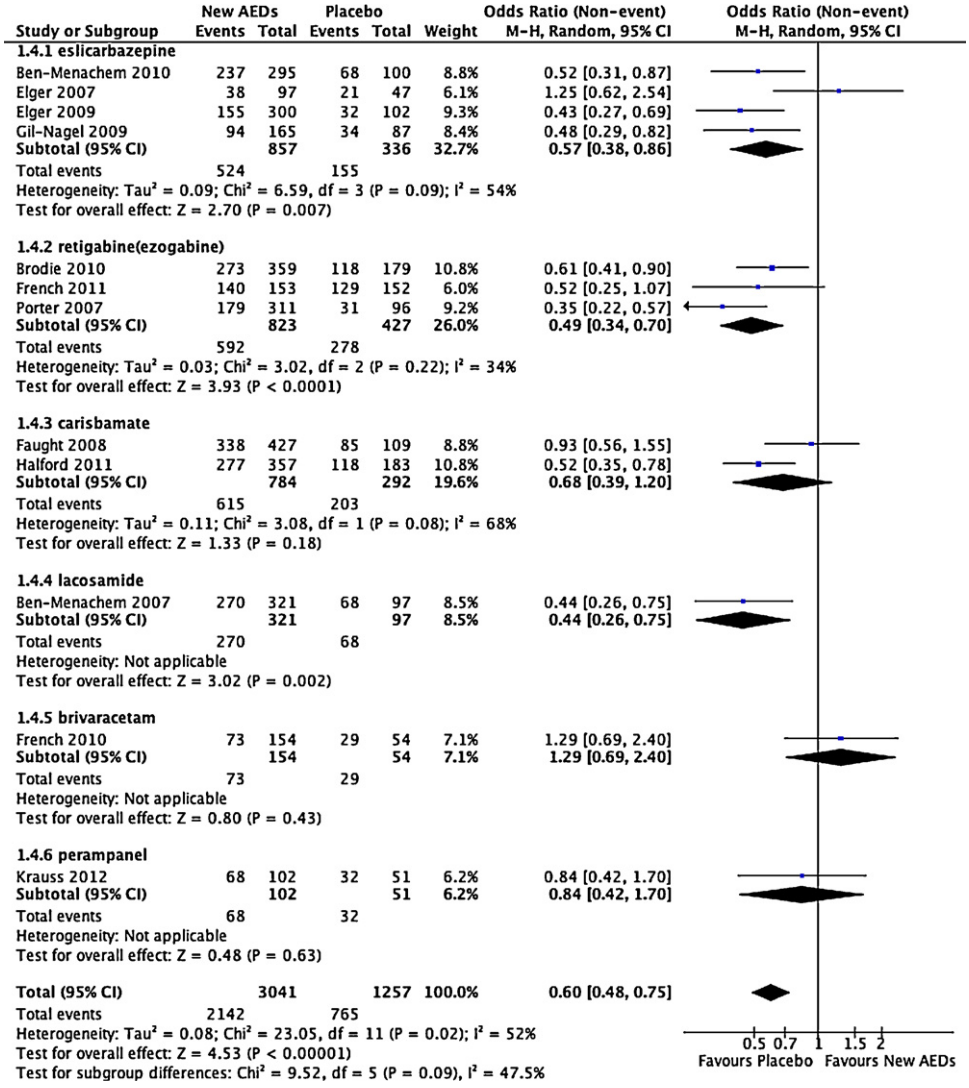

Figure 5 Pooled effects of adverse effects (newer AED vs placebo).

the pooled ORs for responder and withdrawal rates (vs placebo) were 3.00 (95%CI: 2.63, 3.41) and 1.48 (95%CI: 1.30, 1.68), respectively. Indirect comparisons of responder rate based on relative measurements of treatment effect (ORs) favored Topiramate (TPM) (1.52 [95%CI: 1.06, 2.02]) in comparison to all other AEDs. Beyenburg et al. (2012) estimated a placebo-corrected net efficacy of new AEDs. The results of pooled RD were in favor of AEDs over placebo, for seizure-freedom was 6% (95%CI: 4.8, $p < 0.001$) and for responder rate was 21% (95%CI: 19.24, $p < 0.001$). Compared with the results from our study, we estimated the pooled OR was 2.16 (95%CI: 1.82, 2.57) and RD was 15% (95%CI: 12.18, $p < 0.00001$) for responder rates (vs placebo) with medium heterogeneities (37% and 50% for the two estimates). The pooled OR of withdrawal rates (vs placebo) was 1.43 (95%CI: 1.12, 2.10).

Table 4 Newer AED vs All other newer AEDs (Odds Ratio).

New AED	Responder rates	Seizure-free rates	Withdrawal rates	Adverse effects
ESL	1.16 (0.24, 2.08)	0.88 (0.49, 1.27)	0.63 (0.11, 1.15)	1.10 (0.52, 1.68)
RTG	1.41 (0.49, 2.33)	0.85 (0.31, 1.39)	1.48 (0.59, 2.37)	1.28 (0.64, 1.92)
CAR	0.61 (0.08, 1.14)	NA	0.90 (0.32, 1.48)	0.86 (0.29, 1.43)
LAC	0.96 (0.18, 1.74)	1.55 (0.90, 2.20)	1.73 (0.71, 2.75)	1.35 (0.29, 2.41)
BRI	1.79 (−1.50, 5.08)	0.67 (−0.218, 1.57)	0.17 (−0.36, 0.70)	0.43 (−0.15, 1.01)
PER	0.82 (−0.61, 2.25)	NA	0.50 (−0.50, 1.50)	NA

As to the indirect comparison, we dedicated to compare between each newer AED and all the other newer AEDs, rather than indirect comparisons between each newer AED. The combination of all the other newer AEDs can, on one hand, promote the robustness of results (as sample size for each newer AED is relatively small, especially for BRI and PER, with only one RCT for each included). On the other hand, this would also provide some resemblance to clinical practice as it is not uncommon for epileptic patients, especially patients with refractory epilepsy to take more than two kinds of AEDs simultaneously (French and Faught, 2009; Schuele and Luders, 2008). If one AED demonstrates to be more effective than the other AED combination, this AED could be regarded as a replacement to the combination. Additionally, drug interaction between various AEDs and other medications is another primary concern of clinician. Less medication usually comes with less adverse effects, less interaction between different drugs, and obviously more convenience for the patients. This would therefore provide some guidance for clinicians in lieu of results from direct comparison. Nevertheless, the results from the indirect comparisons should be verified and confirmed by future well-designed clinical trials. Last but not least, the indirect comparison was performed based on classical frequentist method instead of Bayesian approach, as the frequentist method is easier to use and more transparent.

Although our study observed that, when using placebo as comparator, BRI, RTG and ESL were probably more effective, whereas CAR and PER may not be as efficacious as aforementioned ones. The generalizability of our results into the clinical practice should be applied with caution. To interpret this, first of all, all the included RCTs were conducted with relatively short duration, ranged from 7 to 18 weeks (referring to the titration plus maintenance phase). The primary outcomes utilized in those studies were seizure-free rates and reduction in seizure frequency per 28 day during the treatment period, all of which are intermediate outcomes in epilepsy management and probably cannot represent the long-term effectiveness. Furthermore, studies with longer duration would be more appropriate to capture the changes in seizure frequency, and with higher possibility of more participant withdrawal and long-term AEs. All of these factors could contribute to the differences in the final outcome. For instance, responder rates positively correlated with treatment duration was reported by one published meta-analysis (Rheims et al., 2011). However, an extension study of one RCT pertaining to ESL observed comparable clinical results to short term research. This study reports that over 1 year follow-up, with 312 ITT population, 84.4% patients continued treatment for at least 6 months, and 76.6% of participants completed 1 year treatment. Patients with slightly increased dose of ESL (from 775 ± 127 mg during the first 4 weeks to 893 ± 234 mg during weeks 41—52) achieved responder rates varied from 48.1% to 53.2% during weeks 5—52. Meanwhile, the seizure free patients per 12-week interval increased over time as well (ranged from 8.7% in weeks 5—16 to 12.5% in weeks 41—52) (Elger et al., 2009). This is the only long-term open-label study about the included newer AEDs performed in conditions more closely reflecting routine clinical practice. Undoubtedly, the maintained effects of ESL from this study could promote confidence in our findings, at least for ESL.

Nevertheless, the use of last observation carried forward (LOCF) analysis gives rise to concerns as well. Particularly, patients who discontinued treatment before the end of the trial, the available data were used to extrapolate to the whole treatment period, with the assumption that the treatment effect is constant and patient respond to such drug without any change over time. However, this assumption bears challenges. As indicated in one study, the responder rates was significantly higher in the LOCF analysis than in the completers' analysis, regardless of placebo or active medication (Rheims et al., 2011), suggesting that the responder rates might be overestimated in the LOCF analysis. For the included studies, 12 out of 15 studies utilized LOCF method to analyze the outcomes, the others did not clearly state which rationale used to deal with the dropped-out participants (Ben-Menachem et al., 2010; French et al., 2010; Gil-Nagel et al., 2009).

Additionally, the treatment period used to calculate the efficacy end point (titration + maintenance vs baseline, or maintenance period vs baseline) poses another uncertainty. Actually, the response to placebo was significantly greater in the maintenance than in the entire treatment period (but the difference was not detect in active medication) (Rheims et al., 2011). Thus, the patients in the placebo arm would have higher responder rates if the data in the maintenance period was employed. Consequently, the relative risk or Odds Ratio would be lower, due to the higher responder rates in placebo. For example, all three RCTs of LAC just used maintenance period to calculate the efficacy outcomes, this offered a possible explanation for their relative low OR than others.

The heterogeneity analyses among synthesized studies did not show heterogeneity in the efficacy outcomes, but medium level of heterogeneity in the safety outcomes (withdrawal rates, adverse effects) was detected. This heterogeneity was associated with lots of factors, such as the study design. For example, dose reduction was allowed in some studies for (Halford et al., 2011; Sperling et al., 2010), but others required patients to have stable dosage of all the AEDs (Brodie et al., 2010; Elger et al., 2007, 2009; Gil-Nagel et al., 2009) or only allowed one reduction for the newer AEDs (Ben-Menachem et al., 2007; Chung et al., 2010; French et al., 2011; Halász et al., 2009; Krauss et al., 2012). The different characteristics of patient gave rise to clinical heterogeneity as well.

Another concern was that in our meta-analysis, all the studies were synthesized without the consideration of different effects of various doses. The subgroup analyses demonstrated that the responder rates showed significant difference between dosages in terms of pooled ORs. For instances, the 1200 mg ESL, 1200 mg RTG, 600 mg LAC exerted superiority in seizure control over other doses. The inclusion of doses with lower efficacy would definitely neutralize the maximum efficacy of individual drug, which is more prominent for ESL 400 mg, this dose is even less than the minimum approved dose. Hence, the synthesis of all the outcomes regardless of dosages may confound the interpretations, leading the final results to be less favorable toward newer AEDs.

Conclusions

In conclusion, in direct comparison, as expected, the newer AEDs are more effective in seizure controls while having higher incidences in withdrawal and adverse effects than placebo. Among the newer AEDs, BRI followed by RTG, might be more preferable in responder rates, but in terms of withdrawal rate, BRI and PER are better tolerated than other newer AEDs. Likewise, results from our indirect comparisons suggest BRI and RTG as superior to all the other newer AEDs in terms of responder rates. In addition, BRI also produces lower withdrawal and adverse effects rates than all the other AED combined. Nevertheless, the results from the indirect comparisons should be verified and confirmed by future well-designed clinical trials.

Conflict of interest

Nothing to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eplepsyres.2012.06.005.

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FULL-LENGTH ORIGINAL RESEARCH

Validation of a Chinese version of the Quality of Well-Being Scale–Self-Administered (QWB-SA) in patients with epilepsy

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Summary

Purpose: Generic preference-based health-related quality of life (HRQoL) instruments are increasingly used to estimate the quality-adjusted life years (QALYs) in cost-effectiveness/utility studies. However, no such tool has been used and validated in epilepsy patients in China. This study was conducted to validate a generic preference-based HRQoL instrument, namely the Quality of Well-Being Scale–Self-Administered (QWB-SA) in Chinese patients with epilepsy.

Methods: Accepted translation procedures were followed to develop the Chinese QWB-SA. An epilepsy group (adults with established diagnosis of epilepsy) and a control group (adults without manifested cognitive problems) were recruited between July and October, 2012, from two tertiary hospitals in China. After giving informed consent, each subject completed both the QWB-SA and the EuroQol (EQ-5D) as well as provided sociodemographic data. Construct validity was examined by six (convergent) and two (discriminative) a priori hypotheses. Sensitivity was compared by ability to differentiate epilepsy-specific variable-based subgroups. Agreement between the QWB-SA and EQ-5D was assessed by intraclass correlation coefficient (ICC) and Bland-Altman plot.

Key Findings: One hundred forty-four epilepsy patients and 323 control subjects were enrolled, respectively. The utility medians (interquartile range, IQR) for the QWB-SA and EQ-5D were 0.673 (0.172), 0.848 (0.275) for epilepsy group and 0.775 (0.258), 1.000 (0.152) for control group, respectively. The difference in utilities between the two measures were significant ($p < 0.0001$). Construct validity was demonstrated by six a priori hypotheses. In addition, the QWB-SA was able to discriminate across different seizure frequency and antiepileptic drug (AED) treatment subgroups. Agreement between the QWB-SA and EQ-5D was demonstrated by ICC (0.725). Finally, the multiple linear regression analysis indicated that group and the EQ-VAS had influences on the utility difference of these two measures, whereas seizure frequency and number of AEDs were predictors of HRQoL as measured by the QWB-SA.

Significance: The QWB-SA is a valid and sensitive HRQoL measure in Chinese patients with epilepsy. Compared to the EQ-5D, the QWB-SA showed superiority in coverage of health dimensions, sensitivity, and ceiling effects. However, future study is still needed to ascertain its responsiveness.

KEY WORDS: Epilepsy, Quality of Well-Being Scale–Self-Administered, EQ-5D, Utility, Validation study, China.

Health-related quality of life (HRQoL) is a multidimensional concept that covers physical health, psychological state, and social relationship (Schipper et al., 1996), thereby describing a comprehensive picture of the individual's overall well-being. Another commonly used measure, quality-adjusted life year (QALY) is a composite metric that integrates HRQoL with the duration of life to provide a single comprehensive expression of health outcome. More specifically, QALY incorporates both quality and quantity of life into one score, thereby enabling the comparisons across diseases and populations. As such, QALY has become a standard measure of HRQoL in cost-effectiveness research in clinical medicine (Gold, 1996).

When assessing HRQoL of interested subjects, health care providers have the choice of using a generic or disease-specific instrument. Disease-specific measures are often more sensitive to subtle changes in the disease of interest, but may ignore changes in other areas of health or functioning. Given the unpredictability of interventions/medications on multiple body systems, it is essential to ascertain health in ways that can capture a subject's overall functioning and wellbeing (Gold, 1996). Hence, in practice, a generic instrument is usually applied together with a disease-specific instrument.

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Epilepsy, as a chronic disorder, has considerable negative effect on people's day-to-day functioning (Baker, 1995). Apart from experiencing seizures and their detrimental impact on cognitive function (particularly memory), those with epilepsy may also experience adverse reactions to antiepileptic drugs (AEDs). In addition, epilepsy is also associated with psychological burden, including anxiety and depression (Wong & Lhatoo, 2000; Vingerhoets, 2006; Ramaratnam et al., 2008). In view of these factors, the traditionally assessed clinical outcomes that measure the treatment effect such as seizure frequency, seizure-free days might not be sufficiently comprehensive to reflect the total impact on the patient's well-being and perception about treatment effect. To capture the patient's own perception of treatment effect, a variety of validated HRQoL measures are available. For epilepsy, the three most commonly reported epilepsy-specific measures were Quality of Life Epilepsy Inventory (QOLIE-10, QOLIE-31, and QOLIE-89), and the two most commonly used generic measures were the Short-Form Questionnaire (SF-18 and SF-36) and World Health Organization Quality of life questionnaire (WHOQOL-BREF and WHOQOL-100; Taylor et al., 2011). Nevertheless, none of the aforementioned instruments could provide a utility score, thus hampering their subsequent uses in the cost-effectiveness/utility research.

Unlike the aforementioned generic instruments, Quality of Well-being Scale (Seiber et al., 2008) was the first instrument specifically designed to measure the quality of life for the estimation of QALYs. It is a preference-weighted instrument combing the three scales of functioning with a measure of symptoms and problems to produce a point-in-time expression of wellbeing that runs from 0 (for death) to 1.0 (for symptomatic full function). With the preference weights derived from a community sample, a unique aspect of QWB-SA version is that a person's utility score reflects a societal perspective on the value of that person's level of functioning and wellbeing (Seiber et al., 2008). The information obtained via QWB-SA would therefore be extremely beneficial for conducting cost-effectiveness/utility research.

Several generic preference-based HRQoL instruments are available in the Chinese versions. For instance, EuroQol (EQ-5D) and Short-form 6D (SF-6D) have been validated in certain Chinese populations (Zhao et al., 2010). However, both EQ-5D and SF-6D, focus only on the functioning aspects, whereas in contrast, QWB-SA has a functioning component complemented by a strong symptom component. Prior work by developers of QWB has demonstrated that on any particular day, nearly 80% of the general population is optimally functional, but less than half of the population experiences no symptoms (Seiber et al., 2008). Consequently, administration of QWB-SA could provide important supporting information that is not captured by EQ-5D or SF-6D.

Our research, therefore, intended to translate and validate the QWB-SA and investigate the psychometric properties of this Chinese version in Chinese patients with epilepsy. At the same time, the performance of QWB-SA was compared with another widely utilized generic preference-based HRQoL instrument: EQ-5D.

Methods

Study design and subjects recruitment

The cross-sectional study recruited participants from two tertiary hospitals in China: Renmin Hospital of Wuhan University, and the Fifth Hospital of Wuhan (Wuhan, Hubei, China) between July and October 2012. The study was approved by the institutional review board of the two study sites. After informed consent was received from each participant (age >16 years), a convenience sample of inpatients or outpatients with the diagnosis of epilepsy and a control group (without manifestation of cognitive problems) were recruited. Attending physicians or consultant neurologists/epileptologists were responsible for initially identifying patients with epilepsy. The diagnosis of epilepsy was based on the clinical history, symptoms, examinations, electroencephalography (EEG; epileptic discharges), neuroimaging (magnetic resonance imaging [MRI], computed tomography [CT]) with the consensus between two physicians (SQP and LX). Each subject was interviewed by a trained interviewer using standardized questionnaires containing QWB-SA and EQ-5D/visual analog scale (VAS). Other information including sociodemographic data (for both epilepsy patients and controls) and epilepsy specific data (for epilepsy patients) were collected simultaneously.

Instruments

QWB-SA

The QWB-SA includes five sections. The first section assesses the presence/absence of 19 chronic symptoms or problems (e.g., blindness, hearing loss), followed by assessment of 25 acute physical symptoms (e.g., headache, breathless, chest pain), and 14 mental health symptoms and behaviors (e.g., sadness, blue, frustration). The remaining sections are assessments of persons' mobility (including use of transportation), physical activity (e.g., walking and carrying stuff), and social activity (completion of role expectation like work, school). Each item in the QWB-SA is described as a health state to be rated on a 0–100 scale (Visual Analog Scale [VAS]) (Seiber et al., 2008). Each participant recalls the answers to the particular QWB-SA question within the last 3 days before the day of the survey. Once all the subjects have provided ratings, preference weight of the corresponding item is then estimated using the following formula (Anderson & Zalinski, 1988):

$$\text{Item weight} = 1.0 - (\text{mean rating}/100)$$

To calculate the QWB-SA utility, each section is to be computed, namely, CPX (acute and chronic symptoms), MOB (self-care and mobility), PAC (physical activity), and SAC (self-care and usual activity). Scoring algorithm and preference weights are then provided by the University of California, San Diego (UCSD) Health Services Research Center. In our current study, the use of QWB-SA was authorized by the QWB-SA copyright holders.

EQ-5D/VAS

The EQ-5D comprises five dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension has three response levels (no problems, some problems, severe problems). The EQ-5D descriptive system can theoretically generate 243 health states, with a utility score ranging from −0.59 to 1.00. The utility scoring algorithm adopted in our study was developed using Time Trade-Off (TTO) based preference scores from a United Kingdom general population (Dolan, 1997). EQ-VAS is a 20-cm vertical visual analog scale ranging from 100 (best imaginable health state) to 0 (worst imaginable health state) to represent the overall health of the day. Each respondent classifies and rates their health status on the day of the survey. The simplified Chinese version of EQ-5D/VAS is an official version authorized by the EuroQol Group. The validity of this version has been reported recently by Zhao et al. (2010).

Translation process

Forward and backward translation

Two Chinese physicians (LG and LX) translated the English version of QWB-SA into simplified Chinese independently. The two Chinese versions of QWB-SA were consolidated into one via thorough discussion of the two translators and the inputs of two professors (SQP and SCL). Next another two bilingual physicians who were blind to the original QWB-SA as well as the study design performed the back-translation process. Finally, the two back-translations were submitted to the developers for appraisal.

Culture adaptations

To evaluate the equivalence with the original version, the initial Chinese version of QWB-SA was sent to two consultant physicians and a pharmacist. Considering the number of motor vehicles per 1,000 people was only 83 (WebDataSource) but there are >520 million bicycles (including electric ones) in China (WebDataSource), and together with the similar physical and mental requirements for driving and riding, one key change was proposed by these experts to make the content of QWB-SA applicable to China.

Items 5b and 6c "drive a motor vehicle" were replaced by "ride a (electric) bicycle or do the housework."

Pilot testing

Forty subjects including hospital general staff (n = 20), interns (n = 12), nurses (n = 4), and outpatients of a neurology clinic (n = 4) were interviewed to complete the draft Chinese QWB-SA. During the process, a couple of respondents neither drove a car nor rode a (electric) bicycle for commuting (Items 5b and 6c), thus "do the housework" was added. Furthermore, from the qualitative input of the pilot study, wording and phrasing were further refined accordingly to avoid confusion in understanding and were then integrated into the final simplified Chinese version.

Data analyses

Descriptive statistics

Descriptive statistics were used to characterize the sample and the distribution of QWB-SA and EQ-5D/VAS scores. Continuous variables were presented by mean, standard deviation/standard error (SE), median, and interquartile range (IQR) where applicable, whereas categorical variables were shown by the number and proportion of the entire sample in corresponding group. The differences between epilepsy and control groups were examined by analysis of variance (ANOVA) (if the distribution was normal) or Mann-Whitney *U*-test (if the distribution was abnormal) in the case of continuous variables, or chi-square test in the case of categorical variables.

Construct validity

To test the convergent validity, the associations between QWB-SA utility and EQ-5D/VAS were assessed at subscale and scale levels. According to the literature and clinical experience, six a priori hypotheses were tested with expected moderate to strong correlation coefficients (ρ):

1. Correlation between QWB-SA utility score and EQ-5D utility score.
2. Correlation between QWB-SA utility score and EQ-VAS.
3. Correlation between QWB-SA acute and chronic symptoms (CPX) with EQ-5D pain/discomfort and anxiety/depression.
4. Correlation between QWB-SA self-care and mobility (MOB) with EQ-5D mobility.
5. Correlation between QWB-SA physical activity (PAC) with EQ-5D mobility and usual activity.
6. Correlation between QWB-SA self-care and usual activity with EQ-5D usual activity and self-care.

Correlation coefficients were computed as Spearman's rank correlation coefficient (ρ), with $\rho > 0.5$ considered as strong correlation, 0.35–0.5 as moderate correlation, and 0.2–0.34 as weak correlation (Juniper et al., 1996).

The discriminative validity was assessed based on criterion validity. Abilities of QWB-SA and EQ-5D to discriminate between epilepsy and general populations as well as different levels of self-rating health status according to QWB-SA and EQ-VAS were examined. Specifically, patients with epilepsy were expected to have lower utility scores on both QWB-SA and EQ-5D than the general population. In addition, subjects with poorer self-rated health status would have lower utility scores as well. The five levels health statuses (excellent, very good, good, fair, poor) according to QWB-SA were adopted as the grouping factor. At the same time, EQ-VAS was also employed as an indicator for self-reported health status, and subsequently categorized into four subgroups: <65 (bad), 65–79 (fair), 80–89 (good), and 90–100 (excellent) (Barton et al., 2008).

Sensitivity of QWB-SA and EQ-5D

This analysis was undertaken for the epilepsy group only. Precisely, two-step analyses were performed to assess the sensitivity of the two measures toward epilepsy characteristics that are known to affect health and quality of life. For example, as shown in a review for determinants of HRQoL for patients with epilepsy, seizure frequency is negatively correlated with HRQoL (Taylor et al., 2011). If the measure could better differentiate HRQoL for patients with distinctive seizure characteristics, the measure might be considered as sensitive to this disease cohort. At first, correlations between sociodemographic or epilepsy-specific variables and HRQoL utility scores were assessed via Spearman's correlation coefficient with p-value < 0.1 to identify candidate predictors. Then, a series of one-way ANOVA analyses (or independent-samples *t*-test) were carried out to further investigate the different effect of epilepsy-specific variables on utilities. Relative efficiency (RE) statistics were also calculated to compare two utility instruments regardless of statistical significance. The RE statistic is the ratio between two F-ratios (or *t*-statistics) from the one-way ANOVA (or independent-samples *t*-test) for each measure, with higher RE suggesting stronger validity. Lastly, multiple linear regression (MLR) was run to investigate the candidate predictors that were ascertained to be significantly correlated with QWB-SA and EQ-5D in the univariate analysis.

Levels of agreement between QWB-SA and EQ-5D

The mean and median utility scores between these two instruments for the entire sample and within each group were compared. Both Wilcoxon's signed-rank test and Spearman's rank correlation were adopted to investigate the association between these two utility scores. In order to address the limitations of simple correlation, the agreement between utility scores of QWB-SA and EQ-5D was assessed by intraclass correlation coefficient (ICC; calculated with two-way random effects model based on absolute agreement and coefficient >0.7 indicates a strong agreement) and Bland-Altman plot. Bland-Altman plot was used to evaluate the agreement between two different instruments or measurements by investigating the existence of any systematic difference (e.g., fixed bias) between the measurements and to identify possible outliers (Bland & Altman, 1986). If no clinically important differences are observed within 95% confidence intervals (CIs), the two methods may be used interchangeably. The one-sample *t*-test was undertaken to compare the mean difference of utility scores with 0, with p-value > 0.05 implying the total agreement between QWB-SA and EQ-5D.

Factors affecting utility difference between QWB-SA and EQ-5D

In investigating the factors attributing to the differences between two instruments, multiple linear-regression was performed to test the socioeconomic characteristics that related to the variance with the difference in the utility set as the dependent variable. At the same time, groups (epilepsy or control group), age, levels of education, marital status, working status, QWB-SA self-rating health status, and EQ-VAS for global wellbeing were selected as the independent variables.

All the statistical analyses were performed on SPSS 20.0 (SPSS Inc, Chicago, IL, U.S.A.). p-value < 0.05 was considered as statistically significant.

Results

Characteristics of subjects

In total, 467 subjects completed both the QWB-SA and EQ-5D with 144 in the epilepsy group. There were statistically significant differences between the epilepsy and control groups in terms of age ($p = 0.033$), gender ($p < 0.0001$), working status ($p = 0.029$), and level of education ($p < 0.0001$; Table 1).

Description statistics of QWB-SA and EQ-5D

For utility of QWB-SA, the mean (standard deviation, SD) was 0.657 (0.135) for epilepsy group and 0.802 (0.155) for control group, and the median (IQR) was 0.673 (0.172) for epilepsy group and 1.000 (0.152) for control group. For utility of EQ-5D, the mean (SD) for epilepsy group was 0.828 (0.206) and 0.923 (0.132) for control group, whereas the median (IQR) was 0.848 (0.275) for epilepsy group and 1.000 (0.152) for control group. Utility scores on QWB-SA and EQ-5D were significantly different between the two groups ($p < 0.0001$), whereas the EQ-VAS did not show a difference ($p = 0.052$). Two of four sections of QWB-SA, namely CPX ($p < 0.0001$) and SAC ($p < 0.0001$), were significantly different between epilepsy and control groups. More specifically, epilepsy patients tended to experience more problems in these two sections (Table 1).

Given the significant differences between the epilepsy and control groups in terms of age, gender, working status,

Table 1. Characteristics of subjects and distribution of QWB-SA and EA-5D utility scores

Characteristics	Epilepsy group N = 144	Control group N = 323	p-Value
Age in years			
Mean ± SD	33.11 ± 13.044	36.15 ± 16.406	0.033
Median ± IQR	30.57 ± 22.00	31.67 ± 27.00	
Range	16–65	16–86	
Gender (male)	75 (52.1%)	127 (40.7%)	<0.0001
Han ethnicity (%)	142 (98.6)	308 (98.7)	0.926
Marital status (%)			
Unmarried	71 (49.3)	123 (39.4)	0.182
Married	70 (48.6)	184 (59.0)	
Divorced	2 (1.4)	2 (0.6)	
Widow/widower	1 (0.7)	3 (1.0)	
Working status (%)			
Employed	65 (45.1)	175 (56.1)	0.029
Unemployed	69 (54.9)	137 (43.9)	
Year of education (%)			
≤6 years	16 (11.1)	16 (5.0)	<0.0001
7–12 years	106 (73.6)	144 (44.5)	
>12 years	22 (15.3)	163 (50.4)	
Age of epilepsy onset (median ± IQR)[a]	18.00 ± 13.50	–	–
Duration of epilepsy (median ± IQR)[a]	6.00 ± 13.00	–	–
Seizure frequency (%)[a]			
<1/year	6 (4.3)	–	–
1–11/year	63 (44.7)	–	
≥12/year	72 (51.1)	–	
Seizure types (%)[a]			
Simple partial	7 (5.0)	–	–
Complex partial	78 (55.3)	–	
Absence	18 (12.8)	–	
Clonic	27 (19.1)	–	
Tonic–clonic	11 (7.8)	–	
Epilepsy syndromes (%)[a]			
Localization-related	107 (75.9)	–	–
Generalized	24 (17.0)	–	
Unknown localization	10 (7.1)	–	
Antiepileptic treatment (%)[a]			
Monotherapy	66 (46.8)	–	–
Polytherapy	75 (53.2)	–	
QWB-SA			
Mean ± SD	0.657 ± 0.135	0.802 ± 0.155	<0.0001
Median ± IQR	0.673 ± 0.172	1.000 ± 0.152	
Range	0.261–0.934	0.308–1.000	
CPX			
Mean ± SD	−0.315 ± 0.103	−0.190 ± 0.144	<0.0001
Median ± IQR	−0.324 ± 0.116	−0.225 ± 0.256	
Range	−0.531–−0.066	−0.523–−0.000	
MOB			
Mean ± SD	−0.002 ± 0.008	−0.002 ± 0.013	0.794
Median ± IQR	0.000 ± 0.000	0.000 ± 0.000	
Range	−0.031–0.000	−0.089–0.000	
PAC			
Mean ± SD	−0.006 ± 0.019	−0.005 ± 0.020	0.731
Median ± IQR	0.000 ± 0.000	0.000 ± 0.000	
Range	−0.072–0.000	−0.072–0.000	
SAC			
Mean ± SD	−0.018 ± 0.038	−0.001 ± 0.008	<0.0001
Median ± IQR	0.000 ± 0.000	0.000 ± 0.000	
Range	−0.150–0.000	−0.096–0.000	

Continued

Table 1. Continued.

Characteristics	Epilepsy group N = 144	Control group N = 323	p-Value
EQ-5D			
Mean ± SD	0.828 ± 0.206	0.923 ± 0.132	<0.0001
Median ± IQR	0.848 ± 0.275	1.000 ± 0.152	
Range	0.079–1.000	0.002–1.000	
EQ-VAS			
Mean ± SD	79.57 ± 16.419	82.64 ± 13.939	0.052
Median ± IQR	80.00 ± 20.00	85.00 ± 11.00	
Range	30–100	10–100	

[a]In total, these data were retrieved for only 141 epilepsy patients.

Table 2. Distribution of QWB-SA self-rated health status and EQ-5D results

Group	Excellent (%)	Very good (%)	Good (%)	Fair (%)	Poor (%)
Epilepsy	2 (1.4)	26 (18.1)	53 (36.8)	56 (38.9)	7 (4.9)
Control	37 (11.5)	86 (26.6)	94 (29.1)	98 (30.3)	8 (2.5)
		EQ-5D (%)			
Level	Mobility	Self-care	Usual activity	Pain/discomfort	Anxiety/depression
1					
Epilepsy	133 (92.4)	133 (92.4)	122 (84.7)	94 (65.3)	75 (52.1)
Control	314 (97.2)	316 (97.8)	312 (96.6)	255 (78.9)	270 (83.6)
2					
Epilepsy	11 (7.6)	9 (6.3)	19 (13.2)	49 (34.0)	64 (44.4)
Control	7 (2.2)	7 (2.2)	11 (3.4)	65 (20.1)	52 (16.1)
3					
Epilepsy	0	2 (1.4)	3 (2.1)	1 (0.7)	5 (3.5)
Control	2 (0.6)	0	0	3 (0.9)	1 (0.3)

and level of education, the adjusted means for QWB-SA and EQ-5D are presented in Table S1.

The Shapiro-Wilk normality test showed that QWB-SA and EQ-5D utility scores were not normally distributed ($p < 0.0001$). The distribution of QWB-SA self-rating health status and EQ-5D are presented in Table 2. Particularly, for QWB-SA self-rating health status, from Fair to Very good, a decreasing trend was observed in both groups, with more subjects having excellent health status in the control group (11.5% vs. 1.4%). For EQ-5D, higher celling effects were observed in domains of mobility (92.4%), self-care (92.4%), and usual activity (84.7%) for the epilepsy group (Table 2).

Construct validity

Convergent validity

Convergent validity was demonstrated by moderate to strong correlation coefficients (0.365–0.590, $p < 0.0001$) of all the six a priori hypotheses between QWB-SA and EQ-5D on both scale and subscale levels (Table 3). The univariate analyses indicated that age, education level, working status, EQ-VAS score, and QWB-SA self-rating health status all contributed to the differences in the utility scores of QWB-SA and EQ-5D for either or both group(s) (Table S2). For example, there was a gradual reduction for utilities of both QWB-SA and EQ-5D in the control group with increasing age and decreasing education level, but the same effect was observed in the epilepsy group with increasing age only (Fig. 1). In the epilepsy group, working status alone contributed to the variation in the utility, with employed epilepsy patients reporting higher utilities on both instruments ($p = 0.005$; Table S2).

Discriminative validity

There was no significant correlation between MOB and AD ($p = 0.085$). However, weak correlations were observed between CPX and SC (−0.174), PAC and AD (−0.211), MOB and AD (−0.205), PAC and AD (−0.115), and MOB and SC (−0.120), which indicated lower correlations between different constructs (Table 3).

Discriminative validity was also confirmed via the know-group hypotheses, with epilepsy patients generating lower utility scores. Furthermore, congruent with the decreasing EQ-VAS score or the decline in QWB-SA self-rating health status, utilities of QWB-SA and EQ-5D also declined simultaneously. QWB-SA score also showed convergent validity with self-rating health status (Table S2).

Table 3. Correlation between QWB-SA and EQ-5D or EQ-VAS

	EQ-5D						
QWB-SA	M	SC	UA	PD	AD	Utility	EQ-VAS
CPX	−0.220	−0.174	−0.273	−0.402	−0.554	0.587	0.411
MOB	−0.365	−0.120	−0.226	−0.205	−0.080 (p = 0.085)	0.178	0.190
PAC	−0.533	−0.363	−0.425	−0.211	−0.115 (p = 0.013)	0.295	0.224
SAC	−0.373	−0.447	−0.509	−0.242	−0.163	0.303	0.183
Utility	0.258	0.236	0.326	0.400	0.524	0.590	0.415
						Pearson 0.569	

Underlined figures corresponded to the six a priori hypotheses being tested.
CPX, acute and chronic symptoms; MOB, self-care and mobility; PAC, physical activity; SAC, self-care and usual activity; M, mobility; SC, self-care; UA, usual activity; PD, pain/discomfort; AD, anxiety/depression.
$p < 0.01$ otherwise indicated.

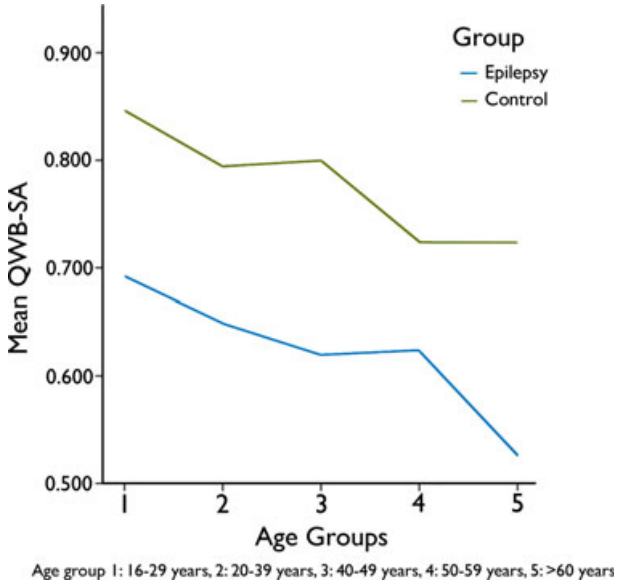

Figure 1.
QWB-SA utility scores by age groups.
Epilepsia © ILAE

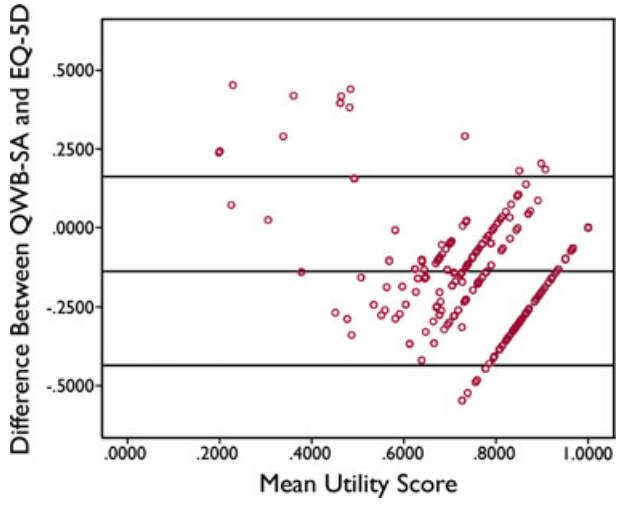

Figure 2.
Bland-Altman plot of difference in utility scores between QWB-SA and EQ-5D.
Epilepsia © ILAE

Sensitivity of QWB-SA

The Spearman's correlation coefficients identified seven variables significantly correlated with utility of QWB-SA and five factors with EQ-5D (Table S3). In addition, one-way ANOVA further indicated that there were significant differences in the utilities of QWB-SA according to varying seizure frequency and antiepileptic treatment. RE statistics also showed that after QWB-SA had stronger discriminative validity than the EQ-5D (except for ability to discriminate patients with different numbers of AEDs; Table S4). Subsequent MLR showed seizure frequency ($p = 0.039$) and AEDs treatment (mono vs. polytherapy; $p = 0.035$) as predictors of the utility on the QWB-SA. In contrast, there was no predictor for utility on the EQ-5D (Table S5).

Agreement between QWB-SA and EQ-5D

In our study, generally, subjects got higher utility scores on EQ-5D than QWB-SA in both groups. According to the one-sample *t*-test, a statistically significant difference was observed between utilities of QWB-SA and EQ-5D ($p < 0.0001$). However, when it came to the ICC, it also showed a strong correlation between these two measures, with ICC of 0.725 (95% CI 0.671, 0.771) for the entire sample. Again, a higher ICC was detected among patients with epilepsy (0.771, 95% CI 0.681, 0.835; Table S6).

Nevertheless, the minimal clinically important difference (MCID) for the EQ-5D is reported to range from 0.04 to 0.10 (Brazier et al., 2004; Le et al., 2013), and for the QWB-SA from 0.02 to 0.05 (Le et al., 2013). In our current study, the 95% CI of utility difference via the Bland-Altman analysis was −0.4508 to 0.1621 (Fig. 2), which demonstrated a difference between the two measures.

Table 4. Multiple linear regression analyses for utility differences between QWB-SA and EQ-5D

Independent variables	Dependent variable (utility differences)	
	Coefficient (95% CI)	p-Value
Age in years	0.001 (−0.001, 0.002)	0.891
Groups	0.053 (0.020, 0.086)	**0.002**
Education	−0.001 (−0.006, 0.005)	0.835
Ethnic minority	−0.003 (−0.124, 0.118)	0.964
Marital status	−0.020 (−0.058, 0.018)	0.310
Working status	−0.004 (−0.034, 0.026)	0.781
QWB-SA self-rated health status	−0.004 (−0.021, 0.012)	0.601
EQ-VAS	−0.001 (−0.002, 0.000)	**0.016**

Utility of QWB-SA is the subtrahend.
Significance level is $p < 0.05$ for the bold values.

Factors associated with the disagreement between QWB-SA and EQ-5D

When the difference between the QWB-SA and EQ-5D was modeled as a dependent variable, with age, education level, marital status, working status, different groups, QWB-SA self-rating health status, and EQ-VAS self-health rating scores modeled as independent variables, the results from multiple regression indicated that, except for EQ-VAS self-health rating scores ($p = 0.018$) and different groups ($p = 0.002$), other factors did not influence the disagreement between QWB-SA and EQ-5D. Furthermore, even with these significant factors, the magnitudes of the influence were very small, for example, the coefficients were −0.001 and 0.053 for EQ-VAS scores and different groups, respectively (Table 4). Therefore, no significant demographic variable or global quality of life (as measured by EQ-VAS and QWB-SA self-rating health status) was identified to contribute significantly to the different utilities between QWB-SA and EQ-5D; other nondemographic variables or the fixed bias between the two instruments might have caused such difference.

Discussion

Given that QALYs have been widely adopted as the effectiveness outcome in cost-effectiveness/utility analysis studies, the utility generated from generic preference-based HRQoL instruments is an important determinant in making clinical as well as health care allocation decisions. In the case of epilepsy, which is the most common neurologic disorders affecting people of all ages (Hauser et al., 1991; Forsgren et al., 2005; Preux & Druet-Cabanac, 2005), no generic preference-based HRQoL measure has yet been validated in epileptic patients in China. With the increasing numbers of new antiepileptic drugs/devices/technologies being invented and introduced, cost-effectiveness/utility analysis will be needed to assess their cost-effectiveness. Hence, a validated HRQoL instrument that could calculate QALYs would be the most useful and greatly in demand. Our study is the first to translate and validate such an instrument (QWB-SA) in Chinese epilepsy patients.

Studies have been conducted previously to investigate the psychometric properties of generic preference-based HRQoL instrument in English-speaking patients with epilepsy. In general, EQ-5D/UK/US, 15D, SF-6D, HUI-2, and HUI-3 were shown to be reliable utility instruments in an epilepsy population (Stavem et al., 2001; Langfitt et al., 2006). In addition, compared to EQ-5D/VAS, the following instruments seemed to be more capable of discriminating between patients with different seizure controls and seizure severity: HUI-2 and HUI-3, SF-6D. This would suggest better psychometric advantages of the SF-6D over the other preference instruments for epilepsy patients. Although 15D and the assessment of Quality of life (AqoL) were sensitive to variability at the upper end of the HRQoL continuum as well, the studies were not targeted at epilepsy patients (Langfitt et al., 2006).

The construct (convergent, discriminative, sensitivity) validity of QWB-SA has been successfully demonstrated in our study. Most importantly, the sensitivity of the QWB-SA was demonstrated by its ability to discriminate between different seizure frequencies and antiepileptic treatment (mono vs. poly) groups, which is of clinical importance. In addition, seizure frequency and antiepileptic treatment were found to be predictors of HRQoL as measured by the QWB-SA rather than the EQ-5D. Lastly 77 (16.5%) versus 275 (58.9%) subjects on the QWB-SA and the EQ-5D scored 1.0 (perfect health), respectively, which suggested that the QWB-SA has fewer ceiling effects.

The utility of the QWB-SA was substantially lower than that of the EQ-5D in both epilepsy and control groups. It was worth noting that the disagreement on utility scores for these two instruments was not uncommon and had been observed by previous large sample studies (N = 3,844; Fryback et al., 2007; Bentley et al., 2011; Khanna et al., 2011). The means for EQ-5D and QWB-SA were reported to be 0.89 and 0.67, respectively (Fryback et al., 2007), whereas subjects with arthritis reported utilities ranging from 0.77 to 0.80 on EQ-5D, and from 0.56 to 0.59 on QWB-SA. The same difference was also observed in the utility scores of subjects without arthritis (Khanna et al., 2011). Furthermore, when the participants were categorized according to body mass index (BMI), the utility score for the EQ-5D was also higher than the QWB-SA among normal, overweight, and obese subjects (Bentley et al., 2011). There might be two explanations for this observation: first, unlike the EQ-5D, which utilizes the time trade-off to elicit the preference-weight for each health state, the QWB-SA adopts VAS, and the utility scores derived from VAS tend to be inherently lower than the TTO or Standard Gamble (Fryback et al., 2007). Second, the large acute and chronic symptom weight in the QWB-SA may cause the utility to be lower than the EQ-5D, as the latter does not include detailed

symptoms. The difference in utility between EQ-5D and QWB-SA would raise a huge concern in future cost-effectiveness analysis, because the variation in utilities will definitely cause differences in the calculation of QALYs, and subsequently the incremental cost-effectiveness ratio (ICER). For example, in an analysis evaluating an antirheumatoid agent, it was reported that four kinds of HRQoL instruments (EQ-5D, HUI2, HUI3, and SF-6D) provided different QALYs and hence different ICERs (Marra et al., 2007). Hence, even if one AED generated obviously desirable ICER in indirect comparison with another AED, a decision could not be easily made because distinctive HRQoL measures with different sensitivities might have been utilized. Therefore, when conducting a cost-effectiveness analysis, the decision in choosing the ideal generic HRQoL measure has to balance the sensitivity and the generalizability of the instrument.

In our study, age- (Fig. 2) and education-by-group effects were observed on both the QWB-SA and the EQ-5D for the epilepsy or control populations. Generally, there was a downward trend in utility with increasing age (in both patient and control groups) and decreasing education level (in control population). However, our current results of the associations with age and education level observed in the epilepsy cohort were not in line with those of previous studies. According to a review of HRQoL determinants, age was not associated with HRQoL, whereas education level might be correlated although the conclusion was not consistent (Taylor et al., 2011). Nevertheless, the normative data of the QWB-SA reported a descending trend of utility with increasing age (Seiber et al., 2008). Therefore, the inherent attributes of the QWB-SA might be sensitive to identify changes in HRQoL affected by age, as the acute and chronic symptoms might occur more often in aged subjects, whereas other HRQoL measures such as the EQ-5D do not take the specific symptoms into account.

Furthermore, working status was another contributing factor of HRQoL for the epilepsy group. For both the QWB-SA and the EQ-5D, employed patients got higher scores even after age and level of education were controlled (e.g., the estimated QWB-SA utilities were 0.686 and 0.632 for employed and unemployed epilepsy patients, respectively). Still, the impact of employment status on the HRQoL of epilepsy patients was inconsistent across studies. Several studies showed unemployment associated with poorer HRQoL (Buck et al., 1999; Gilliam et al., 1999; Mollaoglu et al., 2004; Liou et al., 2005; Elsharkawy et al., 2009; Tlusta et al., 2009), whereas others reported no correlations (Choi-Kwon et al., 2003; Djibuti & Shakarishvili, 2003; Alanis-Guevara et al., 2005; Thomas et al., 2005; Mosaku et al., 2006; Tracy et al., 2007; Zhao et al., 2008; Giovagnoli et al., 2009). Even so, it should be noted that the sample size of three studies was <115, which indicated low statistical power (Thomas et al., 2005; Mosaku et al., 2006; Zhao et al., 2008). A recent study also reported that fully employed epileptic patients might have worse HRQoLs, owing primarily to the discrimination of and misconception about epilepsy in the work place (Mahrer-Imhof et al., 2012). So accordingly, the inconsistency in this result would necessitate future study to confirm.

As to the epilepsy-specific variables, in our multivariate analysis, seizure frequency was shown to be a predictor of HRQoL as measured by the QWB-SA. In addition to suggesting the better sensitivity of the QWB-SA over the EQ-5D, this is of clinical importance when evaluating the therapeutic effects of AEDs. If the HRQoL instrument is insensitive to changes in seizure frequency, the generated QALY and other clinical merits might be underestimated resulting in rejection of valuable therapy. Although numbers of AEDs were shown to be another predictor of utility by the QWB-SA in the present study, again, this association was not consistent across studies (Gilliam et al., 1999; Choi-Kwon et al., 2003; Johnson et al., 2004; Thomas et al., 2005; Tracy et al., 2007). Actually, it is well acknowledged that antiepileptic monotherapy may have several advantages compared to polytherapy in terms of better tolerability, improved adherence, fewer interactions, and lower cost (Guberman, 1998). In addition, adverse effects of AEDs have been shown to be positively associated with decreased HRQoL (Luoni et al., 2011). Therefore, it is reasonable to expect patients who are taking more than one AED to experience more toxic effects of medication, and consequently have poorer HRQoL. Yet, the correlation between numbers of AEDs and HRQoL requires future study to confirm.

The QWB-SA normative data (mean $\pm$ SD) reported that the utilities for clinical and control (general outpatient medical sample) cohorts were 0.599 ± 0.1629 to 0.648 ± 0.1257 and 0.602 ± 0.1323 to 0.67 ± 0.1286 for various age groups (range from 18 to >71 years) (Seiber et al., 2008). Studies were also conducted utilizing the QWB-SA to investigate HRQoL for different disease cohorts. For instance, a study that recruited inpatients and outpatients with depression found that the QWB-SA scores for inpatients were substantially lower than those for outpatients (0.383 ± 0.118 vs. 0.479 ± 0.115) (Pyne et al., 2003). Other reported QWB-SA utilities included family medicine controls (0.6427 ± 0.1349) and subjects with arthritis (0.4966 ± 0.1542) (Frosch et al., 2004); as well as presurgery cataract subjects (0.595 ± 0.134) (Rosen et al., 2005). The epilepsy data from our data set were comparable to the QWB-SA normative data as well as those from the general medical controls, although the utilities in our controls seemed to be higher than the controls from aforementioned studies. There might be several reasons underlying this. First of all, the controls from our data set were substantially younger (36.15 ± 16.406) as HRQoL would decline with increasing age (Seiber et al., 2008). Second, the participants were generally relatives/caregivers of patient group, medical school students, and hospital general staff, most may enjoy better health than subjects from outpatient medical

samples or family medicine controls as included in the QWB-SA normative sample.

Nevertheless, several limitations should be noted. First of all, interrater reliability and responsiveness were not tested due to the cross-sectional design of our study. Admittedly, responsiveness is an important psychometric property of an HRQoL instrument, especially for epilepsy due to its chronic nature and unpredictability of seizures, thus requiring treatment adjustment from time to time. Second, heterogeneity existed between our two groups in terms of age, gender, level of education, and employment status. As identified by our study, the factors age, education, and employment might have associations with quality of life; the variation in these demographic data would somewhat introduce bias to the result. Nonetheless, even when age and education level were adjusted, utilities of the QWB-SA and the EQ-5D still showed differences between two groups. Third, the preference weights utilized to estimate the utilities of the QWB-SA and the EQ-5D were not originated from Chinese subjects (one from America, the other from United Kingdom). However, it was found that the preference scoring does not vary significantly, and the results are similar across different countries (Drummond et al., 2005). Nevertheless, future study to address the responsiveness of the Chinese QWB-SA and to ascertain the preference weights from societal perspective of China is still needed.

In conclusion, from the present study, the QWB-SA was shown to cover more dimensions of HRQoL, have better sensitivity, fewer ceiling effects, and less skewed distribution than the EQ-5D. Hence, it is potentially a more suitable HRQoL measure for patients with epilepsy in China.

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Disclosure

None of the authors has any conflict of interest to disclose. All the authors confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this study is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Adjusted means for QWB-SA and EQ-5D for epilepsy and control groups.

Table S2. Univariate analyses for QWB-SA and EQ-5D.

Table S3. Spearman's correlation coefficients between HRQoL scores and demographic variables (Epilepsy group).

Table S4. Results of one-way ANOVA according to epilepsy-specific variables.

Table S5. Multiple linear regression analysis for QWB-SA and EQ-5D.

Table S6. Intraclass Correlation Coefficient (ICC), Pearson correlation and Spearman rho between QWB-SA and EQ-5D.

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COST-UTILITY ANALYSIS OF LIRAGLUTIDE VERSUS GLIMEPIRIDE AS ADD-ON TO METFORMIN IN TYPE 2 DIABETES PATIENTS IN CHINA

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Objectives: The aim of this study was to evaluate the long-term cost-utility of liraglutide versus glimepiride as add-on therapy to metformin in patients with type 2 diabetes mellitus (T_2DM), based on the results of clinical trial conducted in Asian population.
Methods: The validated UKPDS Outcomes Model was used to project life expectancy, quality adjusted life-years (QALYs), incidence of diabetes-related complication and cost of complications in patients receiving those regimens. Baseline cohort characteristics and treatment effects were derived from an Asian study. China-specific complication costs and utility score were taken from local studies. Patients' outcomes were modeled for 30 years and incremental cost-effectiveness ratios were calculated for liraglutide compared with glimepiride from the healthcare system perspective. Both future costs and clinical benefits were discounted at 3 percent. Sensitivity analyses were performed.
Results: Over a period of 30 years, compared with glimepiride, liraglutide 1.8 mg was associated with improvements in life expectancy (0.1 year) and quality adjusted life-year (0.168 QALY), and a reduced incidence of diabetes-related complications leading to an incremental cost-effectiveness ratio per QALY gained versus glimepiride of CNY 25,6871 (DEC 2010, 1 USD = 6.6227 CNY).
Conclusions: Long-term projections indicated that liraglutide was associated with increased life expectancy, QALYs, and reduced complication incidences comparing with glimepiride. When the UK cost of liraglutide was discounted by 38 percent, liraglutide would be a cost-effective option in China from the healthcare system perspective using the 3X GDP/capita per QALY as the WTP threshold.

Keywords: Cost-effectiveness, Cost-utility analysis, Liraglutide, Glimepiride, Type 2 diabetes mellitus, UKPDS Outcomes Model

Type 2 Diabetes Mellitus (T_2DM) is a serious progressive endocrinology disease characterized by insulin resistance and/or impaired insulin secretion, which imposes great financial burden to health systems internationally. To date, there are approximately 20 million diabetes sufferers in China, and the number is expected to reach 50 million in 2025 (30).

According to COED-2 study conducted in Europe, a breakdown of cost drivers showed hospitalization contributed 55 percent of all direct medical costs for patients with T_2DM, whereas insulin and other anti-diabetic drugs' costs only accounted for 7 percent of total healthcare costs. Furthermore, this study also recognized that the presence of different diabetic-related complications was the single factor having the largest impact on costs of patients with T_2DM, thus, highlighting complication costs as a substantial contributor of the direct medical cost burden of T_2DM (13).

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist, which is an incretin hormone analogue. It has just been introduced into China on October 9, 2011. As an anti-diabetic agent, liraglutide is the first once-daily human GLP-1 analogue with actions of stimulating insulin secretion from β-cell in glucose-dependent manner, inhibiting glucagon secretion, hepatic glucose output, decelerating gastric emptying and reducing appetite and food intake (8;10;20;27). It has been indicated in early studies that incretin-based therapy is a promising option in the continuum of T_2DM management (31).

The efficacy and safety of liraglutide in different populations have been extensively reported by a global phase 3 developmental program. The program comprised of six randomized controlled trials conducted at more than 600 sites in 40 countries involving more than 4,000 patients. In LEAD 1 to LEAD 6 trials, substantial and sustained improvements in HbA_{1c}, fasting plasma glucose and postprandial glucose have been achieved with liraglutide treatment (2;9;17;21;28;43). Recently, a study conducted in an Asian population using glimepiride as comparator also showed similar results (41).

However, the acquisition costs for liraglutide is high when compared with other available anti-diabetic treatments. It is imperative to ascertain whether the administration of liraglutide is cost-effective in the long-term, as healthcare decision makers will need these data to determine its optimum place in therapy and justify its value for money.

Hence, we conducted an economic evaluation of liraglutide using the UKPDS Outcome Model to estimate the long-term cost-effectiveness comparing liraglutide and glimepiride both as add-on therapy to metformin in treating T_2DM.

Authors acknowledge UKPDS Outcomes Model.

Table 1. Changes from Baseline and Modelled Management Costs and Utility Decrements

	HbA1c reduction from baseline(%)	Changes in body weight	SBP reduction (mmHg)	Changes in TC(mmol/L)	Changes in HDL(mmol/L)
Liraglutide 0.6mg	1.14	−1.80†	3	–	–
Liraglutide 1.2mg	1.36	−2.35†	3‡	−0.02	−0.02
Liraglutide 1.8mg	1.45	−2.44†	3‡	−0.30	−0.03
Glimepiride 4mg	1.39	+0.08	0.91	0.09	−0.02

	Annual cost			Utility decrement	
	Year			Year	
Condition	1		>1	1	>1
	Fatal	Non-fatal			
Ischemic Heart Disease		33592	5997	−0.090	−0.090
Myocardial Infarction	40050	40050	9200	−0.055	−0.055
Heart Failure	13319	13319	8096	−0.108	−0.108
Stroke	12097	15609	7029	−0.164	−0.164
Amputation	15688	15688	12505	−0.280	−0.280
Blindness		10366	8000	−0.074	−0.074
Renal Failure	98639	98639	79143	−0.263	−0.263

*Comparing with Glimepiride
† $p<0.0001$
‡ $p<0.05$

MATERIALS AND METHODS

Model Description

The UKPDS Outcomes Model forecasts long-term life expectancy, quality adjusted life expectancy and cost consequences in patients with T_2DM (4). Our data used in the modeling were drawn from local clinical trials, and when local data were not available, the opinions from experts were supplemented.

Treatment Effects

Treatment effects were taken from the Asian study comparing liraglutide with glimepiride, both as add-on to metformin (41). This study was conducted in several Asian countries including China, South Korea, and India using a similar study design as LEAD-2 trial except the lack of metformin plus placebo arm (21). Among the patients recruited, Chinese subjects from seventeen different sites accounted for 51.3 percent of total 928 participating subjects. After a treatment period of 16-week, liraglutide led to improvement in glycemic control similar to that with glimepiride but with less frequent major and minor hypoglycemia, significant weight loss and reduced systolic blood pressure. Treatments with liraglutide 1.2 and 1.8 mg were non-inferior to glimepiride in terms of HbA_{1c} reduction. Liraglutide was associated with an improvement in HbA_{1c} of 1.14 percent (0.6 mg), 1.36 percent (1.2 mg), and 1.45 percent (1.8 mg), respectively. Meanwhile, Glimepiride 4 mg led to a 1.39 percent reduction in HbA_{1c}. These reduction rates were modeled as an initial decrease from baseline levels (Table 1) followed by a natural progression in line with that observed in the UKPDS (32). Overall, results obtained in country subgroups were similar to the whole population (41).

Simulated Cohort

The baseline characteristics and risk factors of the simulated cohort of 1000 subjects were based on the Asian study (41). Additional baseline risk factors (cholesterol and HDL cholesterol) were supplemented with data from the Shanghai diabetes studies (12) and other published sources (31;34;40) (Supplementary Table 1, which can be viewed online at www.journals.cambridge.org/thc2012061). The effects of liraglutide and glimepiride in lowering HbA_{1c}, body weight, systolic blood

pressure, and lipid profile were obtained from Asian trials and economic evaluation regarding liraglutide (Table 1) (33;41). Data regarding the development of seven major diabetes-related complications was based on the study conducted by Palmer et al. (25). The risk factors at diagnosis of T_2DM were obtained from two published studies of Chinese patients newly diagnosed with T_2DM (18;42).

Costs and Perspective

The economic evaluation was undertaken from the health care system perspective, thus we included costs of managing diabetes, anti-diabetic treatments, and addressing clinical complications.

The usage of health resources was abstracted from previous published literatures regarding the economic evaluation of anti-diabetic treatment in Chinese diabetes population (25;26;39) and inflated to 2010 value (Table 1 and Supplementary Table 2, which can be viewed online at www.journals.cambridge.org/thc2012061). Acquisition costs of liraglutide, glimepiride, and metformin were derived from publications (39) or official web sites (22) or estimation of experts (in the case of glimepiride) (Supplementary Table 2). Because none of the current therapies influence the progressive loss of beta-cell function, most people with T_2DM will eventually require insulin. Therefore, our treatment duration was set to 5 years in attempt to replicate clinical practice.

Utilities

In our model, we used quality adjusted life-years (QALYs) gained as our principal outcome. The initial utility score was adapted from a study conducted in sixteen hospitals in China to investigate the association between side effects of oral anti-diabetic drugs and self-reported mental health and quality of life among patients with T_2DM (3). Based on this study, patients with non–insulin-treated T_2DM were assumed to have an EQ-5D score of 0.92 (3). Disutilities associated with diabetes-related complications were obtained from UKPDS and another study (4;15) (Table 1).

Discounting and Time-horizon

Both costs and QALYs were discounted at a rate of 3 percent, according to the recommendation made by World Health Organization (WHO) (36). The time horizon was set to 30 years to capture the long-term mortality and morbidity of diabetes. The administration of liraglutide was set to 5 years, after which the same insulin treatment was used in both groups (33), so both outputs would continue to discount at a rate of 3 percent in the subsequent years.

Cost-utility Analysis

In our Monte-Carlo simulation, we set the number of internal loops per subject as 1,000 to address parameter uncertainty and estimate confidence intervals regarding the main outputs (5). An incremental cost per QALYs gained was calculated to compare each of different treatment regimens. However, there is no official Willingness-to-Pay (WTP) per QALY threshold in China. According to the recommendation of the Commission on Macroeconomics and Health of the World Health Organization, the maximum value of one year of healthy life is around one to three times the Gross Domestic Production (GDP) per capita (35). Some studies had used this recommendation to establish the threshold for their economic evaluations (1;19;25). Because the GDP per capita was CNY 29,748 (USD 4,428) in China in 2010 according to National Bureau of Statistics of China, we take CNY 100,000 (USD 15,099) as threshold in our evaluation. (DEC 2010, 1 USD = 6.6227CNY)

Sensitivity Analysis

We conducted several one-way sensitivity analyses to assess the effect of varying primary model parameters on the final outcomes. To explore the uncertainty around the cost data reported by different studies, two analyses were performed with the complication costs and management costs increased and decreased both 20 percent. The impact of discount rate was addressed by using different discount rates to costs and benefits (0 percent and 6 percent, respectively).

Additionally, the time horizon was also changed to investigate the influence of various time periods on projected outcomes. Because the initial utility score of T_2DM patients in China might not be identical with those captured by the UKPDS study, we incorporated UKPDS utility outcome into sensitivity analysis to test the stability of our outcome as well. Furthermore, we reset the current level of HbA_{1c} and systolic blood pressure equivalent in all four groups, to identify which aspect of the profile contributed most to the outcomes under the same treatment effect. Lastly, prolonged treatment duration (liraglutide and glimepiride treated for 10 years) and varied acquisition cost of liraglutide (10 percent, 25 percent, 50 percent, and 75 percent discount off the official price) were evaluated in the sensitivity analyses.

RESULTS

Clinical Outcomes

Over a period of 30 years, liraglutide (1.8 mg) treatment was associated with improvements in discounted life expectancy of 0.1 years per patient compared with glimepiride (12.5 [95 percent confidence interval {CI}: 11.6,13.5] versus 12.4 [95 percent CI: 11.5,13.3]) (Table 2). When the health-related quality of life (HRQoL) was included in the analysis, liraglutide 1.8 mg treatment was associated with a 0.168 QALYs increase per patient compared with glimepiride (11.3 [95 percent CI 10.4,12.1] versus 11.1 [95 percent CI 10.3,11.9]). However, the liraglutide 0.6 and 1.2 mg treatments were not superior to glimepiride in terms of life expectancy and QALYs over 30 year's simulation.

Nevertheless, patients received liraglutide therapy (of all three doses) enjoyed a reduced cumulative incidence of

Table 2. The Results of Cost-Effectiveness Analysis (In CNY)

Outcome	Liraglutide 0.6mg	Liraglutide 1.2mg	Liraglutide 1.8mg	Glimepiride 4mg
Life expectancy	11.8(10.9–12.7)	12.0(11.1–13.0)	12.5(11.6–13.5)	12.4(11.5–13.3)
Total QALYs (95% CI)	10.6(9.8–11.4)	10.8(10.0–11.7)	11.3(10.4–12.1)	11.1(10.3–11.9)
Total cost of complications	80916.50 (72156.89,89676.12)	82096.25 (73321.96,90870.53)	84503.41 (75601.62,93624.02)	88120.51 (77810.90,98414.37)
Total costs	103382.25	127027.75	151900.66	108746.32
ICER	–	–	256871	Comparator

Table 3. Cumulative Incidence of Diabetes Related Complications over 30-year Period

	Cumulative incidence%			
Condition	Liraglutide 0.6mg	Liraglutide 1.2mg	Liraglutide 1.8mg	Glimepiride 4mg
Ischemic Heart Disease	9.702	9.754	9.455	10.567
Myocardial Infarction	24.694	23.484	22.37	25.214
Heart Failure	7.424	7.3935	6.978	7.974
Stroke	8.39	8.102	7.82	11.065
Amputation	3.122	3.172	3.156	4.170
Blindness	5.813	5.939	5.604	5.435
Renal Failure	1.206	1.28	1.315	2.398

most diabetes-related complications compared with glimepiride (Table 3). The reduction of incidences ranged between 0.996 and 3.245 incidences for ischemic heart disease, myocardial infarction (MI), heart failure, stroke, amputation, and renal failure. The most notable decrease occurred in the incidence of MI which accounted for the second largest complication costs. Another relatively significant reduction reducing from 2.398 (glimepiride) to 1.206 (liraglutide 0.6 mg) took place in the incidence of renal failure, which constituted the largest amount of complication costs. In comparison, glimepiride treatment only showed a maximum advantage in a reduced incidence of blindness of 0.504.

Cost Outcomes

Treatment with liraglutide was associated with an increased direct cost compared with glimepiride primarily due to higher drug acquisition costs, which would be partially offset by lower diabetes-related complication costs. Direct medical cost of administration liraglutide (1.8 mg) over 5 years were CNY 45,479 higher per patient than glimepiride, while the complication costs averted by using liraglutide was CNY 7,204.01, 6,024.26, 3,617.106 for 0.6 mg, 1.2 mg, and 1.8 mg doses, respectively (Table 2).

Evaluation of Cost-effectiveness

From our base-case analysis, administration of liraglutide (1.8 mg) was associated with an ICER of CNY 256,871 per QALY gained (95 percent CI: 132159, 440762). Because the 0.6 and 1.2 mg liraglutide were not superior to glimepiride in terms of gain in life expectancy or QALYs, no attempt was made to calculate the ICER for those groups (Table 2). Comparing with the WTP per QALY threshold in China adopted in our current study, we cannot conclude liraglutide as cost-effective when using glimepiride as the comparator.

Sensitivity Analyses

Sensitivity analyses indicated that the base case findings were most sensitive to variation in the systolic blood pressure benefit of liraglutide and the assumption regarding the time horizon. Shortening the time horizon diminished the clinical benefits associated with liraglutide in terms of complication avoided as diabetes-related complications require time to develop. As a result, the ICER of liraglutide 1.8 mg versus glimepiride was increased from CNY 256,871 to CNY 1,262,286 when shortening time horizon from 30 years to 10 years. Discount rate also exerted positive influence on the consequences. However, variations in the cost of complications, initial utility score and the effect of reducing the level of HbA_{1C} had little impact on the incremental findings (Table 4).

Table 4. Results of Sensitivity Analyses

	Life expectancy			QALYs			Total cost of complications			
Sensitivity analysis	L 1.8	G	Differences (CI)	L 1.8	G	Differences (CI)	L 1.8	G	Differences (CI)	ICER
Base case 30-year time horizon	12.5	12.4	0.125 (0, 0.2)	11.3	11.1	0.168 (0.1, 0.3)	84503.41	88120.51	3617.106 (1402.8, 5831.4)	256871 (132159, 440762)
10-year time horizon	7.8	7.8	0.020 (0, 0.1)	7.1	7.1	0.035 (0, 0.1)	49642.76	50941.78	1299.018 (863.9, 1734.1)	1262286 (437450, 44615000)
20-year time horizon	11.5	11.4	0.065 (0, 0.1)	10.4	10.2	0.141 (0.1, 0.2)	76017.36	78836.47	2819.109 (1301.7, 4336.5)	311726 (205710, 441770)
40-year time horizon	12.7	12.5	0.137 (0, 0.2)	11.4	11.2	0.184 (0.1, 0.3)	85571.85	89247.09	3675.241 (1326.9, 6023.6)	234224 (131517, 441520)
Discount rate of 0%	16.4	16.2	0.199 (0.1, 0.3)	14.8	14.5	0.267 (0.1, 0.4)	112939.04	118434.22	5495.179 (1812.7, 9177.7)	154596 (90753, 436660)
Discount rate of 6%	10.0	9.9	0.080 (0, 0.1)	9.0	8.9	0.111 (0.1, 0.2)	66449.64	68968.63	2518.992 (1109.8, 3928.2)	398680 (207755, 443690)
Complication costs increased by 20%	12.5	12.4	0.123 (0, 0.2)	11.3	11.1	0.168 (0.1, 0.3)	89147.37	93943.80	4796.432 (2088.8, 7504.0)	249857 (126583, 433900)
Complication costs decreased by 20%	12.5	12.4	0.123 (0, 0.2)	11.3	11.1	0.168 (0.1, 0.3)	79859.33	82297.06	2437.730 (707.9, 4167.5)	263897 (137703, 447710)
Initial utility score at 0.785	12.5	12.4	0.123 (0, 0.2)	9.6	9.5	0.151 (0.1, 0.2)	84503.41	88120.51	3617.106 (1402.8, 5831.4)	285797 (198240, 440760)
Same effect in reducing HbA1c	12.5	12.4	0.112 (0, 0.2)	11.3	11.1	0.161 (0.1, 0.2)	84503.41	88494.02	3990.613 (1801.9, 6179.3)	265726 (196500, 436770)
Same effect in reducing Sys BP	12.5	12.5	0.032 (0, 0.1)	11.3	11.2	0.060 (0, 0.1)	84467.49	87044.05	2576.563 (878.3, 4274.8)	736598 (412040, 44601000)
Cost of liraglutide reducing 10%*	12.5	12.4	0.125 (0, 0.2)	11.3	11.1	0.168 (0.1, 0.3)	84503.41	88120.51	3617.106 (1402.8, 5831.4)	209077 (109703, 373390)
Cost of liraglutide reducing 25%§	12.5	12.4	0.125 (0, 0.2)	11.3	11.1	0.168 (0.1, 0.3)	84503.41	88120.51	3617.106 (1402.8, 5831.4)	156496 (42254, 272170)
Cost of liraglutide reducing 50%†	12.5	12.4	0.125 (0, 0.2)	11.3	11.1	0.168 (0.1, 0.3)	84503.41	88120.51	3617.106 (1402.8, 5831.4)	56229 (−58012, 171904)
Cost of liraglutide reducing 75%‡	12.5	12.4	0.125 (0, 0.2)	11.3	11.1	0.168 (0.1, 0.3)	84503.41	88120.51	3617.106 (1402.8, 5831.4)	Dominant
Treatment duration for 10 years	12.6	12.4	0.246 (0.1, 0.4)	11.4	11.1	0.293 (0.2, 0.4)	83995.65	87791.90	3796.257 (1644.6, 5947.9)	306309 (212525, 446565)

*treatment with Liraglutide 1.8mg were 64641.10 after discount

§ treatment with Liraglutide 1.8mg were 50534.25 after discount

† treatment with Liraglutide 1.8mg were 33689.50 after discount

† treatment with Liraglutide 1.8mg were 16844.75 after discount

Sensitivity analysis by varying the treatment effect produced cost-effectiveness findings very similar to those in the base case. In the analysis, assuming that glimepiride had the same effect as liraglutide in reducing systolic blood pressure created an ICER of CNY 736,598 per QALY gained, providing evidence that this parameter is the main clinical driver in the modeling study. Whereas eliminating the benefit of liraglutide in reducing the level of HbA_{1c} (although this result was not statistically significant in the Asian study), the modeling finding was relatively stable, with an ICER of CNY 265,726 per QALY gained. Similarly, although the QALY gained was augmented (0.125), prolonging treatment duration to 10 years did not decrease the cost per QALY probably because increased acquisition cost of liraglutide cannot be compensated by the reduced complication costs. In contrast, the sensitivity analyses by varying the acquisition cost for liraglutide had significant influences on the ICER outcome. Specifically, a reduction of the drug price of liraglutide by 50 percent, would result in an ICER of CNY 56,229 per QALY, rendering liraglutide as a cost-effective option against the CNY 100,000 WTP threshold (Table 4).

DISCUSSION

In the UK, the National Institute for Health and Clinical Excellence has issued recommendations for the optimum management of T_2DM (22;23). According to the recommendations, liraglutide may be considered as a third-line option in combination with metformin and sulphonylurea or in dual therapy (with metformin or sulphonylurea) in certain circumstances (22;23). However, the relative high acquisition cost may prevent its use. So a modeling analysis to project the long-term outcomes and benefits based on the clinical trials and epidemiologic studies of liraglutide is necessary. This is of particular importance in the Asian setting where health care resources are relatively limited.

In the Asian setting, a study group using CORE Diabetes Model had performed an evaluation based on the same clinical trial data as we used (41). As a conference abstract, detailed information was not provided and neither the ICER was reported, but their results were in favor of liraglutide 1.2 and 1.8 mg over glimepiride on the ground that it improved the life expectancy and quality adjusted life-years by 0.051 year and 0.107 QALY, respectively (38). So to the best of our knowledge, our study is the first economic evaluation regarding the long-term cost-utility analysis using efficacy, utility score and costs data from local studies, implemented in UKPDS Outcomes Model. Our analysis provided evidences that administration of liraglutide was associated with improvements of life expectancy and quality adjusted life expectancy, as well as reduced incidence of diabetes-related complications compared with glimepiride.

However, the ICER value obtained from our cost-utility analysis exceeds the threshold of CNY 100,000 per QALY, thus we cannot conclude liraglutide as cost-effective when using glimepiride as comparator. To interpret the results of modeling analysis, we can see that the greater reduction of HbA_{1c} from baseline, the higher liraglutide dose is required with corresponding increasing costs. Therefore, if lower dose of liraglutide demonstrates better performance on this parameter, the cost-effectiveness profile of liraglutide would be improved. Our sensitivity analysis showed that even with same effect in reducing the level of HbA_{1c}, liraglutide was still superior to glimepiride in terms of life expectancy, quality adjusted life expectancy and cost of complications probably because of the benefit in lowering systolic blood pressure and lipid profile. Additionally, the sensitivity analysis identified acquisition cost of liraglutide as another major factor underlying the ICER outcome. A reduction of acquisition cost used in our model by at least 50 percent is required to produce an acceptable ICER against our predefined threshold.

There were economic evaluations worldwide performed regarding liraglutide for T_2DM, which were unanimously in favor of liraglutide compared with traditional antidiabetic comparators (7;11;24;29). Additionally, liraglutide was also compared with other kinds of GLP-1 analogs such as exenatide (33;36). Both studies concluded that liraglutide was a cost-effective treatment option for T_2DM when comparing to exenatide.

Economic evaluations comparing the effect of liraglutide with glimepiride were performed in different countries as well. Davies et al. (6) estimated an incremental cost per QALY gained for 1.2 and 1.8 mg liraglutide versus glimepiride as £9,449 and £16,501, respectively. A Health Technology Assessment (HTA) report submitted by Nova Nordisk also presented an ICER of £13257 and £19837 separately for liraglutide 1.2 and 1.8 mg when glimepiride was used as the comparator (23). Comparing to the recommended threshold for economic evaluation (£20,000) in UK, all the results favored liraglutide.

The difference in cost-effectiveness result arising from our modeling study could be interpreted from two aspects. First, the initial utility score used in our model was much higher than the UKPDS default utility. We derived such utility score from a T_2DM based population under oral anti-diabetic drugs treatment in China (3). Because the profile of participants in that particular study was not identical with the Asian study (41), this may lead to overstating the utility of those Asian cohort (for example, the participants in the Asian study had longer duration of diabetes and higher HbA_{1c} levels). When comparing with the demographic data of the UKPDS (4), the subjects from the UK study had higher mean age and longer diabetes duration than the Asian and Chinese cohort (41). Moreover, a proportion of them had a history of diabetes-related complications, thus providing a reasonable explanation for the poorer HRQoL compared with ours (4). However, it was worth noting that the utility score did not have major influence on the findings. When we performed the sensitivity analysis using the same utility score from UKPDS study, the ICER was relatively stable (CNY 285,797 per QALY gained).

The second explanation came from the intrinsic limitations of the UKPDS Outcomes Model. This model only predicts the first event in any single category of diabetes-related complications, and does not allow series of events such as sequential amputations to be modeled directly as such multiple events in the UKPDS data were relatively infrequent (5). Furthermore, the benefits of reduction in weight and other treatment-related adverse events were not taken into consideration. Lastly, comparing with CORE diabetes outcomes model, UKPDS Outcomes Model does not incorporate certain important diabetes-related complications, including peripheral vascular disease/peripheral artery disease, retinopathy, foot ulcer/diabetic foot syndrome, neuropathy/peripheral neuropathy/nerve and vascular system. The benefits (in terms of reduced incidences of these complications and their associated costs, and improved health-related quality of life) may not be fully captured and therefore underestimated. As such, the use of UKPDS Outcomes Model may result in an overestimation of incremental cost-effectiveness ratio to some extent (4;15). This offered an important interpretation for our unfavorable results toward the use of liraglutide.

There are also some limitations in our study. Because the Asian trial just included members with HbA_{1c} ranged between 7.0 percent and 11.0 percent, the subjects with more unsatisfactory blood glucose control were excluded. This selection bias may affect the generalizability of the results from applying into real-life clinical setting. The duration of T_2DM also posed an uncertainty. Patients of T_2DM with varying duration of disease may have different response to the anti-diabetic drugs because their pancreatic function would deteriorate with disease progression. Another limitation is that the UKPDS Outcomes Model was developed based on the data of 3642 patients (white, Asia-Indian, and Afro-Caribbean) with T_2DM from UK, the risk equation derived from this population may not be applicable to other racial groups including Chinese. Another concern is that the majority of efficacy data in our model were based on the Asian study of relatively short duration (in our case, 16 weeks). In T_2DM, inadequate treatment durability is a key concern because it complicates ongoing glycemic control over time (14). Furthermore, we assumed that all the simulated subjects adhere to the original treatment through their lifetime without considering treatment discontinuation, however, this is true with all modeling practices. This assumption may not represent true clinical practice, because patients with unsatisfied glycemic control would switch to other therapies like insulin injection when the target level of blood glucose and HbA_{1c} were not achieved.

By adopting CNY 100,000 (USD 15,099) per QALY gained as the threshold, we calculate the maximum acquisition cost to make liraglutide (18 mg) cost-effective would be CNY 228.02 (USD 34.43). This new maximum price of liraglutide is 62 percent of CNY 369.2 (USD 55.75) of the drug cost that was used in our modeling.

As shown in Supplementary Table 4, if we adopted the 1–2 times GDP per capita as WTP thresholds, our result would show liraglutide to be a cost-effective option among the developed Asian countries or regions, namely, Hong Kong, Taiwan, South Korea, Singapore, Macau, and Japan. Whereas among the Asian developing countries, even when we used three times of GDP per capita, the results would still exceed the cost-effective threshold.

One of the critical uncertainty impacting cost-effectiveness in our modeling was the drug cost which we derived from British National Formulary (22). However, if different WTP thresholds were to be used for different countries, the acquisition cost for liraglutide must be different in different countries for the drug to be considered cost-effective. Differential drug pricing for different countries is not an unreasonable assumption or option because the price of a specific drug has the negotiable procurement discount and other consideration that the company would apply for marketing the drug. Thus we estimated the cost-effective price of liraglutide in different settings based on the data from present study. Except for the high income economies (where one time GDP per capita was used), one to three times of GDP per capita were used as the WTP per QALY threshold to calculate the cost-effective price of liraglutide in different economic settings (Supplementary Tables 3 and 4, which can be viewed online at www.journals.cambridge.org/thc2012061). From this exercise, the cost-effective price of liraglutide is estimated to range from USD 20.08 to 21.08 in low income regions, and from USD 54.51 to 56.00 in high income economies. These estimates would provide some suggestions for the pharmaceutical companies when seeking reimbursement for liraglutide in distinctive healthcare systems and for health administrators or health insurance to negotiate price.

Furthermore, the approved doses of liraglutide (1.2 mg) did not show to be superior to glimepiride in terms of improvements in life expectancy and QALYs gained in our present study. Undoubtedly, the lower dose would mean lesser costs of liraglutide, if future RCT could demonstrate better therapeutic effects of 1.2 mg liraglutide versus glimepiride, the cost-effective profile of liraglutide would be different and so will be the ICER for liraglutide.

Finally, another theoretical consideration would be whether different WTP threshold should be applied for different diseases as WTP is highly associated with the physical and psychological effects of specific illness. However, this is an issue that can apply in the evaluation of all new drugs and not unique for this case.

Because the healthcare system differs from country to country, health resource usage and medication cost due to T_2DM could vary substantially. Furthermore, even with identical reduction in HbA_{1c} after treatment with liraglutide as shown in the Asian trial, QALYs gained could still be different due to psychological and cultural factors. Hence, CUA study should use local cost and effectiveness data to be truly reflective of the cost-effectiveness for the specific jurisdiction, and the results are difficult to be transferable. However, we have partially overcome this problem but using per capita GDP of individual countries and the recommended WHO WTP thresholds to

estimate the "cost-effective" price for a new drug. Such approach could provide valuable guidance for drug price setting and reimbursement.

In conclusion, our present modeling suggested that the administration of liraglutide was associated with improvements in life-year and QALYs gained, and lower incidences in diabetes-related complications than glimepiride regardless of country-specific issues. However, the economic status of individual country would exert substantial influence in interpreting the cost-effectiveness analysis. As such, the incremental cost-effectiveness ratio is not just positively connected with the effectiveness and acquisition cost of that drug, but also with country-specific issues.

POLICY IMPLICATIONS

Based on the long-term simulation in our model, 1.8 mg liraglutide was associated with improvements in life expectancy, QALYs gained, and decreased incidences in diabetes-related complications, comparing to glimepiride. When the UK cost of liraglutide was discounted by 38 percent, the administration of liraglutide would be cost-effective in China using CNY 100,000 per QALY as the WTP threshold. If adopting three and one time of GDP per capita per QALY as the WTP threshold, the cost-effective price of liraglutide 18 mg is estimated ranging from USD 20.08 to 21.08 in low income regions and from USD 54.51 to 56.00 in high income economies. This information would assist policy makers and health insurers in deciding the reimbursed price for liraglutide for their respective regions.

SUPPLEMENTARY MATERIAL

Supplementary Tables 1–4: www.journals.cambridge.org/thc2012061

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CONFLICTS OF INTEREST

All authors report they have no potential conflicts of interest.

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Chapter 5. Health-related quality of life (HRQoL) and Willingness to pay per Quality-adjusted Life year (WTP/QALY) Threshold-- A Study in patients with epilepsy in China

Abstract

Objectives

To assess the Health-related quality of Life (HRQoL) and Willingness-to-Pay (WTP) per QALY amount of patients with epilepsy in China.

Methods

Adults with epilepsy and a healthy control were recruited in two tertiary hospitals in China. Participants completed two indirect utility elicitation instruments (QWB-SA and EQ-5D) and a WTP questionnaire. Correlations between socio-demographic or epilepsy specific variables and HRQoL or WTP/QALY were assessed to identify the candidate predictor. Multiple linear regression model was adopted to investigate the predictive performances of identified candidate predictors. Data analyses were performed on SPSS 20.0 (SPSS Inc, Chicago, IL, USA).

Results

For both utilities of QWB-SA and EQ-5D, epilepsy patients were statistically lower than the control group ($p<0.0001$). In terms of the WTP/Month, percentage of WTP accounting for the monthly income and the WTP/QALY, values from the epilepsy group were substantially higher than the control group ($p<0.0001$). The MLR model identified working status ($p=0.05$) seizure types ($p=0.022$), income ($p=0.006$), self-rating health state ($p<0.05$) as predictors of HRQoL while income ($p=0.000$), self-rating health state ($p<0.05$) statistically contributed to the variations in WTP/QALY value for the epilepsy group. The WTP/QALY values were nearly two times of GDP/capital in China in 2012 (USD 5417).

Conclusions

Epilepsy patients had substantially lower HRQoL than the healthy population. Seizure types, working status, monthly income and self-rating health state could be considered as predictors of HRQoL of this cohort. WTP/month and WTP/QALY value of epilepsy patients were considerably greater than the general population, which revealed increased intangible cost for the sufferers.

Keywords

Health-related Quality of Life; Willingness-to-Pay (WTP)/Quality-adjusted Life Year (QALY) threshold; Epilepsy; Cost-effectiveness analysis

5.1 Introduction

Epilepsy, as a chronic disorder, has considerable negative impact on people's day-to-day functioning (69), including impact on cognitive function, self-esteem and excessive psychological burden (e.g. depression and anxiety) (70-72). However, although HRQoL of epilepsy patients has been investigated in a series of studies, most of these studies were performed in developed countries. Within the developing countries, the relatively few studies unanimously adopted epilepsy-specific or generic non-preference-based instruments (e.g. QOILE-89, QOLIE-31, SF-36, WHOQOL-BREF) to assess the HRQoL (73-76), thus no utility could be obtained from those measures, consequently, cannot be integrated into cost-effectiveness analysis. In contrast, Quality of Well-being Scale-Self Administered (QWB-SA) (77) version and EuroQol (EQ-5D) are generic preference-based instruments, which could estimate the Quality Adjusted Life Years (QALYs). QALY provides a common currency to assess the extent of the benefits gained from a variety of interventions.

Furthermore, in order to make any health resource allocation nowadays, it is necessary to go beyond assessing just effectiveness of the new drugs or health technology to perform a cost-effectiveness or cost-utility analysis. Common decision rules indicate that an intervention is "good value for money" if the Incremental Cost-effectiveness Ratio (ICER) falls below certain cost effectiveness threshold. The chosen threshold reflects the acceptable value of a health gain within a specific decision-making context. In practice, many economic evaluations adopted 1 to 3 times of the specific country's Gross Domestic Production (GDP) per capital as the Willingness-To-Pay (WTP) per QALY threshold according to recommendation by World Health Organisation (WHO). However, controversies still abound with this suggested threshold, with researchers arguing that it might be too arbitrary to apply to all settings (67).

Another popular approach to define the cost-effectiveness threshold is through the use of contingent valuation. Despite its popularity, there are issues with the obtained WTP estimates. First, these estimates can vary substantially by the elicitation method used (e.g. ex post and ex ante perspectives can create different WTP values). Second, it is important that the WTP estimates obtained are relevant to the decision-making context. Nevertheless, in spite of these issues, WTP studies could provide valuable information to policy makers on the magnitude of individuals' preferences and may better reflect societal value (78).

Moreover, rather than using decision rules such as league tables or ICER threshold value recommended by WHO, it may be

more reasonable to allocate health care resources based on societal WTP for health care benefits (79). This is particularly important for developing countries, as the threshold value recommended by WHO may be over-estimating the WTP values (74, 79). Adopting these recommendations would therefore likely lead to inappropriate decision making. Hence, the investigations on societal WTP for health care benefits should be a "research priority" (80).

Unfortunately, there is a paucity of this type of studies, particularly in developing countries. Nevertheless, a WTP/QALY threshold study on chronic prostatitis patients by measuring the utility (measured by EQ-5D and SF-6D) and WTP simultaneously has been conducted recently in China by Zhao et al (66). In that study, based on the indirect preference elicitation method (using EQ-5D and SF-6D), WTP/QALY was successfully elicited for both chronic prostatitis and general populations with higher WTP/QALY value in chronic prostatitis group. In addition, the reported values were close to the lower bound of the WHO recommended WTP/QALY threshold, but the authors suggested that the type of disease may have an impact on the threshold value.

In view of extreme limited access to advanced antiepileptic treatments and constraints in healthcare resources, patients with epilepsy in China (and in this case also other developing countries) might experience more problems than their western counterparts. There is a strong rationale for assessing their HRQoL to evaluate the impact of their anti-epileptic treatment.

Therefore, our study intended to assess the HRQoL of epilepsy patients using QWB-SA and EQ-5D. At the same time, we attempted to value QALY by WTP approach in epilepsy patients and compare HRQoL and WTP/QALY values with the general population. To the best of our knowledge, the empirical WTP/QALY threshold estimations are only available in two Asian countries (one was for general population only and the other was for both chronic prostatitis and general populations) (65, 66) and there is only one study investigated the WTP value for epilepsy patients from Norway (81). As WTP/QALY threshold plays a significant role in healthcare resource allocation, our study would contribute to the resolution of some of the controversies in determination of an ICER threshold value, especially in countries/regions with limited resources.

5.2 Methods

Subjects

The cross-sectional study recruited participants between July and October 2012 from two tertiary hospitals in China: Renmin Hospital of Wuhan University, and the Fifth Hospital of Wuhan (Wuhan, Hubei, China) with specific Institutional Review Board approval. After informed consent was received from each adult participant, a convenient sample of inpatients or outpatients with diagnosis of epilepsy and a control group (without manifestation of cognitive problems) were recruited. Healthy controls were primarily from the relatives of the epilepsy patients, medical students, interns, and hospital general staff. Each subject was interviewed by a trained interviewer using standardised questionnaires containing QWB-SA, EQ-5D/VAS and WTP questionnaire.

Instruments

QWB-SA

The QWB-SA assesses the presence/absence of symptoms or problems, persons' mobility, physical activity and social activity. Each participant recalls the answers to particular QWB-SA question within the last three days prior to the day of the survey. The preference-weights were derived from a community sample (82). Scoring algorithm and preference weight are provided by the University of California, San Diego (UCSD) Health Services Research Centre. Use of QWB-SA in our study was authorised by the QWB-SA copyright owner and the validity of Chinese language QWB-SA was reported by our study group previously (83).

EQ-5D/VAS

The EQ-5D-3L comprises of five dimensions including mobility, self-care, usual activity, pain/discomfort and anxiety/depression. The utility scoring algorithm adopted in our study was developed using Time Trade-Off (TTO) based preference scores from a UK general population (84). Studies valuing EQ-5D-3L based on this algorithm have been performed in Chinese population previously (85). EQ-VAS is a 20cm vertical visual analogue scale ranging from 100 (best imaginable health state) to 0 (worst imaginable health state) to represent the overall health of the day.

WTP questionnaire

The contingent valuation method was adopted to elicit the WTP value. During this process, a respondent would be provided with an initial bid and asked whether they would like to pay this amount of money on a monthly basis to move from his/her current health state to a perfect health state. If subjects answered positively (negatively), then the amount was increased (decreased) until respondents declined (accepted) the specified amount. The positive or negative answer to the first price offer of the respondent provided the criteria for the next price offered (79). In order to minimize the starting bid bias, 5 different initial bids US$ 139, US$ 224, US$ 300, US$ 399, and US$ 689 representing low, low to middle, middle, middle to high, and high average monthly income in China were randomly assigned to respondents (National Bureau of Statistics of China, 2012). The maximum bidding amount offered would be dependent on respondent's monthly income (maximum price permitted for the close-ended iterative bidding was 10 times of the subject's own monthly income). Besides, each respondent would be reminded that the payment cannot be covered by the healthcare insurance and would reduce the amount of money that could be used in other ways before they respond to the bidding game question. This WTP questionnaire has been used in our study group previously (66).

Data analyses

HRQoL

The differences between epilepsy and control groups were assessed by independent sample ANOVA (if the distribution was normal) or Manny-Whitney U-test (if the distribution was abnormal) in case of continuous variables, or chi-square test in case of categorical variables. Correlations between socio-demographic or epilepsy specific variables and HRQoL utility scores were assessed via Spearman's correlation coefficient with p-value less than 0.1 to identify candidate-predictors.

Multiple Linear Regression (MLR) analysis was performed to investigate the associations between afore-mentioned candidate-predictors and HRQoL utility scores.

WTP/QALY

The WTP/QALY value was calculated as the ratio of the WTP for a move from a given health scenario to perfect health, to the QALY that would be gained by a move from that scenario to a perfect health state (86). Analyses were based on subjects who fully completed the questionnaire. Continuous variables were compared using Mann-Whitney U test and Chi-square tests were used to compare the categorical variables. The WTP/QALY ratio for each participant was computed through the following formula (66, 86):

$$WTP/_{QALY} = \frac{12 \times WTP/Month}{1 - utility(current\ health)}$$

As the monthly payment was elicited, life expectancy and discount rate were not considered. Due to arithmetic attribute of the formula, subjects with perfect health states (defined as utility of 1) were excluded from WTP/QALY calculation. Correlations between socio-demographic or epilepsy specific variables and WTP/QALY value were assessed via Spearman's correlation coefficient with p-value less than 0.1 to identify candidate-predictors. In addition, MLR analysis was undertaken to assess the associations between candidate-predictors and WTP/QALY value. To allow for better interpretation, the monthly income were groups into four categories, ≤US$ 224(9), US$ 225 to 300 (lower-middle), US$ 301 to 689 (upper-middle), and US$ ≥700 (high) (National Bureau of Statistics of China, 2012).

All data analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

5.3 Results

Participants

Overall, 144 epilepsy patients and 312 healthy controls completed the QWB-SA and EQ-5D. Among those, 41 participants in control group failed to complete the WTP questionnaire, 25 healthy subjects reported perfect health state on QWB-SA, while 59 epilepsy patients and 164 control subjects reported full utility on EQ-5D, thus, they were excluded from the corresponding analyses.

Demographic variables

There were statistically significant differences between epilepsy and control groups in terms of age ($p=0.033$), gender ($p<0.0001$), working status ($p=0.029$), education ($p<0.0001$) and monthly income ($p<0.0001$). (Table 5.1)

Description statistics of QWB-SA and EQ-5D

Utility scores for both QWB-SA and EQ-5D were significantly different between two groups ($p<0.0001$), whereas the EQ-VAS did not show difference between two groups ($p=0.052$). (Table 5.1)

Table 5. 1 Characteristics and HRQoL results of epilepsy patients and control population

	Epilepsy n=144	Simple partial n=7	Complex partial n=83	Secondary generalised n=50	Tonic-clonic generalised n=4	Control n=312
Age (Mean±SD)	33.11±13.044	27.43±12.040	33.95±12.930	31.66±12.847	43.75±16.540	34.52±15.662
16-29	68(47.2)	5(71.4)	36(43.4)	26(52.0)	1(25)	144(46.2)
30-39	31(21.5)	0	20(24.1)	10(20.0)	1(25)	36(11.5)
40-49	28(19.4)	2(28.6)	16(19.3)	10(20.0)	0(0)	54(17.3)
50-59	11(7.6)	0	9(10.8)	1(2.0)	1(25)	47(15.1)
≥60	6(4.2)	0	2(2.4)	3(6.0)	1(25)	31(9.9)
Gender (Male%)	52.1	0	57.8	48.0	75.0	38.8
Han Ethnicity (%)	142(98.6)	7(100.0)	82(98.8)	49(98.0)	4(100.0)	308(98.7)
Education (Mean±SD)	10.56±2.961	10.00±3.162	10.41±2.745	11.02±3.298	9.00±2.449	13.16±2.871
≤6	16(11.1)	1(14.3)	7(8.4)	7(14.0)	1(25.0)	16(5.1)
7-12	106(73.6)	5(71.4)	66(79.5)	32(64.0)	3(75.0)	139(44.6)
>12	22(15.3)	1(14.3)	10(12.0)	11(22.0)	0	157((50.3)
Marital status (%)						
Unmarried	71(49.3)	4(57.1)	42(50.6)	24(48.0)	1(25.0)	123(39.4)
Married	70(48.6)	2(28.6)	40(48.2)	25(50.0)	3(75.0)	184(59.0)
Divorced	2(1.4)	1(14.3)	1(1.2)	0	0	2(0.6)
Widow/widower	1(0.7)	0	0	1(2.0)	0	3(1.0)
Working status (%)						
Employed	65(45.1)	4(57.1)	37(44.6)	22(44.0)	2(50.0)	175(56.1)

Unemployed	69 (54.9)	3(42.9)	46(55.4)	28(56.0)	2(50.0)	137(43.9)
Age of onset(Mean±SD)	23.22±14.726	19.43±11.688	24.90±14.396	20.12±14.553	33.50±22.927	-
Duration(Mean±SD)	9.64±9.142	8.86±11.393	8.80±7.852	11.11±10.710	10.25±10.404	-
Brain trauma/disease(%)	31.94(n=46)	42.86(n=3)	30.12(n=25)	32.00(n=16)	50.00(n=2)	-
Brain surgery(%)	15.28(n=22)	14.29(n=1)	16.87(n=14)	12.00(n=6)	25.00(n=1)	-
Head CT/MRI(%)	30.56(n=44)	14.29(n=1)	33.73(n=28)	26.00(n=13)	50.00(n=2)	-
EEG(%)	43.06(n=62)	71.43(n=5)	39.76(n=33)	42.00(n=21)	75.00(n=3)	-
Refractory epilepsy (%)	25.69(n=37)	14.29(n=1)	25.30(n=21)	28.00(n=14)	25.00(n=1)	-
Seizure frequency (%)						
Daily	3.47(n=5)	0(n=0)	3.61(n=3)	4.00(n=2)	0(n=0)	-
Weekly	11.81(n=17)	0(n=0)	8.43(n=7)	20.00(n=10)	0(n=0)	-
Monthly	29.17(n=42)	42.86(n=3)	22.89(n=19)	36.00(n=18)	50.00(n=2)	-
Bimonthly	10.42(n=15)	0(n=0)	9.64(n=8)	12.00(n=6)	25.00(n=1)	-
Quarterly	21.53(n=31)	0(n=0)	31.33(n=26)	10.00(n=5)	0(n=0)	-
Half-yearly	9.03(n-13)	28.57(n=2)	10.84(n=9)	4.00(n=4)	0(n=0)	-
Yearly	10.42(n=15)	28.57(n=2)	10.84(n=9)	6.00(n=3)	25.00(n=1)	-
More than yearly	4.17(n=6)	0(n=0)	2.41(n=2)	8.00(n=4)	0(n=0)	-
QWB-SA						
Mean±SD	0.657±0.135	0.681±0.146	0.636±0.135	0.687±0.127	0.671±0.174	0.802±0.155
Median±IQR	0.673±0.172	0.744±0.216	0.673±0.134	0.676±0.133	0.707±0.321	1.000±0.152
QWB-SA self-rating health status						
Excellent	2(1.4)	0	1(1.2)	1(2.0)	0	37(11.5)
Very good	26(18.1)	0	14(16.9)	12(24.0)	0	86(26.6)

Good	53(36.8)	5(71.4)	28(33.7)	17(34.0)	3(75.0)	94(29.1)
Fair	56(38.9)	2(28.6)	36(43.4)	17(34.0)	1(25.0)	98(30.3)
Poor	7(4.9)	0	4(4.8)	3(6.0)	0	8(2.5)
EQ-5D						
Mean±SD	0.828±0.206	0.890±0.148	0.798±0.211	0.867±0.203	0.854±0.170	0.923±0.132
Median±IQR	0.848±0.275	1.000±0.275	0.848±0.275	1.000±0.204	0.863±0.302	1.000±0.152
EQ-VAS						
Mean±SD	79.57±16.419	74.43±20.239	79.63±16.835	79.80±15.935	84.50±6.403	82.64±13.939
Median±IQR	80.00±20.00	69.00±38.00	80.00±20.00	80.00±20.00	85.00±11.50	85.00±11.00
Income						
≤1500 (USD 241)	9(6.3)	0	4(4.8)	4(8.0)	1(25.0)	0
1501-2000 (USD 241-321)	25(17.4)	2(28.6)	17(20.5)	5(10.0)	1(25.0)	4(1.6)
2001-3000 (USD 321-482)	43(29.9)	1(14.3)	24(28.9)	17(34.0)	1(25.0)	83(33.7)
3001-4000 (USD 482-643)	44(30.6)	3(42.9)	24(28.9)	16(32.0)	1(25.0)	113(45.9)
4001-5000 (USD 643-803)	12 (8.3)	1(14.3)	8(9.6)	3(6.0)	0	43(17.5)
≥5000 (USD 803)	11(7.6)	0	6(7.2)	5(10.0)	0	3(1.2)

Description statistics of WTP/Month, and WTP/QALY

Among the subjects with completed WTP questionnaire, epilepsy patients reported lower utility scores on both QWB-SA and EQ-5D than the control group ($p<0.0001$). In terms of the WTP/Month and WTP as percentage of the monthly income, the values from the epilepsy group were substantially higher than the control group (both $p<0.0001$). Likewise, the WTP/QALY value showed the same trend. (Table 5.2)

The starting bid might introduce a bias to the final result, and to address this, the Kruskal-Wallis H test was undertaken to assess differences in WTP value for five starting bids. The results indicated that there was no significant influence on the final WTP value by the different initial bids.

Table 5. 2 Utilities, WTP/month and WTP/QALY Values [Median (IGR)]

	Utility and WTP				WTP/QALY			
	Epilepsy	Control	p-value	N	Epilepsy	N	Control	p-value
Total	N=144	N=271						
QWB-SA	0.673(0.172)	0.775(0.258)	<0.0001	144	8799.265 (10570.02)	246	1740.388 (4523.505)	<0.0001
EQ-5D	0.848(0.275)	1.000(0.152)	<0.0001	85	9446.073 (12843.369)	107	2916.54 (5700.217)	<0.0001
WTP/month	241.014(184.777)	48.203(160.676)	<0.0001	/	/	/	/	/
Percentage	0.465(0.267)	0.100(0.267)	<0.0001	/	/	/	/	/

Money was presented as US dollars, 1USD=6.2237 CNY (January, 2013)

WTP: Willingness-to-Pay; QALY: Quality-adjusted life years; IGR: Inter-quartile range; QWB-SA: Quality of Well-being Scale-self administered version; EQ-5D: EuroQol; Percentage: calculated via WTP/Month divided by monthly income.

Relationships between socio-demographic or epilepsy specific variables and HRQoL

For the epilepsy group, age (-0.260, p=0.002), marital status (0.188,p=0.024), working status (0.213, p=0.010), seizure types (-0.138, p=0.098), age of epilepsy onset (-0.190, p=0.023), refractory epilepsy (-0.220,p=0.008), seizure frequency (-0.178, p=-0.033), monthly income (0.296, p=0.000), QWB-SA self-rating health state (-0.525, p=0.0.000), and EQ-VAS (0.475,p=0.000) were found to be positively or negatively correlated with utility scores of QWB-SA according to Spearman's correlation coefficients. While the utility scores of EQ-5D were shown to be associated with age (-0.254,p=0.002), marital status (0.174,p=0.037), working status (0.282, p=0.001), seizure types (-0.165, p=0.048), age of epilepsy onset (-0.175, p=0.036), brain trauma/disease (-0.137, p=0.101), brain surgery history (-0.152, p=0.070), QWB-SA self-rating health state (-0.441, p=0.000), and EQ-VAS (0.538, p=0.000). (Table 5.3)

Table 5. 3 Spearman's correlation coefficients between HRQoL scores and demographic variables (Epilepsy group)

Instruments	Age	Marital status	Working status	Diagnosis	Age of onset	Duration of epilepsy	Brain injury /disease	Brain surgery history	Current AEDs	Refractory epilepsy	Seizure frequency	Monthly income
QWB-SA	**0.260 (0.002)**	**0.188 (0.024)**	**0.213 (0.010)**	**-0.138 (0.098)**	**-0.190 (0.023)**	-0.047 (0.577)	0.056 (0.508)	0.030 (0.725)	-0.122 (0.145)	**-0.220 (0.008)**	**0.178 (0.033)**	**0.296 (0.000)**
EQ-5D	**0.254 (0.002)**	**0.174 (0.037)**	**0.282 (0.001)**	**-0.165 (0.048)**	**-0.175 (0.036)**	-0.039 (0.644)	**0.137 (0.101)**	**0.152 (0.070)**	-0.053 (0.526)	-0.116 (0.165)	0.043 (0.613)	**0.149 (0.074)**

Significant level for univariate analysis was set as p<0.10.

Table 5. 4 Spearman's correlation coefficients between HRQoL scores and demographic variables (Control group)

Measures	Age	Marital status	Working status	Education	QWB-SA health status	EQ-VAS	Monthly income
QWB-SA	**0.309 (0.000)**	**0.139 (0.013)**	-0.057 (0.303)	**0.156 (0.005)**	**0.345 (0.000)**	**0.393 (0.000)**	-0.091 (0.133)
EQ-5D	**0.323 (0.000)**	**-0.020 (0.000)**	-0.007 (0.894)	**0.258 (0.000)**	**0.404 (0.000)**	**0.463 (0.000)**	-0.024 (0.689)

Significant level for univariate analysis was set as $p<0.10$.

Results for control group was presented in Table 5.4.

Relationships between socio-demographic variables or epilepsy specific variables and WTP/QALY

For QWB-SA utility score based WTP/QALY calculations by epilepsy group, working status (0.141, p=0.091), duration of epilepsy (-0.149, p=0.074), refractory epilepsy (-0.242, p=0.003), QWB-SA self-rating health state (-0.332,p=0.000), EQ-VAS (0.235, p=0.005) and monthly income (0.752, p=0.000) were significantly associated with WTP/QALY $_{QWB\text{-}SA}$ values. When WTP/QALY value was derived from EQ-5D utility score, it was only statistically correlated with working status (0.220, p=0.043), QWB-SA self-rating health state (-0.333, p=0.002), and monthly income (0.296, p=0.000) (Table 5.5). Results for control group was presented in Table 5.6.

Table 5. 5 Spearman's correlation coefficients between WTP/QALY and demographic variables (Epilepsy group)

Measures	Age	Marital status	Working status	Diagnosis	Age of onset	Duration of epilepsy	Brain injury /disease	Brain surgery history	Current AEDs	Refractory epilepsy	Seizure frequency	QWB-SA health status	EQ-VAS	Monthly income
QWB-SA (n=144)	0.119 (0.154)	0.109 (0.192)	**0.141 (0.091)**	-0.052 (0.534)	0.046 (0.581)	**-0.149 (0.074)**	-0.065 (0.440)	-0.121 (0.149)	-0.042 (0.613)	**-0.242 (0.003)**	0.128 (0.125)	**-0.332 (<0.0001)**	**0.235 (0.005)**	**0.752 (<0.0001)**
EQ-5D (n=85)	0.034 (0.643)	0.042 (0.706)	**0.220 (0.043)**	-0.123 (0.263)	-0.028 (0.799)	-0.050 (0.646)	-0.174 (0.112)	-0.091 (0.409)	-0.060 (0.587)	0.101 (0.358)	0.026 (0.814)	**-0.333 (0.002)**	0.171 (0.117)	**0.296 (<0.0001)**

Significant level for univariate analysis was set as p<0.10.

Table 5. 6 Spearman's correlation coefficients between WTP/QALY and demographic variables (Control group)

Measures	Age	Marital status	Working status	Education	QWB-SA health status	EQ-VAS	Monthly income
QWB-SA (n=246)	**0.259 (0.000)**	0.071 (0.269)	0.035 (0.589)	-0.064 (0.316)	**0.197 (0.002)**	**-0.126 (0.048)**	**0.155 (0.015)**
EQ-5D (n=107)	**0.297 (0.002)**	**0.279 (0.004)**	0.074 (0.451)	0.126 (0.195)	**-0.238 (0.013)**	0.020 (0.840)	**0.232 (0.016)**

Significant level for univariate analysis was set as $p<0.10$.

Multiple linear regression analyses for HRQoL

Epilepsy group

Two models were utilised to investigate the relationships between socio-demographic, epilepsy specific variables and utility scores of the two instruments with statistically significantly factors (identified by Spearman's correlation) as independent variables. In the first model, 22.6% of variation in utility scores of QWB-SA was accounted for by the model while only seizure types (Standardised coefficient β -0.179, p=0.022) and monthly income (β 0.217, p=0.006) statistically contributed to the model. In terms of model two, QWB-SA health state (β -0.296, p=0.000), EQ-VAS (β 0.279, p=0.000), and monthly income (β 0.172, p=0.013) significantly contributed to the model with 42.1% of variation in utility scores being accounted for by the model. For utility scores derived from EQ-5D, the two models accounted for 14.9% and 37.0% variations in utilities respectively. Particularly, working status (β 0.166, p=0.050) in model one, QWB-SA health state (β -0.251, p=0.002) and EQ-VAS (β 0.345, p=0.000) in model two were shown to positively contribute to the variation. (Table 5.7)

Table 5. 7 Multiple Linear Regression analyses for HRQoL scores of Epilepsy Patients

		QWB-SA				EQ-5D	
Model 1 Enter	R^2	Standardised coefficient β	Significance	Model 1 Enter	R^2	Standardised coefficient β	Significance
	0.226				0.149		
Age		0.149	0.290	Age		0.197	0.179
Marital status		0.102	0.289	Marital status		-0.056	0.579
Working status		0.143	0.078	**Working status**		**0.166**	**0.050**
Diagnosis		**-0.179**	**0.022**	Diagnosis		-0.109	0.173
Age of onset		0.092	0.462	Age of onset		0.058	0.653
Seizure frequency		0.165	0.172	Brain injury/disease		-0.045	0.661
Refractory epilepsy		-0.060	0.535	Brain surgery history		0.176	0.091
Income		**0.217**	**0.006**	Income		0.144	0.077

Model 2 Enter	R^2	Standardised coefficient β	Significance	Model 2 Enter	R^2	Standardised coefficient β	Significance
	0.421				0.370		
Age		0.068	0.584	Age		0.081	0.534
Marital status		0.151	0.076	Marital status		-0.009	0.920
Working status		0.095	0.196	Working status		0.091	0.235
Diagnosis		-0.121	0.078	Diagnosis		-0.064	0.361
Age of onset		0.031	0.283	Age of onset		0.059	0.600
Refractory		0.018	0.833	Brain injury/disease		-0.065	0.471
Seizure frequency		0.110	0.212	Brain surgery history		0.118	0.195
QWB-SA Health state		**-0.296**	**0.000**	**QWB-SA Health state**		**-0.251**	**0.002**
EQ-VAS		**0.279**	**0.000**	**EQ-VAS**		**0.345**	**0.000**
Income		**0.172**	**0.013**	Income		0.085	0.235

Control group

Both age (β -0.226, p=0.002, and β -0.173, p=0.014) and EQ-VAS (β 0.240, p=0.000, and β 0.356, p=0.000) contributed to the model statistically in predicting utility scores for QWB-SA or EQ-5D. In addition, QWB-SA utility scores could be predicted by QWB-SA health state as well (β -0.142, p=0.027) (Table 5.8)

Table 5. 8 Multiple Linear Regression analyses for HRQoL scores of control population

		QWB-SA				EQ-5D	
Enter	R^2	Standardised coefficient β	Significance	Enter	R^2	Standardised coefficient β	Significance
	0.199				0.266		
Age		**-0.226**	**0.002**	**Age**		**-0.173**	**0.014**
Marital status		0.045	0.477	Marital status		0.041	0.503
Education		0.016	0.828	Education		0.037	0.537
QWB-SA Health status		**-0.142**	**0.027**	QWB-SA Health status		-0.109	0.077
EQ-VAS		**0.240**	**0.000**	**EQ-VAS**		**0.356**	**0.000**

Multiple linear regression analyses for WTP/QALY

Epilepsy group

For either QWB-SA or EQ-5D based WTP/QALY calculation, QWB-SA health state (β-0.134, p=0.049 and β -0.248, p=0.003) and monthly income (β 0.640, p=0.000 and β 0.629, p=0.000) could be regarded as predictors of the WTP/QALY value with around 50% variation in the WTP/QALY value predicted in the two models. Besides, EQ-VAS also contributed to the variations in the QWB-SA based WTP/QALY values (β 0.640, 0.000) (Table 5.9).

Table 5. 9 Multiple Linear Regression analyses for WTP/QALY of Epilepsy Patients

		QWB-SA			EQ-5D

Model 1 Enter	R^2	Standardised coefficient β	Significance	Model Enter	R^2	Standardised coefficient β	Significance
	0.510				0.497		
Working status		-0.051	0.415	Working status		-0.103	0.209
Duration		0.121	0.055	**QWB-SA health state**		**-0.248**	**0.003**
Refractory epilepsy		0.036	0.573	**Monthly income**		**0.629**	**0.000**
QWB-SA health state		**-0.134**	**0.049**	/		/	/
EQ-VAS		**-0.156**	**0.022**	/		/	/
Monthly income		**0.640**	**0.000**	/		/	/

Control group

Since the residual distribution of $WTP/QALY_{QWB\text{-}SA}$ values in control group was not normal, logarithm transformation was applied to this value. However, neither QWB-SA nor EQ-5D based WTP/QALY values was satisfactorily predicted by the models (R^2 0.099 and 0.104 respectively). When WTP/QALY was calculated based on QWB-SA utility, age (β 0.175, p=0.009) and QWB-SA health state (β -0.199, p=0.012) were predictors of WTP/QALY values, whereas $WTP/QALY_{EQ\text{-}5D}$ value was only predicted by monthly income (β 0.239, p=0.018). (Table 5.10)

Table 5. 10 Multiple Linear Regression analyses for WTP/QALY of control population

		QWB-SA[a]			EQ-5D

Enter	R^2	Standardised coefficient β	Significance	Enter	R^2	Standardised coefficient β	Significance
	0.099				0.104		
Age		**0.175**	**0.009**	Age		0.098	0.441
Monthly income		0.128	0.723	Marital status		0.066	0.572
QWB-SA health state		**-0.199**	**0.012**	QWB-SA health state		0.170	0.091
EQ-VAS		-0.007	0.930	**Monthly Income**		**0.239**	**0.018**

[a] Log-transformed WTP/QALY was applied.

5.4 Discussion

The burden of epilepsy to a sufferer not just encompasses the unpredictability of seizures, but also includes the social exclusion as a result of negative attitudes towards patients with epilepsy. Hence, the primary treatment goals should not just be to reduce the seizure frequency and seizure severity, but also to promote the quality of life of those being affected. As such, factors that impact the quality of life could become the potential targets of antiepileptic management. Furthermore, WTP/QALY, which theoretically incorporates costs of pain, suffering, anxiety or fatigue because of a disease, and therefore would also measures intangible cost (particularly in this case, for epilepsy). Hence, quantifying WTP/QALY and the associated factors for epilepsy patients would provide a more accurate picture on the global burden of this disease. To the best of our knowledge, there was only one study adopting WTP method to measure how much epilepsy patients were willing to pay for an imaginary new technology, which would cure epilepsy permanently (81). Although the high responsive rate indicated great acceptability, the associations between WTP and other preference measures were low (Spearman's correlation coefficients ranged from -0.09 to -0.12 for WTP and SG or TTO). In addition, only 59 subjects completed the study without a control group (81). Nevertheless, the median WTP amount was USD 20,000 (which could inflate to USD 30,984 in 2012), accounting for 47% of annual household income in this afore-mentioned study. In term of the proportion of WTP constituted income, our result (46.5%) was comparable to this one.

With cost-effectiveness/utility analysis increasingly adopted by various jurisdictions, quantifying the threshold of cost effectiveness analysis would offer a benchmark for interpreting economic evaluation. Using the stated preference data to quantify the WTP/QALY has been explored previously by our study group, and this elicitation method for WTP/QALY ratio was found to be acceptable and feasible, as well as produce meaningful answers among Asian subjects (66).

Pertaining to the WTP/month and WTP/QALY values in our study, the value for epilepsy group was substantially higher. For patient group, QWB-SA self-rating health state and monthly income were capable to predict either WTP/QALY $_{QWB-SA}$ or WTP/QALY $_{EQ-5D}$ value. Besides, EQ-VAS was another predictor of WTP/QALY $_{QWB-SA}$ value. When it came to healthy population, age and QWB-SA self-rating health state statistically contributed to the variation of WTP/QALY $_{QWB-SA}$, whereas monthly income was the sole predictor of WTP/QALY $_{EQ-5D}$. Two interesting findings are worth noting here: firstly, more predictors were identified for WTP/QALY $_{QWB-SA}$ than WTP/QALY $_{EQ-5D}$, which might indicate better sensitivity of QWB-SA as the utility elicitation instrument. Additionally, age was also capable of predicting WTP/QALY$_{QWB-SA}$ values for healthy population only, with more advanced age associated with greater WTP per QALY value. Since the negative association between HRQoL $_{QWB-SA}$ and age was shown in the normative data for QWB-SA as well as in our dataset, it might mean that the proportional increase in the WTP of the healthy respondents with increasing age would exceed the magnitude of the

decrease in the utility as measured by QWB-SA. This was supported by the WTP/QALY value increases with increasing age in our study. In another word, this finding suggested that the WTP value disproportionally increases with age. Nonetheless, this finding was not consistent, one study based on a community sample observed that there was a negative association between age and WTP/QALY (87). However, another review study reported that relative to baseline assumption of 40 years, the WTP/QALY value would decrease by 7% for those aged at 35 years and increase by 9% for those aged at 45 years, which was similar to our finding (88). Although different elicitation methods and targeted populations were used in the studies, this inconsistency still warrants future investigations.

The median of WTP/QALY $_{QWB\text{-}SA}$ or WTP/QALY $_{EQ\text{-}5D}$ value for epilepsy group were nearly two times of the GDP per capita in China (International Monetary Fund, 2012, USD 5417 for China), but fell within the range of World Health Organisation (WHO)'s recommendation (1-3 times of the GDP per capita). Comparing to the result from a previous WTP study (66), epilepsy patients afforded greater amount of WTP and WTP/QALY values than chronic prostatitis patients based on the same indirect utility elicitation method (EQ-5D), and this might reflect the different impacts on patients by these two chronic diseases.

In our study, WTP/QALY $_{QWB\text{-}SA}$ and WTP/QALY $_{EQ\text{-}5D}$ values were a great deal higher than the general population suggesting that the WTP/QALY value is context-specific. In theory, the perceptions of WTP question for epilepsy patient and healthy subjects are essentially different. For patients, the scenario provided is probably perceived as a curative treatment whereas for healthy respondent, the scenario offered is more like considering a prevention as they are not experiencing health problems at the moment of the study. Since the WTP amount for prevention is remarkably less than the amount for treatment, an obvious difference in WTP estimated from treatment and prevention situations was previously reported (65, 89). According to a prospect theory, the preference of an individual is related to a reference point (90), in our study, epilepsy patients were in declined health states comparing to health subjects, thus the reference points for two cohorts were essentially distinctive. This would offer another explanation for the huge gap in WTP amount between two groups other than the inherent difference in intangible cost for two distinct cohorts. Taking together, these results also imply that one ceiling threshold should not be applied to all the interventions when deciding resource allocation.

Our present results showed that working status, seizure types, monthly income, self-rating health state might be predictors of HRQoL of epilepsy patients, which is in line with a previous study (91). In contrast, epilepsy-specific parameters like age of epilepsy onset, duration of epilepsy, epileptic discharge (EEG), seizure frequency, and AEDs did not statistically

contribute to the variation in HRQoL in our study. This is supported by a review which indicated, except for seizure frequency, severity and psychological factors, other disease variables had only affected HRQoL in limited studies (91). Furthermore, the proportion of HRQoL variance explained by the MLR model was low in our study, ranging from 14.9% to 42.1% corresponding to different models and utility measures. This might due to the insensitivity of generic preference-based HRQoL instrument is unable to capture the characteristics inherent to a specific disease. In addition, depression and anxiety have been demonstrated to exert high impact on HRQoL, but were not independently assessed in our study, thus not included in the MLR model (92, 93).

Our study was subject to some limitations as well. First, direct utility elicitation method such as SG or TTO would be superior to the indirect method as utilised in the present study. However, a higher convergent validity was observed between WTP/QALY $_{QWB\text{-}SA}$ and WTP/QALY $_{EQ\text{-}5D}$ in current study than study adopting SG and TTO (79). Second, since epilepsy, generally, is not a life-threatening disease, as reported by previous literatures, a QALY gained by improving the quality of life or extending a life is worth less than a QALY gained by saving a life, so the WTP/QALY estimation derived from this cohort might not be comprehensive enough to reflect the societal perspective (94-97).

5.5 Conclusions

Epilepsy patients had substantially lower HRQoL than the healthy population. Seizure types, working status, monthly income and self-rating health state could be considered as predictors of HRQoL of this cohort. WTP/month and WTP/QALY value of epilepsy patients were considerably greater than the general population, which also revealed increased intangible cost for the sufferers. Nevertheless, it is questionable to apply one WTP/QALY threshold to all the situations.

Chapter 6. Burden of epilepsy: a prevalence-based cost of illness study of direct, indirect and intangible costs for epilepsy

Abstract

Objectives

We aimed to gauge the burden of epilepsy in China from a societal perspective by estimating the direct, indirect and intangible costs.

Methods

Patients with epilepsy and controls were enrolled from two tertiary hospitals in China. Patients were asked to complete a Cost-of-Illness (COI), Willingness-to-Pay (WTP) questionnaires, two utility elicitation instruments and Mini Mental State Examination (MMSE). Healthy controls only completed WTP, and utility instruments. Univariate analyses were performed to investigate the differences in cost on the basis of different variables, while multivariate analysis was undertaken to explore the predictors of cost/cost component.

In total, 141 epilepsy patients and 323 healthy controls were recruited. The median total cost, direct cost and indirect cost due to epilepsy were US$949.29, 501.34 and 276.72 respectively. Cost for AEDs accounted for 78.7% of the direct medical cost while patients' and caregivers' productivity costs constituted the major component of indirect cost. The total national economic burden of epilepsy from the societal perspective was US$3.80 billion (Interquartile Range, IGR: 2.53-12.39) or US$11.35 billion (IGR: 5.78-25.95) (including the under-productivity loss) in 2012. The intangible costs in terms of WTP value (US$266.07 vs. 88.22) and utility (EQ-5D, 0.828 vs. 0.923; QWB-SA, 0.657 vs. 0.802) were both substantially higher compared to the general population.

Conclusions

Epilepsy is a cost intensive disease in China. The median total cost was US$949.29 (IGR: 632.17-3096.43) with direct cost as the major component. According to the prognostic groups, drug resistant epilepsy generated the highest total cost

whereas patients in seizure remission had the fewest cost. Age, seizure frequency, self-rating impact on work capability, prognostic groups, MMSE scores and utility of EQ-5D could be predictors of the total cost.

Keywords

Cost of illness; epilepsy; utilisation; China

6.1 Introduction

Epilepsy is the most common neurologic disorders affecting people of all ages. The prevalence of this disorder is estimated at between 0.52% and 1.5% (58-60). Due to the recurrent nature, some patients may require lifetime treatment, and the management employed mainly is anti-epileptic drugs (AEDs) (61, 98).

Epilepsy is well recognised to pose heavy economic burden on society and individual, as indicated in many cost-of-illness (COI) studies (58, 99-103). With increasing attention towards containing health care expenditure, the economic consequences of managing epilepsy would not be spared the scrutiny. This is especially so with the advent of second-generation AEDs, the promotion of vagal nerve simulators as well as the surgical options, all of which potentially contributing to a substantial increase in the costs of managing epilepsy.

Besides increasing the utilisation of health care resources, many patients with epilepsy also suffer from other co-morbidities, with mood disorders like depression being the most prominent one (70-72). In addition, negative psychological and social impacts are commonly detected among patients with epilepsy (104). These include a reduction in self-esteem, a higher probability of anxiety and unemployment/underemployment (105, 106), a lower marriage rate (107, 108), and difficulty with learning (109). Moreover, the mortality of this population is higher than their healthy counterparts (110, 111). All these factors contribute to the increase in the direct, indirect and intangible costs to patients and society.

To assess the economic burden of epilepsy, Cost-of-Illness (COI) studies are commonly employed to estimate the maximum amount that could potentially be saved or gained if a disease were to be eradicated. Knowledge of the economic costs of an illness can help policy makers to set priority in health care manpower planning, resource allocation and prevention policy. Besides, cost-of-illness studies also provide important information for cost-effectiveness and cost-benefit analysis by providing a framework for the cost estimation in these analyses (49).

To date, there were two studies estimating the economic burden of epilepsy in China (112, 113), one study estimated both the direct and indirect cost (112) whereas the other one only calculated the direct cost (113). However, neither study took the caregiver's productivity cost nor the intangible cost into consideration. In fact, in cost analysis, the relevant productivity changes are those arising from both the patient and family member taking time off work in order to receive health

care(114). Thus, for a comprehensive COI study, cost of both patients' and caregiver's productivity should be included. In addition, intangible costs could be measured and valued, through the utility or willingness-to-pay (WTP) approach" (115). The inclusion of intangible cost would provide a more comprehensive estimation of the economic burden of the disease.

Hence, we aimed to estimate the direct, indirect, and intangible cost of epilepsy in China from a societal perspective. Specifically, a bottom-up, prevalence-based approach was adopted to compute the direct and indirect cost due to epilepsy, while utility and WTP values of each individual were elicited and compared with general population to describe the intangible cost. Hence, besides providing an estimate of the direct and indirect cost of managing epilepsy, the results from our study would also provide an estimate of intangible cost of epilepsy, which is seldom reported explicitly. For informing public health, the results obtained would thus provide some important benchmark values for decision makers in assessing the economic burden of epilepsy internationally.

6.2 Methods

Subjects

The cross-sectional study recruited participants from two tertiary hospitals in Hubei Province, China: Renmin Hospital of Wuhan University, and the Fifth Hospital of Wuhan between July 2012 and January 2013. The study was approved by the Institutional Review Board of the two study sites. After informed consent was received from each participant (age>16 years), a convenient sample of inpatients or outpatients with the diagnosis of epilepsy and a control group (without manifestation of cognitive problems, primarily from the relatives or caregivers of patients with epilepsy, hospital general staff, interns and nurses) were recruited. Attending physicians or consultant neurologists/epileptologists were responsible for initially identifying the patients. The diagnosis of epilepsy was based on clinical history, symptoms, examinations, EEG (epileptic discharges), and neuroimaging (MRI, CT) with the consensus between two physicians (SQP and LX). Each participant was asked to complete a Cost-of-Illness (COI) questionnaire, a Willingness-to-Pay (WTP) questionnaire, two indirect utility elicitation instruments (EuroQol, EQ-5D and Quality of Well-Being Scale, Self-administered, QWB-SA), and a cognitive impairment-screening tool (Mini Mental State Examination, MMSE). The epilepsy-specific data were extracted from the medical record of corresponding individual where applicable.

Instruments

COI questionnaire

The questionnaire included two parts: first part assessed health or non-health resource usages during the past 12 months including antiepileptic treatment (AEDs or other kinds of treatment except for surgery), numbers of outpatient visits/hospitalisations/rehabilitation care/nursing home/examinations/laboratory tests/emergency room visits/absenteeism [both the patient and caregiver], means of transportation to the hospital, special equipment/food/ home alteration due to epilepsy, and formal or informal domestic care. Second part assessed the costs of aforementioned variables and the productivity loss due to absenteeism and early retirements of patient and caregiver. Finally, each participant was asked to rate the impact of disease on work capability and how much was lost due to the illness (out of a possible 100%).

The cost of each unit was derived from the Hubei Province Price Bureau (for list of all the licensed drugs, medical examinations, laboratory tests and the individual prices), National Bureau of Statistics of China (for the annual income of each province within China), and The People's Government of Hubei Province (for the minimum wage per hour, document series number [2011] No.69). Besides, the prices of local taxi, public transportation fares (including bus/travel bus, train/subway) were obtained from local transport authority. The direct cost was calculated via summation of all the cost items (each cost item was computed via the numbers of usage of each resource multiplied by the cost per unit). The indirect cost was calculated based on the human capital method, which included the costs of working days loss due to sick leave or visits to hospital (each hospital visit was treated as a day loss), loss of early retirement, and productivity loss of caregiver. The average wage per hour was assigned to each subject (both patient and caregiver) to conservatively estimate the loss due to sick leave or visits to hospital regardless of their occupations. If patient reported early retirement, the average annual income of Hubei province was input to represent one-year loss due to premature retirement. In addition to this, the under-productivity loss was computed by multiplying the individual's self-rating percentage loss in productivity by the average income of Hubei province. All costs were expressed in US dollars (exchange rate 1 USD=6.2353 CNY, December 2012).

Each participant was assigned to one of the category on the basis of a previous study (112): A. epilepsy in remission for more than 2 years; B. epilepsy remission for 1-2 years with occasional seizures (seizures do not require treatment adjustment in the opinion of the treating physician); C. active epilepsy, i.e., relapsing seizure but in the opinion of the treating physician, treatment adjustment may be able to improve the seizure occurrence; D. drug resistant epilepsy, i.e.,

complete seizure control is not achieved with trials of two appropriate antiepileptic drugs (70), and outcome is extremely difficult to be improved by drug changes in the opinion of the treating physician.

Intangible cost

WTP valuation

The contingent valuation method was adopted to elicit the WTP value. A respondent would be provided with an initial bid and asked whether they would like to pay this amount of money on a monthly basis to move from his/her current health state to a perfect health state. If subjects answered positively (negatively), then the amount was increased (decreased) (i.e., doubled or halved) until respondents declined (accepted) the specified amount. The maximum bidding amount offered would be dependent on respondent's monthly income (maximum price permitted for the close-ended iterative bidding was 10 times of the subject's own monthly income) (79). If the respondent was willing to pay less than the minimum offered bid or higher than the maximum offered bid, his/her WTP amount was determined using open-ended questions. In order to minimize the starting bid bias, 5 different initial bids of US$139, US$224, US$300, US$399, and US$689 representing low, low to middle, middle, middle to high, and high average monthly income in China were randomly assigned to respondents (National Bureau of Statistics of China, 2012).

Utility

QWB-SA

The QWB-SA assesses the presence/absence of symptoms or problems, persons' mobility, physical activity and social activity. Each participant recalls the answers to particular QWB-SA question within the last three days prior to the day of the survey. The preference-weights were derived from a community sample (77). Scoring algorithm and preference weights are provided by the University of California, San Diego (UCSD) Health Services Research Centre upon request. Use of QWB-SA in our study was authorised by the QWB-SA copyright owner and the validity of Chinese language QWB-SA was reported by our study group previously (83).

EQ-5D/VAS

The EQ-5D comprises of five dimensions including mobility, self-care, usual activity, pain/discomfort and anxiety/depression. The utility scoring algorithm adopted in our study was developed using Time Trade-Off based preference scores from a UK general population(84). EQ-VAS is a 20cm vertical visual analogue scale ranging from 100 (best imaginable health state) to 0 (worst imaginable health state) to represent the overall health of the day. Each

respondent classifies and rates his/her health status on the day of the survey. The simplified Chinese version of EQ-5D/VAS is an official version authorised by the EuroQol Group.

Cognitive status

MMSE

The MMSE is a well-established and widely used cognitive screening tool worldwide. The Chinese version of the MMSE has been extensively deployed in Chinese population across a number of disorders (116-119).

Data analysis

Cost data are usually skewed, as was the case in our study. Thus, we presented the median and the ranges/interquartile range (IGR) of all the cost components. Kruskal-Wallis test was undertaken for comparisons across groups. Spearman's correlation coefficient was constructed to examine the relationship between socio-demographic/epilepsy-specific variables and cost data.

Since the health care expenditures were heavily skewed, so the generalised linear model with a gamma probability distribution and log link function was adopted to explore the predictors of total cost due to epilepsy. Specifically, the total cost was selected as the dependent variable. Other socio-demographic and epilepsy-specific variables that were significantly in the univariate analysis were treated as independent variables. In addition, missed days from work was modelled individually using negative binomial logistical regression for counts of events. All statistical analyses were performed on SPSS 20.0 (SPSS Inc., Chicago, IL, USA). The statistical significant level was a p-value less than 0.05 for all analyses.

6.3 Results

Descriptive statistics

In total, 141 patients with epilepsy and 323 (with 270 subjects completed the WTP questionnaire) healthy controls were enrolled and completed all the instruments from two tertiary hospitals between 4th July 2012 and 20th January 2013. For the epilepsy group, the average age was 31.95 (SD, 13.08), education level was 10.69 years (3.01), age of epilepsy onset was 21.00 (14.08) and duration of epilepsy was 9.32 years (8.74) (Table 6.1). In terms of the prognostic category, there were 8 subjects in the seizure remission group, 33 patients in the occasional seizure group, 58 patients in the active

epilepsy group, and 42 subjects in the drug-resistant epilepsy group.

Table 6. 1 Characteristics of the participants

	Epilepsy	Controls
Number of Subjects	141	323
Age in years, mean (SD)	31.95 (13.08)	36.31(16.55)
Male, n (%)	78 (55.3)	127 (40.7)
Marital status, n (%)		
Single	71 (50.4)	123 (39.4)
Married	69 (48.9)	184 (59.0)
Divorced	1 (0.7)	2 (0.6)
Widowed	0 (0)	3 (1.0)
Han ethnicity n (%)	139 (98.6)	308 (98.7)
Employed, n (%)	61 (43.3)	175 (56.1)
Years of education, mean (SD)	10.69 (3.01)	13.02 (2.93)
Age of onset, mean (SD)	21.00 (14.08)	/
Duration of epilepsy (years), mean (SD)	9.32 (8.74)	/
Seizure types, n (%)		
Simple partial	7 (5.0)	/
Complex partial	78 (55.3)	/
Absence	18 (12.8)	/
Myoclonic generalised	14 (9.9)	/
Clonic generalised	13 (9.2)	/
Tonic-clonic generalised	11 (7.8)	/
Epilepsy syndromes, n (%)		
Localisation-related epilepsies	77 (54.6)	/
Generalised epilepsies	53 (37.6)	/
Epilepsies of unknown localisation	11 (7.8)	/
Refractory epilepsy, n (%)	74 (33.6)	/
Seizure frequency, n (%)		
<1 per year	6 (4.3)	/
1-11 times per year	64 (45.4)	/
≥12 times per year	71 (50.4)	/

Antiepileptic treatment, n (%)		
Monotherapy	65 (46.1)	/
Polytherapy	76 (53.9)	/

Direct medical cost

Inpatient and outpatient care

During the past 12 months, only 18 hospitalisations occurred with a mean hospitalisation of 0.13 per patient, and 23.8% of patients in the drug-resistant epilepsy group were admitted into the hospitals. The outpatient visits for the whole sample totalled 968 a year producing an average of 6.87 per patient per year. Similarly, outpatient care showed an identical trend, with drug-resistant epilepsy group had the highest numbers of outpatient visits (n=381). In terms of the cost for these two components, results showed the differences across prognostic groups were statistically significant ($p=0.012$ and $p<0.0001$ respectively) (Tables 6.2 and 6.3).

Antiepileptic treatment

Three treatment strategies were employed by the majority of patients (82 out of 141), which were Lamotrigine (LTG, N=18), Oxcarbazepine (OXB, N=22) and LTG combined with Valproate (VAP) (N=42). Monotherapy and polytherapy were employed in 46.1% and 53.9% of patients respectively. In addition, 83% of patients were treated by at least one kind of new generation of AEDs. The median cost for AEDs was US$394.53, with the AEDs' cost significantly different across the prognostic groups ($p=0.050$). Besides, only 21 patients (14.9%) received other kinds of antiepileptic treatment, e.g. Chinese herbal medicine, acupuncture. In general, the cost for AEDs constituted 78.7% of the direct medical cost, and 49.5% of the total cost (Tables 6.2 and 6.3).

Medical investigations

Generally, more patients had EEG and biomedical assays during the last 12 months, with the mean of 1.50 (SD, 1.76) and 1.52 (1.80) respectively, whereas AED concentration monitor and brain image scan were less frequently performed. Furthermore, in terms of the utilisations of those four investigations, the four prognostic groups did not show significant differences (all with $p>0.05$). However, the costs of investigations were distinctively different across the four groups ($p=0.024$). The annual per person median cost of investigation was highest in drug-resistant epilepsy group (USD 64.15)

and lowest in remission group (USD 9.62) (Tables 6.2 and 6.3).

Direct non-medical cost

Transportation

The majority of the patients from downtown of the city took the bus/taxi/self-drive or walked to the hospitals (79.4%). However, 29 patients from the suburbs of the city commuted by train or coach. The median cost for transportation was US$19.25 annually and there was significant difference across the prognostic groups (p=0.020). Patients in the drug-resistant epilepsy group (median, US$29.83) spent more on transportation than the other three groups (median, US$17.32, 15.40, and 15.72 respectively) (Tables 6.2 and 6.3).

Equipment/food/special decoration due to epilepsy

Only 15 patients spent money on the equipment/food/special home alteration because of epilepsy and the highest cost was US$481.13 per year with no differences among the groups (p=0.674). More patients in the drug-resistant group (14.3%) purchased special goods for epilepsy. In comparison, no one in the remission group invested on those merchandizes (Tables 6.2 and 6.3).

Indirect cost

124 patients (87.9%) came to the hospital with at least one companion and the average absenteeism from work was 9.31 days per patient annually. For the patients within their working ages (18-60 years), 30 subjects (21.3%) prematurely retired due to epilepsy. However, only 7 patients (5%) required everyday care from their caregivers. 70.2% of patients had absenteeism from their works during the last year. Furthermore, 102 out of 141 patients deemed the disease negatively impact on their working capabilities with significant differences between the four groups (p=0.013). In particular, epilepsy reduced on average the self-rating working capability by 36.74% (out of possible 100%). The self-rating working capability loss was highest in drug-resistant epilepsy group (59.29%) and lowest in the remission group (22.50%). The median indirect cost was US$276.72 per year per patient, with patients' and caregivers' productivity as the major component. In addition, the differences in early retirement, caregiver's costs, and loss due to under-productivity were significant across the prognostic groups (p=0.020, p<0.0001 and p<0.0001 respectively) (Tables 6.2 and 6.3).

Table 6. 2 Patterns of resource uses

	SR (N=8)	OS (N=33)	NDR (N=58)	DR (N=42)	Total (N=141)
Hospital admission	1 (12.5%)	3 (9.1%)	2 (3.4%)	12 (23.8%)	18 (11.3%)
Outpatient visit	45 (100%)	173 (100%)	369 (100%)	381 (100%)	968 (100%)
Investigation					
Brain CT/MRI	2 (25.0%)	14 (42.4%)	38 (56.9%)	37 (71.4%)	91 (56%)
EEG	3 (37.5%)	24 (66.7%)	56 (69.0%)	63 (78.6%)	146 (69.5%)
Biomedical assay	19 (75.0%)	30 (63.6%)	75 (67.2%)	64 (71.4%)	188 (68.1%)
AED concentration monitor	1 (12.5%)	6 (15.2%)	7 (10.3%)	2 (4.8%)	16 (9.9%)
Means of transportation					
Walk	0(0%)	2 (6.1%)	1 (1.7%)	0 (0%)	3 (2.1%)
Bus	3(37.5%)	22 (66.7%)	38 (65.5%)	29 (69.0%)	92 (65.2%)
Taxi	0(0%)	0(0%)	4 (6.9%)	5 (11.9%)	9 (6.4%)
Self-drive	1(12.5%)	4 (12.1%)	3 (5.2%)	0 (0%)	8 (5.7%)
Train	0(0%)	2 (6.1%)	2 (3.4%)	2 (4.8%)	6 (4.3%)
Travel bus	4 (50%)	3(9.1%)	10 (17.2%)	6 (14.3%)	23 (16.3%)
Special equipment/decoration/food	0 (0%)	3 (9.1%)	6(10.3%)	6 (14.3%)	15 (10.6%)
Number of companion	6 (75.0%)	34 (90.9%)	56 (86.2%)	43 (90.5%)	139 (87.9%)
Absenteeism	42 (87.5%)	201 (78.8%)	476 (74.1%)	594 (54.8%)	1313 (70.2%)
Early retirement	1 (12.5%)	4 (12.1%)	9 (15.5%)	16 (38.1%)	30 (21.3%)
Care from caregivers	1(12.5%)	0(0%)	0(0%)	6 (14.3%)	7(5.0%)
Impact on work capability	4 (50.0%)	22 (66.7%)	38 (65.5%)	38 (90.5%)	102 (72.3%)
Loss of productivity (%)	22.50 (34.12)	24.85 (27.85)	29.14 (29.16)	59.29 (31.50)	36.74 (33.07)

Footnote: SR – Seizure Remission; OS –Occasional Seizures; NDR- Non-drug Resistant Seizures; DR-Drug Resistant Seizures.

Table 6. 3 Cost of epilepsy per year (In USD) [Median (Range)]

	SR (N=8)	OS (N=33)	NDR (N=58)	DR (N=42)	Total (N=141)	P-value
Total cost	555.43 (336.17, 9146.99)	875.74 (347.05, 4601.36)	790.10 (221.66, 5127.84)	2856.93 (503.00, 12862.15)	949.29 (221.66, 12862.15)	<0.0001
Direct	390.84 (214.91, 1366.73)	442.00 (178.98, 3762.77)	447.13 (79.23, 2105.75)	610.07 (51.32, 7762.26)	501.34 (79.23, 4492.49)	0.003
Direct Medical	378.65 (176.41, 1289.75)	634.82 (163.58, 3666.54)	406.56 (68.96, 2089.72)	554.42 (129.91, 4428.34)	461.89 (68.96, 4428.34)	0.002
Hospitalisation	0 (0, 641.51)	0 (0, 962.26)	0 (0, 1603.77)	0 (0, 3207.54)	0 (0, 3207.54)	0.012
Outpatient care	8.02 (1.60, 19.25)	8.41 (3.21, 38.49)	9.62 (3.21, 19.25)	9.62 (3.21, 64.15)	9.62 (1.60, 64.15)	<0.0001
AEDs	371.43 (153.96, 504.23)	414.72 (153.96, 1181.66)	394.53 (57.74, 841.98)	394.53 (57.74, 1181.66)	394.53 (57.74, 1181.66)	0.050
Other antiepileptic therapy	0 (0, 0)	0 (0, 3207.54)	0 (0, 1603.77)	0 (0, 80.19)	0 (0, 3207.54)	0.014
Investigations	9.62 (0, 136.32)	39.17 (0, 78.58)	59.34 (0, 165.19)	64.15 (0, 224.53)	59.34 (0, 224.53)	0.024
Direct Non-medical	63.76 (35.06, 222.96)	72.10 (29.20, 653.07)	74.43 (12.92, 418.24)	103.53 (24.54, 736.79)	82.99 (12.92, 736.79)	0.001
Transportation	17.32 (5.13, 115.47)	15.40 (0, 115.47)	15.72 (2.57, 205.28)	29.83 (5.13, 384.91)	19.25 (0, 384.91)	0.020
Special equipment/food	0 (0,0)	0 (0, 240.57)	0 (0, 481.13)	0 (0, 481.13)	0 (0, 481.13)	0.674
Indirect	172.95 (34.59, 7608.29)	207.54 (34.59, 3907.92)	242.13 (69.18, 4219.23)	778.28 (69.18, 7608.29)	276.72 (34.59, 7608.29)	<0.0001
Absenteeism cost	77.83 (0, 207.54)	103.77 (0, 760.98)	103.77 (0, 795.57)	172.95 (0, 2594.26)	103.77 (0, 2594.26)	0.708
Early retirement cost	0 (0, 3804.15)	0 (0, 3804.15)	0 (0, 3804.15)	0 (0, 3894.15)	0 (0, 3804.15)	0.020
Caregiver's cost	34.59 (0, 3804.15)	86.48 (0, 415.08)	103.77 (0, 1282.00)	103.77 (0, 3804.15)	103.77 (0, 3804.15)	<0.0001
Loss due to underproductivity [a]	432.40 (0, 1297.20)	864.80 (0, 1729.60)	864.80 (0,2162.00)	2594.40 (1621.50, 3891.60)	1297.20 (0, 2594.40)	<0.0001

[a] The range of the four subgroups are the same (0, 4324), in order to show the difference, the interquartile range is presented here instead.

Intangible cost

WTP valuation

The average WTP value was US$266.07 per epilepsy patient comparing to US$88.22 for a healthy control, and the difference between the two groups was significant (p<0.0001). However, there was no difference in terms of WTP value across the four prognostic groups or various seizure types, epilepsy syndromes, seizure frequencies (all with p>0.05) (Table 6.4).

Table 6. 4 Intangible cost of epilepsy group vs. control group [Median (IGR)]

	WTP value (USD)	**Utility**	
		EQ-5D	**QWB-SA**
Epilepsy	240.57 (192.45)	0.848 (0.275)	0.673(0.172)
Control	48.11 (160.38)	1.000(0.152)	0.775 (0.258)

Utility valuation

For utility using QWB-SA, the mean was 0.657 (SD, 0.135) for epilepsy group and 0.802(0.155) for control group, and the medians (IQR) were 0.673(0.172) for epilepsy group and 1.000(0.152) for control group.

For utility using EQ-5D, the means for epilepsy group were 0.828 (0.206) and 0.923 (0.132) for control group, while the medians (IQR) were 0.848 (0.275) for epilepsy group and 1.000(0.152) for control group. Utility scores on QWB-SA and EQ-5D were significantly different between the two groups (p<0.0001), whereas the EQ-VAS did not show a difference (p=0.052) (Table 6.4).

Predictors for cost of epilepsy

Univariate analysis

For the socio-demographic variables, total cost (p=0.002) and indirect cost (p<0.0001) could be differentiated by age, with an increasing trend in cost observed with older age. When it came to the epilepsy-specific variables, duration of epilepsy, seizure frequency, and number of AEDs successfully discriminated the total cost or the direct/indirect cost. In addition, patients with different cognitive profiles also had distinctive total costs (p=0.022), with poorer cognition incurred greater cost. Lastly, the QWB-SA self-rating health status also predicted the difference in total (p=0.001), direct (p=0.033) and indirect cost (p<0.0001). Particularly, patients with poorer health status had higher cost (Table 6.5).

Table 6. 5 Univariate analysis of cost

Age	**≤20 (N=31)**	**21-30 (N=47)**	**31-40 (N=26)**	**≥41 (N=37)**	p-value
Total cost	726.75 (3367.76, 8229.75)	807.49 (221.66, 7957.17)	1310.31 (442.61, 8667.86)	1760.92 (389.67, 12862.14)	0.002
Direct cost	506.15 (150.43, 1329.85)	502.94 (79.23, 3762.77)	555.23 (121.89, 2100.94)	447.45 (112.58, 4492.49)	0.727
Indirect cost	207.54 (34.59, 7608.29)	207.54 (69.18, 7608.29)	328.61 (69.18, 7608.29)	726.39 (103.77, 7608.29)	<0.0001
Gender	**Male (N=78)**		**Female (N=63)**		
Total cost	896.55 (347.05, 9146.99)		969.17 (221.66, 12862.14)		0.880
Direct cost	503.74 (150.43, 2291.79)		498.13 (79.23, 4492.49)		0.170
Indirect cost	242.13 (34.59, 7608.29)		276.72 (34.59, 7608.29)		0.647
Working status	**Employed (n=63)**		**Unemployed (N=78)**		
Total cost	896.55 (221.66, 12862.14)		959.74 (336.18, 10094.38)		0.903
Direct cost	508.72 (79.23, 4492.49)		475.36 (112.58, 3762.77)		0.251
Indirect cost	276.72 (34.59, 7608.29)		259.43 (34.59, 7608.29)		0.949
Education	**≤6 years (N=16)**	**7-12 years (N=96)**	**≥13 years (N=29)**		
Total cost	1381.53 (428.65, 5127.84)	877.07 (221.66, 9146.99)	896.55 (336.18, 12862.14)		0.557
Direct cost	493.16 (150.43, 1457.19)	504.55 (79.23, 3763.77)	501.34 (214.91, 4492.49)		0.977
Indirect cost	432.38 (69.18, 4219.23)	242.13 (34.59, 7608.29)	276.72 (69.18, 7608.29)		0.210
Age of epilepsy onset	**≤10 (N=31)**	**11-20 (N=60)**	**21-30 (N=19)**	**≥31 (N=31)**	
Total cost	979.50 (399.75, 9146.99)	800.56 (221.66, 8667.86)	722.84 (491.64, 5396.71)	2960.57 (389.67, 12862.14)	0.129
Direct cost	537.26 (121.89, 2100.94)	500.06 (79.23, 2291.79)	487.23 (276.49, 3762.77)	410.57 (112.58, 4492.49)	0.481
Indirect cost	276.72 (34.59, 7608.29)	242.13 (34.59, 7608.29)	242.13 (69.18, 3907.92)	1176.07 (69.18, 7608.29)	0.126
Duration of epilepsy	**≤2 (N=40)**	**3-5 (N=29)**	**6-15 (N=44)**	**≥16 (N=28)**	

Total cost	1024.65 (421.30, 10094.38)	684.84 (221.66, 5318.46)	1103.06 (399.75, 12862.14)	989.78 (434.78, 6364.70)		0.003
Direct cost	444.73 (112.58, 3762.77)	416.66 (79.23, 1490.87)	519.62 (179.62, 4492.49)	607.03 (121.89, 2105.75)		0.050
Indirect cost	233.48 (69.18, 7608.29)	207.54 (69.18, 3942.51)	397.77 (34.59, 7608.29)	285.37 (103.77, 4219.23)		0.010
Seizure types	**Simple partial (N=7)**	**Complex partial (N=78)**	**Absence (N=18)**	**Myoclonic (N=14)**	**Clonic (N=13)**	**Tonic-clonic (N=11)**
Total cost	806.81 (428.65, 5234.42)	975.82 (221.66, 10094.38)	847.84 (336.18, 4789.37)	1108.35 (421.30, 9146.99)	949.45 (367.76, 5318.46)	743.94 (445.90, 12862.14)
Direct cost	574.79 (308.24, 1215.98)	500.22 (79.23, 3762.77)	532.13 (150.43, 1329.85)	584.74 (230.94, 2015.30)	442.00 (121.89, 1397.53)	461.89 (179.62, 4492.49)
Indirect cost	207.54 (69.18, 3907.92)	276.72 (34.59, 7608.29)	207.54 (103.77, 4011.69)	250.78 (69.18, 7608.29	276.72 (34.59, 4011.69)	380.49 (103.77, 7608.29)
Epilepsy syndrome	**Localisation-related (N=77)**	**Generalised (N=53)**	**Unknown localisation (N=11)**			
Total cost	981.61 (221.66, 10094.38)	878.40 (336.18, 12862.14)	1206.63 (403.63, 8667.86)			0.686
Direct cost	499.09 (79.23, 3762.77)	492.04 (121.89, 4492.49)	508.72 (178.98, 2015.30)			0.884
Indirect cost	276.72 (69.18, 7608.29)	259.43 (34.59, 7608.29)	328.61 (34.59, 7608.29)			0.667
Seizure frequency	**≤1 /year (N=6)**	**1-12 /year (N=64)**	**>12 /year (N=71)**			
Total cost	520.50 (336.18, 755.59)	768.60 (347.05, 9146.99)	1297.37 (221.66, 12862.14)			<0.0001
Direct cost	345.61 (214.91, 530.53)	445.53 (178.98, 3762.77)	534.70 (79.23, 4492.49)			0.039
Indirect cost	129.71 (34.59, 207.54)	207.54 (34.59, 7608.29)	484.26 (69.18, 7608.29)			<0.0001
Antiepileptic treatment	**Monotherapy (N=65)**	**Polytherapy (N=76)**				
Total cost	722.84 (221.66, 5127.84)	1260.65 (389.67, 12862.14)				<0.0001
Direct cost	341.28 (79.23, 2082.66)	538.07 (245.06, 4492.49)				<0.0001
Indirect cost	207.54 (34.59, 4219.23)	319.96 (34.59, 7608.29)				0.009
MMSE	**>27 (N=74)**	**≤26 (N=67)**				
Total cost	812.38 (336.18, 10094.18)	1016.36 (221.66, 12862.14)				0.022
Direct cost	485.46 (112.58, 2200.38)	508.72 (79.23, 4492.49)				0.262
Indirect cost	207.54 (34.59, 7608.29)	345.90 (69.18, 7608.29)				0.008

QWB-SA self-rating status	Excellent (N=2)	Very good (N=22)	Good (N=56)	Fair (N=54)	Poor (N=7)	
Total cost	599.10 (442.61, 755.61)	584.25 (290.60, 4070.69)	886.15 (221.66, 5396.71)	1103.06 (336.18, 12862.14)	4582.23 (1534.95, 8667.86)	0.001
Direct cost	400.46 (270.40, 530.53)	424.68 (112.58, 3762.77)	531.65 (79.23, 2200.38)	485.46 (150.43, 4492.49)	915.43 (508.72, 2291.79)	0.033
Indirect cost	138.36 (138.36, 138.36)	153.96 (25.66, 3958.11)	250.78 (69.18, 4219.23)	397.79 (69.18, 7608.29)	3804.15 (622.62, 7608.29)	<0.0001

The Spearman's correlation also showed the significant correlations between total cost and utility (EQ-5D and QWB-SA) (both with p<0.001), EQ-VAS (p=0.008), QWB-SA self-rating health status (p<0.0001), and MMSE (p=0.020) (Table 6.6).

Table 6. 6 Correlation between total cost of epilepsy and other factors (correlation coefficient, p-value)

	Total cost	Direct cost	Indirect cost
EQ-5D	-0.286(0.001)	-0.111(0.189)	-0.301(<0.0001)
EQ- VAS	-0.221 (0.008)	-0.169 (0.045)	-0.209 (0.013)
QWB-SA	-0.338 (<0.0001)	-0.106(0.210)	-0.402 (<0.0001)
QWB-SA self rating health status	0.307 (<0.0001)	0.095 (0.262)	-0.408 (<0.0001)
WTP	-0.077 (0.362)	-0.017 (0.843)	-0.032(0.703)
MMSE	-0.197(0.020)	-0.069(0.413)	-0.252(0.003)
Self rating negative impact on work	-0.367 (<0.0001)	-0.112 (0.185)	-0.542 (<0.0001)

To investigate the difference in cost based on types of AEDs, treatment strategy with more than 10 subjects was extracted for further exploration, which included LTG (N=18), OXB (N=22), and LTG combined with VAP (N=42) groups. The result showed significant differences across these three AED's groups, with patients on LTG incurred the lowest total cost (p=0.010) (Table 6.7).

Table 6. 7 Cost estimation based on different AED's treatment

	Total cost	Direct cost	Indirect cost
LTG (N=18)	833.39† (365.74, 4270.15)	457.46‡ (272.76, 2118.43)	375.93§ (52.20, 3947.80)
OXB (N=22)	1644.54 (398.69, 4655.14)	566.39‡ (309.62, 1094.62)	1078.16 (52.20, 4026.10)
LTG+VPA (N=42)	2323.47 (453.51, 12308.65)	900.45 (427.41, 4569. 66)	1423.02 (26.10, 8261.01)
Significance	0.000	0.000	0.007

†LTG generated less total cost than LTG+VPA, p=0,010
‡LTG+VPA created higher direct cost than either LTG or OXB, p<0.05
§ LTG borne less indirect cost than LTG+VPA, p=0.033

Mutivariate analysis

The generalised linear model identified seizure frequency (p=0.022), prognostic groups (p=0.018) (Figure 1), self-rating impact on work capability (p=0.020), MMSE scores (p=0.002), age (p<0.0001), and utility of EQ-5D (p=0.035) were able to predict the total cost. For example, one unit increase in the MMSE score (better cognition) was associated with a 4.8% decrease in the log-transformed total cost. Similarly, one unit increase in EQ-5D utility attributed to a 63.8% decrease in the log-transformed total cost. However, other factors like utility of QWB-SA (p=0.055), QWB-SA self-rating health state (p=0.589), duration of epilepsy (p=0.054) and number of AEDs (p=0.275) failed to retain the significances (Table 6.8). For days of absenteeism, the multivariate analysis showed only self-rating impact on work capability (p<0.0001) and age (p=0.020) significantly contributed to the model. For example, comparing to people without self-deemed reduction in working capability, patient with such decrease was associated with a 1.182 increase in the log count of the missed days from work (Table 6.9). However, no variable statistically contributed to the differences in numbers of hospitalisation and outpatient care.

Table 6. 8 Multivariate analysis for total cost (generalised linear model with gamma distribution)

Parameter Estimates							
Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	9.204	0.5690	8.089	10.319	261.653	1	<0.0001
Number of AEDs							
Monotherapy	-0.150	0.1378	-0.420	0.120	1.190	1	0.275
Polytherapy	0[a]	.	.	.	.	.	.
Seizure frequency							
≤1/year	-1.649	0.6136	-2.852	-0.446	7.223	1	0.007
2-11/year	-0.003	0.1674	-0.331	0.325	0.000	1	0.985
≥12/year	0[a]	.	.	.	.	.	.
Prognostic groups							
In remission	0.588	0.5246	-0.440	1.616	1.256	1	0.262
Occasional seizures	-0.480	0.2375	-0.946	-0.015	4.090	1	0.043
Active epilepsy	-0.469	0.1870	-0.835	-0.102	6.279	1	0.012
Refractory epilepsy	0[a]	.	.	.	.	.	.
Self rating health state							
Excellent	-0.598	0.6224	-1.818	0.622	0.924	1	0.336
Very good	-0.277	0.3361	-0.935	0.382	0.677	1	0.411
Good	-0.432	0.2972	-1.014	0.151	2.108	1	0.147
Fair	-0.361	0.2861	-0.922	0.200	1.594	1	0.207
Poor	0[a]	.	.	.	.	.	.
Impact on work capability							
Positive	0.365	0.1567	0.058	0.672	5.416	1	0.020
Negative	0[a]	.	.	.	.	.	.
Age	0.020	0.0051	0.010	0.030	15.044	1	<0.0001
Duration of epilepsy	-0.015	0.0078	-0.030	0.000	3.708	1	0.054
EQ-5D	-0.638	0.3021	-1.230	-0.045	4.453	1	0.035
MMSE score	-0.048	0.0159	-0.080	-0.017	9.219	1	0.002
(Scale)	0.457[b]	.0508	0.367	0.568			
Dependent Variable: Total Cost							

Model: (Intercept), number of AEDs, seizure frequency, prognostic groups, QWB Health state, Impact on work capability, age, duration, EQ5D, MMSE scores
a. Set to zero because this parameter is redundant.
b. Maximum likelihood estimate.

Table 6. 9 Multivariate analysis for days of absenteeism (negative binomial regression model)

Parameter Estimates							
Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	3.223	1.2201	0.831	5.614	6.976	1	0.008
Number of AEDs							
Monotherapy	0.105	0.2412	-0.368	0.578	0.190	1	0.663
Polytherapy	0[a]	.	.	.	.	.	.
Seizure frequency							
≤1/year	0.437	1.0157	-1.554	2.427	0.185	1	0.667
2-11/year	0.149	0.3059	-0.451	0.748	0.237	1	0.626
≥12/year	0[a]	.	.	.	.	.	.
Prognostic groups							
In remission	-0.860	0.9305	-2.683	0.964	0.854	1	0.356
Occasional seizures	-0.642	0.4542	-1.533	0.248	2.000	1	0.157
Active epilepsy	-0.562	0.3460	-1.240	0.116	2.640	1	0.104
Refractory epilepsy	0[a]	.	.	.	.	.	.
Self rating health state							
Excellent	-1.142	0.9740	-3.051	0.767	1.375	1	0.241
Very good	-0.473	0.5736	-1.597	0.651	0.680	1	0.410
Good	-0.312	0.4983	-1.289	0.664	0.393	1	0.531
Fair	-0.637	0.4938	-1.604	0.331	1.662	1	0.197
Poor	0[a]	.	.	.	.	.	.
Impact on work capability							
Positive	1.182	0.3177	0.559	1.804	13.836	1	<0.0001
Negative	0[a]	.	.	.	.	.	.
Age	-0.022	0.0097	-0.041	-0.003	5.379	1	0.020
Duration of epilepsy	0.013	0.0135	-0.014	0.039	0.904	1	0.342
EQ-5D	-0.263	0.4973	-1.238	0.711	0.281	1	0.596

MMSE score	-0.013	0.0348	-0.081	0.055	0.142	1	0.706
Lost of productivity	-0.003	0.0047	-0.012	0.006	0.378	1	0.538
(Scale)	1[b]						
(Negative binomial)	1[b]						
Dependent Variable: days of absenteeism Model: (Intercept), number of AEDs, seizure frequency, prognostic groups, Health state, Impact on work capability, Age, duration, EQ-5D, MMSE scores, lost of productivity.							
a. Set to zero because this parameter is redundant.							
b. Fixed at the displayed value.							

Cost of epilepsy in China

In 2012, the total population in China was 1,359,470,000, and the prevalence of epilepsy in China was 2.89% (69), hence, epilepsy sufferers would approximately be 4 million in 2012. Based on the estimation of present study, the total direct medical cost for epilepsy was US$18.1 billion in 2012 for China. The national statistics (National Health and Family Planning Commission of the People's Republic of China) indicated that the total health care expenditure was CNY 2891.44 billion (US$463.72 billion) in 2012. Thus, the total medical cost of epilepsy accounted for 3.9% of total health care costs. Furthermore, the total economic burden of epilepsy from the societal perspective would be US$3.80 billion (IGR: 2.53, 12.39) and US$11.35 billion (IGR: 5.78-25.95) with under-productivity loss in 2012. Per patient total cost of epilepsy constituted 17.5% (IGR: 11.67%-57.16%) or 52.4% (IGR: 26.7%-119.76%) (with under-productivity loss) of the Gross Domestic Production (GDP) per capita in China (USD 5417, 2012).

6.4 Discussion

Cost of illness study is used generally to inform the economic burden of a disease, and aid the decision making for health resource allocation. To the best of our knowledge, our study is the first to quantify the direct, indirect and intangible cost due to epilepsy in China. Along with the overall cost of epilepsy, our study also compared the differences in total cost based on disease severities. In our study, the total cost of epilepsy accounted for 21.95% (IGR: 14.6%-71.62%) of the annual personal income of residents of Hubei province (US$4323.61). Furthermore, the intangible costs in terms of WTP value and utility were both substantial comparing to the general population. All together, the burden of epilepsy in China is huge for both patient and society.

In the present study, cost for AEDs accounted for 78.7% of the direct medical cost, which was higher than previously reported (40% and 65%)(112, 113). Nevertheless, participants in the present study had the fewest hospital admissions during the past one year with a mean of 0.12 per patient compared to 0.47(112) and 0.2 (113) in the previous reports. According to other COI studies of epilepsy, two primary direct cost components were hospitalisation and AEDs (100, 103, 120-125), which could explain the discrepancy in results. With respect to the indirect cost, productivity loss of patient exceeded the cost of early retirement probably because only 30 patients (21.3%) prematurely withdrew from the labour market. Actually, more than 72% of the patients in our study claimed reduced work capabilities due to the disease and the average loss in productivity was fairly high (36.7% per person). When a monetary value was assigned to productivity loss, the median indirect cost was increased from USD277 to USD1902, constituting 67% of the total cost (Table 6.3). In contrast, in our study the productivity loss of caregivers was modest, with only 7 out of 141 patients required informal care, and most of the caregiver's productivity cost was due to the absenteeism from work.

The robustness of our result in indirect cost could be demonstrated by the consistency with other indirect cost estimations. From the identified COI studies, the indirect cost (adjusted to 2012 value) ranged from US$146 to 10228 from developing to developed countries (112, 124, 126-133), accounting for between 23.5% and 83.3% of the total cost. To interpret this huge variation more meaningfully, the raw cost data was converted to percentage of GDP/Capita of individual country based on the method of a previous study(134). After the transformation, the indirect cost expressed as percentage of the GDP/Capita ranged from 5.13% to 25.68% (Table 6.10). As such, the indirect cost from our study (5.11%) was very close to the lower bound value. However, when under-productivity loss was included in the indirect cost, our estimation (35.11%) exceeded the upper bound primarily because none of the studies included this component of loss. Considering patients with epilepsy have higher possibilities to experience psychological problems (135), social stigma (136), as well as poorer quality of life, all contributing to their reduced work performance, ignoring the under-productivity loss would result in substantial underestimation of the total economic burden of this disease. Consequently, our results could fill the knowledge gap on the under-productivity loss of epilepsy as well as provide a quick reference check of the indirect cost especially for countries with similar economic status.

Table 6. 10 Comparison of indirect cost across countries (In 2012 USD values)

	Total cost	Indirect cost	Proportion of indirect cost	GDP/Capita	Percentage of indirect cost accounting for the GDP/Capita
	Mean or Median				
Spain (Sancho. 2008)	10832	2546	23.5%	32077	7.94%

Spain (Pato. 2011)	3915	2318	59.2%	32077	7.23%
India (Thomas. 2001)	484	353	73.0%	1514	23.34%
India (Krishnan. 2003)	228	146	64.1%	1514	9.65%
USA (Ivanova. 2010)	15982	3756	23.5%	48328	7.77%
Denmark (Jennum. 2011)	19657	15332	78.0%	59709	25.68%
Germany (Hamer. 2006)	13497	8328	61.7%	44111	18.88%
Sweden (Bolin. 2011)	12279	10228	83.3%	57638	17.75%
Switzerland (Gessner. 1993)	10134	4054	40.0%	79052	5.13%
China (Zhen. 2009)	824	293	35.6%	5417	5.42%
Present study [a]	949	277	29.19%	5417	5.11%
Present study [b]	2838	1902	67.01%	5417	35.11%

[a] Including direct and indirect costs (patient and caregivers productivity cost and premature retirement cost)
[b] Including direct and indirect costs (patient and caregivers productivity cost, premature retirement cost, and under-productivity cost)

The comparability of the current results with other results from developed countries is somewhat restricted by the differences in health care systems and economic status across countries. For example, in many developed countries, inpatient care usually constitutes the largest part of direct cost according to a number of COI studies (122-124, 129, 132, 137-139). In contrast, in the present study, only 11.3% of patients required hospitalisation during the last year, which may be caused by the treatment pattern difference across countries. Another difference is that, in China, the general practitioner (GP) is not responsible for the management of patients with epilepsy. Instead, all patients with epilepsy will be referred to the neurologist/epileptologist. This management by specialist physicians may also explain the fewer hospitalisations. In addition, due to cultural and social norms, patients with disability or difficulty in everyday life would be taken care at home by family members rather than at the rehabilitation centre/nursing home, this also contributes to the difference in the total cost. For example, in a UK study, community-based health care accounted for 3.90% of the direct cost (125). Nonetheless, even the results from developing countries seemed to be inconsistent with our study. For instances, two Indian and a Nigerian studies reported the annual per person direct costs were US$80, 106 and 208 (inflated to the values in 2012) respectively (the GPD/capita was US$1514 for India and US$1522 for Nigeria in 2012). However, the composition of the total costs shared certain similarities with the costs of AEDs accounted for the most part amongst all these developing countries (130, 133, 140).

In the multivariate analysis, it was identified that age, seizure frequency, prognostic groups, self-rating impact on work capability, MMSE scores and utility of EQ-5D could be the potential predictors for total cost. It should be noted that the cost

to address cognitive problem and other comorbidity were not included in the present estimation, hence, the different cost was primarily caused by the intrinsic difference in the disease severities. Furthermore, there was a positive correlation between age and cost of epilepsy (Beta coefficient 0.198) (the difference was primarily caused by the variation in indirect cost, according to univariate analysis), which might be important for health care policy formulation. The unemployment or underemployment rate for epileptic population is higher than the general population (110, 141-146) and patients with epilepsy face greater difficulty in finding and maintaining regular employment (105, 147). Therefore, it is beyond argument that policy and intervention should be implemented not just to reduce the cost of the disease from the societal perspective but also promote the individual's personal status, identity, self-worth (106) and quality of life (110, 148).

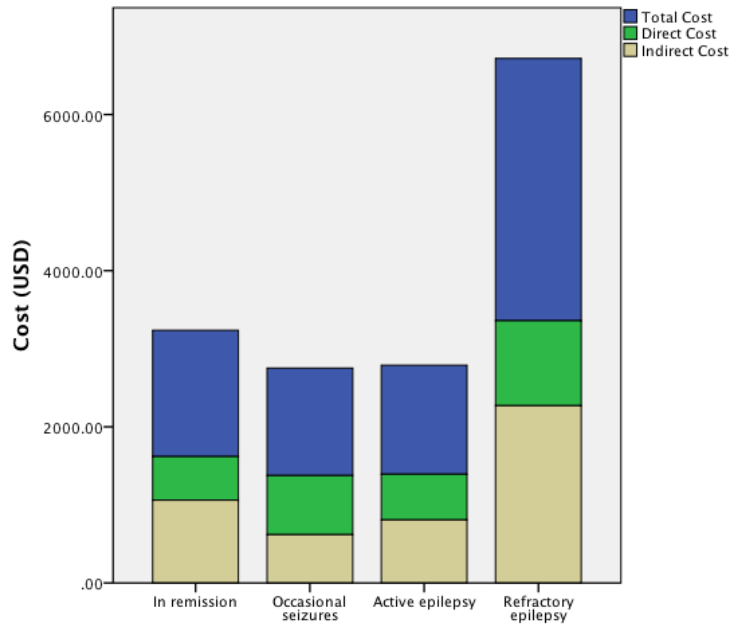
In addition, reduced cognitive function also indicated increased total cost in the multivariate analysis. Patients with epilepsy experienced cognitive problems in various cognition domains, such as reduced intelligence, attention, problems in memory, language, and executive functions (149). In our univariate analysis, indirect cost rather than direct cost was different between two MMSE score based groups. Besides, when direct cost was selected as dependent variable in the multivariate analysis, only number of AEDs significantly contributed to the model ($p<0.0001$) whereas MMSE scores did not retain the significance ($p=0.256$). Therefore, we may infer that due to underlying cognitive problems, patients may suffer more severe reduction in productivity. Meanwhile, patients with such problems might be more likely to require attention from their family members, which could result in higher caregiver's loss.

Moreover, our study also confirmed that seizure frequency is an independent determinant of health resource utilisation for epilepsy patients as reported in other studies (138, 150) (Figure 1). Additionally, in our study, the intangible cost measured by utility of EQ-5D also appeared to be significantly associated with total cost, which may also have policy implications. As reported by previous studies, differences in quality of life could potentially lead to the variations in the health resource utilisation (150) or total cost of care (151). Consistent with the reported studies, our current study also showed poorer utility in EQ-5D could predict increased total cost due to epilepsy.

An important novelty of the present study was the measurement of intangible cost via both utility and WTP valuations. To the best of our knowledge, only one study ever estimated the intangible cost due to epilepsy through assessing the HRQoL (utilising Quality of Life in Epilepsy Inventory-10, QOLIE-10) (131). Nevertheless, this epilepsy-specific HRQoL instrument cannot reflect patients' preferences for health outcomes whereas the utility measures can. Therefore, it might be more appropriate to assess the intangible cost using utility measures. Based on two measures (WTP and utility), patients with

epilepsy had substantially higher intangible cost than the general population. It has been stated that "the psychological and social consequences of epilepsy are more disabling than the seizures themselves"(135). Although patient in seizure remission might have fewer direct and indirect cost benefited from satisfactory seizure control, they may still have serious psychological problems(135). Additionally, even patients in remission might worry about the stigma of epilepsy label (136). Altogether, it is important to include the intangible cost to avoid substantially underestimating the burden of epilepsy.

Figure 6. 1 Differences in cost based on prognostic groups



Several limitations of our study should be noted. First, the subjects in the study were enrolled from two local hospitals, which may limit the representativeness of the result for entire China. Second, the results may suffer from some potential recall inaccuracies. However, in order to reduce the recall inaccuracy, all patients were asked to bring the relevant outpatient medical chart and discharge record and completed the questionnaire with the presence of their caregivers. In addition, all inputs were also cross-checked with the hospital records. Third, for the intangible cost comparisons between epilepsy and general populations, due to the difference in demographic characteristics of recruited subjects, the results need to be interpreted with some caution. Nevertheless, after controlling for the heterogeneous demographic variables, the difference between the two groups was still significant.

6.5 Conclusions

Epilepsy is a cost intensive disease in China. The median total cost was US$949.29 (IGR: 632.17-3096.43) with direct cost accounting for the larger part. Using the prevalence derived from a review, the annual total cost of epilepsy was US$3.80 billion (IGR: 2.53-12.39) or US$11.35 billion (IGR: 5.78-25.95) (with under-productivity loss) in 2012 for China. Per patient total cost of epilepsy would consume 17.5% (IGR: 11.67%- 57.16%) of the Gross GDP per capita in China. Within the cost components, cost for AEDs was the most prominent component of direct cost. Besides, the intangible cost of epilepsy was substantially different according to the WTP value and utility comparisons between epilepsy patients and healthy controls. Lastly, age, seizure frequency, self-rating impact on work capability, prognostic groups, MMSE scores and utility of EQ-5D could potentially predict the total cost for this population. Future study using the prospective method is recommended to confirm the accuracy of our estimation.

Chapter 7. Conclusions

7.1 Major findings

In this concluding chapter, the major findings from the series of studies in this thesis could be summarised as follows:

In the first section of the thesis (Chapter 2), a systematic review and meta-analysis of RCTs for newer antiepileptic drugs was performed to summarise the evidence on the efficacy and safety outcomes. This chapter gave an example on how to identify and summarise the evidence in guiding clinical recommendation development and essential drug list formulation with the intention to promote quality use of medicines when local information was not available. Due to the substantial time and cost required in performing clinical trials locally, it would be both time and cost saving to develop the clinical guidance based on the readily available evidence, which is crucially important for developing countries. With the convergence in clinical practice patterns and availability of multinational designed clinical trials, it is also feasible to pool the clinical evidence from various sources for local use. As a result, in this study, it was found out that the newer generation AEDs as add-on therapy for patients with drug resistant partial onset seizures were more effective than monotherapy alone in terms of higher seizure free and responder rates, by accompanied with greater incidences in adverse effects. From the same study, it was also indicated that brivaracetam followed by retigabine might be more preferable than the other newer AEDs. This information could aid the formulation of the clinical guidelines for patients with drug-resistant partial onset seizures and placement of different newer AEDs in the clinical guidelines. In addition, it could also assist the formulation of essential drug list and reimbursement decision-making.

Given the limitations of efficacy and safety outcomes in assessing patient relevant outcomes, the importance of incorporating patients' values in the decision-making process has been well recognised. For patients with chronic diseases, it is even more important to integrate the patients' values into either clinical or policy

decision-making to deliver quality healthcare services. However their clinical use in China is relatively limited due to a lack of validated instruments. Therefore, in the Chapter 3, we firstly translated and validated a health utility measure (77) in Chinese patients with epilepsy. We demonstrated the Chinese-language QWB-SA to be a sensitive and reliable utility measure in both patients with epilepsy and general population. Comparing to another widely use generic utility tool --EQ-5D, QWB-SA is able to differentiate various disease subgroups and has less ceiling effects. Additionally, more disease-specific variables were identified to associate with utility of QWB-SA than EQ-5D. This information can help clinicians and policy-makers in choosing a sensitive and reliable utility measure. Last but not least, with the increasing usefulness of economic evaluation in reimbursement decision-making amongst developing countries, the utility that derived from QWB-SA could be integrated into the cost-effectiveness/utility analysis.

Due to the extreme constraints in the healthcare budget in developing countries, it is imperative for decision makers in these countries to ascertain the value for money for any healthcare decision-making. Thus, in Chapter 4, we utilised a decision-analytic model to simulate the clinical and economic consequences of administrating liraglutide in Chinese patients with T_2DM. As a result, this study demonstrated that, although liraglutide was associated with fewer costs for diabetes-related complications, longer life expectancy and higher QALYs, using the price populated in the model, liraglutide was not a cost-effective anti-diabetic agent in China. However, if the price of liraglutide could be discounted, its administration could become cost-effective in a series of Asian developing countries. These findings could be employed as benchmarks by decision-makers when negotiating the price with pharmaceutical companies for individual jurisdictions. This is especially useful to China, to the best of our knowledge, liraglutide has been marketed since 2011 in China, whereas it has not been listed in the national or provincial drug reimbursement list at the time of our study.

Following the previous chapter, in Chapter 5, through the empirical study eliciting the WTP/QALY value on patients with epilepsy and general population, we examined the validity of decision-making threshold proposed by WHO (1-3 times of GDP/Capita) and demonstrated that it may be possible to be applied in the

Asian setting. The adoption of such a threshold would provide a quick reference value when decision-makers intend to interpret the result from CEA/CUA studies to arrive at an overall conclusion about the cost-effectiveness of a particular medicine. Besides, using two indirect utility elicitation measures (QWB-SA and EQ-5D), we also identified that several socio-demographic and/or epilepsy-specific variables were the predictors of HRQoL for those two populations.

In Chapter 6, through a prevalence-based COI study gauging the economic burden of epilepsy in China, we demonstrated that the COI study could be a helpful analytic tool for healthcare planning, disease prioritising, benefits assessment and resource allocation. From this study, it was found out that epilepsy is a cost-intensive disease in China and pharmaceuticals cost constituted the largest component for the direct medical costs while productivity loss was substantial to the society. Moreover, the cost due to epilepsy was positively associated with disease severity, cognitive function, Health related quality of life and age of the subjects. Besides, the intangible cost, which was firstly reported, was also considerable in terms of both utility and WTP values. The results from this study could be adopted by decision-makers in resource allocation, policy formulation and disease prioritising processes with a timely manner and fill the knowledge gap on burden of epilepsy in China, especially the intangible cost.

In conclusion, the results from the studies presented in this thesis would systematically contribute new knowledge to the feasibility and applicability of the concept of quality use of medicines in developing countries from a micro perspective. It demonstrated the feasibility to apply the concept of quality use of medicines in developing countries with limited healthcare resources. Though in developing countries, tackling the drug quality and ensuring the access to drugs are primary and more pressing goals in regulating the medicines uses, with the increasing availability of sophisticated drugs and consumer expectation, the subsequent excessive growth in healthcare expenditure will eventually make the quality use of medicines another major focus for attention. Several important implications are worth noting: first, due to the discrepancy in the utility between health utility measures (QWB-SA and EQ-5D), cautions should be paid when choosing an appropriate measure either in measuring patient preference for healthcare outcome or integrating the values into cost-

effectiveness/utility analysis. Second, in terms of drug price negotiation, with relatively simple adaptation, a reference value of drug could be easily derived from threshold of ICER. All these efforts would facilitate the understanding on quality use of medicine for clinicians and policy-makers, especially for developing countries, where quality use of medicines would maximise the usefulness of existing resources and deliver the best healthcare outcomes.

7.2 Limitations

The limitations of the each study have been thoroughly discussed in the individual chapters. It will be briefly stated in this concluding chapter.

Firstly, the representativeness of the subjects recruited in the study was restricted by the limited sample size and sampling method for a number of reasons including logistical difficulty and time constraints. Particularly, sample of the general population was enrolled conveniently from the relatives of patients, hospital general staff and medical students, which may be not fully representative. As such, the utility from our studies may be lack of generalisability to the nationwide population in China. Therefore, future study with larger sample size and well-designed sampling process would be required to confirm our results.

Second, the WTP value in the study was elicited through indirect approach (QWB-SA and EQ-5D). Without doubt, direct utility elicitation method such as standard gamble or time-trade-off would be superior to the indirect method as utilised in the present study. However, either standard gamble or time-trade-off method was hard to understand and respond for participants, thus, indirect methods might serve as a substitution to direct methods.

Third, the COI study was performed via a retrospective manner in this thesis, which is subject to potential bias. However, in order to reduce the recall bias, all patients were asked to bring the relevant outpatient medical

chart and discharge record and completed the questionnaire with the presence of their caregivers. In addition, all inputs were also cross-checked with the hospital records. Thus, we believed the inaccuracies were controlled to the least extent.

7.3 Recommendations for future studies

In this final section, we would like to propose a few ideas and make some suggestions for future research.

- Head-to-head comparisons among newer generation of antiepileptic drugs for patients with drug resistant partial onset seizures are strongly encouraged to ascertain the relative efficacy and safety of those drugs, and to compare with the results from our meta-analysis.

- National survey with larger sample size and well-designed sampling process is encouraged to provide the reference for baseline information on health related utility index in China as well as other developing countries. Besides, it is recommended to estimate the utility index algorithms of either QWB-SA or EQ-5D for Chinese population. This is important because the variation in descriptive systems and preference weights may potentially distort the final results. Additionally, this will also have important implication especially if the derived QALY would be used in the cost-effectiveness/utility analysis. Furthermore, the longitudinal responsiveness of QWB-SA and EQ-5D in patients with epilepsy needs to be further explored to better support their clinical application.

- Due to the uncertainty of modelling study in exploring the cost-effectiveness of various drugs, economic evaluations are recommended to perform along with clinical trials using patient-level data to avoid substantial assumptions when simulate the treatment effects and related costs.

- In the present thesis, the results from WTP/QALY elicitation suggested that the QALY values are context specific. Therefore, future studies are encouraged to determine the specific type of QALY value or disease

specific QALY value when measuring its monetary value. Besides, direct valuation approach, e.g. standard gamble or time-trade-off might be more desirable to quantify the patient preference value for health outcomes.

- The cost-of-illness study, especially for chronic diseases, should assess the life-time cost due to that disease for all the incidence-based cases in a prospective manner, as the results for incidence cases might be more informative to disease prevention, resource allocation, and healthcare planning.

- The quality use of medicines should be guided and realised via the sound policy regulation. Therefore, studies investigating the quality use of medicines from a macro approach are in need as well.

In summary, future studies would provide more valuable information on the application of quality use of medicines in developing countries and help to improve the healthcare outcomes ultimately.

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