CONDUENT

Texas Medicaid

Anticonvulsant Drug Use Evaluation

Educational RetroDUR Mailing	❑Initial Study ☑Follow – up /Restudy

Executive Summary

Purpose:	To promote safe, cost-effective use of anticonvulsant medications.		
Why Issue was Selected:	Anticonvulsant medications are among the most commonly prescribed classes of medications. Claims data indicates that in the Texas Medicaid Fee-For-Service Program there were 19,724 prescriptions for anticonvulsants in a recent 365 day period at the total cost of $2,316,606. Various anticonvulsants are associated with risks for drug-disease interactions as well as other potential toxicities.[1,2] These variables have an impact on the cost/benefit ratio of the use of these medications.		
	Performance Indicators	**Exceptions**	
		(<18 Years) FFS	**(<18 Years) MCO**
	1. Increased Risk of Adverse Drug Event (IADE): Anticonvulsants and drug-disease interactions	(2) 25	(189) 2,875
	2. Nonadherence with anticonvulsants	(4) 20	(2,171) 4,909
	3. Increased Risk of Adverse Drug Event (IADE): Anticonvulsants and recommended monitoring • Hepatic monitoring • Renal monitoring • Platelet/Coagulation monitoring/CBC • Serum Bicarbonate • Ophthalmologic Exam	 (31) 107 (1) 13 (30) 105 (21) 57 (2) 31	 (4,595) 13,266 (519) 2,455 (4,046) 12,228 (3,301) 8,223 (817) 4,467
Setting & Population:	All patients with drug therapy with an anticonvulsant in the most recent 45 days.		
Types of Intervention:	Cover letter with individual patient profiles.		

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Main Outcome Measures:	The performance indicators in this proposal will be re-measured.
Anticipated Results:	Increased awareness of appropriate monitoring for potential anticonvulsant toxicities may reduce the risk for negative outcomes.

Performance Indicator #1: Increased Risk of Adverse Drug Event (ADE): Anticonvulsants and drug-disease interactions

Why has this indicator been selected?	Several anticonvulsants are associated with box warnings and/or contraindications relating to their use in patients with certain concomitant illnesses. Patients taking an anticonvulsant in the presence of a contraindication or warning are at increased risk for adverse events.[1,2]
Candidates (denominator):	All patients receiving an anticonvulsant drug therapy as listed (see Appendix A) during the most recent 45 days.
Exception criteria (numerator):	Candidates who have a history of a contraindicated/warned medical condition (see Appendix A) in the past 2 years.

Performance Indicator #2: Nonadherence with Anticonvulsants

Why has this indicator been selected?	To identify patients with a seizure disorder who are nonadherent with prescribed anticonvulsant medications.
Candidates (denominator):	All patients with a history of a seizure disorder in the past 2 years receiving current anticonvulsant drug therapy in the most recent 45 days and chronic therapy in the last 90 to 135 days.
Exception criteria (numerator):	Candidates who received less than 60 days of anticonvulsant therapy in the last 90 day period of claims activity are considered nonadherent.

Performance Indicator #3: Increased Risk of Adverse Drug Event (ADE): Anticonvulsants and recommended monitoring

Why has this indicator been selected?	Selected anticonvulsants are associated with box warnings relating to potential complications associated with their use. Official prescribing information for these agents suggests monitoring that should be employed to minimize the risk for complications.[1,2]
Candidates (denominator):	All patients receiving a selected anticonvulsant drug therapy (see Appendix B) during the most recent 45 days.
Exception criteria (numerator):	Candidates who do not have the recommended monitoring documented in the past 365 days (see Appendix B).

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References:

1. FDA Label Information (package inserts). DailyMed. U.S. National Library of Medicine. Available at: https://dailymed.nlm.nih.gov/dailymed/index.cfm. Accessed 9/2020.
2. Drug-Drug Interactions and Drug-Disease Contraindications. First Databank, Inc. San Francisco, CA. 2020.

Appendix A: Drug-Disease Interactions with Select Anticonvulsants[1,2]

ANTICONVULSANT	MEDICAL CONTRAINDICATIONS/ WARNINGS
Carbamazepine, Felbamate	Aplastic Anemia or Agranulocytosis
Valproic Acid Analogs	Pancreatitis, Urea Cycle Disorders
Lacosamide	Congestive Heart Failure, Cardiac Conduction Problems such as AV Block or Sick Sinus Syndrome
Clonazepam, Valproic Acid Analogs, Felbamate	Liver Impairment
Phenobarbital, Primidone	Porphyria
Phenytoin, Carbamazepine	Cardiac Conduction Disorder
Rufinamide, Cenobamate	Familial Short QT Syndrome

Appendix B: Recommended Anticonvulsant Monitoring[1]

ANTICONVULSANT	RECOMMENDED MONITORING
Carbamazepine	Baseline and periodic Hepatic and Renal Function
Carbamazepine, Felbamate, Stiripentol	Baseline and periodic Complete Blood Count
Cannabidiol, Felbamate	Baseline and periodic Hepatic Function
Carbamazepine, Vigabatrin	Baseline and periodic Ophthalmologic Exam
Topiramate, Zonisamide	Baseline and periodic Serum Bicarbonate
Valproic Acid Analogs	Baseline and periodic Hepatic Function and Platelet Function/Coagulation tests

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Flag	Internal	External
34	Compliance: Anticonvulsants	Compliance: Anticonvulsants: According to submitted pharmacy claims, it appears your patient may be nonadherent with the identified chronic anticonvulsant therapy. Prescription data suggests your patient received less than 60 days of maintenance therapy in a 90-day period. Please review this information to determine the best course of action for your patient.
129	# Candidates	
10253	IADE: Selected Anticonvulsants and Blood Dyscrasias	IADE: Selected Anticonvulsants and Blood Dyscrasias: According to pharmacy and medical claims data, it appears your patient is receiving the indicated anticonvulsant and has a history of agranulocytosis or aplastic anemia. A history of such blood dyscrasias is considered a contraindication to the use of these anticonvulsants, as they are associated with hematologic toxicity. Because of the low incidence of severe hematologic reactions, data is not available to accurately assess potential risk factors. Duration of therapy cannot be relied on to predict the potential risk as some cases have occurred after prolonged use. Patients on these anticonvulsants should be monitored for decreases in blood cell counts and the medication should be discontinued if any significant bone marrow depression is detected. Please review this information and determine if action is necessary with your patient.
10254	IADE: Valproic Acid Products and Pancreatitis	IADE: Valproic Acid Products and Pancreatitis: According to pharmacy and medical claims data, it appears your patient is receiving a valproic acid product and has a history of pancreatitis. A black boxed warning in the prescribing information for valproic acid products indicates that cases of life-threatening pancreatitis have been reported in both children and adults receiving these medications. In some cases the pancreatitis has been hemorrhagic with rapid progression to death. Cases have been reported shortly after initial use as well as after several years of use. Please review the use of a valproic acid product in your patient and determine if an alternative therapy should be considered.
10255	IADE: Valproic Acid Products and Urea Cycle Disorders	IADE: Valproic Acid Products and Urea Cycle Disorders: According to pharmacy and medical claims data, it appears your patient is receiving a valproic acid product and has a history of urea cycle disorder (hyperammonemia). Official prescribing information for valproic acid products indicates that such use is contraindicated. Hyperammonemic encephalopathy, sometimes fatal, has been reported following use of valproic acid products in patients with urea cycle disorders. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving a valproic acid product should receive prompt treatment (including discontinuation of the valproicacid product) and be evaluated for underlying urea cycle disorders. Please review the use of a valproic acid product in your patient and determine if action or an alternative therapy should be considered.

10258	IADE: Selected Anticonvulsants and Liver Impairment	IADE: Selected Anticonvulsants and Liver Impairment: According to pharmacy and medical claims data, it appears your patient is receiving a valproic acid product, felbamate or clonazepam and has a history of liver dysfunction. Official prescribing information for each of these anticonvulsants indicates that such use is contraindicated. Valproic acid products and felbamate have been associated with hepatotoxicity and death has occurred as a result of the liver failure. Clonazepam may demonstrate significant toxicity when used in patients with significant hepatic disease. Liver function tests should be monitored at frequent intervals in patients with hepatic disease being treated with one of these anticonvulsants. Please review the use of a valproic acid product, felbamate or clonazepam in your patient and determine if action or an alternative therapy should be considered.
10271	IADE: Carbamazepine or Phenytoin and Cardiac Conduction	IADE: Phenytoin or Carbamazepine and Cardiac Conduction: According to pharmacy and medical claims data, it appears your patient is receiving phenytoin or carbamazepine and has a history of a cardiac conduction disorder. Carbamazepine and phenytoin both have effects on ventricular automaticity and may exacerbate cardiac conduction abnormalities. Please review the use of phenytoin or carbamazepine in your patient and determine if action or an alternative therapy should be considered.
10288	IADE: Phenobarbital or Primidone and Porphyria	IADE: Phenobarbital or Primidone and Porphyria: According to pharmacy and medical claims data, it appears your patient is receiving phenobarbital or primidone and has a history of porphyria. A history of porphyria is considered a contraindication to the use of either of these anticonvulsants in the official prescribing information. Both of these anticonvulsants are associated with increases in porphobilinogen excretion and may induce acute porphyric attacks. Please review the use of phenobarbital or primidone in your patient and determine if action or an alternative therapy should be considered.
10937	IADE: Carbamazepine and Hepatic Monitoring	IADE: Carbamazepine and Hepatic Monitoring: According to pharmacy and medical claims data, it appears your patient is receiving carbamazepine and has not had liver function tests documented in the past year. Hepatic effects, including hepatic failure, have been reported during treatment with carbamazepine. Official prescribing information recommends patients being treated with carbamazepine have baseline and periodic evaluations of hepatic function. Please review your patient's history and determine if action is necessary.

10938	IADE: Valproic Acid Products and Hepatic Monitoring	IADE: Valproic Acid Products and Hepatic Monitoring: According to pharmacy and medical claims data, it appears your patient is receiving a valproic acid product and has not had liver function tests documented in the past year. A black boxed warning in the official prescribing information for valproic acid products indicates that hepatic failure resulting in fatalities has been reported in both children and adults receiving these medications. While most cases have occurred during the first six months of therapy, cases have been reported after several years of use. Periodic evaluations of hepatic function are recommended in patients being treated with valproic acid products. Please review your patient's history and determine if action is necessary.
10939	IADE: Valproic Acid Prod and Monitoring of Platelets/Coags	IADE: Valproic Acid Products and Monitoring of Platelets & Coagulation: According to pharmacy and medical claims data, it appears your patient is receiving a valproic acid product and has not had platelet levels or coagulation function tests documented in the past year. Thrombocytopenia and abnormal coagulation function have been reported during therapy with valproic acid products. Official prescribing information recommends baseline and periodic evaluation of these lab tests. Please review your patient's history and determine if action is necessary.
113935	IADE: Lacosamide and Cardiac Issues	IADE: Lacosamide and Cardiac Issues: According to pharmacy and medical claims data, it appears your patient is receiving lacosamide and has a history of a cardiac conduction disorder and/or congestive heart failure. Lacosamide causes dose-dependent prolongations in the PR interval and may exacerbate heart failure. Caution is urged when using lacosamide in patients with known conduction problems or heart failure with increased monitoring, including possible ECG monitoring recommended. Please review the use of lacosamide in your patient and determine if action or an alternative therapy should be considered.
113938	IADE: Rufinamide and Familial Short QT Syndrome	IADE: Rufinamide and Familial Short QT Syndrome: According to pharmacy and medical claims data, it appears your patient is receiving rufinamide and has a history of cardiac arrhythmias. The effects of rufinamide on cardiac conduction cause QT interval shortening and have been associated with ventricular fibrillation. Its use is contraindicated in patients with baseline short QT intervals. Please review the use of rufinamide in your patient and determine if action or an alternative therapy should be considered.
113984	IADE: Carbamazepine and Renal Monitoring	IADE: Carbamazepine and Renal Monitoring: According to pharmacy and medical claims data, it appears your patient is receiving carbamazepine and has not had renal function tests documented in the past year. Renal dysfunction, including renal failure, has been reported during treatment with carbamazepine. The official prescribing information recommends patients being treated with carbamazepine have baseline and periodic evaluations of renal function. Please review your patient's history and determine if action is necessary.

113985	IADE: Cannabidiol Solution and Hepatic Monitoring	IADE: Cannabidiol Solution and Hepatic Monitoring: According to pharmacy and medical claims data, it appears your patient is receiving Epidiolex (cannabidiol solution) and has not had liver function tests documented in the past year. Cannabidiol solution causes dose-related elevations of liver transaminases (ALT and AST). In general, transaminase elevations of greater than 3 times normal, especially in the presence of elevated bilirubin, are an important predictor of severe liver injury. Early identification of elevated liver enzymes may decrease the risk of a serious outcome. While most cases have occurred early in therapy, cases have been reported after months of use. Periodic evaluations of hepatic function are recommended in patients being treated with cannabidiol solution. Please review your patient's history and determine if action is necessary.
113986	IADE: Selected Anticonvulsants and Ophthalmic Exams	IADE: Selected Anticonvulsants and Ophthalmic Exams: According to pharmacy and medical claims data, it appears your patient is receiving the anticonvulsant indicated on the enclosed profile and has not had an ophthalmic exam in the past year. Eye changes, including retinal abnormalities and vision loss, have been reported during treatment with these agents. The official prescribing information for these anticonvulsants recommends baseline and periodic evaluations of visual acuity. In fact, vigabatrin has a boxed warning about potential vision loss which may be permanent in some cases. Not all cases of vision loss have been recognized by patients until it is severe. Please review your patient's history and determine if action is necessary
113987	IADE: Selected Anticonvulsants and Serum Bicarbonate Levels	IADE: Selected Anticonvulsants and Serum Bicarbonate Levels: According to pharmacy and medical claims data, it appears your patient is receiving the anticonvulsant indicated on the enclosed profile and has not had a serum bicarbonate level in the past year. Metabolic acidosis, which may result in cardiac arrhythmias or osteomalacia or nephrolithiasis if left untreated, have been reported during treatment with these agents. In pediatric patients, this may result in reduced growth rates and decreased maximal height. The official prescribing information for these anticonvulsants recommends baseline and periodic evaluations of serum bicarbonate levels. Please review your patient's history and determine if action is necessary.
115169	IADE: Felbamate and Hepatic Monitoring	IADE: Felbamate and Hepatic Monitoring: According to pharmacy and medical claims data, it appears your patient is receiving felbamate and has not had liver function tests documented in the past year. A black boxed warning in the official prescribing information for felbamate indicates that hepatic failure resulting in liver transplantation or death can occur in patients receiving this medication. Baseline and periodic evaluations of hepatic function are recommended in patients being treated with felbamate. Please review your patient's history and determine if action is necessary.

115170	IADE: Selected Anticonvulsants and Hematologic Monitoring	IADE: Selected Anticonvulsants and Hematologic Monitoring: According to pharmacy and medical claims data, it appears your patient is receiving either carbamazepine, felbamate or stiripentol and has not had a complete blood count (CBC) documented in the past year. Hematologic abnormalities including neutropenia, thrombocytopenia, aplastic anemia and agranulocytosis have been reported during treatment with these agents. Official prescribing information for these anticonvulsants recommends at least baseline and periodic hematologic testing to allow for earlier detection of hematologic changes. Please review your patient's history and determine if action is necessary.
115180	IADE: Cenobamate and Familial Short QT Syndrome	IADE: Cenobamate and Familial Short QT Syndrome: According to pharmacy and medical claims data, it appears your patient is receiving cenobamate and has a history of cardiac arrhythmias. The effects of cenobamate on cardiac conduction cause QT interval shortening and have been associated with ventricular fibrillation. Its use is contraindicated in patients with baseline short QT intervals. Please review the use of cenobamate in your patient and determine if action or an alternative therapy should be considered.

TEXAS
Health and Human Services

Cecile Erwin Young
Executive Commissioner

<<Date>>

«dea»
«name»
«add1»
«add2»
«add3»

RE: Anticonvulsant Drug Use Evaluation

Dear Dr. <<NAME>>:

Thank you for providing quality care for Texas Fee-For-Service (FFS) Medicaid patients. The content of this letter has been approved by the Texas Drug Utilization Review (DUR) Board, whose function is to promote safe and cost-effective drug therapy and provide opportunities for continuous improvement of care.

This retrospective claims review was selected to assist providers in improving the safe use of anticonvulsant medications. Various anticonvulsants are associated with risks for drug-disease interactions as well as other potential toxicities and require routine monitoring.[1] These recommendations are designed to assist you in maximizing outcomes and promoting patient safety for individuals receiving this type of therapy.

Claims data indicates that in the Texas Medicaid Fee-For-Service Program there are approximately 1,125 individuals being treated with an anticonvulsant. This treatment included 19,724 prescriptions for anticonvulsants in a recent 365 day period. The total Texas Medicaid Fee-For-Service performance indicators for all patients (including those <18 years) with opportunities for improving the safe use of anticonvulsants are shown in the table below.

Total Texas Medicaid Fee-For-Service Specific Data

Anticonvulsant Medication Management Indicators	Number of Patients with Opportunities*	
	<18 Years	**≥18 Years**
• Increased Risk of Adverse Drug Event (ADE): Anticonvulsants and drug-disease interactions	2	23
• Nonadherence with anticonvulsants	4	16
• Increased Risk of Adverse Drug Event (ADE): Anticonvulsants and recommended monitoring	85	228

*Based on data through September 7, 2020

The enclosed patient profiles reflect one or more of the above issues and are provided as a medical record reminder for when your patients return for their next appointments.

We acknowledge that there may be clinical variables influencing an individual patient's management that are not apparent in claims data. However, we believe the issues identified may assist you in caring for your patient(s). It is possible that your license number may have been inadvertently assigned to the claim as an

error at the pharmacy during the billing process. **Also, some prescribed medications as well as some recommended laboratory monitoring or physical examinations may not appear on the patient's profile because they may have been privately purchased or were not billable to Medicaid Services.** We thank you for reviewing this information and caring for Texas Medicaid patients, and we welcome the opportunity to discuss any comments or concerns you may have about our quality management program. Please feel free to call our office at 1-866-923-7208 with questions or concerns. If your mailing address is incorrect, it must be updated through the Texas Medical Board online at **http://www.tmb.state.tx.us/page/change-address.**

Sincerely,

Medicaid Drug Use Review Board
Vendor Drug Program H-630

Anticonvulsant Medication Management Indicator Summary
• **Increased Risk of Adverse Drug Event (IADE): Anticonvulsants and drug-disease interactions:**[1,2] Drug-disease interactions with anticonvulsants frequently involve issues that are identified in boxed warnings or precautions in the official prescribing information. Any use of an anticonvulsant in an individual with a medical condition considered a contraindication or significant precaution requiring additional monitoring will be flagged. As an example, several antiepileptic drugs (e.g., carbamazepine, cenobamate, lacosamide, phenytoin, rufinamide) may affect cardiac conduction and cause or worsen arrhythmias in susceptible individuals. As such, these agents should be used cautiously and it may be clinically appropriate to monitor electrocardiograms (ECG) in high risk patients.
• **Nonadherence with anticonvulsants:**[3] Literature indicates that anticonvulsant nonadherence rates among adults with a seizure disorder range from 29-39%. Not taking epilepsy medications as prescribed may compromise the effectiveness of the regimen as well as lead to adverse clinical outcomes, increased mortality and increased healthcare costs.
• **Increased Risk of Adverse Drug Event (IADE): Anticonvulsants and recommended monitoring:** [1,2] The use of certain anticonvulsants is associated with potential toxicities that require routine monitoring. For example, hepatic toxicity is known to occur with cannabidiol, carbamazepine, felbamate and valproic acid, and official prescribing information recommends baseline and periodic assessment of hepatic function for these agents. Periodic hematologic assessments are also recommended for agents that can cause blood dyscrasias (e.g., carbamazepine, felbamate, stiripentol, valproic acid). While not targeted in this retrospective claims review due to lack of specific recommended monitoring frequencies, it may be clinically appropriate to monitor additional parameters for certain medications. For example, periodic hepatic and renal function assessments may be appropriate for patients taking phenytoin, phenobarbital and other anticonvulsants. Carbamazepine and oxcarbazepine can cause hyponatremia, often as a result of syndrome of inappropriate antidiuretic hormone secretion (SIADH). As such, it may be prudent to monitor electrolytes, particularly in patients: taking higher doses, who are elderly or taking concomitant diuretics. Additionally, monitoring may be recommended in specific clinical scenarios. For example, valproic acid analogs and topiramate can cause hyperammonemia, so ammonia levels should be measured in patients taking either of those agents who develop unexplained lethargy, vomiting or changes in mental status.

Clinical Considerations
• **Anticonvulsants and risk of decreased oral contraceptive effectiveness:**[1,2,4] Several anticonvulsants that induce hepatic enzymes are known to decrease the effectiveness of hormone-containing contraceptive agents. While these interactions are not a contraindication, and therefore not targeted in this mailing, the risk of an unwanted pregnancy in individuals who rely on such contraceptives can be a life-changing event. Such individuals should be counseled to use alternative methods of preventing an unwanted pregnancy during combined use of enzyme-inducing anticonvulsants and hormonal contraceptives. (see Table below)
• **Anticonvulsant use during pregnancy:**[1,2,5] Several anticonvulsants are recognized as being potentially teratogenic and, as such, raise serious considerations in the treatment of pregnant women. This issue is not targeted in this retrospective claims review but should be an area of concern for prescribers and females of child bearing age. Clinical risk/benefit discussions should occur with all appropriate individuals in such cases and folate therapy should begin before becoming pregnant if possible. (see Table below)
• **Metabolic considerations:**[6-8] Antiepileptic drugs can cause unintended metabolic consequences. Agents that induce the cytochrome P450 hepatic enzyme system may affect the metabolism of various hormones, cholesterol, vitamins and bone. Agents like phenytoin and carbamazepine may increase serum lipids and this may contribute to the higher rates of cardiovascular and cerebrovascular disease that are seen in patients with epilepsy. Carbamazepine, phenytoin and valproic acid may affect thyroid hormone levels and contribute to weight gain. These same agents can also affect reproductive hormones in men (decreasing testosterone levels) and women (causing symptoms similar to polycystic ovary syndrome). The impact of these metabolic changes on specific clinical outcomes is unknown, but clinicians may want to monitor patients taking these agents more closely. It may be appropriate to consider switching therapy to a different or newer anticonvulsant if a patient experiences undesired metabolic effects.
• **Anticonvulsants and bone health:**[6,8] Studies suggest an association between anticonvulsants, reduced bone density and increased fracture risk. The mechanism is not fully understood and not all anticonvulsants have been implicated. Carbamazepine, phenobarbital and phenytoin have been shown to decrease the absorption of calcium, increase the metabolism of vitamin D and affect bone metabolism. Valproic acid has also been associated with lower bone mineral density and increased risk of fractures. Patients taking anticonvulsants long-term may warrant closer monitoring and assessment of overall bone health.

Anticonvulsant Medications that Decrease Effectiveness of Hormonal Contraceptives[1,2,4]		
• Carbamazepine • Cenobamate • Clobazam • Eslicarbazepine • Felbamate	• Lamotrigine (> 300 mg/day) • Oxcarbazepine • Perampanel • Phenobarbital	• Phenytoin • Primidone • Rufinamide • Topiramate

Anticonvulsant Medications that are Potentially Dangerous During Pregnancy[1,2,5]		
• Carbamazepine • Lamotrigine • Oxcarbazepine	• Phenytoin • Phenobarbital • Primidone • Topiramate	• Valproic Acid Analogs • Vigabatrin • Zonisamide

Selected References (full reference list available upon request):

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