CLINICAL & FORENSIC

Toxicology News

ISSN 2374-9679

September 2016

An AACC/CAP Educational Newsletter for Toxicology Laboratories

Newer Anti-Epileptic Drugs
TDM for Second Generation of AEDs Remains a Work in Progress

By Matthew D. Krasowski, MD, PhD

Medications used to treat and prevent seizures—anti-epileptic drugs (AEDs)—are among the most common drugs for which therapeutic drug monitoring (TDM) is performed (1). The first-generation AEDs, including carbamazepine, phenobarbital, phenytoin, primidone, and valproic acid, were introduced prior to 1990 and are still in use today to varying degrees (2). TDM helps with optimal dosing of the first-generation AEDs, which can be challenging because the drugs have a high degree of inter-individual variability. They also have a relatively high risk of toxicity, with several of the agents also being teratogens, including carbamazepine, phenobarbital, phenytoin, and valproic acid.

The past two decades have seen an entirely new generation of AEDs enter clinical practice, with 17 approved for use in the United States or Europe (3). TDM is commonly used for a subset of these newer AEDs (1,4). The new drugs generally have wider therapeutic indices and less serious adverse effects than the first-generation AEDs (2). This article focuses on seven of them—clobazam, eslicarbazepine acetate, ezogabine (retigabine), lacosamide, perampanel, rufinamide, and tiagabine.

Diverse Structures and Uses

AEDs are structurally diverse (Figure 1) (3). In addition to management of seizures, the newer agents are also used (often off-label) for other neurologic or psychiatric conditions, such as addiction, bipolar disorder, panic attacks, Parkinson's disease, and substance abuse (Table 1) (5,6). Some AEDs now have primary indications for treating migraine and cluster headaches, neuralgias, and neuropathic pain. TDM of AEDs prescribed for clinical uses other than management of seizure disorders has not been well-defined, although serum or plasma concentrations are sometimes used to assess compliance.

The selection of which AED to use for a seizure disorder requires consideration of the etiology and type(s) of the seizures (7). Some seizure disorders are inherited (for example, Dravet spectrum disorders), but most are acquired (such as, head injury or brain malformations) or idiopathic (unknown cause). Characteristic presentations may be described based on cause (for example, febrile seizure), as a syndrome (for example, Lennox-Gastaut), or as a type of epilepsy (for example, temporal lobe epilepsy).

Seizure types are often described as generalized (involving both hemispheres of the brain) or partial (focal). Partial seizures represent approximately 60% of all seizure types. Partial seizures can be simple (no loss of consciousness) or complex (loss of consciousness), and may be associated with autonomic, motor, and somatosensory symptoms. Partial seizures can occur with or without generalization. Generalized seizures may be convulsive (for example, tonic-clonic) or nonconvulsive (for example, absence, formerly called petit mal seizures). Status epilepticus (continuous seizure) is a life-threatening medical emergency.

Most of the newer AEDs are formally indicated for partial seizures but may be used for treatment of a wider range of seizure disorders. Many of them were originally approved as adjunct therapy for refractory seizures (3).

TDM of Second-Generation AEDs

TDM of AEDs can be challenging given that seizures occur irregularly and unpredictably, often with long periods between episodes. Seizures can vary in their presentation and intensity even for a single individual. There is also a wide spectrum of

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Second-Generation AEDs

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disorders, some of which are resistant to medication or surgery. This variety makes it difficult to define a therapeutic range for any drug and individual patient. When treatment involves more than one AED, drug–drug interactions are common, especially if first-generation AEDs are used concomitantly. In addition, toxicity from AEDs can resemble the underlying seizure disorder in clinical presentation. The presence of active metabolites can complicate TDM, which may need to involve the parent drug along with one or more metabolites, or sometimes only metabolites.

TDM for AEDs most commonly uses serum or plasma. Although uncommon, saliva and dried blood spots can be used for some AEDs, and sometimes offer significant practical advantages (8,9).

Therapeutic Ranges

Table 1 shows proposed therapeutic ranges for the newer AEDs. Establishing therapeutic ranges is challenging because of the wide range of concentrations associated with effective management of seizures (1). Therapeutic ranges vary based on seizure subtype and whether the AED is used alone or with other AEDs. It is prudent to target clinical efficacy rather than aiming for a "standard" therapeutic range. Dosing requirements—and hence therapeutic targets—can change with age, clinical status, concomitant drug therapy, organ insufficiency, and pregnancy. Perucca has advocated for "individual therapeutic concentrations" based on good seizure control (10). TDM levels may need to be adjusted when changes occur in the patient that alter AED pharmacokinetics.

TDM for AEDs may also be used early in therapy to ensure that steady-state concentrations have been achieved before efficacy is evaluated, particularly for drugs that have complicated pharmacokinetics (1). TDM is useful during maintenance therapy to identify and avoid problems with drug–drug interactions, to manage changes in dose or drug formulation, and to evaluate compliance, particularly when seizure control is suboptimal. Children can be particularly difficult to manage with AEDs, in part due to nonadherence. Drug concentrations should be also taken into consideration during evaluations of toxicity or sudden death (11).

For special populations, such as pregnant women, the elderly, and uremic patients who have been prescribed AEDs that have a high proportion of protein binding (>90%), it may be appropriate to manage the TDM based on unbound or "free" fraction of drug (12). The classical AED phenytoin provides an example of this. Its free drug concentrations have been well-characterized by using ultrafiltrate and immunoassays calibrated for lower concentrations. The high protein-binding levels of the new AEDs perampanel and tiagabine may make them good candidates for free drug analysis, although it is not currently commonly used (13).

An individual's genetic predispositions may explain some of the inter-individual variation in response to and toxicity of AEDs. Among the newer AEDs, clobazam has the strongest pharmacogenetic association. Clearance of the active *N*-desmethyl metabolite of clobazam is primarily via cytochrome P450 (CYP) 2C19. Patients with low activity of the enzyme CYP2C19 metabolize the drug slowly and therefore require lower doses. In such patients, TDM may help to lower risk of toxicity.

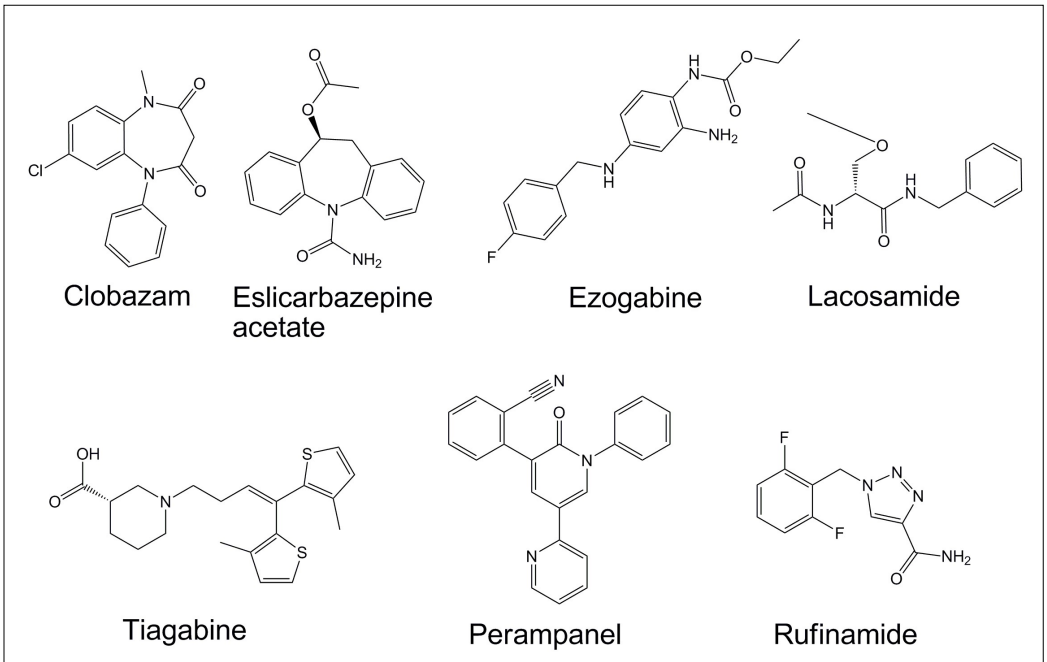

Figure 1. Chemical structures of seven of the newest anti-epileptic drugs

TDM Methodology

Quantitative TDM of the newer AEDs using serum or plasma is performed using both commercial assays and laboratory-developed tests (2). For several of them, including lamotrigine, levetiracetam, and topiramate, homogeneous immunoassays for use in common clinical chemistry analyzers are commercially available. But for most of the new AEDs, immunoassays are either not available or do not perform adequately. TDM for these drugs requires high-complexity methods, such as high performance liquid chro-

matography (HPLC) or gas chromatography (GC). Although many detectors can be used, mass spectrometers (MS) are most common because of their high specificity. Tandem mass spectrometers coupled to liquid chromatography (LC-MS/MS) are the most common high-complexity platforms used to support TDM with serum or plasma today (14). A multi-drug LC-MS/MS reagent kit is currently available (MassTox TDM kit, ChromSystems 92921, Germany), although many laboratories using chromatography techniques have developed their own assays. With the background above, seven of the newer AEDs will be discussed.

Clobazam

A 1,5-benzodiazepine drug, clobazam was first evaluated in the 1970s for anxiolytic properties but was not approved for use as an AED in the U.S. until 2011 (15). It is rapidly absorbed and exhibits linear pharmacokinetics, with a peak serum/plasma concentration in 1–3 hours and a half-life of 10–30 hours. It is particularly effective in Lennox-Gastaut syndrome, an epilepsy syndrome often refractory to other drugs. Its activity is attributed to both the parent drug and *N*-desmethylclobazam, a metabolite generated primarily through a reaction mediated by CYP3A4. The metabolite has a half-life of 36–46 hours and is subsequently inactivated by CYP2C19, leading to a recommendation that poor metabolizers of CYP2C19 be treated with low doses (16). Serum and plasma immunoassays for benzodiazepines may detect clobazam, but quantitation is not accurate. Thus, TDM uses chromatographic methods (17).

Eslicarbazepine Acetate

Eslicarbazepine acetate is a pro-drug that is rapidly metabolized by liver esterases to the active metabolite, eslicarbazepine [(*S*)-licarbazepine, (*S*)-10-hydroxycarbazepine]. It is also a metabolite of oxcarbazepine (itself one of the newer AEDs). Eslicarbazepine acetate was approved in the U.S. in 2013 and in Europe in 2009 (18). TDM focuses on the active metabolite and not the parent drug. Unlike the structurally related, older AED carbamazepine, eslicarbazepine has generally predictable pharmacokinetics and minimal drug–drug interactions (19). Renal clearance is the predominant elimination route for it and its minor metabolites. Its relatively predictable pharmacokinetics mean TDM has a minimal role except in patients with renal impairment. Enantioselective LC-MS/MS methods have been reported for use in serum/plasma (20).

Ezogabine (Retigabine)

Ezogabine (known as retigabine in Europe) was approved in the U.S. in 2010 and in Europe in 2011 for the treatment of partial seizures (18). It has extensive first-pass metabolism by the liver (21). Its serum

Table 1. Clinical Uses, Therapeutic Ranges, and Characteristics of Newer AEDs

Drug name(s)	Common U.S. trade name (year approved)	Primary seizure indication	Nonseizure uses	Therapeutic range (mg/L)	Notes
Clobazam	Onfi (2011)	Lennox-Gastaut	Anxiety, schizophrenia	0.03–0.3 0.3–3.0 (desmethyl metabolite)	*N*-Desmethyl metabolite is active; shows variation based on CYP2C19 metabolizer status
Eslicarbazepine acetate	Aptiom (2013)	Partial seizures	Bipolar disorder	3–35 (eslicarbazepine metabolite)	Chiral pro-drug; provided as *S*-enantiomer
Ezogabine/retigabine	Potiga (2010)	Partial seizures	Migraine headaches, tinnitus, neuropathic pain	Not established	*N*-acetyl metabolite has weak pharmacological activity
Lacosamide	Vimpat (2008)	Partial seizures	-	5–15	Generally predictable pharmacokinetics
Perampanel	Fycompa (2012)	Partial seizures	-	Not established	Substrate of CYP3A4
Rufinamide	Banzel (2008)	Lennox-Gastaut	-	3–30	Wide therapeutic range but individuals tend to have narrow response range
Tiagabine	Gabitril (1998)	Partial seizures	Panic attacks, movement disorders	0.02–0.2	Chiral, provided as *R*-enantiomer; extensive metabolism, CYP3A4 substrate

half-life is 6–10 hours and protein-binding is estimated at 80%. Its clearance decreases in the elderly, mainly attributable to age-related declines in renal function (21). Approximately 20–30% of the dose is excreted unchanged by the kidneys (22). Both renal and hepatic impairment decrease its clearance rate. It has minimal drug–drug interactions. There is little information on the role of TDM in patient management, with no therapeutic range established yet. An LC-MS/MS method for determining serum/plasma concentrations has been reported (23).

Lacosamide

Lacosamide was approved in both the U.S. and Europe in 2008 for the treatment of partial-onset seizures (24). It has excellent oral bioavailability and minimal serum protein binding. Drug–drug interactions appear to be minimal. A therapeutic range of 5–15 mg/L has been proposed (18). HPLC and LC-MS/MS procedures for measurement in plasma or serum have been reported (13). Its generally predictable pharmacokinetics limit the routine need for TDM other than to establish individualized therapeutic ranges or to manage therapy in patients with liver or kidney failure.

Perampanel

Perampanel was approved in 2012 in the U.S. and Europe for adjunctive therapy of partial seizures (25). Because of its potential for abuse, it is regulated as a schedule III drug in the U.S. (26). It is rapidly absorbed following oral administration (27). The serum half-life was 52–129 hours after a single dose and 66–90 hours after two weeks of therapy in a clinical trial of adult men. Perampanel is heavily bound to serum proteins (>95%). Monitoring of free drug fractions, although not commonly used, may theoretically be beneficial. Perampanel is primarily metabolized by CYP enzyme oxidation followed by glucuronidation. Its clearance rate is reduced in patients with renal and hepatic insufficiency. There is minimal information on the role of TDM in patient management, with no therapeutic range established.

Rufinamide

Rufinamide is approved in the U.S. and Europe for the treatment of Lennox-Gastaut syndrome (28). It has high bioavailability (85% or higher), with increased absorption when taken with food. It is extensively metabolized to inactive metabolites that are mainly excreted renally. Rufinamide metabolism is increased by concomitant therapy with liver enzyme inducers such as carbamazepine, phenytoin, phenobarbital, rifampin, and St. John's wort (an herbal antidepressant). TDM is currently not well-defined (28). In clinical trials for the treatment of epilepsy, treatment has succeeded with a wide range of concentrations (3–30 mg/L). However, individual patients appear to have a narrower range of concentrations related to good clinical response, so an individual therapeutic concentration strategy might be warranted (28). Concentrations can be determined by HPLC with ultraviolet/visible or MS detection (13).

Tiagabine

Tiagabine is approved in the U.S. for adjunctive therapy of partial seizures (3). Its use has been limited by adverse side effects, particularly a propensity to trigger seizures and nonconvulsive status epilepticus, which can be life-threatening in rare cases (29). It is rapidly absorbed, with excellent bioavailability. It exhibits a high degree of binding to serum proteins (>95%), with a potential for interactions with drugs such as valproic acid, which can displace tiagabine from serum protein binding sites (30). Tiagabine is extensively metabolized by the liver, with faster clearance in children compared with adults. Inducers of liver metabolism increase its metabolism (31). Its serum half-life is 5–9 hours in patients not on concomitant liver enzyme inducers. Liver failure increases its half-life to 12–16 hours (32).

Tiagabine's variable metabolism makes TDM potentially useful. A broad therapeutic range of 20–200 ng/mL (0.02–0.2 mg/L) has been proposed based on a multicenter study (33). GC/MS, HPLC, and LC-MS/MS methods have been reported for measuring serum/plasma concentrations (13). Comparison studies of tiagabine measurements between different clinical laboratories noted a high degree of variability, higher than seen with other second-generation AEDs (34).

Summary

The newer generation of AEDs has expanded the therapeutic options for managing seizure disorders as well as other neurologic and psychiatric conditions. Overall, the newer AEDs have fewer adverse effects and wider therapeutic margins than the first generation. TDM of the new AEDs is evolving and more research is needed to delineate the therapeutic ranges (including for nonepilepsy uses) and to document the benefits of TDM in clinical practice. There is also limited information on their toxicity, a situation likely to should change as overdose cases are analyzed.

Learning Objectives

After reading this article the reader will be able to identify clinical applications of seven of the newest anti-epileptic drugs and their potential advantages over older anti-epileptic drugs. The reader will also be familiar with clinical situations in which therapeutic drug monitoring is most likely to be helpful for these drugs.

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The author has nothing to disclose.

NACB Creates Guideline on Tests For Monitoring Pain Management

By Paul J. Jannetto, PhD, and Loralie J. Langman, PhD

The National Academy of Clinical Biochemistry (NACB) recently released a draft of a new laboratory medicine practice guideline (LMPG) on the use of laboratory tests to monitor drug therapy in pain management patients. The comment period closed on Sept. 6, but the guideline, "Using Clinical Laboratory Tests to Monitor Drug Therapy in Pain Management Patients," can be viewed on the AACC website (1).

The NACB LMPGs are created using evidence-based approaches to address specific questions about the appropriate use of diagnostic laboratory testing. The new pain management LMPG provides recommendations on which drugs and drug classes should be tested for routinely; the clinical utility of urine and alternative specimen types; assay formats (laboratory -based vs. point-of-care); assay types (screening vs. definitive); specimen validity testing; pharmacogenomics testing; and the reporting, communication, and interpretation of test results back to clinicians.

Literature Review Process

A multidisciplinary guideline committee made up of clinical laboratory professionals, pain management clinicians, other healthcare professionals, clinical experts, and other stakeholders began the process by defining all the questions the guideline should address using the PICO(TS) strategy for construction of the questions. PICO(TS) stands for the (P)atient population, (I)ntervention, (C)omparator, (O)utcome, (T)ime period, and (S)etting.

The committee's systematic review of the literature, which covered from January 2000 to February 2015, identified 7,647 articles. Using the DistillerSR software to document the review process, each abstract was then independently reviewed by two committee members to move it forward to the full text review phase. Any discordance was resolved by a third person. A total of 2,352 articles underwent a full text review and 562 of those were ultimately used to formulate the recommendations. Finally, the strength of each recommendation was graded using an approach described in a 2011 Institute of Medicine report.

Important Recommendations

A few of the most important recommendations include:

- First-line definitive testing (qualitative or quantitative) is recommended for detecting the use of relevant over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances in pain management patients. Definitive urine drug testing specifically identifies or quantifies a drug, its metabolites, or both.
- Quantitative definitive urine testing is not more useful than qualitative definitive urine testing at detecting outcomes in pain management patients. Furthermore, quantitative definitive urine testing should not be used to evaluate dosage of administered drug or adherence to a prescribed dosage regimen. However, quantitative urine definitive testing can be used to identify variant drug metabolism, pharmaceutical impurities, or metabolism through minor routes.
- Specimen validity testing to identify aberrant drug-taking behavior should be used as a supplement to other tools for detecting outcomes in pain management patients. Multiple tools, including specimen validity testing, should be used as a component of urine drug testing to identify the use of relevant over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances in pain management patients.
- Current evidence in the literature does not support routine genetic testing for pain management patients. Genetic testing should be considered to predict or explain variant pharmacokinetics or pharmacodynamics of specific drugs as indicated by repeated treatment failures, adverse drug reactions, or toxicity.
- Data showed that many clinical providers have insufficient knowledge and expertise to correctly interpret urine laboratory test results in pain management patients. Clinicians should contact laboratory personnel for any test result that is inconsistent with the clinical picture or prescribed medications to more effectively interpret urine test results in pain management patients.

Evidence Strength

Each of these recommendations had a strength of "A," which means the NACB strongly recommends

Table 1. Tiers of Testing for Pain Management Drugs

Tier	When to Order	Drug Class	Example Drug or Metabolite
I	Routine monitoring	Amphetamines	Amphetamine, methamphetamine, methylenedioxymethamphetamine (MDMA), methylenedioxyamphetamine (MDA), methylenedioxyethylamphetamine (MDEA)
		Barbiturates	Amobarbital, butalbital, phenobarbital, pentobarbital, secobarbital
		Benzodiazepines	Alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, halazepam, lorazepam, medazepam, midazolam, oxazepam, prazepam, temazepam, triazolam
		Cannabinoids	∆9-tetrahydrocannabinol (THC)
		Cocaine	Cocaine, benzoylecgonine
		Opiates/opioids	6-acetylmorphine (6-AM), buprenorphine, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, tapentado, tramadol
II	High-risk patients with known history of abuse for this medication, Use of the drug is prevalent in local region, Risky polypharmacy, Patient has multiple providers, or Drug is prescribed but patient shows toxicity or lack of efficacy	Alcohol	Ethanol or metabolite
		Anticonvulsants	Carbamazepine, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, pregabalin, rufinamide, tiagabine, topiramate, valproic acid
		Antidepressants	Amitriptyline, citalopram, clomipramine, desipramine, doxepin, duloxetine, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline, venlafaxine
		Antitussive	Dextromethrophan
		Dissociative anesthetic	Ketamine
		Hallucinogens	Lysergic acid diethylamide (LSD), phencyclidine
		Muscle relaxants	Carisoprodol, meprobamate
		Narcotic pain-reliever	Propoxyphene
		Synthetic cathinones	Compounds ever-changing, too numerous to list
III	As clinically indicated	OTC analgesic	Acetaminophen, salicylate
		Antihistamine	Certirizine, chlorpheniramine, diphenhydramine, loratidine
		Antipsychotics	Amisulpride, amoxapine, chlormethiazole, clopenthixole, chlorpiprazine, chlorpromazine, chlorprothixene, cloxazepine, clozapine, distraneurine, dixyrazine, fluentixol decanoate, fluphenazine, haloperidole, loxapine, melperone hydrochloride, methotrimeprazine, olanzapine, oxilapine, perphenazine, phenothiazine, pimozide, quetiapine, risperidone, sulpiride, thioridazine, tiapride, trifluoroperazine, ziprasidone, zotepine
		Synthetic cannabinoids	Compounds ever-changing, too numerous to list

This table is not meant to be a comprehensive list of all drugs that must be tested for in every pain management patient. The list provides examples of drugs from each drug class. The provider should take into account the medications prescribed to the patient, the patient's substance abuse history, other accessible or locally abused drugs, and the patient's clinical presentation when selecting which tests to order. Furthermore, it may be more appropriate to look for and identify a drug's metabolite based on what is found in the matrix tested. For this reason, laboratory tests must include the appropriate parent drug and/or metabolites based on the matrix.

its adoption because there is good evidence that it improves important health outcomes, and the guideline committee concluded that its benefits substantially outweigh its harms.

The first four recommendations had an evidence quality score of "II," which means the evidence was sufficient to determine effects, but the strength of the evidence was limited by the number, quality, or consistency of the studies; generalizability to routine practice; or indirect nature of the evidence. The fifth recommendation had an evidence quality score of "I," which means the evidence included consistent results from well-designed, well-conducted studies in representative populations.

Part of the reason for the lower evidence quality scores for the first four recommendations was that, although the guideline focuses on the pain management population, much of the available evidence was gathered in other settings, including substance abuse and workplace drug-testing populations.

Breadth of Tests

The new guideline also attempted to address the breadth of tests being ordered routinely on pain management patients. Table 1 shows the three main tiers of drugs and drug classes that are being recommended to test for based on risk. This table is not meant to be a comprehensive list of all drugs in every pain management patient, but instead should be used as a guideline.

Conclusion

The new guideline on the use of laboratory tests to monitor drug therapy in pain management patients is the first evidence-based guideline that attempts to provide some details around the types of tests, the analytes, and the frequency of laboratory testing for the benefit of both laboratories who perform the tests and the clinicians who order them. This guideline also identified several gaps in the literature where evidence was weak or lacking, so the authors hope this prompts people to perform these clinical studies to facilitate future recommendations.

Learning Objectives

After reading this article, the reader will understand the evidence-based recommendations for laboratory testing to support the monitoring of controlled or illicit substances in pain management patients. The reader will also be able to identify the benefits and limitations of various types of compliance monitoring for chronic pain patients.

Reference

1. Using clinical laboratory tests to monitor drug therapy in pain management patients. The National Academy of Clinical Biochemistry laboratory medicine practice guidelines. https://www.aacc.org/science-and-practice/practice-guidelines/using-clinical-laboratory-tests-to-monitor-drug-therapy-in-pain-management-patients (Accessed September 2016).

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The authors served on the committee that created the guideline described in the article.

Gabapentin and Pregabalin: *Although They Were Thought to Pose Little Risk, their Abuse is Growing*

By Christine Snozek, PhD

A study presented at the 2016 AACC annual meeting in Philadelphia highlights a growing concern in pain management patients and other populations: the abuse of nonopioid medications such as the antiepileptic drugs (AEDs) gabapentin and pregabalin. These drugs, often used to treat neuropathic pain, drug or alcohol withdrawal, and other nonseizure indications, were originally thought to have minimal risk of abuse. However, growing evidence in case reports and larger studies shows that misuse of them does occur and is becoming more common.

Quigley et al. presented a study of 323 patients from pain (~90%) and rehabilitation (~10%) clinics whose urine specimens were tested for gabapentin in addition to opioids, benzodiazepines, and other drugs (1). Seventy of the 323 (22%) were positive for gabapentin despite having no record of a gabapentin prescription, suggesting misuse of the drug. Sixty-six of those 70 patients were also positive for at least one of the following: opioids, cyclobenzaprine, benzodiazepines, or other drugs.

International Review

This prevalence is in line with the rates of gabapentin misuse summarized in a recent international review by Smith et al. (2). Despite low prevalence of gabapentin misuse in the general population (1%), misuse rates increased to 40–65% in patients with gabapentin prescriptions and to 15–22% in individuals known to abuse opioids. Effects reported varied widely, including sedation, sociability, euphoria, and "highs" similar to cocaine, amphetamines, or marijuana. Data from poison centers and autopsy reports indicated that misuse of gabapentin can lead to more severe consequences as well, such as seizures and death. Populations at risk for AED misuse included pain management patients as well as former and current substance abusers.

Similarly, a review by Schjerning et al. described the current literature regarding recreational

use and abuse of pregabalin (3). Although preclinical studies did not demonstrate abuse potential, in clinical studies, patients reported feelings of euphoria and feeling "dazed" or "drunk." Misuse of pregabalin was reported at relatively low prevalence in the general population, but there were indications of overuse of prescribed pregabalin in a subset of patients. The authors note that pregabalin abuse was more common in users with a history of substance abuse; this finding is concerning given the apparent utility of pregabalin in easing withdrawal from certain drugs of abuse.

Although gabapentin and pregabalin are used recreationally by themselves, published literature and user self-reports (for example, at www.erowid.org) suggest that both can enhance the euphoric effects of drugs such as opioids. Reported doses and effects vary widely, particularly when they are used in combination with alcohol or other drugs.

A Need for Screening?

These studies suggest that routine screening for gabapentin and pregabalin in the pain management population might be prudent, but some logistical hurdles could slow the adoption of that practice. First, many current assays for these AEDs are intended for therapeutic drug monitoring, so the targeted sample matrix is serum or plasma, whereas drug screening is generally performed using urine specimens. Inclusion of gabapentin and pregabalin into routine screening workflows would therefore require validation of suitable assays in urine, collection of a simultaneous serum sample, or movement toward alternate matrices such as oral fluid.

Furthermore, detection of misuse of legitimately prescribed gabapentin and pregabalin presents additional challenges. Certainly, the presence of these drugs in a patient who does not have a prescription is likely to represent misuse. However, testing protocols that allow detection of more subtle forms of misuse (particularly overuse) of prescribed medications are much more complicated to define. Unfortunately, the wide therapeutic intervals and lack of correlation between dose and urine concentration make it difficult to clearly determine when a patient is taking more than the prescribed dose. For these and other reasons, the recent National Academy of Clinical Biochemistry pain management guideline does not recommend routine screening for gabapentin and pregabalin in all patients (see page 6) (4).

In summary, initial perceptions that gabapentin and pregabalin had minimal abuse potential led to their widespread use in numerous on- and off-label indications. Subsequent studies have revealed that these AEDs are used recreationally both on their own and in combination with other drugs. Clinicians and laboratorians who support pain clinic, emergency department, and similar practices should be aware of the prevalence and potential abuse of these drugs.

Learning Objective

After reading this article, the reader will be able to describe the prevalence and concerns regarding misuse of gabapentin and pregabalin.

References

1. Quigley K, Adhlakha V, Reddy P, et al. Prevalence of gabapentin abuse among clinical patients. Abstract B-324. Described in http://www.news-medical.net/news/20160803/Study-finds-high-rate-of-misuse-ofc2a0seizure-and-pain-drug.aspx (Accessed August 2016).
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4. Using clinical laboratory tests to monitor drug therapy in pain management patients. The National Academy of Clinical Biochemistry laboratory medicine practice guidelines. https://www.aacc.org/science-and-practice/practice-guidelines/using-clinical-laboratory-tests-to-monitor-drug-therapy-in-pain-management-patients (Accessed September 2016).

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The author has nothing to disclose.

The authors summarize data from postmortem cases, drugged driving cases, and in vivo and in vitro metabolism studies in the literature. They discuss the extraction procedures from biologic matrices and describe standard analytical methods—including immunoassay, gas chromatography-mass spectrometry, and liquid chromatography-tandem mass spectrometry—as well as more esoteric methods.

By Barry Levine, Justin M. Holler, and Shawn P. Vorce, the 204-page, spiral-bound book costs $24 ($20 for AACC members). It can be ordered online (www.aacc.org and click on the "Store" link) or by calling (800) 892-1400 or (202) 857-0717.

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