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Pharmacogenetics of Addiction

How Good is the Evidence?

By Erin Kaleta, PhD

Addictions are psychiatric disorders that involve the persistent, compulsive need to use a substance despite adverse consequences. The definition of substance abuse in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) includes the following psychiatric criteria:

- Spending a large amount of time obtaining, using, or recovering from the substance;
- Using larger amounts of the substance for longer periods of time than expected;
- Continuing substance use despite suffering social or occupational consequences;
- Wishing persistently to discontinue use; and
- Building tolerance to the substance and symptoms of withdrawal.

With substance-use disorders now affecting 9.35% of the U.S. population, addiction is considered a public health crisis. As high as it is, the estimated prevalence of substance-use disorders is likely a gross underestimate based on the well-known lack of systematic reporting. Furthermore, with so many affected people, the cost to the U.S. healthcare system is huge (1).

Identifying the causes of addiction has been difficult due to contributions from both environmental and genetic factors. However, extensive research has uncovered specific genes that contribute to addiction. We now know that addictions are frequently inherited. These findings are useful for tailoring specific pharmacotherapies that alter the effects of addictive substances, as well as creating new treatment options for substance abuse. So far, however, reports of responses to these therapies has been mixed, which may imply that other genetic factors affect the metabolism of such drugs and therefore the efficacy of treatment.

Pharmacogenetic Targets of Addictions

Pharmacogenetics uses analysis of a particular genetic profile to predict a patient response to a specific medication. The focus of such testing is primarily mutations in genes responsible for drug-metabolizing enzymes, transporters, or pharmacological receptors. Identifying patients who have genotypes that predict a favorable response to medication is particularly relevant in addiction disorders, because the trial-and-error process of treatment can put patients at risk of a relapse.

To date, many studies have addressed potential pharmacogenetic targets for treating addiction, including naltrexone for alcohol dependence and bupropion for nicotine dependence. Table 1 presents an overview of outcome from these pharmacogenetic-based studies.

The mesolimbic pathway represents one biological target that is conserved across multiple substance abuse disorders (Figure 1). Activation increases the release of dopamine into the nucleus accumbens of the brain, stimulating the reward sensation. Blockage of dopamine reuptake, which occurs with cocaine and amphetamines, also affects this pathway by activating the dopaminergic neurons affected by alcohol and opioids. These attributes make this pathway an attractive target for pharmacogenetics because they suggest a heritable effect that may be independent of the particular addictive substance.

Researchers also have conducted extensive studies of the mu-opioid receptor (MOR) in this mesolimbic pathway. To date, more than 200 polymorphisms have been characterized. The most common variant is a single nucleotide polymorphism

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Addiction Pharmacogenetics

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(SNP) at position 118 where an A>G mutation in exon 1 of the *OPRM1* gene occurs. This base change causes a missense mutation, substituting an asparagine residue for aspartic acid in the protein sequence.

Researchers have speculated that this mutation may cause: 1) the loss of an N-glycosylation site in the extracellular domain that is responsible for receptor activation; 2) a three-fold increase in the binding affinity of β-endorphin; and/or 3) a decrease in expression of the receptor mRNA and protein with respect to the wild type allele. It occurs within the general population at frequency of 0.1–0.4 and shows variation in different ethnic groups. Several studies have attempted to correlate the mutation with alcohol dependence, but the findings have been inconsistent and conflicting. A meta-analysis of 28 studies found no significant correlation between this variant and alcohol dependence, suggesting that the mutation may be a risk factor for progressing to alcohol dependence, but that it is not the sole factor contributing to the addiction (3).

Pharmacogenetic Studies of Alcohol Addiction

The drug Naltrexone is an MOR antagonist that blocks the euphoria stimulated by dopamine release in response to β-endorphin, the same pathway associated with alcohol consumption. Individuals' responses to naltrexone treatment vary widely. In fact, not all individuals with alcohol dependence respond to naltrexone, suggesting a potential pharmacogenetic factor. There also is strong evidence that alcohol dependence is hereditary, which supports involvement of pharmacogenetic factors. The focus has been on the MOR SNP 118 A>G mutation that occurs at the highest frequency, although researchers also have investigated other mutations and found little evidence to suggest a role in naltrexone response variability.

Three large scale clinical trials on the pharmacogenetics of naltrexone have been published. One trial conducted at the University of Pennsylvania involved randomization of individuals to naltrexone (n = 71) or placebo (n = 59) across three groups: one varying the length of naltrexone treatment; a second varying the psychosocial interventions; and a third that randomized treatment with naltrexone, nefazodone, and placebo (4). The findings showed that carriers of the MOR SNP 118 A>G allele had a lower relapse rate with an odds ratio for no relapse of 3.52 (p = 0.044) and a longer time for returning to heavy drinking with an odds ratio of 2.79 (p = 0.040) versus the MOR SNP 118 A/A genotype. No such effect was seen with placebo. These findings were supported in a second clinical trial, the Combined

Table 1. Pharmacogenetic Outcome Studies

Drug	Gene	Odds Ratio	Outcome Measured	References
Naltrexone	OPRM1 118 A>G	3.52 5.75 NS	Relapse rate at 12 weeks Alcohol reduction at 16 weeks Relapse rate at 12 weeks	Oslin 2003 Anton 2008 Gelernter 2007
Bupropion	DRD2 Taq1 A2/A2	3.25 1.7	Abstinence at 6 months Abstinence at 12 months	David 2007
Varenicline	CHRNA4 CHRNB2	2.52 NS 1.89 NS	Abstinence at 12 weeks Abstinence at 12 months Abstinence at 12 weeks Abstinence at 12 months	King 2012

* NS = Not significant finding

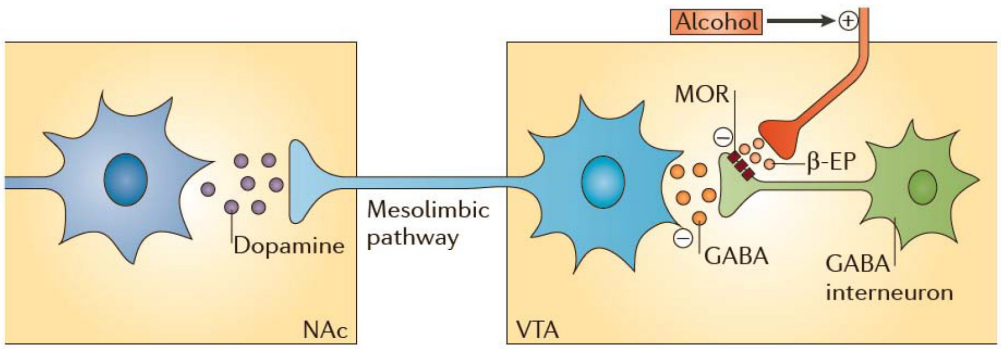

Figure 1. Schematic of the mesolimbic pathway on the nucleus accumbens (NAc) and ventral tegmental area (VTA) neurons and involvement of β-endorphin (β-EP) on the mu-opioid receptors (MOR).
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Pharmacotherapies and Behavioral Interventions (COMBINE) study (5). In this large, multi-site study, 604 patients received either 100 mg/day of naltrexone (n=301) or placebo (n=303). All participants received basic medical management, and 50% received additional combined behavioral interventions. The researchers found statistically significant effects for naltrexone in the group of patients who received only basic medical management. In addition, they found that participants on naltrexone who were carriers of the MOR SNP 118A allele had more abstinent days ($p = 0.07$) and fewer heavy drinking days ($p = 0.04$). The findings were further supported by other measures of good clinical outcome, such as abstinence, a decrease in drinks/week, and fewer than three alcohol-related problems in the last 8 weeks of treatment, with an odds ratio of 5.75 for MOR SNP 118A carriers taking naltrexone ($p = 0.005$). The researchers suggested that the reason for lack of correlation of the genotype with naltrexone treatment versus placebo in the group also receiving combined interventional therapy stems from the general increase in benefit that patients experience as a result of such intensive behavioral therapy, which is designed specifically for treating substance abuse. Overall, the findings of the two trials are in agreement with the literature and suggest that the MOR SNP 118 A>G mutation causes a functional difference in the MOR.

The Veterans Affairs (VA) Cooperative Study, however, failed to support these results (6). In this clinical trial, researchers divided 213 patients into two groups: one group received 50 mg/day naltrexone for 12 months or 50 mg/day naltrexone for 3 months followed by 9 months of placebo ($n = 149$); and a third received placebo ($n = 64$). The overall effect of naltrexone on the entire study population showed benefit regardless of genotype, with an odds ratio of relapse in the placebo group of 2.10 versus those treated with naltrexone and an increase in the time to relapse with a hazard ratio of 0.59 for treated versus placebo. Analysis of a subset of the study groups by genotype, however, showed no significant difference between patients homozygous for MOR SNP 118A versus carriers of the 118G allele, which is in direct conflict with earlier studies.

There are many possible explanations for why this study's results did not agree with the other two studies, including smaller size of the study group ($n = 604$ versus $n = 213$ in the VA study), which limits the statistical power especially in a study that is designed to monitor only a moderate change in response to treatment with low odds ratios, and a potentially higher severity of alcohol dependence in the VA population. Another possibility is that patients who are on naltrexone therapy longer build tolerance to the medication, decreasing its overall effect in the Veterans Affairs study compared to the shorter treatment periods in the COMBINE and University of Pennsylvania studies.

Overall, while the literature regarding pharmacogenetics of naltrexone therapy is not totally consistent, there is evidence suggesting a positive benefit for treating patients with specific genotypes. Therefore, in the future, healthcare providers may want to use such tests to identify patients most likely to benefit from the therapy.

Pharmacogenetic Studies of Nicotine Addiction

Twenty-three percent of the U.S. population smoke cigarettes. Because smokers account for at least 30% of all cancer-related deaths, nicotine addiction is a major public health concern (7). Similar to opioids, nicotine exerts its effects primarily on receptors in the brain that stimulate the dopaminergic pathway by binding neuronal nicotinic acetylcholine receptors (nAChRs). Studies show that despite many attempts, only 15% of smokers are successful in quitting. Several pharmacological agents have shown benefit for smoking cessation, most notably the nicotine replacement therapies, bupropion and varenicline. Individuals can have vastly different responses to these drugs, suggesting pharmacogenetic factors play a role.

Bupropion, marketed as Zyban, is the most widely studied pharmacotherapy for smoking cessation. This medication inhibits the re-uptake of dopamine and norepinephrine by binding the dopamine transporter, and it also acts as an antagonist to the nAChR. Three genetic variants have been studied for bupropion pharmacogenetics of nicotine dependence: the cytochrome P450 enzyme 2B6 (*CYP2B6*), the variable number of tandem repeats (VNTR) in the dopamine transporter gene *SLC6A3*, and the dopamine receptor D2 (*DRD2*).

Researchers suspected involvement of the *CYP2B6* gene because it is involved both in nicotine metabolism and bupropion pharmacokinetics. Studies have demonstrated, however, that the effect of variants in this gene are independent of bupropion and are caused by slower rates of nicotine metabolism in *CYP2B6* variants. Similarly, *SLC6A3* studies failed to demonstrate a correlation between abstinence and bupropion treatment.

Some studies have associated the *DRD2* Taq1A A2 allele of the tyrosine kinase gene *ANKK1* with greater benefit from bupropion treatment. The A2 allele involves a C>T polymorphism in the intronic region 3' to the *DRD2* gene that results in lower nAChR density on cells. Researchers have found that individuals homozygous for this polymorphism

(A2/A2) have a 3-fold greater response than heterozygous carriers as measured by abstinence at 6 months after initiating treatment (8). This finding was supported by results from a meta-analysis of two key clinical trials that correlated pharmacogenetics of bupropion with the *DRD2* Taq1A A2 allele. The study demonstrated a correlation between the A2/A2 genotype and smoking cessation with bupropion therapy, with an odds ratio of quitting with this genotype of 3.25 at 6 months, and 1.7 at 12 months.

More recently, a new pharmacotherapy for smoking cessation has gained interest. Varenicline, marketed as Chantix, acts as a partial agonist for the nAChR. It binds more weakly than nicotine to the receptor, thereby reducing the reward sensation associated with nicotine intake while also reducing cravings, similar to nicotine replacement therapy. Targets of pharmacogenetics for varenicline involve the nicotinic receptor subunit genes *CHRNA4* and *CHRNB2*, with an odds ratio of smoking abstinence at 12 weeks of 2.52 and 1.89, respectively (9). Neither of these targets, however, was associated with continued abstinence when treatment was discontinued.

Since varenicline was approved as a treatment only recently, few studies have been published on its pharmacogenetics. Additional gene targets may well be identified in the future.

Challenges to Overcome

Overall, pharmacogenetic studies of addiction have been moderately successful in identifying genotypes that confer a favorable response to treatment medications, most notably naltrexone and bupropion. It is important to note, however, that substance abuse is not strictly heritable; it also has a large environmental component that may greatly impact patient outcomes. In most cases, it is impossible to completely remove a patient from all external driving forces of addiction.

Furthermore, the published studies in this area often disagree about the effectiveness of these medications, and the increase in response with certain genotypes is often only a moderate improvement with low odds ratios. Moreover, it is difficult to accurately measure the benefit of treatment for substance dependence. Measures are largely subjective and depend on abstinence rates from self-reporting. Although not always effective at maintaining abstinence, these drugs may act by decreasing symptoms of withdrawal in patients, an outcome that would not be captured by monitoring relapse rates.

The genetics of addiction are likely very complex, involving the interaction of many genes as well as the environment. Future studies that look for gene-gene interactions in association with pharmacotherapy may shed more light on the pharmacogenetics of addiction. In the meantime, physicians should choose treatment options that best meet individual patients' needs and incorporate both behavioral therapy and pharmacotherapy.

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Erin J. Kaleta, PhD, is a clinical chemistry fellow in the Department of Laboratory Medicine and Pathology at the Mayo Clinic in Rochester, Minn. Email: erin.kaleta@mayo.edu

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Carisoprodol

Now a Schedule IV Controlled Substance

By Nicole V. Tolan, PhD and Loralie J. Langman, PhD, DABCC, DABFT

The Drug Enforcement Administration (DEA) issued a final ruling late last year making carisoprodol a Schedule IV controlled substance under the Controlled Substances Act (CSA). Until this ruling went into effect on January 12, 2012, the drug had been classified as a controlled substance in 18 states and monitored in a number of state prescription programs. While meprobamate, a major metabolite of carisoprodol, has been classified as a schedule IV controlled substance for more than 40 years, these two substances did not share the same federal distinction until just this year. It wasn't until 2009 that DEA issued a Notice of Proposed Rulemaking in the Federal Register which resulted in the new scheduling.

Branded as Soma, Soprodal, and Vanadom, carisoprodol is a carbamate derivative that was first synthesized in 1959 and marketed as a centrally acting skeletal muscle relaxant. The Food and Drug Administration (FDA) subsequently approved the drug for relief of discomfort associated with acute, painful musculoskeletal conditions in adults most commonly due to low-back and neck injury, intervertebral disk disorders, and lumbago (1). Meprobamate, marketed as Miltown and Equanil, has well-documented risks for addiction and abuse and produces sedative, hypnotic, anxiolytic, muscle relaxant, and anticonvulsant effects.

DEA's motivation for adding carisoprodol to Schedule IV of the CSA is evident throughout the literature. Investigators have demonstrated its involvement in a number of emergency room visits, cases of driving while under the influence, poison control center reports, drug-facilitated sexual assaults (DFSA), and autopsy findings (1–5).

Carisoprodol Metabolism

In the liver, the polymorphic cytochrome P450 enzyme 2C19 (CYP2C19) metabolizes carisoprodol to meprobamate. Hydroxycarisoprodol is also thought to be a major biotransformation product of the drug, producing hydroxymeprobamate upon metabolism. Glucoronidation of each of the compounds can occur prior to excretion in the urine (6). Theoretically, as a substrate of CYP2C19, carisoprodol could alter the metabolism of other substrates of this enzyme, such as warfarin. However, researchers have yet to elucidate the full impact of co-administration of carisoprodol with other CYP2C19 substrates, inhibitors, or inducers.

Common Carisoprodol Intoxication Side Effects

Symptoms of carisoprodol intoxication include decreased consciousness, lethargy, dizziness, ataxia, confusion, horizontal gaze nystagmus, hand tremor, involuntary movements, seizures, agitation, and hypotension. Patients with clinical presentations uncharacteristic of central nervous system depressants are likely to have consumed carisoprodol along with other substances. Conversely, at supratherapeutic carisoprodol concentrations, patients also present with symptoms of hypertension, tachycardia, involuntary choreiform movements, shivering, and tremor (7). These adverse drug reactions are not similar to γ-aminobutyric acid-like effects; therefore, researchers have postulated that they result from serotonin syndrome. Withdrawal symptoms include muscular pain, headaches, anxiety, insomnia, irritability, and seizures, which likely add to the complexity of the other symptoms described above (2).

Increased Risk of Misuse and Addiction

FDA recommends against chronic use of carisoprodol, as continued administration for more than 2–3 weeks increases the risk for misuse, dependence, and withdrawal. Physicians should suspect misuse when chronic users request the drug by name, refuse alternatives, or repeatedly miss diagnostic evaluation appointments, but make the necessary appointments for prescription refills.

Combined use of carisoprodol with other drugs, such as narcotic pain relievers, benzodiazepines, and alcohol, can dangerously enhance the CNS depressant effects, which have been reported to be similar to those of heroin (5). Patients who use carisoprodol in combination with other pharmaceuticals are at a higher risk for abuse or dependence. Such is the case for many older adults who commonly take numerous prescriptions daily and is suggested by the nearly 4-fold increase of carisoprodol-related emergency room visits of patients ≥50 years of age.

Carisoprodol Testing

A number of methods exist for the measurement of carisoprodol within serum and urine, including colorimetric, gas chromatography, and liquid chromatography mass spectrometry. Non-specific colorimetric methods are unable to distinguish carisoprodol from its metabolites (6). To limit availability of carisoprodol without prescription, physicians monitor patient compliance, preferably by testing a urine specimen. The Society of Forensic Toxicologists recommends 50 ng/mL as the minimum detection limit

for carisoprodol and meprobamate (8) in the context of common DFSA drugs and metabolites. Laboratories frequently detect carisoprodol in the presence of other drugs in patients, including benzodiazepines, opiates, and cannabinoids (3). Detecting carisoprodol with these drugs, however, is subject to the ability to detect carisoprodol on an initial drug screen. When laboratories perform more sensitive reflex testing, they may fail to capture a number of individuals taking carisoprodol alone and falsely inflate the perceived combinatorial use of carisoprodol.

Conclusion

Numerous pharmacologic and non-pharmacologic alternatives for managing musculoskeletal pain are available that lack the mind-altering effects of carisoprodol. Before prescribing the drug, physicians should exercise caution and identify patients with a history of addictive behaviors to avoid prescribing carisoprodol for patients with a higher risk of abuse.

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Nicole V. Tolan, PhD, is a clinical chemistry fellow at Mayo Clinic in the Department of Laboratory Medicine and Pathology, Rochester, Minn. Email: tolan.nicole@mayo.edu.

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Loralie J. Langman, PhD, DABCC, DABFT, is the director of the Toxicology and Drug Monitoring Laboratory at Mayo Clinic in the Department of Laboratory Medicine and Pathology, Rochester, Minn. Email: langman.loralie@mayo.edu.

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The Scientific Working Group in Toxicology
The Who, What, and Why

By Robert Middleberg, PhD, DABFT, DABCC

Scientific Working Groups (SWG) originated in the early 1990s as a means to improve the practices of various disciplines and to build consensus with federal, state, and local forensic community partners. Originally sponsored by the Federal Bureau of Investigation (FBI), today other agencies such as the National Institute of Justice (NIJ) within the Department of Justice (DOJ) also support SWGs. In fact, at least 20 such groups exist today representing varied forensic science disciplines ranging from DNA (Scientific Working Group for DNA Analysis Methods; SWGDAM) to firearms and tool marks (Scientific Working for Firearms and Toolmarks; SWGGUN).

Until recently, forensic toxicology in the U.S. operated independently of a formal SWG. Instead the field relied upon self-regulation by guidance from groups like the Society of Forensic Toxicologists (SOFT), the American Academy of Forensic Sciences (AAFS), the American Board of Forensic Toxicology (ABFT), and the Forensic Toxicologist Certification Board (FTCB). However, complying with guidance from these organizations has been completely voluntary.

SWGTOX's Inception

SWGTOX was created after the National Academy of Science (NAS) published a report on the state of forensic sciences in the U.S. The report prompted Presidential and Congressional actions to correct some of the problems NAS identified. Consequently, in 2009, the Forensic Toxicology Council (FTC) commissioned the SWGTOX, which received initial funding from SOFT and ABFT.

When the group was commissioned, three co-chairs were appointed to oversee one of three requisite committees: Standards, Practice, Protocols and Accreditation; Education, Ethics, Outreach and Certi-

The Forensic Toxicology Council created the Scientific Working Group for Toxicology in April 2009.

The mission of SWGTOX is to:

1. Develop and disseminate consensus standards for the practice of forensic toxicology in the U.S., including:
   - quality assessment and quality control
   - requisite practices
   - education and training requirements
   - accreditation and certification
2. Develop a code of professional conduct for forensic toxicologists and laboratories.
3. Identify general and specific areas of research and development related to forensic toxicology.
4. Promote public awareness of forensic toxicology.

For the purposes of SWGTOX, forensic toxicology includes:

1. Post-mortem toxicology
2. Human performance toxicology, encompassing:
   - operating a conveyance
   - drug-facilitated crimes
   - other human performance toxicology
3. Non-regulated employment drug testing
4. Court-ordered toxicology, such as probation, parole and child services
5. General forensic toxicology performed for legal purposes, such as non-lethal poisoning investigation

fication; and Research, Development, Testing and Evaluation. In the initial meetings, the co-chairs created an organizational and governance structure and proposed by-laws for the group. The leaders also drafted a mission statement, which later was modified during early SWGTOX meetings (See box above). The group expects to produce standards of practice in all forensic toxicology disciplines; however, its scope of activities does not include those specialized areas in which mandated, codified rules and regulations currently exist.

Governance and Structure

SWGTOX held its first meeting in December, 2010. At that meeting, members approved the by-laws and created an executive committee comprised of the three appointed co-chairs and two at-large members. Since then, SWGTOX has met three times with the support of the NIJ and FBI. Recently, the group voted in favor of a single chair, consistent with proposed universal SWG by-laws, and also appointed an executive secretary. No one receives any form of payment for participation in SWGTOX work.

The executive committee appoints SWGTOX members to the various committees. Members have voting privileges and are selected from a diverse group of individuals with government, private, and academic backgrounds who have the appropriate expertise. Members change as demand requires, so the length of service is at the discretion of the executive committee. Consultants and invited guests do not have voting privileges and represent the non-North American international community, as well as those with particular specialized skills and knowledge. Currently, SWGTOX has approximately 40 members and 16 consultants, and is lim-

Table. Progress of SWGTOX Committees and Groups

Committee/ Subcommittee/ Task Group	Expected Work Product	Status as of July 2012
Guide and Code of Professional Conduct	Standard	Published Dec. 6, 2011
Research, Development, Testing and Evaluation	Review	Public comment period closed May 23, 2012; in review
Method Validation	Standard	Out for public comment until August 16, 2012
Quality Management	Standard	In process; likely to be submitted for public comment following the next several standards
Certification and Education	Standard	In process; almost ready for public comment
Accreditation	Standard	In process; almost ready for public commment
Quality Control	Standard	New; ongoing
Analytical Procedures	Standard	New; ongoing
Training and Competency	Standard	New; ongoing
Uncertainty and Traceability	Standard	New; ongoing
Proficiency Testing	Standard	New; ongoing
Breath Testing	Standard	New; ongoing
Definitions	Document	New; ongoing
Mass Spectrometric Standards	Standard	Subcommittee forming

ited to no more than 50 members at any given time.

To tackle SWGTOX's mission, the leadership creates various subcommittees and task groups. These groups have worked extremely hard, both at meetings and on their own time. Thanks to their diligence, SWGTOX has accomplished a remarkable amount of significant work in only 1 1/2 years (See table page 7).

Standards adoption requires a rigorous review and voting process, including a 60-day public comment period. When documents are ready for public comment, the group notifies relevant organizations so that they can inform their membership. Once the comments have been vetted and the document has been amended as needed, a final vote of SWGTOX members takes place. Documents for review and comment, as well as adopted standards and other relevant materials, can be found on the SWGTOX website, www.SWGTOX.org.

Toward Better Practice

SWGTOX members want to provide a way for forensic toxicology practitioners and other interested parties to play an active role in setting consensus standards for the field. At the same time, the group aspires for flexibility to avoid being restrictive or dictatorial.

A group of extraordinarily dedicated individuals have sacrificed their personal time to participate in the work of SWGTOX. You can also participate by reading proposed standards and commenting on them; volunteering in your particular area of expertise; and providing general feedback on the processes.

Together we can facilitate change and bring much needed uniformity to the practice of forensic toxicology in the U.S. On behalf of SWGTOX, I invite you to participate. After all, as Dr. Seuss said in the Lorax, "Unless someone like you cares a whole, awful lot, things aren't going to get better, they're NOT!"

Robert Middleberg, PhD, DABFT, DABCC, is vice president, quality assurance and laboratory director and forensic toxicologist at NMS Labs, Willow Grove, Pa. He also is chair of SWGTOX. Email: robert.middleberg@nmslabs.com

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