It's Not the Drug! It's so Much More!

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Drugs cause addiction. Drugs cause epidemics. A drug can be considered the work of the devil or sometimes a savior. Governments, drug companies, and media minions pay homage to the drug. Regulatory powers chant "It's The Drug!" The Food and Drug Administration FDA declares, "It's the drug!" The Drug Enforcement Administration (DEA) enforces the maxim, "It's the drug!" And, the pharmaceutical industry highly profits from the notion "It's the drug!"

The challenge is how to persuade non-believers to reject the simple explanation that "It's The Drug!" Perhaps it is best to start with concepts already accepted and believed in? One concept comes from the Greeks: "One man's food is another's poison." This premise recognizes the importance of context. Human responses to common foods vary greatly, let alone to substances used to treat medical conditions or alter consciousness. Physicians readily acknowledge that a poison in one context could be life-saving in another.

In medicine, we prescribe drugs based on the proper context and when we can predict likely results based on clinical trials. We make a diagnosis, run tests, and make predictions accordingly. We rarely expect the response to a drug to be universal and without possible side effects or untoward effects. Even when the expected result is likely to be beneficial, a diversity of responses can and should be expected. People and clinical contexts vary. It is not only the drug itself that determines outcomes.

To understand the effects of a drug it is wise to ask: "What are the specific properties of the drug and how does a variety of contextual variables influence outcomes, when the specific drug is used?" What are some of the contextual variables that influence the "effect" of a drug? Here we speak in large part to the immense and complex field of clinical pharmacology and medicine in general. No one is prepared to provide an exhaustive list nor to prioritize all the possible variables. The point is: It is not simply the drug! Other important variables are in play, such as the dosage, the age of the recipient, and the method by which the drug is administered, to name a few.

Dose is important. One dose of insulin can be therapeutic and another fatal. The age and size of the recipient, along with co-occurring conditions and substances used, are important variables that help predict the effects. Genetic variables and the history of exposure to similar substances can be critically important. A dose of methadone, which could be fatal for a young person, could be only a small fraction of the dose required to treat an adult with severe pain or an opioid use disorder.

How a drug is administered is most important. Some drugs have no effect at all, when consumed by mouth. Yet, it is possible that a therapeutic dose by mouth could be fatal, if taken intravenously, smoked, or injected.

The above list of variables is truly a short list among the hundreds of other known variables. It is all quite complex and that is why society has physicians, who are responsible for deciding what drug might or might

not be helpful for a given patient. The drug when administered by a knowledgeable and experienced clinician can play a dramatic role in promoting safe and effective outcomes. As a seasoned physician, I appreciate the role that pharmacists and other members of the team have in assuring the safe and effective use of drugs. Regulations and criminal deterrence have their place, as well. The physician is only one player in a cast of characters with critical parts in a complex script. I argue, and it might surprise many, that a physician has quite limited control over the multitude of variables, which impact drug use within our society.

Drug use patterns are strongly influenced by "cultural variables." These same variables can also play a major role in determining use or misuse of a drug. A glaring example is our current response to the opioid epidemic. We see certain medications or doses of medications commonly blamed. For example, along with heroin, methadone and fentanyl are now commonly judged to be "bad" opioids because of overdose rates and other complications. Physicians are afraid to prescribe methadone and fentanyl, because, when misused or poorly prescribed and monitored, they, as is the case with most powerful medications, are dangerous. Clearly, methadone and fentanyl are very helpful drugs when used properly. They have likely helped saved many more lives than they have taken. What's more both drugs have significantly reduced suffering and preserved functioning in patients with pain or opioid use disorders. Because they are potent opioids with unique pharmacological properties they can be readily misused. This does not mean that they are "bad" drugs or that they should never be used.

To further highlight cultural influences regarding opioids, I know of no other example where laws have been so written to regulate a proven medically effective drug. Fatalities and poor health associated with alcohol and tobacco are higher and more significant than with opioids, yet these former substances are legal and relatively uncontrolled compared to opioids. Tobacco is arguably as addictive as any opioid including heroin. What's more opioids when properly used save lives and dramatically improve health. Hard to make a similar argument especially for tobacco.

In Washington State, laws are on the books to specifically require physicians to get consultations and adhere to onerous requirements based on prescribing a patient a higher dose of an opioid. Now, as a comparable example, consider when a higher dose of insulin is clearly justified in a diabetic patient. While a higher dose is more dangerous than a lower dose, it is indicated, because of more serious diabetes and associated complications. A higher dose does not mean that prescribing a higher dose of insulin is "bad" or necessarily "dangerous." While the mortality rate for patients on higher doses of insulin is significantly higher than those on lower doses, no laws, as is now the case for opioids in Washington State, have put restrictions on the dosage of insulin to be prescribed.

Even the FDA, which is the governmental agency responsible for determining the relative safety and effectiveness of a drug, acknowledges that it only provides guidelines to prescribers. The clinical variables that can be at play in general clinical medicine can never be duplicated in clinical trials. Clinical trials allow us to address probabilities not certainties, particularly for a given patient. Yet political pressures and cultural beliefs about drugs have prompted laws to be written and enforced regarding specifics in the prescription of opioids.

To further highlight cultural influences in how we judge and think about drugs, particularly drugs which can be abused, imagine what would happen, if we passed laws limiting which patients could be admitted to hospitals based upon the high rate of complications and rate of mortality associated with patients previously admitted. What if hospitals were regulated in such a fashion as to promote cherry picking their

patients? The sickest would be excluded because they would be most likely to die in the hospital. The public outcry would be deafening! And appropriately so! Whereas, we “outlaw” higher doses of opioids except with specific guidelines and everyone nods approval. The politicians, bureaucrats, and even some academicians are reassured by the reduction in overdoses associated with opioid prescriptions. It would be as if we started celebrating the lower rate of hospital complications and deaths by limiting very ill people from being admitted to hospitals. The suffering and complications from poorly managed pain and opioid use disorders were not formally measured following the implementation of the Washington State Pain Rules. The consequences were nonetheless readily apparent. Overdoses from heroin and other non-prescribed opioids skyrocketed. Many patients on Chronic Opioid Agonist Therapy for chronic pain suffered immensely and some likely died as a result of poor access.

Note, rates of overdoses from prescribed opioids vary significantly from one Washington State county to another. Indeed, the correlation between amount of opioids prescribed and the rate of overdoses clearly did not substantiate the belief that “It’s the drug!” or that the dose of the drug is what matters most. In some cases the counties with the highest rate of opioid prescribing had among the lowest rates of overdoses and vice versa. Lastly, I cannot think of another example in history where specific medical care was legislated and became potentially criminal if not followed.

Further evidence for the importance, if not the primacy, of cultural influences are common. Consider that many “experts” still consider diversion a side effect of opioids. Diversion refers to the intentional misdirection of appropriately prescribed opioids from the patient to “the street.” Common sense supports that a substance that helps one “feel better” might be more likely shared or misused. Nonetheless, the major influence on the likelihood of diversion of a substance lies in its availability. The pharmacological properties of a drug, by themselves, have limited influence on the probability of diversion. If one cannot readily obtain a substance legally, a drug one wants or needs, the diversion of prescriptions and purchases from illegal sources are encouraged. It’s the cultural setting “It’s not the drug!”

Cultural factors, for better and for worse, dominate the likelihood for diversion and misuse. “It’s not the drug!” It’s the context in which the drug is legislated, enforced, prescribed, administered, stored, used, and misused. Regulations, financial incentives, available alternatives, and other human factors, which determine availability, all dominate the likelihood and extent of diversion. It’s not a side effect of the drug and clearly is not listed as such by the FDA!

In closing, based on clinical, pharmacological, and cultural influences, it is evident that “It’s not the drug!” In reality, it is only the drug in combination with a multitude of other variables. These variable, often more than the drug itself, is what determines outcomes. Drugs can save lives, drugs can kill. It depends. “It’s not simply the drug”