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Therapeutics & Toxins News

Inside this issue:

Drug treatments for neuropathic pain

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Pain is the most common reason people seek health care services in the United States and is estimated to cost over $600 billion yearly (1). Chronic pain is the number one cause of long-term disability with approximately 100 million American adults affected (1, 2). Worldwide, more than 1.5 billion people suffer from chronic pain and approximately 3-4.5% of the global population suffers from neuropathic pain (NP) (3). However, unlike other forms of pain, NP management is particularly challenging as; (i) it is long-lasting and intense, (ii) it is usually sensed in seemingly normal body parts, and (iii) it is unresponsive to over-the-counter pain relievers. NP is pain caused by lesions of the peripheral or central nervous system. It typically manifests with positive (e.g. pain, dysesthesia, hyperalgesia, allodynia) and negative (e.g. sensory loss: tactile hypoesthesia or anesthesia, thermal hypoesthesia, pinprick hypoalgesia, loss of vibrational sensation) sensory phenomena (4, 5). Common causes of NP include trauma resulting in nerve injury and deafferentation, inflammation, metabolic diseases (e.g. diabetic neuropathy), infections (e.g. herpes zoster with resulting postherpetic neuralgia), toxins (e.g. chemotherapy), tumors and primary neurological diseases (5, 6). NP is not a specific entity, but consists of diverse pain states including: painful peripheral mononeuropathy and polyneuropathy, deafferentiation pain, sympathetically maintained pain and central pain. Some of the pathophysiological properties responsible for causing NP include: sensitization of nociceptors, ectopic impulse generation, central sensitization (pronociceptive facilitation at the spinal dorsal horn), disinhibition (failure or inhibition of normal inhibitory mechanisms), and central reorganization (7, 8, 9).

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Peripheral nerve injury results in the sensitization of nociceptors. This in part is due to the release of proinflammatory cytokines (interleukins, TNFα), inflammatory mediators (bradykinin, prostaglandins) and growth factors (nerve growth factor). These chemicals promote hyperalgesia and allodynia, by lowering the threshold of nociceptors thereby furthering the stimuli (8, 9). After neuronal damage, the differential expression, distribution and abnormal activity of sodium channels at the site of the lesion, leads to the production of ectopic impulses resulting in symptoms such as paraesthesias, dysaesthesias, and lancinating pain. In addition, activation of calcium channels following increased expression at the site of the lesion leads to the release of substance P and glutamate. The development of allodynia has been shown to correlate with the level of expression of the α2δ subunit of voltage-gated calcium channels (VGCCs) in the dorsal root ganglia (8, 10). Pathophysiological changes in the dorsal root ganglion due to peripheral neuronal damage result in the removal of the inhibition on the N-methyl-D-aspartate (NMDA) glutamate receptor subtype, by a magnesium ion. This disinhibition of the NMDA receptors results in the amplification and prolongation of the harmful stimuli in the spinal dorsal horn (8, 11). [Continued on page 5]

".Chronic pain is the number one cause of long-term disability with approximately 100 million American adults affected."

Acetaminophen: a household liver toxin

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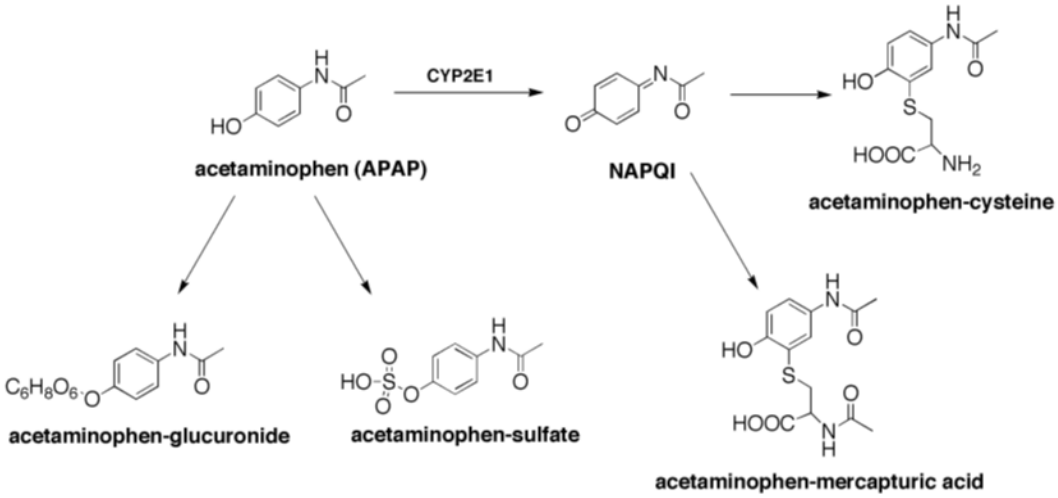
Acetaminophen (N-acetyl-p-aminophenol, APAP) (Figure 1) is a drug that has been commonly used in the United States for pain relief and fever reduction since the 1970's [1-3]. Acetaminophen is available in both prescription and over the counter (OTC) medications, either alone (ie: Tylenol) or in combination with other drugs (ie: Excedrin or Percocet). Despite the prevalence of acetaminophen in many household medicine cabinets, accidental or intentional overdose and the associated toxicity are real concerns. In 2010, acetaminophen, both alone and in combination, was in the top 25 substances associated with fatalities [4]. By 2012, acetaminophen toxicity has become the number one cause of acute liver injury in the United States [5,6]. Increasing awareness of both acetaminophen containing medications and proper dosing limits are important steps in reducing the incidents of toxicity.

Acetaminophen is commonly available as an oral tablet and has a bioavailability of 88% [7]. Protein binding of acetaminophen is relatively low, at ~10-30% , and the peak serum concentration of acetaminophen following an oral dose occurs as rapidly as 20 minutes, or as long 2 hours, in the case of extended-release tablets [2,7]. The half-life ($t_{1/2}$) of acetaminophen in therapeutic concentrations is 1-3 hours and increases at toxic doses [1,2]. Acetaminophen is a reducing agent, resulting in indirect inhibition of cyclooxygenase enzymes and a decrease in prostaglandin production [2,3,7].

Figure 1: Metabolism of acetaminophen; NAPQI, N-acetyl-p-benzoquinoneimine.



"In 2010, acetaminophen was in the top 25 substances associated with fatalities."

Acetaminophen is metabolized through a number of pathways (Figure 1). Acetaminophen metabolism occurs predominantly in the liver, and yields glucuronide (~45-60 %) and sulfate (~30 %) conjugates [1-3]. The glucuronide and sulfate metabolites are excreted in urine, along with a small amount (~2-5%) of unmodified acetaminophen [1,2,8]. Acetaminophen also undergoes oxidation by CYP2E1 to produce N-acetyl-p-benzoquinoneimine (NAPQI), a toxic metabolite [1-3,6]. Following therapeutic doses of acetaminophen, NAPQI combines with glutathione to produce cysteine or mercapturic acid conjugates [1,2]. In the event of an overdose, the sulfation pathway is saturated and glutathione supplies are depleted, resulting in an accumulation of NAPQI [2,6]. In the absence of glutathione, NAPQI forms protein adducts and also binds to sulfhydryl groups of proteins in hepatocyte mitochondria, leading to decreased mitochondrial function and eventually cell death [2,3,6,9]. The initial signs and symptoms of acute acetaminophen toxicity, which occurs following a single ingestion, can be non-specific and include nausea, vomiting and abdominal pain [2,3]. As hepatotoxicity progresses, decreased liver function is indicated by increased aspartate aminotransferase (AST) levels, followed by abnormal alanine aminotransferase (ALT), glucose, bilirubin and pH values [2,5].

Acetaminophen: a household liver toxin
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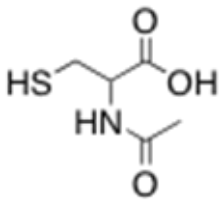
The signs and symptoms of chronic acetaminophen toxicity, which occurs following multiple ingestions over hours or weeks, can also be non-specific, but may include abdominal pain or hepatic tenderness [10]. Chronic acetaminophen toxicity leads to hepatotoxicity as indicated by laboratory tests of liver function, including elevations in AST, ALT and bilirubin [10,11].

Serum concentrations of acetaminophen can be measured by spectrophotometry, immunoassay or gas chromatography-mass spectrometry (GC-MS) [3,12-14]. The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines issued in 2003 lists acetaminophen as an assay that must be offered STAT by laboratories supporting emergency departments [15]. Spectrophotometric and immunoassay methods are quick but may be subject to interferences, particularly the interference of bilirubin in spectrophotometric assays [3, 16]. Chromatographic methods for detecting acetaminophen are considered reference methods [3] and GC-MS assays are available at reference laboratories to detect acetaminophen as part of drug screens [12,13]. Serum concentrations of acetaminophen and the time post-ingestion can be interpreted together using the Rumack-Matthew nomogram to assess the risk of hepatotoxicity [2,8]. The treatment line of the Rumack-Matthew nomogram is the plasma concentration of acetaminophen above which treatment with N-acetylcysteine (NAC) is indicated. NAC (Figure 2) was approved by the FDA in 1985 for oral use [2]. NAC acts as a glutathione precursor and is able to bind to NAPQI and reduce hepatotoxicity [2,8]. NAC therapy is most beneficial if administered within 10 hours of acute acetaminophen ingestion [2,8], underscoring the importance of rapid turnaround times for acetaminophen assays. The Rumack-Matthew nomogram may not be useful in all situations of acetaminophen toxicity. The nomogram is designed for use in cases of acute toxicity where the time since ingestion is known [8]. The Rumack-Matthew nomogram may also not be useful in instances involving extended release formulations of acetaminophen, in which the pharmacokinetics are designed to be different from traditional acetaminophen formulations [8,17]. Finally, the Rumack-Matthew nomogram is not applicable to cases of chronic toxicity, since serum acetaminophen concentrations may not be outside the therapeutic range [10,15,17]. Even in the absence of an interpretation based on the nomogram, patients suspected of chronic acetaminophen toxicity should be treated with NAC [10,17].

Despite the risk and prevalence of hepatotoxicity that accompanies acetaminophen use, the FDA considers this medication to be safe when used within the recommended daily limit, which is 4 g/day [18]. Unintentional overdose can occur if patients are unaware that medications may contain acetaminophen in combination with other drugs [5]. Over 200 drug preparations contain acetaminophen in combination with additional active components [1]. In addition, some individuals may be at increased risk for acetaminophen-induced hepatotoxicity, such as individuals with renal failure, alcoholics, or individuals who are malnourished [1,5, 18]. The first step in avoiding hepatotoxicity from acetaminophen use is to read the labels of all medications to determine if acetaminophen (sometimes listed as APAP) is present, and closely monitor the cumulative dose ingested throughout a day.

"Unintentional overdose can occur if patients are unaware that medications may contain acetaminophen in combination with other drugs."

Figure 2: N-acetylcysteine (NAC).



N-acetylcysteine

Acetaminophen: a household liver toxin
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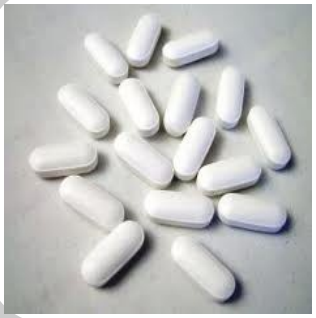

Drug treatments for neuropathic pain
(continued from page 1)

A decrease in the inhibitory synaptic transmission by gamma-amino butyric acid (GABA) and glycine bring about the disinhibition of nociceptive input at the spinal inhibitory network, and an increase in pain sensitivity (8, 12). Another effect of peripheral neuronal injury in some NP syndromes is neuronal plasticity in the central nervous system (CNS). The amount of central reorganization has been shown to positively correlate with pain intensity in NP patients. Fortunately, several studies show that with treatment, central reorganization might be reversible resulting in relieve of pain symptoms (8, 13-15).

Despite increase in understanding of the complex NP mechanisms, proportional increase in successful pain management in people with NP has been slower. The difficulty of treating NP partly accounts for the myriad of drug treatments available. Most of these clinically available drug treatments for NP are borrowed from other therapeutic areas, such as anticonvulsants, tricyclic antidepressants, α_2-adrenergic agonists, and N-methyl-D-aspartate (NMDA) antagonists. Traditional pain therapy, such as opioids is not commonly used for this purpose.

"Anticonvulsants such as gabapentin and pregabalin are drugs that were originally introduced for the treatment of epilepsy. However, their efficacy in the treatment of NP became increasingly evident and has been approved for the treatment of NP in several countries."

Opioids

NP was traditionally thought to be non-responsive to opioids. Certain studies however suggest that some NP states will respond to opioids at higher doses than needed in nociceptive pain states (16, 17). Morphine (Figure 1) and oxycodone have been shown to relieve NP; nevertheless, they did not consistently show positive effects on mood, quality of life and disability (18-20). Tramadol which is a weak opioid also has serotonin-noradrenaline reuptake inhibition properties which likely contribute to its analgesic effects in NP treatment (21). The synthetic opioid, methadone, has NMDA-antagonist properties making it potentially beneficial for NP management (22).

Anticonvulsants

Anticonvulsants such as gabapentin and pregabalin are drugs that were originally introduced for the treatment of epilepsy. However, their efficacy in the treatment of NP became increasingly evident and has been approved for the treatment of NP in several countries. Gabapentin was first used as an antieleptic in the early 1990s and was soon found to be useful in the treatment of NP (23). Pregabalin (Figure 1) on the other hand, is a newer drug that has been used in Europe since 2004 and recently became approved in the US for the adjunctive therapy of partial seizures in adults and the treatment of pain due to diabetic peripheral neuropathy and post-herpetic neuralgia in adults (24, 25). Both drugs are analogs of GABA and their effectiveness in the management of NP lies in their ability to bind with high affinity to the α2δ subunit of VGCCs and inhibit calcium influx, ultimately resulting in a reduction in NP (25, 26). Although gabapentin and pregabalin have similar modes of action, pregabalin demonstrates; higher efficacy at lower doses, better bioavailability, kidney clearance without significant metabolism, and almost no drug-drug interactions (24).

Another category of anticonvulsants has also been shown to have some efficacy in NP management, by an alternate mechanism (sodium channel blocking). These include carbamazepine, oxcarbazepine, phenytoin, and lidocaine (27). Lamotrigine is also potentially helpful in NP due to HIV, stroke, and diabetic neuropathy, but substantial evidence indicative of its widespread use is lacking (28-31).

Antidepressants

Tricyclic antidepressants (TCAs) were one of the first classes of drugs shown to be effective in NP management (32). TCAs for example amitriptyline (Figure 1) modulate pain by blocking sodium channels beyond other mechanisms of action (8). Despite their efficacy, a high prevalence of unpleasant anticholinergic side effects, such as dry mouth, constipation, and sedation, limit adherence to treatment in several patients (5).

NMDA antagonists

NMDA receptor antagonists such as ketamine (Figure 1) have been shown to have efficacy in the management of NP syndromes such as post-herpetic neuralgia and complex regional pain syndrome (CRPS) (8, 33). The mode of action of NMDA receptor antagonists is by blocking NMDA receptors. Inhibition of NMDA receptors leads to NP suppression. Ketamine was first synthesized in 1963, however, it was not until a couple of years later that the first report of its clinical use was published (17, 34). Despite its useful attributes, ketamine has psychotropic effects for which the *R*(-) isomer has been implicated (35), which has limited its use.

Drug treatments for neuropathic pain
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α_2-adrenergic agonists

Several hypotheses have been proposed as to how α_2- agonists modulate pain. Some of these include; enhancement of descending inhibitory pathways, direct inhibition of neuronal firing at receptor sites and decreasing the production of substance P. Although initially intended for use as a nasal decongestant, clonidine (Figure 1) is the most commonly used α_2-agonist (17). A recent randomized trial has shown topical clonidine to be effective in the management of foot pain in diabetic neuropathy (36).

Therapeutic drug monitoring (TDM) in NP varies with the class of drug used, the patient's clinical status, risk for toxicity and the need to check compliance. For the most part, monitoring of serum/plasma trough concentrations is the most beneficial. Similar principles are employed in the methods used for the TDM of these different drug classes. Opioid TDM can be measured by immunoassay, TOF-MS, GC-MS or LC-MS/MS. Anticonvulsants such as gabapentin can be measured by capillary electrophoresis, HPLC-MS, or GC-MS. Likewise, antidepressants can be measured by immunoassay, GC-MS or LC-MS/MS. TDM of the other drug classes (NMDA antagonists and α2-adrenergic agonists) is not routinely done.

In summary, NP is a complicated symptomatic disease with complex mechanisms. Although NP management has been challenging, diverse drug classes are currently available for its treatment. Though not originally intended for pain therapy, these drugs demonstrate efficacy in the treatment of NP.

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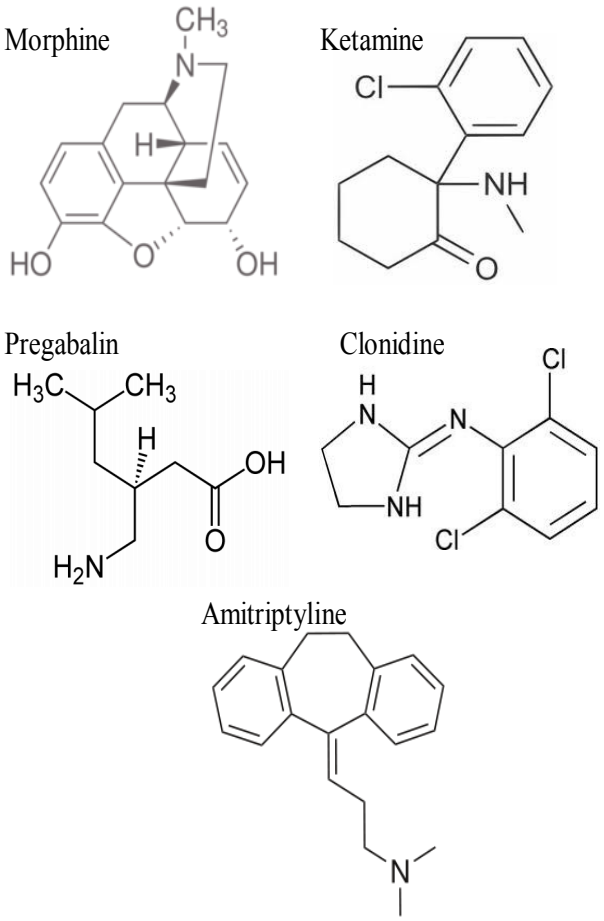

Figure 1: Drugs from different classes for the treatment of neuropathic pain

Drug treatments for neuropathic pain
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Table 1: Pharmacokinetics of selected drugs for the treatment of neuropathic pain (37-42)

	Morphine	Pregabalin	Amitryptiline	Ketamine	Clonidine
Absorption	Readily absorbed	Rapid	Completely but slowly absorbed	Only 17% of oral dose absorbed	Absorption $T_{1/2}$= 0.6 0.2 h
Oral Bioavailability	40 %	≥ 90	≥89 %	Low	75%
Peak plasma concentrations	15-20 min of intramuscular and subcutaneous administration 30-90 min after oral	0.7-1.5 h	2 – 4 h	12 – 30 min (After intravenous administration)	2 h after dose
Half-life ($T_{1/2}$-plasma)	1.3 - 6.7 h	4.6-6.8 h	8 - 51 h	3 – 4 h	5 – 20 h
Volume of distribution (Vd)	2 – 5 L/kg	0.5-0.6 L/kg	6 – 10 L/kg	3 - 5 L/kg	3.2 – 5.6 L/kg
Plasma protein binding	35%	Minimal	94%	30%	20-40%
Elimination	87% excreted in urine, mainly as glucoronidated derivatives	98% excreted in urine	80% excreted in urine mainly as inactive metabolites	100% excreted in urine mainly as hydroxylated derivatives	65% excreted in urine and 22% excreted in feces

"NP is pain caused by lesions of the peripheral or central nervous system. It typically manifests with positive (e.g. pain, dysesthesia, hyperalgesia, allodynia) and negative (e.g. sensory loss: tactile hypoesthesia or anesthesia, thermal hypoesthesia, pinprick hypoalgesia, loss of vibrational sensation) sensory phenomena."

Table 2. Clinical features, pathophysiology, and drug treatments for selected neuropathic pain syndromes (27)

Neuropathic pain syndrome	Pain-related clinical feature	Cause	Pathophysiology	Some common drugs for pain management
Painful diabetic neuropathy	Burning pain in lower legs	Hyperglycemia	Prolonged exposure to high levels of glucose → nerve damage (demyelination and axonal loss)	Pregabalin Gabapentin Clonidine
Postherpetic neuralgia	Unilateral dermatomal pain and allodynia	Varicella zoster virus infection	Nerve damage → changes in the expression of voltage-gated sodium and potassium channels, and upregulation of pain-associated receptors	Topical lidocaine Pregabalin
Trigeminal neuralgia	Sudden stabbing or electric-shock-like facial pain	Neurovascular contact or neurovascular conflict	Compression of the trigeminal nerve as it exits the brainstem by a swollen blood vessel or tumor	Carbamazepine Baclofen
HIV-related neuropathy	HIV-infection	Symmetrical painful paraesthesias	Not well understood → could be HIV-mediated nerve damage	In some patients: Desipramine Nortriptyline Lamotrigine Topical lidocaine Capsaicin patch
Complex regional pain syndrome (CRPS); Type 1 and 2	Regional pain	Type1 – Tissue injury other than nerve Type 2 – nerve injury	Nerve injury → increase noradrenergic sensitivity	Antidepressants Topical lidocaine Anticonvulsants

Drug treatments for neuropathic pain
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"Common causes of NP include trauma resulting in nerve injury and deafferentation, inflammation, metabolic diseases (e.g. diabetic neuropathy), infections (e.g. herpes zoster with resulting postherpetic neuralgia), toxins (e.g. chemotherapy), tumors and primary neurological diseases."

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"Worldwide, more than 1.5 billion people suffer from chronic pain and approximately 3-4.5% of the global population suffers from neuropathic pain."

FROM THE HOT SEAT:

Greetings TDM/Toxicology Division Members!!!

Thank-you for taking the time to read our newsletter. There are many exciting professional development and networking opportunities, in the fields of therapeutic drug management and clinical toxicology, to put on your calendars. I want to highlight two:

The Division has provided "Patron" sponsorship for the upcoming International Congress of Therapeutic Drug Monitoring and Clinical Toxicology that will be held in Salt Lake City, UT September 22-26, 2013: http://iatdmct.com/ There will be a fantastic all-day event focused on antiepileptic drugs, and several plenary lectures, symposia, workshops, roundtables, and opportunities for research presentations. The scientific program will be well-balanced between TDM, toxicology, and pharmacogenetics. Registration for the meeting should be available in mid-to-late January, 2013, and the abstract deadline is February 28, 2013. Everyone is strongly encouraged to submit! There will also be several events (and discounts) specifically planned for Young Scientists (under 41 yrs old). Please make plans to attend this unique international congress!!!

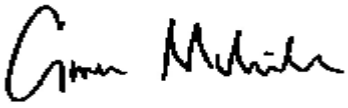
The Division will be hosting a lunch meeting, open to all members, at the 2013 annual meeting in Houston. Please join us for lunch from noon-2pm on Monday July 29th at a to-be-determined location, hosted by Dr. Don Wiebe, the incoming Chair for 2013-14. Look for more details in the coming months. Don can be contacted by email at: da.wiebe@hosp.wisc.edu

Related to this meeting,
** **We need nominations for the 2013 Young Investigator Award!** **
Please nominate your young colleagues on or before April 1, 2011. Nominations should be sent to the attention of Dr. Jim Ritchie, our incoming Chair-Elect, at jritchi@emory.edu and information about the award is on our Division website: http://www.aacc.org/members/divisions/tdm/pages/default.aspx#

"TDM/Tox Division lunch meeting will be held on July 29th from 12-2pm."

I am very much looking forward to seeing and visiting with you at these, and other upcoming meetings! And, I appreciate having had opportunity to serve as Chair for the Division these past two years. Please feel free to contact me with any questions, concerns, or requests related to the TDM/Toxicology Division, or the upcoming IATDMCT meeting, at gwen.mcmillin@aruplab.com

Sincerely,



"Abstract submission Deadline: February 28, 2013"

UPCOMING MEETINGS OF INTEREST

MASS SPECTROMETRY: APPLICATIONS TO THE CLINICAL LAB (MSACL)
Annual Meeting
February 9—13, 2013, Sheraton Hotel & Marina, San Diego, CA.
www.msacl.org

SOCIETY OF TOXICOLOGY (SOT)
Annual Meeting
March 10—14, 2013, Henry B. Gonzalez Convention Center, San Antonio, TX.
www.toxicology.com

MIDWEST ASSOCIATION FOR TOXICOLOGY AND THERAPEUTIC DRUG MONITORING (MATT) Annual Meeting
April 25—26, 2013, Cleveland Clinic, Cleveland, OH
www.midwesttox.org

ASSOCIATION OF CLINICAL SCIENTISTS (ACS)
Annual Meeting
May 22—25, 2013, Omni Parker House Hotel, Boston MA.
www.clinicalscience.org

"The Congress for the International Association of Therapeutic Drug Monitoring and Clinical Toxicology will be held in Salt Lake City, Utah from Sept. 22-26, 2013."

AMERICAN ASSOCIATION FOR CLINICAL CHEMISTRY (AACC)
Annual Meeting
July 28—August 1, 2013, Houston TX.
www.aacc.org

THE INTERNATIONAL ASSOCIATION OF FORENSIC TOXICOLOGISTS (TIAFT)
Annual Meeting
September 2—6, 2013, Madeira, Portugal
www.tiaft.org

THE AMERICAN ACADEMY OF CLINICAL TOXICOLOGY
North American Congress of Clinical Toxicology (NACCT)
September 27—October 2, 2013, Hyatt Regency Atlanta, GA.
www.clintox.org

SOCIETY OF FORENSIC TOXICOLOGISTS (SOFT)
Annual Meeting
October 28—November 1, 2013, Orlando, FL.
www.soft-tox.org

Please contact Dr. Kamisha Johnson-Davis at kamisha.johnson-davis@aruplab.com if you are interested in joining the editorial board or if you have ideas or article contributions for this newsletter.

American Association for Clinical Chemistry
Improving healthcare through laboratory medicine

DRUGS IN THE NEWS

FDA requires lower recommended doses for certain sleep-aid drugs containing zolpidem (Ambien, Zolpimist, Edluar).

The FDA issued a draft guidance document to assist industry in developing new formulations of opioid drugs with abuse-deterrent properties.

FDA Drug Safety Communication: Pradaxa (dabigatran etexilate mesylate) should not be used in patients with mechanical prosthetic heart valves.

Recent FDA Approved Drugs

Eliquis (apixaban)
Treatment: **Venous thromboembolism in patients with non-valvular atrial fibrillation**
Fulyzaq (crofelemer)
Treatment: **Antidiarrheal drug for HIV/AIDS patients**
Sirturo (bedaquiline)
Treatment: **Multi-drug resistant tuberculosis**
Juxtapid (lomitapide)
Treatment: **Homozygous familial hypercholesterolemia (HoFH) - Rare cholesterol disorder**
Iclusig (ponatinib)
Treatment: **Chronic myeloid leukemia and acute lymphoblastic leukemia**