Managed Care Integrated Care Summit on Epilepsy

MEETING REPORT AND FINDINGS

AMCP Academy of Managed Care Pharmacy®

This monograph is based on the presentations, deliberations, and conclusions of a meeting held October 15, 2013, San Antonio, Texas.

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Introduction

Health plan, insurer, and pharmacy benefit management executives tend to focus their attention on disease categories associated with high incidences, expensive medical treatments, or high inpatient costs. Diseases not fitting most of these criteria are subject to few (if any) prior authorization requirements, have high generic utilization, and are not highly publicized (for any number of reasons). Furthermore, they are not usually the focus of intense quality improvement and management by medical and pharmacy executives.

This does not lessen the critical challenges associated with diseases that are not in the spotlight of managed care. Epilepsy is an excellent example. It is a complex disorder with an array of etiologies and seizure types.[1] It results in a spectrum of disability, from near-normal quality of life and participation in the workforce to near incapacitation or developmental disorders that prevent patients from integrating into society. Epilepsy is the fourth most common neurological disorder in the United States, with 150,000 new cases per year[1] and an estimated current adult population with epilepsy of 2.3 million[2] and 480,000 children.[3] According to the Centers of Disease Prevention and Control, the US economic burden related to epilepsy is about $15.5 billion.[4]

The ability of the medical community to attain seizure-free status for patients with epilepsy remains a story of mixed clinical success. Adherence to available medications is problematic. Many of the frequently used drug treatments for epilepsy have been available as generics for several years, but questions about the effectiveness of some formulations remain. In addition, medical science is still seeking better ways to prevent both the etiology of epilepsy and seizures in patients with active disease.

From a managed care health policy standpoint, epilepsy treatment should begin to regain some attention. The increased access to health care coverage as a result of the Affordable Care Act (ACA) may mean additional covered enrollees with epilepsy. As the baby boomer population ages, the number of older individuals at risk for epilepsy from stroke, brain tumor, and other neurologic conditions increases.[1] Finally, the drug arsenal to treat epilepsy has been growing (though, to date, not through the introduction of specialty products targeting epilepsy).

Managed care pharmacy and pharmacists are uniquely positioned to examine, revise, and implement strategies that can improve patient lives within the larger clinical and business goals of their organization. To that end, AMCP convened a summit meeting of clinical experts and managed care executives to remove epilepsy from the shadows and to:

- Review the clinical evidence and the value of current drug therapy in epilepsy treatment
- Identify gaps that exist in the process of epilepsy care that might hinder achieving optimal epilepsy outcomes
- Describe data needs for covering, adopting, and integrating new epilepsy treatments into practice
- Formulate managed care strategies that can improve access to optimal pharmacotherapy and improve those outcomes

The *Managed Care Integrated Care Summit on Epilepsy* was held in San Antonio, Texas on October 15, 2013. This monograph summarizes the unmeet needs of the epilepsy population and current perspectives to address each of the above objectives, based on the proceedings of the summit. This includes insights, comments, and recommendations by presenters and panelists who devoted their time and efforts to reconsider this puzzling disorder and how managed care organizations can improve both public health and individual patient outcomes.

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Drug Therapy for Epilepsy: Achievements and Challenges

Until the 1990s, the primary pharmacologic options for the treatment of epilepsy were phenobarbital, carbamazepine, valproate, and phenytoin. These medications have a long history of demonstrated efficacy in seizure treatment, but also safety and tolerability issues which have hindered their effectiveness. Since 1990, 14 new molecular entities in several different drug classes were approved for use as anticonvulsants (Table 1); however, scant evidence exists that these second-generation agents are more effective than the older agents.[1,2] Even though these agents are considered to be safer and to have fewer drug interactions than their predecessors,[3] the vast majority of these agents still have notable safety issues, from aplastic anemia and liver toxicity to kidney stones, weight disturbances, and even increased seizure activity.[4] The era of third-generation antiepileptic agents, ushered in with the introduction of lacosamide and rufinamide, may offer yet more advantages.[3]

A Heterogeneous Disease That Requires Individualized Treatment

Despite new developments in epilepsy treatment evolving over the past 20 years, clinical management remains a challenge for both clinicians and their patients. A significant proportion of patients with epilepsy continue to experience seizures and other symptoms. Between 60% and 70% of patients with new onset seizures respond to some extent to currently available

Table 1: Drugs Approved by the FDA for the Treatment of Epilepsy Since 1990

Year	Nonproprietary Name	Brand Name	Generic Available?
1992	Felbamate	Felbatol	Yes
1993	Gabapentin	Neurontin	Yes
1994	Lamotrigine	Lamictal	Yes
1997	Topiramate	Topamax	Yes
1998	Tiagabine	Gabitril	Yes
2000	Levetiracetam	Keppra	Yes
2000	Zonisamide	Zonegran	Yes
2000	Oxcarbazepine	Trileptal	Yes
2004	Pregabalin	Lyrica	No
2008	Rufinamide	Banzel	No
2009	Lacosamide	Vimpat	No
2009	Vigabatrin	Sabril	No
2011	Clobazam	Onfi	No
2011	Ezogabine	Potiga	No
2013	Perampanel	Fycompa*	No

Note: Carbamazine (Tegretol), valproic acid (Depakene)/divalproex (Depakote), and phenytoin (Dilantin) were introduced decades earlier, and are available in generic formulations.

** Yet to be released commercially.*

antiepileptic drugs; the percentage of patients who remain free of seizures remains unacceptably low.[4] An underlying problem with current therapies is that they do not address the mechanism generating the seizures.[4]

The heart of the challenge may be that epilepsy is not a single neurological disorder with a single etiology. It is a grouping or spectrum of seizure disorders that vary not only by the type and frequency of seizures but by their cause. There is different underlying pathophysiology for similar seizure types.[5]

Therefore, it is not surprising that no one therapy is an effective treatment for all of the variants (Table 2). For example, some agents work better for patients with partial seizures, whereas others work better for those with absence seizures.[6] As alluded to earlier, a drug that demonstrates effectiveness in partial-onset seizures may actually cause more events in a patient with primarily generalized seizures.[7]

Owing to the complexity of the disorder, clinicians who do not commonly manage patients with epilepsy may find it difficult to stay current as new therapies are introduced. As a result, these clinicians may be hesitant to try new agents and rely on older pharmacologic treatments. However, since epilepsy is a heterogeneous disorder with wide variation in clinical presentation and cause, clinicians must be cognizant of the many treatment options and diligently select the agent that is most likely to control seizures on a patient specific basis.[4]

What Is the Best Outcomes Indicator for Epilepsy Treatment?

When evaluating a new anticonvulsant drug's efficacy, the FDA has historically considered a reduction in seizure frequency of at least 50% to be the benchmark. However, this measure has limited utility in practice and in comparative effectiveness research (CER).[8] It also is based on dosages used during the investigational phase of testing; in clinical practice, initial and maintenance dosages used may be far different than those evaluated by the FDA for approval.[7]

Clinicians routinely seek to reduce the frequency of seizures as much as possible, with the desired outcome being seizure freedom. This is a far different measure of success than the 50% reduction in seizure frequency that is used in clinical trials.

The overall effectiveness of the agent may be more accurately described by a composite outcome, such as "retention rate" (which addresses efficacy, tolerability, and adherence).[7,8] For the most common type of epilepsy, partial seizures, the International League Against Epilepsy endorsed the retention endpoint as most accurately reflecting the overall goal for the treatment of patients.[2] The organization's recent guideline emphasizes the treatment goal should go beyond simply reducing seizures. The guideline advises clinicians to choose treatments that enhance the quality of life with the

Table 2. Efficacy of Some Modern Antiepileptic Drugs Against Common Seizure Types and Syndromes

Seizure Type/Syndrome	FBM	GBP	LEV	LTG	OXC	PGB	TGB	TPM	VBG	ZNS
Partial	+	+	+	+	+	+	+	+	+	+
Secondary generalized	+	+	+	+	+	+	+	+	+	+
Tonic-clonic	?+	?+	+	+	+	?	?	+	?+	+
Absence	?+	–	?+	+	–	?	–	?	–	?+
Myoclonic	?	–	+	*	–	?	?	+	–	+
Lennox–Gastaut	+	?	?	+	0	?	?	+	?	?
Infantile spasms	?	?	?	?+	0	?	?+	?+	+	?+

**Lamotrigine may worsen myoclonic seizures in some cases.*

+ = Proven efficacy; ?+ = probable efficacy; 0 = ineffective; – = worsens control; FBM = felbamate; GBP = gabapentin; LEV = levetiracetam; LTG = lamotrigine; OXC = oxcarbamazine; PBG = pregabalin; TGB = tiagabine; TPM = topiramate; VBG = vigabatrin; ZNS = zonisamide.

Source: Hitiriz 2006.

fewest side effects and the best seizure outcome, which is an amalgamation of different clinical endpoints, and may then result in greater medication retention rates. This involves an individualized approach to treatment.[7]

Balancing Safety and Efficacy

Through a number of different mechanisms of action, epilepsy medications are intended to alter brain activity.[2,4] This raises the specter of central nervous system side effects, which can include headache, dizziness, somnolence, impaired cognition, vision problems, and depression, among others (Table 3).

In addition, many epilepsy medications are hepatically metabolized, are highly protein-bound, and frequently inhibit or induce metabolic pathways.[1,4,9] Drug interactions not only increase the risk of toxicity, but may also decrease efficacy leading to suboptimal seizure control.[2,9]

Table 3. Main Characteristics of Some of the Newer Antiepileptic Drugs

Compound	Putative Modes of Action	Elimination and Metabolites	Main Safety Issues or Concerns
Felbamate	Glutamate reduction	Hepatic metabolism; active metabolites	Hepatic failure; aplastic anaemia
Gabapentin	Calcium-channel modulation	Not metabolized, urinary excretion unchanged	Paradoxical increase in seizures
Lamotrigine	Sodium-channel inhibition; glutamate reduction	Hepatic metabolism by glucuronidation	Idiosyncratic rashes, rarely Stevens–Johnson syndrome, toxic epidermal necrolysis, liver failure, aplastic anemia, multiorgan failure
Levetiracetam	Synaptic vesicle protein modulation	Urinary excretion	Behavioral problems
Pregabalin	Calcium-channel modulation	Not metabolized, excreted unchanged	Weight gain; rarely increased seizures
Oxcarbazepine	Sodium-channel inhibition	Hepatic metabolism	Idiosyncratic rash; hyponatraemia
Tiagabine	GABA augmentation	Hepatic metabolism	Increased seizures; non-convulsive status
Topiramate	Glutamate reduction; sodium-channel modulation; calcium-channel modification	Not extensively metabolized, with renal excretion	Weight loss; kidney stones; impaired cognition
Vigabatrin	GABA augmentation	Not metabolized 85% excreted unchanged	Visual field defects, increased seizures
Zonisamide	Calcium-channel inhibition	Urinary excretion	Rash; rarely blood dyscrasias
Lacosamide	Enhances slow inactivation of voltage-gated sodium channels	Urinary excretion, no active metabolites	Suicidal thinking; dizziness, ataxia, blurred vision; nausea, vomiting
Ezogabine	Possibly through enhancement of transmembrane potassium currents	Urinary excretion, metabolized through glucuronidation and acetylation; primary metabolite is active	Retinal abnormalities, vision loss; dizziness, somnolence, fatigue, confusional state, vertigo, tremor
Perampanel	AMPA-receptor antagonism	Extensively metabolized, about 50% excreted through urine and feces	Aggression and hostility (behavioral and mood changes), dizziness, somnolence, fatigue, irritability

Sources: Duncan 2006 and prescribing information for lacosamide, exogabine, and perampanel.

Another consideration is the fact that patients with epilepsy often have multiple co-morbidities[9–11]; it is therefore important that the clinician have the flexibility to prescribe drugs that will balance effectiveness, possible drug interactions, and side effects for individual patients.

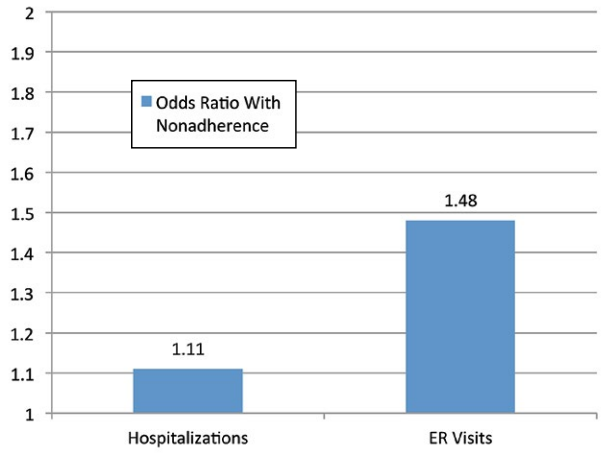
Nonadherence in Epilepsy

Depending on the medication used, as many as 53% of patients do not take their epilepsy medications as prescribed, contributing not only to suboptimal seizure control but additional health care costs related to hospitalizations and possible injury.[11] Over a mean follow-up of 27 months, an average of 39% of patients taking various epilepsy treatments were found to be nonadherent, ranging from 32% for patients taking phenytoin to 53% for individuals receiving gabapentin.[11]

The extent to which nonadherence actually contributes to excess morbidity or mortality in epilepsy is unknown. However, it would not be unreasonable to assume that poorly controlled epilepsy symptoms place individuals at a higher risk of seizures, and therefore, at higher risk of injury during specific activities (e.g., driving, swimming, and even walking). Patients with epilepsy are also at risk for sudden unexplained death, generally during a seizure.[12,13] Although sudden unexplained death in epilepsy (SUDEP) is poorly understood, studies have shown that patients who succumb as a result of it have subtherapeutic blood levels of epilepsy drugs in their system, pointing to nonadherence as a possible cause.[14]

Figure 1. Odds Ratio With Nonadherence

The impact of nonadherence in epilepsy: 11% increased likelihood of hospitalizations with nonadherence ($P = .013$) and 48% increased likelihood of visits to the emergency room with nonadherence ($P < .0001$).



Source: Davis 2008.

Beyond patient perceptions of medication effectiveness and tolerability, other general reasons for medication nonadherence include an inability to pay the cost of drugs or the copayments, inconvenient or challenging dosing regimens (and route of administration), patient or caregiver health literacy limitations, cultural beliefs, and other social and economic factors.[15–17] Although patients must be educated on the importance of taking their medications as prescribed, their unique circumstances must be fully considered in conjunction with clinical goals, drug selection and patient safety.

Faught and colleagues[18] demonstrated that nonadherence with epilepsy medications also results in significant health costs that are related to increased utilization of emergency rooms, hospitalizations, and inpatient days (Figure 1). The total incremental cost of services resulting from nonadherence to antiepilepsy drugs is $18,492 per patient annually, which far outweighs the total annual drug costs not spent as a result of nonadherence ($749).[18]

Socioeconomic Aspects and Access to Therapy

The issues of access to care, nonadherence, and paying for drugs are compounded by socioeconomic status and their insurance coverage. Economic analyses have revealed that patients with epilepsy (even in patients who are adherent) incur $4,522 in additional health costs annually compared with the general population. Complicating the significant costs associated with epilepsy is the fact that patients have, on average, significantly lower annual incomes, which can result in difficulties paying for treatment.[19]

Whereas 74% of the general population had private insurance coverage in 2008, only 49% of those with epilepsy did so. Forty-one percent of those with epilepsy were publicly insured.[19] Only 10% had no insurance in 2008. It is not known how implementation of the Affordable Care Act will affect these figures, but perhaps fewer will be without insurance (either private, through exchanges; or public, through Medicaid expansion).

Generic Drugs and Epilepsy

Generic drug substitution plays an ever-greater role in managed care pharmacy as a method of cost containment. In 2012, the generic substitution rate across diseases was 78%, according

to a Government Accountability Office report.[20] The majority of prescriptions are written to allow generic substitution, and health plans incentivize the use of generics through low copayments as well as reimbursements based on maximum allowable cost pricing.

Although data on the specific generic utilization rate in epilepsy are difficult to obtain, as Table 1 indicates, generics for the commonly used older medications are widely available. A 2013 study revealed that a Medicaid recipient is at nearly 2.5-fold likelihood of being prescribed a generic anticonvulsant product compared with a patient with private coverage. A Medicare beneficiary was 16% more likely to be dispensed a generic anticonvulsant than a person with private insurance.[21] This may relate to differences in coverage policies and formulary access to branded versus generic drugs.

Considerable controversy has brewed for several years as to whether generic substitution should be practiced in epilepsy as it is in other disease states.[22] Specifically, researchers have questioned whether clinical and economic outcomes achieved with the generic products are equivalent to those of their branded counterparts. Retrospective studies have suggested that patients with epilepsy using the generic agents use more health resources than those treated with brand-name drugs. In a study of 33,600 patients, Labiner and associates[23,24] found that the average patient receiving generic versions of carbamazepine, gabapentin, phenytoin, primidone, or zonisamide had $3,186 greater annual medical services costs than patients dispensed the branded versions of these medications. This effect was noted regardless of degree of seizure control or types of epilepsy. On the other hand, Erickson and colleagues[25] found that clinical and economic outcomes of patients treated with branded or generic versions of lamotrigine or divalproex were the same, but the latter were associated with more drug discontinuations, dosage changes, or additional therapies used. In another study of topiramate in epilepsy, the use of multiple generics (i.e., generic to generic switching) was associated with 65% greater risk of hospitalization and a 44% greater risk of longer hospital stays compared with brand product utilization.[26] It should be noted that well-designed prospective studies have not yet been published to support these findings.

These studies suggest that the generic drugs do not seem to yield identical effects, despite having the same chemical structure of the innovator medications. One explanation favored by researchers is that the antiepileptic drugs may have a narrow therapeutic index that is not optimally matched by the generic agents because of bioequivalence differences. The FDA stipulates that generic drugs must demonstrate bioequivalence to the branded agent by matching key pharmacokinetic measures at the 90% confidence interval around the mean of those measures within a window of 80% to 125% when compared with the branded product.[22] If a patient is switched from a generic version at the low end of the range to another that is at the high end of the range, the result may be potential side effects, lack of effectiveness, or both. Therefore, when switching a branded anticonvulsant drug to a generic, or one generic to another, clinicians (and managed care executives) should consider continued anticonvulsant response as well as any new clinical issues that might occur.

To further understand and explore the concerns over bioequivalence the Food and Drug Administration has commissioned and funded two separate studies. The first study, being conducted by the University of Maryland, is prospectively evaluating the bioequivalence related changes in patient blood levels when switching from brand to generic epilepsy drugs. A second study is examining similar affects associated with switching patients from a generic with “high-end” bioequivalence to a generic with “low-end” bioequivalence. Investigators are also evaluating bioequivalence variation even if the patient is maintained on the same brand or generic product. Results of both studies, which do not include clinical outcomes data, have not yet been published, but the general consensus among epileptologists and pharmacy researchers is to exercise caution when switching a patient with well-controlled epilepsy from brand to generic or from one generic to another generic.[5]

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Unmet Needs in Epilepsy Drug Treatment and Patient Care

Limited Comparative Effectiveness Research (CER) on Epilepsy Treatments

Despite the growing number of treatments now available for patients with epilepsy syndromes, little information exists today with regard to which drug has the greatest efficacy (either for individuals or for populations), which has the best safety profile, and which is associated with the greatest adherence or retention rates.[1]

The general lack of good quality CER based on higher levels of evidence may impede clinician choice of existing therapy and perhaps access to new epilepsy drugs. One challenge involves the stated objective of many clinical trials: If the goal of a study is to demonstrate "superiority" to existing medications but fails to do so, does this mean that conclusions of "noninferiority" in this study are valid or convincing?[2]

A problem that has long plagued clinical decision makers is that a randomized placebo-controlled trial (RCT) may show 50% efficacy for drug A. However, does another RCT demonstrating 45% efficacy for drug B in a seemingly similar group of patients mean that drug B's efficacy is inferior to drug A? A further complication is that the outcomes measures used in past clinical studies—a reduction in seizure frequency of 50%—may not be the best outcomes comparator, nor is it consistently used in studies of today's newest epilepsy interventions.[1] It becomes apparent that CER results are lacking in epilepsy.[1]

In 2011, the Agency for Healthcare Research and Quality (AHRQ) attempted to collate and draw conclusions in its report "Effectiveness and Safety of Antiepileptic Medications in Patients with Epilepsy."[1] The reviewers found in general that the older drugs (carbamazine, phenytoin, and valproic acid) worked as well as the newer agents in obtaining seizure-free results. They found little evidence to support the notion that newer drugs presented improved safety profiles, which positively affected adherence with the drug regimen. Yet, the results remain controversial for several reasons, including a low level of available evidence (such as trials with seizure-free outcomes as the primary endpoint) and inadequate data to make all needed comparisons. Further, the review ignored unique patient groups, did not utilize clinically relevant outcomes and generally compared new drugs as a group with older drug as a group. As a result, AHRQ's conclusions have limited value in crafting managed care strategies applicable to large patient populations and reinforces the challenges associated with clinical management of the individual patient.[1,3,4] A related unmet need is better clarity in terms of side-effect profiles of the various agents used to treat epilepsy. Although placebo-controlled trials do provide information about an individual product's safety, RCTs are not usually of sufficient duration to inform regarding the drug's long-term use and drug interactions seen in actual practice. This type of information is increasingly gathered in postmarketing experience, and therefore, may be more available to some extent for older anticonvulsants. New investigations with long time horizons *using real-world experience* may help fill this important gap.

The efficacy of combination drug therapy in patients with refractory epilepsy is also difficult to interpret. Several reviews from the Cochrane database evaluated the effectiveness of different drugs as add-on therapy in focal and partial-onset epilepsy.[5–10] These trials generally utilized small patient populations and varied in terms of outcomes tested (and duration), making determinations of effectiveness elusive. In fact, no specific combinations have been proven to be clinically effective, and in some cases, may even be harmful. Clinicians are often required to rely on medical judgment combined with trial and error. Large-scale analysis of existing retrospective claims data (possibly some available through managed care prescription and medical claims) may help shed some light on the effectiveness of combination therapy.

Epilepsy is one of the few disorders in which brand-to-generic and generic-to-generic drug switching may be a concern, as a result of the narrow therapeutic index of anticonvulsant medications. Knowledge in this area is incomplete, particularly as to the bioequivalence and clinical outcomes associated with switches from one formulation of a medication to another. In addition, there are questions about whether significant patient variability in response is an issue with one formulation versus another. This includes the identification of certain population subgroups who may be most vulnerable to altered outcomes when switched to products at the lowest or highest values of the FDA's accepted bioequivalence range. The results of prospective studies underway on anticonvulsant drug switching will help form the basis for managed care pharmacy policy and decision making.

Pharmacy Engagement in Epilepsy Care

As described on the preceding pages, epilepsy is a multifaceted disorder for which much room for improvement in treatments and outcomes still exists. The principal challenges seem to involve optimizing seizure control, improving drug selection and adherence (considering drug safety and possible interactions between epilepsy medications and those used for comorbid conditions), and cost implications.

Clinical pharmacists are well positioned to help in many of these areas, both at the individual patient level and through population-based programs. However, few models exist in which pharmacists are actively performing medication therapy management services or providing other important consulting directly to the epilepsy care team. Older anecdotal reports of clinical pharmacist participation in epilepsy clinics have been published.[11,12] A report from the United Kingdom indicated that clinical pharmacists conducting an annual review of epilepsy therapy in a general practice setting resulted in changes to medical regimens in a quarter of the patients; these were based on myriad drug-related, medical, and patient lifestyle recommendations.[13]

Although pharmacy consulting models in epilepsy are rare, a best practice example is available from Kaiser Permanente Colorado.[14] In this integrated model, a full-time clinical pharmacy specialist is integrated into a neurology office, spending approximately 40% of her time on epilepsy care and encounters. Kaiser Permanente Colorado model ultimately requires an integrated electronic medical record (EMR), electronic prescribing mandates, an organization commitment to utilizing pharmacy consulting expertise in clinical care teams, among other structural (e.g., risk-sharing setting) and philosophical (e.g., clinician acceptance) criteria.[14]

The value of clinical pharmacist services in anticoagulation services and clinics has long been demonstrated both with older agents[15] and with newer anticoagulant products.[16] This drug class has long been understood to have a narrow therapeutic index, and clinical pharmacy specialist experience in anticoagulation management may be instructive regarding pharmacy's possible role in reviewing and monitoring epilepsy drug therapy. This can be incorporated as an important part of team-based epilepsy care.

Reimbursement methodology may influence the viability of these integrated care teams. For example, the perspective from a fee-for-service practice may be that ancillary health professionals are added expenses that can only be supported by evidence of return on investment. This can be quite different in a capitated group practice or accountable care organization, where care efficiency, rather than fee generation, is emphasized. Therefore, integrated epilepsy teams, which include clinical pharmacy experts, may have the best chance for successful development in systems that accept risk (which may also apply to the patient-centered medical home concept).

Medical and Pharmacy Benefit Design Considerations

Mandatory generic substitution is prevalent throughout the health insurance and pharmacy benefit management industry today. If one considers the clinical issues involving drug switching with anticonvulsant drugs, then it may be beneficial for pharmacy benefit designs (and purchasing policies) to incorporate an exception process by which generic medications are not always considered interchangeable with branded anticonvulsant products, and a generic agent may not necessarily be interchangeable with another generic drug. This may entail a different approach to purchasing generic medications—considering allowing access only to select products demonstrating a narrower variation in bioequivalence against a standard (usually the innovator brand).

The new health insurance exchange raises a separate consideration—access to medications available through low-cost plans offered on health exchanges. Most of the bronze and silver plans include high deductibles, with or without separate pharmacy deductibles.[17] Plan sponsors on the federal health exchanges developed these low-cost plans to attract greater enrollment of the newly insured. Pharmacy benefits may also be influenced by this objective to keep premiums low. As a result, coverage decision making for anticonvulsants that have off-label uses (or other frequent indications, like neuropathic pain, in the case of gabapentin) may focus on managing the broader utilization rather than easing access for patients with epilepsy. This is partially driven by the fact that many plans cannot determine the patient's diagnosis at the time of dispensing.

The spectrum of health plans available to patients with epilepsy offer pharmacy benefits that differ by formulary, copay/coinsurance, number of tiers, and use of prior authorization and step therapy. It may be beneficial to educate individuals with epilepsy and their caregivers as to how different insurance coverage policies can affect their access to medications. On the other hand, pharmacy benefit decision makers should ensure that their pharmacy benefit policies improve access to epilepsy care, not create barriers to that care.

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Recognizing the Spectrum of Epilepsy Conditions

Although the majority of adult patients classified as having epilepsy experience partial onset or generalized seizures, epilepsy is a spectrum of disorders that include relatively rare syndromes (e.g., Dravet syndrome, infantile spasms) that may require very specific therapy. As more is learned about the underlying pathophysiology of epileptic seizures, highly individualized treatments are likely to be implemented. Additionally, polytherapy and nonpharmacologic treatment approaches may be necessary. Treatments may not be as straightforward as prescribing a generic anticonvulsant.

A separate challenge is the ability to distinguish between epileptic and nonepileptic events, which are sometimes called psychogenic seizures or pseudoseizures. They are episodic, paroxysmal events but are not caused by abnormal electrical activity in the brain and thus not considered part of the spectrum of epilepsy. About one-quarter of patients referred to an epilepsy center to be evaluated for surgery have non-epileptic seizures.[18] It is not unusual for patients with diagnosed epilepsy to suffer nonepileptic episodes as well as typical seizures. On the other hand, some people without a history of epilepsy may suffer seizures from other causes, including brain tumor, caused by epilepsy. Distinguishing between these epileptic and pseudoseizure events is key to providing appropriate care.

Identifying Patients With Epilepsy

Although the diagnosis of epilepsy is not generally considered to be a challenge, sometimes identifying a health plan's population with epilepsy through the claims database can be. Without that identification, steps to directly improve patient care are limited. For example, this can be useful for identifying patients with side effects associated with a specific medication, which may be eased with a change to another anticonvulsant.

A reason for this gap is the disconnect between the medical and pharmacy data within many plans. However, another important problem is the ambiguity of the pharmacy record itself: Several anticonvulsant drugs (e.g., gapapentin, pregabalin, topiramate) are used for multiple indications, and the diagnosis is not ordinarily indicated in pharmacy claims. To accurately identify patients in a typical health plan with epilepsy, the managed care executive would need to query both the medical and pharmacy databases. An illustration of this is the identification of patients with renal calculi: This information resides in the medical database through a search for the appropriate CPT code. The pharmacy database must be cross referenced to identify if any of those plan members with renal calculi are taking topiramate, for which kidney stones are a known side effect.[19]

Further, difficulty in confirming the diagnosis can create barriers to the development of programs that medical executives and clinicians can use to improve care of members with epilepsy (e.g., personal outreach, referral to case management).

Patient Access to Optimal Care

In some cases, patients with active epilepsy have been seeing primary care physicians who have been treating them for many years, despite a lack of improvement. The family physician or internist may be reluctant to try a different regimen based on his or her comfort level or lack of awareness of all available options. This raises a few questions:

- Although seizure-free status is the ideal goal, what is realistic under usual care settings?
- How can provider education be improved to enable clinicians to keep up with the state of the art in epilepsy care?
- Does the patient have access to care from a neurologist or epilepsy specialist?
- Will insurers participating in health exchanges offer only narrow provider networks, possibly excluding local epilepsy centers or specialists?
- Will patients with epilepsy be well served by nurse practitioners or physician assistants in areas with physician shortages?

According to a study by the American Academy of Neurology, the current supply of neurologists is 11% below demand, and by 2025, this gap will grow to 19%. The average wait times to see a neurologist are also increasing, from 28 business days in 2010 to 35 business days in 2012.[20] As of 2011, nearly 150 specialized epilepsy centers were operating in the US.[21] As many as 6 epileptologists work at any one center, and the Institute of Medicine (IOM) suggests there is a shortage of these subspecialists outside of the areas served by these centers.[21]

Fewer than 25% of patients with uncontrolled seizures see an epileptologist.[21] With access to a team-based epilepsy center, seizure frequency may be improved, and even if the patient cannot attain seizure-free status, reduction in the number of medications taken by the patient or the side effects resulting from the anticonvulsant medical regimen may be possible.

Limited Resources and Epilepsy Improvement Programs

Priorities in terms of quality improvement must be balanced against available resources, and for several disease states, including epilepsy, this results in relatively low visibility, compared with oncology, autoimmune, and other high cost

disorders. The reasons for this are manifold: Many epilepsy medications have been used for more than 15 years and are available as generics; it has a low prevalence coupled with somewhat low medical expenditures; and although several medications are available to treat epileptic disorders, other interventions are rarely used and/or still under clinical development (e.g., deep nerve brain stimulation, brain tissue excision).

For epilepsy, limited resources, in terms of personnel and funding, may be the overriding reason for not scrutinizing this category more carefully. The impact of this problem can be illustrated by the example used previously—even if a pharmacy and medical director can find the resources to analyze the incidence of kidney stone treatment claims in patients taking topiramate, is there time and staff available to contact individual physicians to do peer-to-peer education? Many other priorities (e.g., appropriate prescribing of relatively expensive specialty drugs) will compete for the resources required to successfully complete the project.

One way to ensure epilepsy is an area of focus is to develop quality criteria that are credible, measurable, and meaningful. This can form the basis for new HEDIS or other quality-reporting standards. Currently, there is no one clinical quality measure for epilepsy that is universally accepted, as is the case for diabetes (HbA1c) or cholesterol (total cholesterol, HDL, and LDL levels), for example, which galvanizes health plan action for accreditation and quality reporting. If these accepted measures of epilepsy care quality can be shown to improve through integrated care management, medication therapy management, or both, managed care organizations may be convinced to fund these programs (or find a source of funding).

Health Information Technology Gaps

Having capable health information technology (HIT) systems, and utilizing the systems accurately and to their fullest extent are separate issues. The need to improve quality and coordination of care through electronic medical records (EMRs) and incentives from the federal government to pay for their implementation have spurred the growth in HIT.[22,23] As of April 2013, approximately 80% of hospitals and more than half of physicians' offices have adopted EMRs.[22] Managed care's efforts to improve care quality rely heavily on HIT systems (consider again the topiramate–kidney stone example), particularly in the areas of claims analysis for quality improvement projects, HEDIS reporting, and accreditation.

Reimbursement is also highly reliant on HIT today, both in the provider's office and from the Medicare Advantage or Medicaid managed care plans' perspective. This implies the need for accurate coding to ensure appropriate reimbursement. Although provider-entered diagnostic coding (ICD-9 or ICD-10) for epilepsy seem to be accurate for correctly identifying epilepsy-related services,[24,25] identification of epilepsy through procedure codes for services, such as electroencephalogram or laboratory testing (not all new anticonvulsants require lab testing), or drug claims are not.[24] Providers also should consider that using an ICD-10 code to gain optimal reimbursement does not necessarily mean that is the correct code for registering quality information.

Another problem that may hinder the accuracy of the information in the EMR relates to the patient. A patient who arrives at an emergency room may have impaired cognition and relate incorrect medication dosing. Electronic medical records that can be read and annotated across care settings can ensure that clinical decisions made in the ER are based on an accurate understanding of the patient's medication regimen, clinical status, and history.

This highlights the criticality of interoperable HIT systems for smoothing transitions of care. A patient's journey from pediatric care to adult-based care, from primary care provider to specialist, from emergency room or inpatient stay to home care or back to primary care should be followed in the EMR to assist coordination among the individual care providers, consistency in medical therapy, and avoidance of preventable adverse drug events or increased seizure frequency.

Addressing Adherence

As noted, nonadherence rates for epilepsy medication regimens average 39%.[26] Although this is within the range seen for patients with other chronic diseases,[27] there remains a significant opportunity to improve epilepsy medication adherence to both improve seizure control and reduce health costs related to nonadherence.

Adherence is affected by a multitude of factors, some related to the patient, others related to the plan, the medication itself, or the environment. Health literacy is a key issue. The health literacy of most Americans is disappointingly low, according to the National Assessment of Adult Literacy, which indicated that only 12% of Americans have a "proficient" health literacy level.[28] In addition, 36% of adults have limited health literacy and an additional 5% are not fluent in English. The reasons for low health literacy are diverse, including socioeconomic factors, education levels, cultural perceptions, cognitive deficits, among others. Low health literacy directly affects patient and caregiver ability to understand instructions on following the medical regimen, and it hinders learning about the disease and its management, as well as setting appropriate expectations for disease outcomes.[28]

In epilepsy, adherence can be seriously affected by memory loss, which may be attributable either to the epilepsy medications, the seizures themselves, or both.[29] Furthermore, a patient living alone who experiences a partial seizure may only notice that an amount of time has passed during which he or she cannot recall their activity. This may be the only hint that a seizure has occurred.

Lack of transportation (to the physician's office, clinic, or pharmacy) may also represent another impediment to adherence. Many patients with epilepsy do not drive and are dependent on either public transit or family and friends for transport. Locating assistance with transportation may prevent missed office appointments and medicine refills from the pharmacy. A further possible way to ease transportation challenges is to synchronize prescription refill dates—for the patient taking multiple medications, coordinate the refills to occur at the same time each month, eliminating multiple trips to the pharmacy.[30]

To some extent, benefit design can help or hinder adherence, relating to affordability of medicines.[31,32] For most generic epilepsy drugs, access/affordability issues are minimized, but cost sharing for branded medications can be substantial, particularly in plans with pharmacy deductibles.

Adherence is also affected by the frequency of the medication regimen—evidence has shown that adherence is better with a once-daily medication compared with one taken three or four times daily.[33] Efforts to simplify the medication routine can yield significant improvements.

Other Considerations in Patients With Epilepsy

Patients with epilepsy have a relatively higher incidence of a broad spectrum of somatic and psychiatric comorbid conditions compared with patients without epilepsy.[21] These include depression and anxiety,[34] heart disease, hypertension, stroke, diabetes, emphysema, bronchitis, dermatitis, arthritis, and asthma,[35] among others. There are many interrelated reasons for the comorbidities, such as a high level of inactivity leading to cardiovascular issues,[35] but little is known about the exact mechanisms behind the comorbidities. More work is needed to determine the effect of these comorbidities on epilepsy status, as well as the implications of effective epilepsy treatment on these comorbidities themselves, especially major depressive disorder.

Pregnancy in women with epilepsy is an important issue that deserves greater attention. For most pregnant women, the risk of seizures outweighs the risks of the medications in pregnancy; therefore, women often cannot stop medications during pregnancy without serious concerns of seizure recurrence.[36] The American Academy of Neurology produced guidelines in 2009 to address this area. A Canadian study found that patient knowledge of the impact of epilepsy on pregnancy is low.[37] Managed care plans should be actively involved in counseling, and direct this subset of patients to helpful resources to consider epilepsy treatment options and their risks in pregnancy, as well as to help in planning for pregnancy.[36]

Greater consideration should be devoted to training and education, such as a "seizure action plan," for school counselors, teachers, and nurses; directors of social activities (e.g., boy/girl scouts, Little League, day camps and sleepaway camps); and worksite managers to help recognize seizures when they do occur. This applies not only to grand mal seizures (which are more readily identified as epileptic events) but the subtle seizures that are more difficult to notice. With this training, it may even be possible for lay persons who spend significant time with the patient to notice seizure activity that the parents had not recognized.

Patient Engagement and Accountability

In most disease states, it is acknowledged that adherence and overall patient engagement cannot be achieved without the patient having some "skin" in the game. This does not necessarily have to take the form of cost sharing. In Medicaid, beneficiary cost sharing is minimal. Instead, patient engagement can be the result of collaborative planning with the clinical staff, ensuring that patients acknowledge their epileptic syndrome (i.e., not an occasional "fainting spell"), gaining an awareness to distinguish between the onset of an epileptic seizure versus a nonepileptic event, and keeping a record of their seizures (perhaps through a daily diary).

This type of engagement, as with initiatives to improve adherence, can be challenging in some patients with epilepsy because of cognitive deficits. Developmental disabilities are often seen in younger patients with epilepsy, and elderly patients with epilepsy may demonstrate impaired cognition as well.[21] Yet, the expectation is that either the patient or caregiver will adhere to the medical regimen, or at least report problems that interfere with their taking the medication as directed.

This highlights the need for a collaborative plan, in which the patient or caregiver understands the rationale for the treatment, goals of the treatment, and why it is important to adhere to the regimen. The collaborative plan would consider a patient's living situation, life priorities, insurance status, access to transportation, work status and capability, education, and support system. If he or she perceives that they are being issued instructions by the doctor, or that they did not take part in developing the treatment plan, the likelihood of patient "buy-in" is reduced, seriously

limiting the clinician's ability to minimize the patient's symptoms and to improve that person's quality of life.

In many of these areas, caregivers for patients with epilepsy play a critical role. For young patients, their parents; for elderly patients, their children or healthcare workers; and for adult patients, their spouses or other caregivers must be involved in care planning and support to ensure not only optimal adherence but patient engagement for best possible outcomes.

One problem that erodes patient engagement and challenges best care is repeatedly moving from one physician to another, which fosters opportunities for lost or inaccessible records, disjointed efforts at care planning, and poor patient follow-up. In state Medicaid programs, this may occur when patients leave a Medicaid managed care plan for a fee-for-service provider and then sometime soon join another (or the same) plan. Real-time exchange of information, as described here, may also be enabled by community linkage through health information exchanges.

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Recommendations and Action Steps

Employ More Team-Based Approaches

Kaiser Permanente Colorado serves as a model for other integrated health plans in its use of a collaborative approach to epilepsy care, incorporating clinical pharmacy into the heart of the program.[14]

Even non-integrated plans can try innovative approaches to improving epilepsy care through teams. One example is to check the daily member discharge summaries, calling patients within 24 hours after leaving the hospital, to try to arrange an upcoming physician visit. If patients can't visit the physician, a nurse or other healthcare professional can visit them, helping to reduce confusion around the medication regimen, which may have been a factor in the hospitalization, and lead to improved adherence.

Ensure Patients Access Case Management

Patients with epilepsy should have access to case management or integrated care management, which can provide personal outreach, improve care coordination, and help patients to efficiently use the health benefits they have. Health plans and insurers should utilize protocols that trigger case management contact upon identification of a new patient with epilepsy or one who has had a recent related hospitalization.

Empower Pharmacists to Engage More Directly in the Care of Patients with Epilepsy

Lack of time, limited resources, and inadequate incentives are all cited as reasons why pharmacists do not participate more in patient care. Epilepsy adds yet another dimension: It is a complex disease that requires a delicate touch to optimize seizure and balance side effects. Perhaps some pharmacists believe that they will require significant training before reaching a comfort level in providing medication therapy management services, including pharmacotherapy counseling, to patients with epilepsy.

In California, Governor Brown recently elevated pharmacists' status as healthcare providers, allowing them to initiate certain prescriptions and to provide clinical advice and patient consultation.[38] This may motivate other states to expand pharmacy's scope of practice and serve as a model for those wanting to take similar action.

Review Potential Opportunities With Existing and Innovative Prior Authorization Systems

Prior authorization (PA) systems used today ask the clinician to provide specific information before patients can access specific medications, tests, and procedures. It may be possible to utilize patient data from providers entered for PA purposes as a form of feedback: Capturing information on medications that are not working as anticipated, identifying adherence problems or adverse events, or flagging patients associated with higher cost care (such as brain imaging). Importantly, evaluation of existing PA data will be less useful if an infrastructure is not in place to evaluate patient outcomes on the interventions requested through the PA.

New PA approaches, such as the uniform electronic prior authorization standards,[39] may facilitate communication between the provider and the pharmacy and may enable the addition of more pertinent information systematically into the prescription PA process.

Connect With the Pharmaceutical Industry for Public Outreach and Education Programs

Pharmaceutical manufacturers often have the resources to assist in epilepsy education, especially with regard to the Medicaid population. For example, Medicaid managed care plans do not usually have the ability to adequately reach community centers with disease awareness messaging. Epilepsy poses an opportunity for partnering with the pharmaceutical industry to help broaden the educational messages on the disease state (rather than a specific product), including seeking seizure-free status, what to do (and not to do) if a person is having a seizure, and resources available to help patients improve their own care. This may increase the recognition and general awareness of the disease state and prompt patients to see a doctor if they have been on a medication for many years and still experience seizures.

Whereas pharmaceutical company activity in patient education tends to wane as their particular product ages and nears patent expiration, new product launches represent opportunities for new, refreshed initiatives. Managed care organizations should seek out pharmaceutical manufacturers and other organizations that are bringing new technologies to the market as partners for patient education.

Tools like outcomes-based pharmaceutical contracting, which encourage manufacturers to accept risk, may motivate them to work with the managed care plan as part of the team to improve (and prove) patient outcomes on their medication.

In terms of branded products, pharmaceutical manufacturers make copayment coupons available to patients to defray the higher cost sharing if their products are placed in nonpreferred copayment tiers, or even tier 2 branded tiers. From the standpoint of the patient, copayment coupons are helpful as long as the program extends. Consider the patient who uses a new branded agent and has achieved good clinical results but has been using copay coupons to help pay for the product for an extended period. The manufacturer discontinues the couponing program and the patient is suddenly faced with the real out-of-pocket cost of this product. He or she may ask the physician to change therapies to one on a lower copayment tier, which can alter the patient's seizure status. Payers are well positioned to help the patient navigate the couponing process and make them aware of these forms of payment assistance. This may represent an opportunity to increase visibility and accessibility of patient assistance programs as well as other insurance options.

Improve Communication Between the Medical and Pharmacy Claims Systems

Outside of integrated organizations, medical and pharmacy claims still largely exist in separate databases. The ability to query both to identify patients with epilepsy or to evaluate treatment is hindered by limited communication between the databases, slow speed of retrieval of data from the medical or pharmacy silos, and difficulty in interpreting the information that is available. Each of these areas need to be examined and developed to give pharmacists, clinicians, and case managers the ability to identify, *in real time,* patients with epilepsy and those in whom care can be improved.

Improve the Interoperability of EMRs

To address the transitions in care gaps, better interoperability among EMRs is necessary. Not all patients are admitted to hospitals within a health system, nor utilize physicians within the network, and these raise the probability that patient encounter information is lost or does not get captured accurately.

Work Towards the Creation of a National Epilepsy Data Repository

The development of a centralized general database or registry of patients, coordinated through a nonprofit third party (e.g. Epilepsy Foundation or other public organization), could be a useful step towards gaining data necessary for CER. This repository can provide national, de-identified patient information, which may be accessed by researchers and perhaps even health plans to assist coverage decision making. At present, a registry for pregnancy in epilepsy does exist (http://www.epilepsybirthcontrolregistry.org/), but this is not the case for other patients with seizure disorders.

Develop a Useful Quality-Reporting Metric for Epilepsy Care

In 2012, the IOM called for the creation of a national quality-reporting measure for epilepsy care,[21] which would focus organizational quality teams for accreditation purposes, to better compete in the market, and indirectly improving population-based care. This information should be easily recordable and captured in data queries for both analysis and reporting purposes.

However, it needs to be based on a meaningful metric; for example, "number of patients with epilepsy with uncontrolled seizures" may not be specific enough to be useful, considering the lack of agreement on the definition of "uncontrolled seizures" (e.g., percent of patients who are not seizure free or have fewer than a specified number of seizures per month) and the spectrum of epilepsy (focal-partial vs. generalized disease vs. Dravet's disease or other), including type of seizures experienced.

The development of epilepsy quality-reporting measures implies a discussion on their possible financial implications, as current pay-for-performance and value-based purchasing is founded in clinical and administrative quality measures. Such a measure or group of measures relating to epilepsy care can conceivably be incorporated into Medicare Star ratings as well as reimbursement bonuses for practices.

Medicare has taken a first step, incorporating 3 epilepsy-care related measures for the first time in 2014 into its Medicare's Physician Quality Reporting System. The 3 measures were developed by the American Academy of Neurology:[40] (1) percentage of patient visits with a diagnosis of epilepsy who had the type(s) of seizure(s) and current seizure frequency(ies) for each seizure type documented in the medical record, (2) all visits for patients with a diagnosis of epilepsy who had their etiology of epilepsy or with epilepsy syndrome(s) reviewed and documented if known, or documented as unknown or cryptogenic, and (3) all female patients of childbearing potential (12–44 years old) diagnosed with epilepsy who were counseled about epilepsy and how its treatment may affect contraception and pregnancy at least once a year. Physicians treating Medicare patients who meet these requirements are eligible for additional payment.

Stakeholders' Recommendation Matrix

Stakeholder	Recommendations
Patients	• Take ownership, accountability, responsibility for their own care • Communicate better with providers • Don't be satisfied with the status quo regarding seizure frequency (understand treatment options)
Caregivers	• Take ownership of the patient's care
Patient Advocacy Groups	• Provide more information to patients about the resources available to them and encourage its exploration (patient empowerment) • Be the public advocates for developing epilepsy quality measures • Help lead in the definition and improved diagnosis of the various forms of epilepsy • Issue policy statements aimed at improving care and outcomes
Providers	• Review patients' records with long-standing epilepsy and reevaluate their seizure status • Seek out information on newer epilepsy treatments and education on which interventions work best with certain epilepsy disorders and which do not • Work with health plans and insurers to establish the most effective referral patterns and processes associated with management of epilepsy • Design treatment plans that consider the patient's out-of-pocket costs, available health benefits, and their personal circumstances (access to transportation, other caregivers, etc)
Pharmacists	• At the community pharmacy level: Seek information to provide to patients with epilepsy; seek to strengthen the pharmacy educator role • Define clinical pharmacists' preferred role as collaborator on the clinical team • Actively seek opportunities to expand clinical pharmacy activity in epilepsy (e.g., medication reconciliation, medication therapy management) • Share best practices in epilepsy team-based management
Payers	• Offer benefit designs that encourage the use of specialist care when appropriate • Encourage access and adherence to best medical therapy • Apply quality improvement–based evaluation to determine where provider network performance in epilepsy can improve (e.g., in diagnosis, seizure outcomes, adverse events, specialty referral, case management referral) • Focus on the need for comparative effectiveness research to better inform coverage decision making (especially for new epilepsy medications)
Community	• Work to destigmatize epilepsy through education in schools, community centers, and in media and social events • Create support strategies for patients with epilepsy in the community
Health Systems	• Ensure EMR interoperability between providers and the hospital/health system • Work with HIT vendors to be sure their systems capture data that are unique or critical to epilepsy care and incorporate appropriate guidance or quality checks (e.g., social worker or case management referral) • Regard epilepsy as a spectrum of diseases and not as a single, unique disorder • Understand the unique needs of the patients with epilepsy as it relates to overall case management and transitions of care
Manufacturers	• Assist with education in epilepsy care, especially public awareness campaigns • Disseminate available research data through peer-reviewed publications • Focus R&D efforts on unmet needs in epilepsy care through innovative mechanisms of action (rather than reformulation of existing products) • Emphasize the availability of patient assistance programs to optimize patient access to antiepileptic medications • Engage with key coverage decision makers as early as possible in the clinical development process

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