Preface

Drug Testing and Toxicology: Redefining the Plague of Darkness

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Editor

The book of Exodus recounts the experience of the plague of darkness during Pharaoh's rule. The narrative discusses the imposing nature of the Darkness that occurred throughout the land of Egypt as a "darkness which may be felt… a thick darkness, where no one could see another person, and no one could rise from his place."[1]

What's old is new again. Although the narrative is thought to have occurred over three thousand years ago, modern day reports of increasing pain and treatment over the last two decades may offer another insight into this experience. As the plague imposed a sense of complete and utter isolationism where one afflicted could not interact with another nor shed the enveloping sense of imprisonment, so too can the pain experience impose similar overtones.

Pain is becoming a pervasive state of being. It has garnered its own cadre of diagnostic codes, given rise to multiple treatment modalities, pain specialties and subspecialties, devices, and—since 2005—has recruited September to be its own awareness month.[2] Pain can be likened to darkness. Numerous books, publications, and narratives have described the experience of pain as fostering intense isolationism, hopelessness, worthlessness, despondency, nonacceptance, lack of productivity, familial discord, social outcast state, and other intimations of a lone and dark existence.[3–5] In addition, the social and physical relationships of pain are thought to share underlying biological processes.[3]

Over the past two decades, the number of people suffering from some manner of pain, and the narcotic prescriptions that are tethered to pain symptoms, has increased four- to tenfold depending on how data are collected and/or stratified and can account for over 80% of physician visits.[6,7] Many of these initial acute pain experiences progress to chronic pain conditions, which afflicts patients for years. Recent data estimate that as many as one in three individuals suffer from some manner of pain; over

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125 million people (US) reported some pain over a 3-month period and that approximately 50 million Americans, and over half of various populations in general, suffer from chronic pain.[8,9] As health care providers, we feel obligated to mitigate the suffering of our patients. Oftentimes, treating pain goes hand in hand with the treatment of disease and, of late, frequently it is the only presentation pertaining to the patient's chief complaint.

As conscientious caregivers, we have been able to select from an ever-increasing arsenal of narcotic analgesics, each with its own unique claims for its ability to assuage pain. Indeed, numerous classes of benzodiazepines, opiates, amphetamines, and others have availed themselves as wellsprings of pain obviation. However, these medications come with their own side effects, which require secondary prescriptions. For example, opioid administration has been reported to precipitate adverse effects, including but not limited to sedation, physical dependence, tolerance, hyperalgesia, and notably, constipation.[10] In fact, opioid-induced constipation (OIC) has become such a common and expected gastrointestinal sequelae of patients on opioids, that the rescue pharmacopeia for OIC were repeatedly advertised during the recent Super Bowl 50 commercial spots,[11] further demonstrating the prevalent, almost household, use of narcotic analgesics in our society.

The literature has concordantly mirrored this explosion of pain relief options in that a PubMed search for the limited query of "pain medication review" publications in 1992 would yield 45 review-type articles published in that year, whereas a similar query 20 years later in 2012 would provide a >five-fold increase of over 250 publications per annum, the total number that can be exponentially increased if one removed the limitation of a "review" article from the search query.

In light of increasing pain, the commensurate increase in pain medication prescriptions, and subsequent side effects of select pain medications, many emerging drug offerings promote reduction of side effects, improved dosing and dependency, as well as increased potency and effectiveness. Many such claims have not held up and were likely the result of overzealous advertising campaigns to capture the ever-increasing pain-centric market share in the way Postum coffee alternative marketed itself as an coffee-like beverage that, unlike the villainous coffee bean, would not stunt the growth of children, cause divorce, promote business failures, or be the etiological agent responsible for the completely fictitious disease known as "coffee heart."[12,13]

The current *Pain Paradox*™ poses additional challenges. The ability to note, qualify, and quantify a patient's pain is largely a subjective exercise. Numerous psychosocial variables, including but not limited to age, gender, personality, and ethnicity, among others, affect the manner in which a patient relates to pain,[14] and certain such variables have been reported to help predict responses to pain treatment.[15] To this end, various psychosocioeconomic questionnaires and screening tools (ie, Screener and Opioid Assessment for Patients with Pain, the Opioid Risk Tool, the Oswestry Disability Index, the NIH Patient-Reported Outcomes Measurement Information System) have been employed to attempt to create objective quantification of pain scores and risk stratification for pain patients in how they relate to pain and pain medication prescriptions as well as the risks of succumbing to drug addiction or abuse.

Furthermore, in light of the molecular age of *personalized* or more recently dubbed discipline of *precision medicine*, we may be able to more effectively tailor which analgesic should be preferably prescribed to a patient—based on their genetic polymorphisms—that impact drug absorption, distribution, metabolism, and excretion (ADME). To this end, Genome Wide Association Studies (GWAS) were culled from many individuals being prescribed analgesia (ie, opioids) to identify optimal genetic inputs, which would ideally characterize how a patient's genetic constitution would

translate into an individual's unique enzymatic footprint and thus affect ADME, drug efficacy and function, and help guide prescribing habits.

A caveat to this approach, however, is the understanding that polygenic rather than single major gene effects will foster and translate the likelihood of a patient's response to opiates or other analgesia. In addition, patients enrolled in GWAS studies may be on polypharmacy (drugs, herbs, nutraceuticals, other) for pain and/or other maladies, which may introduce additional variables as well as exert epigenetic effects that contribute or influence genomic and proteomic results.[16] Nonetheless, genetic influences that may be common across different opioid analgesics include polymorphisms in the CYP2D6 gene and findings that the A118G single-nucleotide polymorphism (SNP) of the mu opioid receptor gene and the V158M SNP of the catechol-*o*-methyltransferase gene may alter both analgesic responsiveness and opioid abuse risk,[17] although the value of identifying such polymorphisms in moderating drug-prescribing habits is not without debate.[18]

The *Pain Paradox*™ has given rise to the behemoth aptly dubbed the *Pain Problem*™. This "problem" encompasses all the sequelae that have become an epidemic of national and global concern, including but not limited to death, addiction, diversion, pill pushing, doctor shopping, abuse, and all the damage that this juggernaut leaves in its wake. The morbidity and mortality associated with such behavior have reached epic proportions. Recent reports demonstrate that drug-induced deaths have been on the rise for the last decade, steadily increasing from ~30,000 deaths per year in 2003 to over 45,000 deaths in 2013, which surpasses homicide-, motor vehicle–, and firearm-related deaths, nationally.[19,20] Drug overdose claims the lives of approximately 120 people each day. Disturbingly, the number of deaths attributable to controlled prescription drugs has outpaced those for illicit drugs such as cocaine and heroin combined. Furthermore, with regard to prescription drugs, it is alarming to note that over the last few years, select prescription drugs for pain have precipitated untoward mortality. To this end, the schedule II synthetic opioid fentanyl and its analogues have been responsible for more than 700 deaths across the United States.[19]

The increase in pain combined with the increase in pain prescriptions, many of which can be dispensed without discretion and in considerable quantities at each visit, has availed a unique market for supply and demand. For example, a 30-mg Oxycodone tablet can cost ~$2 at the clinic but can be resold for up to $30 ($1/mg) on the street; at 120 to 150 pills per prescription, the street value for a few refills is enough for a decent used car, or other useful commodities.[20]

In addition to patients-turned-addicts being punished by law enforcement for criminal activity, doctors are being subjected to such as well. A recent ruling from the Supreme Court has provided *patients the ability to sue their physicians*, under "wrongful conduct," for getting them addicted to pain medications,[21] thus fostering distance between physicians and their patients. Additional physician narcotic prescription monitoring initiatives have also been instituted. Some states have created mandatory educational/monitoring initiatives, also known as "pill mill" legislation,[22] requiring all pain management clinics to be certified by their Medical Board on a biennial basis and to be owned and operated by a licensed physician, whereas other states encourage physicians to require opioid education and proactive addiction counseling for patients who are prescribed schedule II or III controlled substances for chronic pain for extended periods,[23] whereas other states keep a watchful eye on how MDs prescribe in that simultaneously prescribing opioids and benzodiazepines can precipitate an audit.[24] Furthermore, *Prescription-Drug Monitoring Programs* (PDMP) are statewide electronic databases that serve to help clinicians identify patients obtaining controlled substances from multiple prescribers (ie, "doctor shopping") for

appropriate pain management. To this end, over 40 states currently have a PDMP program in operation.[25]

So what's a doc to do? Prescribe? Not prescribe? It seems bleak on either front. Then again, maybe not.

It is reasonable to assume that no individual chooses to become an addict. Most start out as your "average Joe" who are prescribed narcotics after surgery, giving birth, sports or back injury in the appropriate manner. In some, the meds stop working efficiently, whether as a result of individualized modulation of pain receptor cell density, tolerance, and the like, thereby fostering the need to seek out (a) increased dosing of the same medication, (b) adding polypharmacy of other classes of pain medication, and/or (c) nonprescribed sources of pain relief. The latter can include illicit drugs as well as alcohol for their sedative synergy. In short order, when one becomes an addict, one is no longer subject to logic, reason, or rationality as their brain chemistry has changed.

But how does the physician know where the patient before him lies on the spectrum of "patient to addict" without the aid of a crystal ball? The clinical laboratory can be very helpful in this regard in that it has matured in step with this conundrum and can provide objective drug compliance and monitoring assistance to aid the physician in managing the patient. The application of toxicology and drug monitoring to one's practice can be very helpful in aiding the physician in answering two basic questions as he/she assesses the patient:

1. Is the patient taking what has been prescribed?
2. Is the patient taking something else?

The rudimentary value of these queries is not to be underscored. Knowing if one's patient is taking what is being prescribed provides an objective determination of pain management as told by the patient's physiology and his/her body fluid prose of parent and metabolite drug signatures. The value of the patient taking something else—and the something else can be prescription medications not disclosed or prescribed by another health care provider, as well as illicit drugs—is also compelling. To this end, recent studies have shown that an unscheduled toxicology assessment of patients scheduled for maxillofacial surgery highlighted that 47% of those patients yielded illicit drug results that were inconsistent with the information obtained by the treating physician/surgeon[26]; almost one-half of patients tested had drugs in their system that were not known to their health care provider. It is likely that any conscientious physician would want to know if the patient they were about to operate on had a sedative/narcotic/illicit on board before subjecting them to anesthesia or other drugs that may interact with the patient's systemic drugs, fostering deleterious outcomes.

Urine drug testing (UDT) has been unfortunately utilized by some to paint proverbial "cross-hairs" on the backs of their patients. Recent studies have reported that physicians use "inconsistent" UDT to "fire" their patients from their clinics.[27] However, this is not unexpected. Part of this binary "flip the switch" attitude is that clinicians themselves are under ever-increasing scrutiny by accrediting, governmental, societal, and federal bodies, among others as outlined earlier, thus adding a relatively new defensive gestalt, which has been ingrained into the health care provider who dispenses such medication. It makes relative sense that a patient who is not squeaky clean in a busy pain clinic to be "let go" by the physician who only has an average of 8 minutes to see his/her patient,[28] rather than take the time to discuss, and/or repeat the UDT on the patient. Such an act theoretically obviates further risk to the clinician's practice and license and can be documented in the patient's chart as the reason for termination of care.

However, UDT may actually improve adherence[29,30] and provide a two-way street for trust, compliance, and management. An objective UDT may be employed to rule out problematic drug use for patients under specific monitoring programs, allow the clinician to search for other causes for pain, lend support to patient self-reporting which can be otherwise unreliable,[31,32] as well as provide objective evidence for increasing pain dosing and/or switching drug classes. The value of properly utilizing UDT is compelling. One can search the Web and easily find all manner of professional and lay press on how UDT results were used to fire employees and sever doctor-patient relationships.[27,33] In contrast, UDTs can be also be appropriately implemented as part of a patient workup to provide objective approaches to drug prescribing and monitoring.[34]

A major issue is understanding what the UDT actually can and cannot do. Many clinicians wrestle with the interpretation of results[35,36] and may inappropriately conclude that, although UDT can detect use of illicit drugs or nonuse of prescribed opioids, it can also diagnose prescription opioid abuse, addiction, or diversion, when in fact it cannot provide such in the routine health care setting.[29] To this end, below are a few guidelines to appropriately approach and interpret a UDT:

First, a health care provider must know what he or she is prescribing to his/her patient. There are those who are habituated to prescribe select narcotics based on clinic formularies, training history, and/or drug representative narrative excerpted from drug manufacturer's boilerplate information packaging.[37] Support systems can be employed for the benefit of the physician by fostering continuing education initiatives, which can modify prescribing habits, by employing support of evidenced-based medicine, expert advisement, and/or institutional support.[37]

Second, one must be well versed in the characteristics of the drug, such as its half-life, parent/metabolite relationships, and drug-drug interactions. Although this practice applies to all drugs, the narcotic analgesic space is unique in that these drugs should be considered lethal weapons if not prescribed properly: a sensitivity to be mindful of and not shared with many other medications. It is unlikely for one to open the newspaper and read a news story on how someone on omeprazole was driving impaired, jumped a divider, and killed drivers in the oncoming traffic lane. Such an event is unfortunately common for those on schedule I or II controlled substances.[38]

Third, one must understand (a) what laboratory assay they are ordering (eg, immunoassay employed in drug *screening* technology versus gas/liquid chromatography/mass spectrometry utilized for drug *confirmatory* testing), (b) which tissue fluid they are submitting for testing (ie, blood, oral swab, urine, and so forth), and (c) be familiar with the expected drug detection timing windows, which often differ among fluids tested. For example, a very common source of confusion can be depicted by a patient that tests negative on an a drug *screen* from an oral swab but positive on a *confirmatory* test from a urine sample, often precipitating disparaging overtones from the physician's clinic regarding the competency of one lab over another. This testing competency argument would be similar to comparing apples to cats. One should be familiar with the understanding that detection windows are routinely shorter for saliva than for urine (ie, 6 hours vs 72 hours), and that the detection sensitivity is greater when assessed via mass spectrometry (gas chromatography or liquid chromatography) than for immunoassay screens (ie, 20 ng/mL versus 300 ng/mL). Furthermore, toxicology assessment on different fluids (blood vs urine), even if collected within minutes of each other, can have different results based on differences in processing methodology, carrier proteins, half-life, and ADME for drugs in unique fluid

compositions, and as such, cannot necessarily be linearly compared with each other.[39,40])

Fourth, it is important to understand and respect the fact that clinical toxicology laboratories, and laboratories in general, are accredited entities that are regulated, audited, and inspected by governmental regulatory bodies (FDA, CAP, COLA, and so forth). There are rules that a lab must abide by to remain in good standing, accredited, competent, and reimbursable by third-party payors for the services they render to the clinician for patient management. A common misunderstanding is the issue of test or retest inconsistencies, which can seem frustrating to the health care provider. Laboratory quantitative values are determined by establishing a standard curve utilizing controls, which will set the minimum and maximum reportable concentration values (ie, 50-500 ng/mL), which a lab is then legally permitted to result to the clinician. Anything above the maximum validated value will often be depicted as "greater than" (ie, >500 ng/mL) no matter what the value. The reason for such is that without validation of reportable concentration values by a verifiable control source, the extrapolated data above the validated maximum may be subject to bias (positive or negative drift, and so forth) and be grossly inaccurate. Conversely, a value below the validated cutoff will often be reported as "less than" (ie, <50 ng/mL) as well as "negative" depending on the standard operating procedure employed by the lab. This approach is necessary for the same reasons as above with the additional caveat that a value below the cutoff may be due to background, processing, and/or method-specific noise. Thus, pressing a laboratory to provide raw data above or below the cutoff that is not in-line with standard controls is doing a disservice to the laboratory as well as the patient.

Moreover, if inconsistencies are found in *different* samples even if taken close in time, those samples can be profoundly different from one another in detection of the analyte of interest; such differences can be due to catabolism of said drug, liver, kidney function, other meds, and hydration status among other items.[41] The conclusion for any inconsistency is merely the most likely reason as a result of eliminating all putative/known causes, yet there are some variables that are out of the lab's control as well as areas that are not easily identified. Thus, sending a fresh sample, where the patient sample procurement is scheduled or unscheduled, can more often than not shed light on such reporting quandaries.

Fifth, UDT results should not be considered gospel to precipitate a decision to terminate, believe, or admonish a patient. Common scenarios that pose difficulty for a clinical service include (a) patients having tested negative for prescribed medication, (b) positive for a nonprescribed medication, (c) presence of illicit drugs, (d) and/or a change in positive/negative status upon retesting. The UDT laboratory results are intended to provide the health care provider with laboratory supplemental data for discretionary use, in conjunction with other clinical patient profiles, presentations, signs, symptoms, history, and physical findings obtained by the patient's primary care provider and do not necessarily reflect timing or dosage of administration. Parent drug or metabolite concentrations are subject to many metabolic factors, including but not limited to hydration, kidney and liver function, time and dose of drug ingestion as stated above,[41] in addition to other factors, including pharmacogenomics and polypharmacy, and so forth. Ideally, in scenarios where there is confusion, suspicion, or inconsistency, the physician should obtain a fresh sample from the patient, preferably at random for additional testing. This will provide a trail of objective UDT data to identify trends of patient drug administration behavior in conjunction with other clinical findings and provide content for a cogent dialogue with the patient. If the physician does decide to terminate care of his/her patient, serial UDT results will also serve to

provide the documentation to justify such a decision when other interventions (addiction clinic, detox referral, and so forth) fail.

It is also important to note that standard UDT is not the same as forensic testing, which requires chain of custody and specific forensic protocols regarding sample collection, which ascertain the fidelity of the sample from patient voiding to result. Standard UDT is often collected in the physician's office and subsequently shipped to the testing lab via courier which does not employ forensic protocols or require forensic lab accreditation.[42]

Sixth, prior to sending a UDT, the clinician should document when the patient last took the medication being tested for. If the patient has not taken the medication (ie, opioid) for the past 72 hours, it may not be detected, depending of the detection window. Furthermore, the level of concern and subsequent management would be different if a patient disclosed that he had **not** taken his opioid prior to his/her negative test result rather than in the context of a strained overtone of an unexpected or inconsistent test result. The rationale of requiring a UDT should always be discussed openly with patients. It is less about catching patients doing something wrong and more about assessing increased prescription misuse risk, patient compliance, and trust in the patient-physician relationship.

In light of the aforementioned complexities encountered with UDT interpretation, clinicians may need access to a laboratory toxicologist to help with both UDT ordering and assessment.[34–36] To this end, recent data[35] suggest that primary care clinicians' lack of education and training to interpret and implement urine toxicology tests may impact their management of patient opioid misuse and/or substance use. The issue for clinicians is how to implement urine toxicology tests as a routine clinical procedure. While tests have become more frequent with the many new medical association guidelines, many clinics do not have sufficient staff or resources to systematically address how often clinicians should test, which substances to test for, and how to implement standardized urine toxicology tests. Clinicians who described using urine toxicology tests routinely to monitor misuse had difficulty interpreting results due to insufficient education and training. As such, clinicians may benefit from additional education and training about the clinical implementation and use of urine toxicology tests. Many such avenues (courses, symposia, associations) are becoming available in e-tutorial format, thereby creating up-to-date information of UDT ordering and management with the click of a mouse.

In summary, the adage, "With great power comes great responsibility," which helped forge Spiderman as a superhero, can be applied to physicians who have the noble task of alleviating pain. Medication can be a powerful ally for the doctor who uses such appropriately to treat the patient. Pain meds are powerful, effective, physiologically altering entities, and as such, require pause prior to putting pen to prescription pad. Such pause includes working with the patient to foster a *subjective* empowering relationship, which includes their personal understanding and recounting of pain as well as an *objective* empowering relationship, which includes disclosing to the patient the value and buy-in for the physical exam, imaging, and other ancillary services, notably the clinical laboratory. The ability to perform a urine toxicology screen and/or confirmation creates an objective baseline snapshot of the patient's on-board pharmacopeia, which should foster trust between the patient and physician as a unit. This Patient-Physician Unit (PPU)™ ideally works together to maintain mutual trust, integrity, and transparency to achieve pain relief and improved health. Although not simple, the Pain Problem™ can be improved upon through appropriately engaging the services, support, and resources of the clinical toxicology laboratory along with

other health care support structures. This collective health care "village" can work synergistically to empower the PPU™, obviate pain, end the plague, and bring light to the darkness.

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