A Tale of Two Drug Testing Technologies: GC-MS and LC-MS/MS

Letters to the Editor

Although the scientific community is becoming increasingly aware that LC-MS/MS is an excellent technology and is equal if not superior to GC-MS in analytical capability, there is virtually nothing in the literature at the time of this writing that directly compares GC-MS with LC-MS/MS in urine drug testing specifically for a pain patient population.

Workplace drug testing has been in practice since the 1970s when the Department of Transportation instituted the requirement that all vehicle operators in jobs regulated by that agency should periodically be checked for the presence of amphetamines and illicit drugs. The confirmatory analytical instrument used in laboratories for that purpose was, and in many cases still is, Gas Chromatography-Mass Spectroscopy (GC-MS), which has been the gold standard for 30 years (1). These instruments have been optimized to measure the NIDA Five (methamphetamine, cocaine metabolite, marijuana, phencyclidine, and morphine). However, limitations of this technology are well known (2).

Cutoffs established in the seventies by SAMHSA were optimized to minimize false positives due to “other substances.” In recent years, urine drug testing has undergone a shift from workplace testing and forensic cases to include another population, pain patients. Physicians treating people with chronic opioid therapy have a need and responsibility to establish medication compliance and to identify illicit drug users as well as “doctor shoppers” and diverters among that population (3). Ease of analysis, ability to measure a large number of pain drugs, as well as the necessity of accommodating patients who may have difficulty producing enough sample volume for multiple analyses by GC-MS have highlighted the benefits of LC-MS/MS (4).

Millennium Laboratories sent out 1,000 urine samples to a leading NIDA-certified diagnostic laboratory over an 8 month period for confirmation testing by GC-MS. Typically, the testing by GC-MS involved confirmation of opioids, benzodiazepines, TCAs, fentanyl, tramadol, and cannabinoids.

From the 1,000 samples sent the following were observed: 67 samples (6.7%) were returned with no tests completed due to “quantity not sufficient” (QNS). An additional 211 samples (21%) were returned with one or more tests not completed due to QNS. A further 110 samples (11%) were returned with one or more individual tests not completed because the lab was “unable to confirm due to an interfering substance.” An additional 17 samples (2%) were returned with one or more tests not completed due to an undefined “invalid result.”

Out of a random selection of 68,000 samples submitted to Millennium Laboratories for confirmation by LC MS/MS over the same period, only 287 (<0.5%) were rejected for QNS, and only 10 individual tests were “unable to confirm for interfering substance.”

Insufficient sample volume for test completion by GC-MS is clearly a significant issue with respect to this study. Testing laboratories using GC-MS typically require a minimum of 10mL of urine to complete a pain management-type panel (2mL per analyte), although it is not uncommon for one or more tests to come back as incomplete due to QNS unless greater volume is provided. Using LC-MS/MS Millennium Laboratories is able to conduct a full panel of tests with as little as 1mL (roughly 20 drops), a volume all but the most infirm person could arguably supply.

Polypharmacy is common among the pain patient population, many of whom are elderly (5). In view of the known problem of drug interferences in GC-MS analyses, it was not surprising that a significant number of the submitted urines were be reported as unable to confirm. In contrast, the tandem mass spectroscopy is
expected to be freer of interferences because the analysis has a second analytical separation step.

This data, although limited because only one other reference laboratory was used, should indicate to physicians that urine drug testing with LC-MS/MS technology may provide them and their patients with benefits over testing by GC-MS.

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**REFERENCES**


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**Are Independent Medical Examiners Truly Independent?**

**To the Editor:**

I appreciated the recent health policy article regarding the facts and fallacies of Independent Medical Examinations (IMEs) (1). However, I was concerned that it failed to mention a significant source of bias in the system. When physicians receive a substantial portion of their income from performing IMEs (or if their hourly rate for IMEs is significantly greater than their hourly rate for patient care), they will not be independent. In fact, they will be financially dependent on those who request their services. Generally, representatives of the payer rather than the patient select the examiner. These payer representatives (commonly workers’ compensation insurance adjusters) have a financial incentive to select those IME providers who tend to recommend that services be denied. The examiners know this dynamic. Some continue to provide unbiased opinions and accept that they may not get many referrals to perform IMEs. Others, unconsciously or intentionally, favor the insurance company interests and get more and more of the IME business. Clearly, those who provide IMEs...
as a major source of income are much more susceptible to being influenced than those who derive only a very small percentage of their livelihood from IMEs. If we are to avoid both the appearance of bias and actual bias in the system, ethical guidelines should require IME providers to avoid being significantly financially dependent on those who request these services. Truly independent medical exams would be offered by specialists who derive the vast majority of their professional income from providing care to patients, not opinions to insurance companies.

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In Response

We appreciate Dr. Spencer’s concern about the bias inherent in the independent medical examinations (IME) process. In some cases, physicians may be more influenced by financial gain than in conducting an unbiased and truly independent appraisal of a patient’s health. While only a small number of physician independent medical examiners may be involved in such dubious practices, it may necessitate the implementation of self-regulation by means of guidelines put forth by specialty societies and the implementation of those guidelines by internal review boards. Among the interventional pain physician community, most societies are drafting or have already issued statements delineating their position on the ethical conduct of performing IMEs. For instance, a recent review by the American Academy of Neurological Surgeons (AANS) highlights that disciplinary action with the potential for expulsion from unethical conduct by physicians performing IMEs (1). They also suggested additional oversight of both plaintiff and defendant physician testimony by members of the organization as well as potential state medical board involvement by means of parallel review programs, thereby ensuring greater effectiveness of the ethical conduct review process (1).

The content of each organization’s guidelines describe different viewpoints regarding key principles needed to uphold the highest ethical standards. For example, some review boards endorse responsible self-limitation of the percentage of total time invested in performing IMEs. Specifically, The American Academy of Neurology (AAN) subjects members who spend more than 20% or more of their time in medico-legal activity to a potential competence review in which the expert must demonstrate that his/her opinions are both objective and not influenced by financial interests (2). Soon to be released ASIPP guidelines recommend that its members, “will be prepared to state whether the testimony given is based on personal experiences, specific clinical references, and/or generally accepted standards in the subspecialty field.” The AAN and American Society of Anesthesiologists (ASA) guidelines advance similar views (2,3). Most specialty organizations provide a basic set of principles with which the examiner should adhere; these usually include clauses advocating recent or active clinical practice in respective specialized fields, expertise in matters for which professional opinions are provided, and condemnation of contracts in which the physician fee is contingent upon content or outcome of the IME (2-4).

Total time spent or total income derived from IMEs may warrant specialty board review on a case by case basis. Potential intervention of state medical boards in select cases of grievous abuse as suggested by the AANS review would maximize examiner adherence to ethical guidelines when performing IMEs. We would endorse possible percentage cutoffs of total time spent or professional income derived from IMEs, but do not
believe that exceeding these cutoffs should necessarily be viewed as benchmarks for alleging physician misconduct.

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Efficacy of Biofeedback in the Treatment of Migraine and Tension Type Headaches

To the Editor:

The disorders of the population are described as “migraine with or without aura and/or tension type headaches, by ICHD-1 criteria” without discriminating between these 3 throughout the whole study (1). Therefore, the results can never lead to the conclusion that “biofeedback ... provided no additional benefit ... in the treatment of migraine and tension type headaches in adults” since such a statement had to be grounded on separate analyses for migraine and tension type headache (TTH). TTH patients might have improved while migraineurs deteriorated. Moreover, the authors do not unveil the distribution of these disorders across groups, so that the biofeedback group might have consisted of e.g. migraineurs only. Consequently, the scope of possible conclusions is restricted to the outcome of “treatment of a subgroup of a group of adults suffering from migraine with or without aura and/or tension type headaches, where it is left unknown if and how many patients suffered from each disorder in the subgroup treated with biofeedback.”

Even within these epistemological limits, the results seem disencouraging: Meta-analyses for biofeedback treatment of TTH (2) and migraine with and without aura (3), although not discussed in Mullally et al (1), exhibited medium effects, where TTH and migraine were treated with various biofeedback modalities including EMG (to reduce pericranial muscle activity in TTH patients) and peripheral skin temperature (TEMP), while the use of photoplethysmography (“blood volume pulse” feedback, BVP) of temporal arteries was reported for migraine treatment only. If however patients with TTH responded to EMG biofeedback and migraineurs...
responded to the TEMP approach, all participants in (1) should have improved because all types of headache which might have been included in the biofeedback treatment group would have been addressed by their specific biofeedback modality.

I doubt, however, that TEMP biofeedback in context of migraine is an adequate comparison object for EMG biofeedback in context of TTH when, as in (1), relaxation techniques are taught anyway. Pericranial hypertension is most likely one physiological cause for TTH, so sound EMG biofeedback may be a causal treatment of TTH by means of pathophysiology. In contrast, while the pathophysiological causes for migraine are still unknown (4), peripheral skin temperature is for obvious reasons not even discussed as a possible cause for migraine (5). To my knowledge, for migraineurs, biofeedback therapists usually use TEMP to teach voluntary inhibition of the sympathetic nervous system, which is relaxation training. If muscular phenomena play no causal role for a certain disorder, EMG is just another measure of tension vs. relaxation. So the examination of EMG and TEMP biofeedback as an addition to “simple relaxation training” in (1) turns out as examination of “biofeedback relaxation training” as an addition to “simple relaxation training” in migraineurs, which is a lot of relaxation, but by no means physiologically causal counteraction like EMG in TTH patients. Since the authors of (1) only communicate that “all [patients] had had migraine and/or tension type headaches,” it is left unclear if there were TTH patients in the biofeedback group, and if yes, how many, leaving open if and how many patients did receive something else than relaxation (i.e. if and how many patients in the biofeedback group received any other therapeutic approach than the relaxation-only group).

Note how the 95% confidence interval for “BFB vs. relaxation” leaves Null for TTH in (2, table 2), while it does not for migraine in (3, table 2), because BFB trials contained a lot of EMG trials (i.e. nothing but another relaxation training) in the latter meta-analysis, which concomitantly exhibited largest mean effect size for BVP (3, table 4). In (1) indeed, BVP would have been a candidate for a credible comparison object as mentioned before because it potentially makes patients learn to counteract the phenomenon of constriction succeeded by dilatation of extra-cranial vessels in migraine attacks (4,6). Another approach might be seen in electroencephalographic feedback of slow cortical potentials at 10 – 20 site Cz addressing cortical migraine generators (4,7,8), which is still experimental.

At last, finding an appropriate individual model of illness is crucial in psychological therapy. Life events, pathophysiology, genetics, family issues, dysfunctional thoughts, relaxation, early childhood traumata, and many other paradigms may play a role in this process. Biofeedback is not appropriate for each patient’s model of illness and might even confuse patients when superimposed on markedly diverging models of illness. When patients were referred to the Harvard Community Health Plan Comprehensive Pain Program, some of them or their referrers probably focused their expectations on other elements of pain management they have heard of being conducted there (meditation, self hypnosis, and art and movement therapy with a pain clinician are reported in 1), keeping models of illness potentially incompatible with biofeedback throughout their participation. It would be interesting to see how patients performed physiologically in biofeedback therapy: Did they become able to self-regulate or were they just “guests” at the psychologist’s?

Although there is a gap between suggestions of biofeedback models, interventions, and training courses — especially concerning electroencephalography (“neurofeedback”) — and the evidence base (cf. 9), the use of certain biofeedback modalities for the treatment of TTH and migraine is already supported by meta-analyses (10). Due to methodological limitations, (1) is unable to challenge these findings.

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In Response:

In our study, subjects with migraine headache with and without aura, tension type headache, or both were randomly assigned to receive instruction in relaxation techniques with education in pain theory or biofeedback in addition to the relaxation/education. The subjects who were treated with biofeedback received instruction in both Temperature and EMG biofeedback without distinction with regard to headache type. The distribution of the headache types in the 2 groups was similar. Treatment with biofeedback did not produce any additional improvement in the frequency or severity of the headaches when compared to simple relaxation techniques. Furthermore, it did not effect a decrease in the number of medications required to treat the headaches over the subsequent 3 years nor did it decrease the number of medical visits specifically for headache over that same period of time (1).

The referenced meta-analyses, with regard to the efficacy of biofeedback in migraine and tension type headache, are interesting but do not address the potential for underlying biases and that is a major limitation of such analyses. Many of the studies regarding the use of biofeedback in the treatment of migraine and tension type headache have been performed by practitioners of biofeedback or by those who routinely utilize the treatment modality in the course of their practice (2, 3). Meta-analyses are also, in general, subject to observer variation and the results must be carefully interpreted. Compiling and analyzing data from multiple trials does not improve upon the quality of the original studies (4).

Our study was initiated to convince insurance carriers that biofeedback should be a routinely covered benefit for patients who suffer from migraine and tension type headache. Unfortunately the results proved otherwise (1).

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References:

A Different Approach to Occipital Neurostimulation-Induced Muscle Spasms

TO THE EDITOR:

We read with great interest the article by Hayek et al (Pain Physician 2009; 12:867-876) and would like to share our own experience with implantation of occipital stimulator leads. Our surgical technique is similar to that described by Hayek et al (1) with the additional modifications that we believe not only decrease the risk of cervical muscle spasms, but also reduce the risk of lead migration and lead tip erosion. We insert cylindrical leads through a midline incision as described by Kapural et al (2), but above the occipital protuberance.

We have found that stimulation of the greater occipital nerves is still possible in this region. In addition, since the scalp is taut in this area, the leads are more firmly positioned, which we believe serves as another barrier to lead migration. The contour of the occipital skull also allows the Touhy needle to follow a firm structure to place the leads 4.5 cm from the midline more easily. The leads, a total of either 1 or 2, are placed under the fascia (galea) to the right and left sides to cover the greater occipital nerves within each region.

We place the leads under the fascia since it does not affect our ability to stimulate and being a tough fibrous tissue, we feel helps to prevent both lead migration and tip erosion. The leads are then anchored to the fascia with non-absorbable suture, and then brought together to the midline where a second anchor is placed. They are then tunneled to either the right or left side of the neck and finally passed over the clavicle for infraclavicular implantation. We like to have our strain relief loop within the neck given the placement of our IPG.

With this technique, we have not experienced any displacement of the leads secondary to movement at the fulcrum of the occipitocervical junction. The authors have performed a combined 400 of these procedures, beginning in 2004. The one disadvantage of this technique is that by going underneath the fascia, there is a small risk of a subgaleal hematoma. We have not experienced this complication to date. We are presenting a technique that was developed after performing several hundred implantations. The technique was devised based on ease of placement and which resulted in less complications. This is not a study, but a well designed study should be done to further assess its efficacy.

Fig. 1. The patient’s head is shaved prior to removal of percutaneous paddle leads and placement of cylindrical leads. Surgical marker is used to proximate placement of each cylindrical lead. In this case, once above the occipital protuberance, 2 cylindrical will be placed to the right-side and left-side within the occipital region. The superior and inferior leads are separated by 2 centimeter in distance.

Fig. 2. Once all leads are brought to the midline and anchored, they are tunneled to either side of the neck and into the infraclavicular region were they are attached to the IPG. Note that a surgical marker is used proximate the coarse of the leads as they are tunneled.
Figures 1-4 illustrate our preparation for lead placement and final view with x-rays.

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In Errata

The P values were missing on page 974 of Falco et al Cross Talk: A New Method for Peripheral Nerve Stimulation. An Observational Report with Cadaveric Verification 2009;12;965-983. The last paragraph in the Outcome Data section found in column 1 on page 974 should read that there were P values of 0.0004 and 0.03 regarding functional improvement as measured by ODI scores prior to and after PNS implantation with cross talk.