PART III: NAMING THE GENOTOXICITY AND & 100,000 PATIENT DAYS DATAPOINT

ABSTRACT

This is the third article in a series of three. In the first article, we showed how two groups of humans behaved differently in an identical situation. Specifically, we showed how the opioid dependent demonstrated symptoms of a neurotoxicity when confronted with an opioid abstinence. This contrasted sharply with the opioid naive who demonstrated no symptoms when confronted with an identical opioid abstinence. In the second article, we showed that Artificial Intelligence saw the two groups, the opioid naive and the opioid dependent, as two genetically separate and distinct populations. Artificial Intelligence saw the two groups as separate and distinct when utilizing three common forms of unsupervised machine learning: Principal Component Analysis, Non-Metric Dimensional Scaling, and PERMANOVA Analysis. The distinction between the two groups was a methylation in the OPRM1 gene in the opioid dependent group that was simply not present in the opioid naïve group. This neurotoxicity associated with the methylation is thus a form of genotoxicity. Here we put forth that, under the World Health Organization (WHO) guidelines, the proper name for this genotoxicity is Severe Opioid Neurotoxic Syndrome. [1] We further demonstrate that the symptoms of this neurotoxicity can be successfully treated long term with buprenorphine. As this genotoxicity is a poisoning, this use of buprenorphine to treat the symptoms of the neurotoxicity firmly establishes buprenorphine as an antidote, a separate classification of medications. [2] We further present here results of over 100,000 patient days using buprenorphine as an antidote for the treatment and prevention of the recurrence of the neurotoxic symptoms as seen in an IRB exempt retrospective chart review (RCR). It is our hypothesis that the maladaptive behavior in the opioid dependent is all driven by a primary neurotoxicity. [3] This neurotoxicity is the result of the opioids as a genotoxic agent. This primary neurotoxicity results in a secondary opioid craving as it is quickly learned that the full agonist opioids can offer a temporary, albeit dangerous, respite from the horrors of the neurotoxicity. This secondary opioid craving thus results in a tertiary pathological consumption of the opioids. As this group has been denied a proper diagnosis and treatment, the only access to a respite from the horrors of the neurotoxicity can be found in illicit, illegal, and dangerous "street" opioids. This failure of a proper diagnosis and treatment has thus contributed to a quaternary opioid overdose event epidemic. In this article, we demonstrate that a proper treatment with the antidote buprenorphine results in a near complete resolution of the primary neurotoxicity. This resolution of the primary neurotoxicity was both complete and sustained for the entire 100,000 patient day study period. Furthermore, as predicted by our hypothesis, resolution of the primary neurotoxicity resulted in a near complete resolution of the follow up sequela including the secondary opioid cravings, the tertiary aberrant opioid usage, and the quaternary opioid overdose events. These follow up sequela of opioid cravings, aberrant opioid usage, and opioid overdose events remained resolved for the entire 100,000 patient day study period.

1). INTRODUCTION

Mental health disorders do not cause a neurotoxicity. Poisonings can cause a neurotoxicity. This specific poisoning from the opioids is known as a genotoxicity. The genotoxicity due to the opioids can be compared to other known genotoxicities such as lead poisoning. Lead exposure results in epigenetic damage such as methylation. [4] These epigenetic damages are implicated in the development of lead neurotoxicity. Opioid exposure results in epigenetic damage such as methylation. It is our hypothesis that this methylation results in a neurotoxicity just as the methylation from lead results in a neurotoxicity.

1.1). GENOTOXICITY

A genotoxicity refers to the "ability of harmful substances to damage genetic information in cells." [5] These harmful substances can cause genomic damage or epigenetic damage that can result in a disease state or toxicity. And that is what has happened in the case of the opioids, a toxicity. Exposure to the opioids results in methylation within the promoter region of the OPRM1 gene. This methylation, when of enough severity, we believe results in a neurotoxicity when opioid abstinence is attempted. While it is our hypothesis that the etiology of the neurotoxicity is due to the formation of a defective mu-opioid receptor resulting from the methylation, this exact mechanism will require additional study.

1.1.1). GENOMIC DAMAGE

Simplified, genomic damage is damage to the sequence of the DNA. [6] This damage can occur at the gene level such as point mutations, insertions, and deletions. Or this damage can occur at the chromosome level such as aneuploidy and translocations. These types of genetic damages are linked to various disease states such as cancer. The opioids have not been linked to these types of genomic damage.

1.1.2). EPIGENETIC DAMAGE

Simplified, epigenetic damage is damage to the DNA that does not involve an alteration in the sequence of the DNA. According to the Center for Disease Control (CDC), epigenetic damage can take the form of DNA methylation, histone modification, and non coding DNA. [7] Epigenetic damage is found in both poisonings and disease states. The opioids have been definitively linked to causing methylation within the OPRM1 gene, the gene that encodes for the mu-opioid receptor. [8, 9, 10, 11, 12] It is our hypothesis that this opioid induced methylation results in the neurotoxicity seen in the opioid dependent when opioid abstinence is attempted. It is our hypothesis that this methylation results in the formation of a normal in number population of the mu-opioid receptor but that the receptors themselves are damaged and unable to function normally. It is this inability of the mu-opioid receptor to function normally that results in the neurotoxicity.
Epigenetic changes are known to be inheritable. How this opioid induced methylation may impact future generations is not currently understood.

1.2). ANTIDOTE

Poisons are substances that cause harm to organisms when sufficient quantities are absorbed, inhaled, or ingested. A toxin is a poisonous substance produced within living cells or organisms. [13] For our purposes, we will consider the opioids as a poison while recognizing that some opioids are produced within the cells of the poppy plant. The study of poisons is known as toxicology. An agent used to treat a poisoning is known as an antidote. Antidotes are agents that negate the effect of a poison or toxin. Antidotes work by either preventing the absorption of the toxin, preventing the end-organ effect, or preventing the conversion of the toxin to more toxic metabolites. [14] In using buprenorphine as an antidote to treat and prevent the recurrence of the neurotoxicity, the buprenorphine is preventing the end-organ effect of the poisoning. The exact mechanism by which the buprenorphine prevents the neurotoxicity is not currently understood. The administration of the antidote, buprenorphine, is required as long as the symptoms of the neurotoxicity require prevention. It is entirely possible, yet currently unknown, that some victims of the poisoning will require life-long treatment with the antidote, buprenorphine.

1.3). PROVIDER/PATIENT RELATIONSHIP IN AN EMERGENCY

When we identified statistically significant catecholamine toxicity in the first article, four changes immediately occurred. First off, the mental health diagnosis of Opioid Addiction/Opioid Use Disorder became an impossibility. A mental health disorder does not cause catecholamine toxicity. Secondly, it became evident that the patients were in a true neuroendocrine emergency. In other words, a true emergency medical condition existed. Thirdly, the use of buprenorphine to treat and prevent the symptoms of the neurotoxicity became the application of an antidote. Antidotes are a separate classification of medications. And fourthly, the provider/patient relationship was forever altered for this population of patients. Due to the existence of an emergency medical condition, the provider/patient relationship was now that of an implied relationship. No further action was required to establish the relationship. The relationship was created the moment that the emergency condition was recognized. In the implied provider/patient relationship, the provider "need not examine a patient, speak to the patient, or see the patient's medical records in order to be engaged in a provider-patient relationship that gives rise to a duty of care." [15] The American Medical Association states that the "practice of medicine….is fundamentally a moral activity that arises from the imperative to care for patients and to alleviate suffering ". Furthermore, "in certain circumstances a limited patient-physician relationship may be created without the patient's (or surrogate's) explicit agreement. Such circumstances include when a physician provides emergency care…..In these circumstances,…….the relationship is implicit." [16]

The antidote buprenorphine became the pharmacological equivalent of the defibrillator. And just as the provider is able to administer a defibrillator in the emergency setting such as cardiac arrest, so may the provider facilitate access to the antidote buprenorphine in the emergency setting. This fact is not altered by the use of telemedicine or any other facilitating technology. No dialogue, visit, encounter, or any other action is required to establish the provider/patient relationship than the existence of the poisoning and the existence of an antidote. No government or authoritative agency/organization should interfere with this implied relationship between the provider and the patient in the setting of an emergency. To aid in the denial of an effective antidote in the setting of a known emergency poisoning is an act of moral depravity.

2). METHODS

2.1). SETTING

The setting is a large multi-state, multi-provider telemedicine program specifically designed for the stabilization of individuals poisoned by repetitive opioid exposure. The program relies exclusively upon the use of buprenorphine as an antidote for the symptoms of the neurotoxicity. As a part of the program requirements, patients complete weekly both a Neurotoxicity Scale and an Opioid Craving Scale. Information is obtained also on aberrant opioid usage and any opioid overdose events. This information is a part of the electronic medical record for each patient.

As this study is a Retrospective Chart Review (RCR), an opinion was requested from the Institutional Review Board as to whether or not an exemption for IRB approval was required. The IRB found that this study was exempt from IRB approval.

Once an IRB exemption was obtained, a very careful and meticulous data harvesting process was implemented. The goal was to make near impossible a breach in patient confidentiality. As the database had been implemented with patient confidentiality in a Retrospective Chart Review a priority, data harvesting and analysis was completed without a single patient identifying detail ever leaving the HIPPA compliant server.

2.2). SUBJECTS

The subjects were men and women over the age of 18. All subjects had taken the opioids previously and for an extended period of time. All subjects experienced symptoms of a neurotoxicity when opioid abstinence was attempted. All subjects were stabilized on a regiment of daily buprenorphine ranging from 4 mgms a day to 16 mgms a day. The inclusion criteria were reflective of these facts:

• Males and females over 18 years of age stabilized on the antidote buprenorphine

• Currently participating in the telemedicine program or just beginning the program

• Participant is in compliance with the guidelines of the program (completing weekly meetings, having had a live telemedicine visit with the provider, current on all drug screens).

In order to avoid the creation of bias, as long as the patient was in compliance with the program, there were very few exclusion criteria:

• Subject is not in compliance with the guidelines of the program. If the subject was not in compliance with the program, no data was ever uploaded to the database. All records in the database are reflective of a compliance.

2.3). NEUROTOXICITY SCALE

We developed the Neurotoxicity Scale for use in our first clinical trial. Unfortunately, we determined an emergency halt to the clinical trial due to widespread catecholamine toxicity before the Neurotoxicity Scale could be statistically validated. We have subsequently submitted this validation in a separate report attached to the three main articles as an addendum.

The Neurotoxicity Scale exceeded expectations in its clinical performance. The scale was not only effective at measuring the severity of the neurotoxicity, but the scale was effective at detecting rapid changes in the neurotoxicity such as when the antidote, buprenorphine, was administered to an individual experiencing neurotoxicity.

2.4). OPIOID CRAVING

We developed the Opioid Craving Scale for use in our first clinical trial. Unfortunately, we determined an emergency halt to the clinical trial due to widespread catecholamine toxicity before the Opioid Craving Scale could be statistically validated. We have subsequently submitted this validation in a separate report attached to the three main articles as an addendum.

The Opioid Craving Scale exceeded expectations in its clinical performance. The scale was not only effective at measuring the severity of the opioid craving, but the scale was effective at detecting rapid changes in the opioid craving such as when the antidote, buprenorphine, was administered to an individual experiencing opioid craving.

2.5). ABERRANT OPIOID USAGE

Aberrant opioid usage is usage of an opioid that was not prescribed or usage of a prescribed opioid in a manner other than it was instructed. Measurement of the aberrant opioid usage relies upon self-reported aberrancy, results of the state Prescription Monitoring Program, and results of the drug screens. But even

with the most diligent of efforts, one can always assume that the aberrant opioid usage will be under-reported. That stated, this inherent under-reporting is offset to some degree by two factors. First off, the participants were honest about aberrant opioid usage when joining the program. Aberrant opioid usage prior to the initiation of the antidote buprenorphine was 100% in this patient population. There is no direct evidence that this honesty would change under treatment. Secondly, aberrant opioid usage after the initiation of the antidote buprenorphine is so low, that even if the estimation was off by 100%, the frequency of aberrant opioid usage would still remain a very rare event.

2.6). OPIOID OVERDOSE EVENTS

Opioid Overdose Events, including death and near death events are also a problematic number to accurately assess on a Retrospective Chart Review. Again, reliance is upon the self-reporting of an event which is only possible in a near death event. It is noted that some states are beginning to enter naloxone administration into the state Prescription Monitoring Program system. This has already proven useful in our management of the program.

2.7). WORLD HEALTH ORGANIZATION (WHO) GUIDELINES FOR NAMING NEW DISEASE STATES

The World Health Organization (WHO) maintains the system known as the International Classification of Diseases (ICD). The World Health Organization recommends that when new diseases are named that "best practices state that a disease name should consist of generic descriptive terms, based on the symptoms that the disease causes (e.g. respiratory disease, neurologic syndrome, watery diarrhea) and more specific descriptive terms when robust information is available on how the disease manifests, who it affects, its severity or seasonality (e.g. progressive, juvenile, severe, winter)." [1] For these reasons outlined, and in an attempt to follow the World Health Organization's guidelines, we propose the name Severe Opioid Neurotoxic Syndrome (SONS).

2.8). STATISTICAL METHODS

3). RESULTS

Data was accumulated in the electronic medical records over time. These are large datasets. We did not want to lose the granularity of the data within the size of the datasets. Therefore, we divided the large datasets into smaller data parcels. For the 5,000 patients experiencing opioid withdrawal at the time of their documentation, we divided this group of 5,000 into five equal groups of 1,000. This division was accomplished based upon date and time of entry into the database. The first 1,000 participants were Withdrawal Group 1. The second 1,000 were Withdrawal Group 2. And so forth until five separate groups of 1,000 were obtained. These results can be found in Table 1.

This pattern was continued with the participants undergoing treatment and stabilization with buprenorphine. The first 10,000 patient encounters of individuals stabilized on buprenorphine were Treatment Group 1. The second 10,000 were Treatment Group 2. And so forth until ten separate groups of 10,000 were obtained. These results can be found in Table 2.

3.1). NEUROTOXICITY SCALE

The data recorded included both participants while in opioid withdrawal and participants while chronically stabilized on buprenorphine. The data included 5,000 patient days while in opioid withdrawal and 100,000 patient days while stabilized on buprenorphine. This data was divided into groups based upon date and time as noted above. The average Neurotoxicity Scale score for each group while experiencing withdrawal was 1,2,3,4,5 respectively. The overall average Neurotoxicity Scale score while the participant was experiencing opioid withdrawal was 46.2. The average Neurotoxicity Scale score for each group while stabilized on buprenorphine was 1,2,3,4, and 5 respectively. The overall average Neurotoxicity Scale score while the participant was chronically stabilized on buprenorphine was 0.1. This drop from 46.2 to 0.1 represents an over 99% improvement in the level of neurotoxicity due to the stabilization with buprenorphine.

3.2). OPIOID CRAVING SCALE

The data recorded included both participants while in opioid withdrawal and participants while chronically stabilized on buprenorphine. The data included 5,000 patient days while in opioid withdrawal and 100,000 patient days while stabilized on buprenorphine. This data was divided into groups based upon date and time as noted above. The average Opioid Craving Scale score for each group while experiencing withdrawal was 1,2,3,4,5 respectively. The overall average Opioid Craving Scale score while the participant was experiencing opioid withdrawal was 27.1. The average Opioid Craving Scale score for each group while stabilized on buprenorphine was 1,2,3,4, and 5 respectively. The overall average Opioid Craving Scale score while the participant was chronically stabilized on buprenorphine was 0.02. This drop from 27.1 to 0.02 represents an over 99% improvement in the level of opioid craving due to the stabilization with buprenorphine.

3.3). ABERRANT OPIOID USAGE

The data recorded included both participants while in opioid withdrawal and participants while chronically stabilized on buprenorphine. The data included 5,000 patient days while in opioid withdrawal and 100,000 patient days while stabilized on buprenorphine. The aberrant opioid usage of the participant experiencing opioid withdrawal had been 100%. The aberrant opioid usage of the participant chronically stabilized on buprenorphine was 0.4%. This drop from 100% to 0.4% represents an over 99% improvement in the level of aberrant opioid usage due to the stabilization with buprenorphine. It is noted that a small subset of the population admitted to a continued opioid craving despite stabilization of the neurotoxicity with buprenorphine (Table 3). On further questioning, this small subset admitted to feelings described as "wanting to get high". While this subset is a small percentage of the larger population at only 0.6%, this group is exhibiting continued high risk activity. This group will require further study and understanding. Fortunately, the overwhelming majority of the population at 99.4% had no further desire to engage with the opioids.

3.4). OPIOID OVERDOSE EVENTS

The data recorded included both participants while in opioid withdrawal and participants while chronically stabilized on buprenorphine. The data included 5,000 patient days while in opioid withdrawal and 100,000 patient days while stabilized on buprenorphine. The reported opioid overdose events of the participants experiencing opioid withdrawal was 15%. This is to say that at some time prior to the encounter with the program, 15% of this population had experienced and survived an opioid overdose event. The reported opioid overdose events of the participants chronically stabilized on buprenorphine was 0%. There were no reported opioid overdose events during the 100,000 patient days in the group chronically stabilized on buprenorphine. This drop from 15% to 0% represents an 100% improvement in the level of opioid overdose

events to the stabilization with buprenorphine.

It is recognized as problematic relying upon a Retrospective Chart Review (RCC) as an accurate means of assessing a true incidence of opioid overdose events in this population. While we may be able to gain some insights and estimates from a RCC, a prospective format may be able to provide a more accurate insight into the true incidence of opioid overdose events in a population chronically stabilized on buprenorphine.

4). DISCUSSION

This article concludes the third in a series of three articles. In the first article, we demonstrated how the opioid naive and the opioid dependent behaved differently when confronted with an identical clinical scenario. When confronted with opioid abstinence, the opioid naive exhibited no symptoms. When confronted with an identical opioid abstinence, the opioid dependent exhibited symptoms of a neurotoxicity. The first article went on to demonstrate the effectiveness of the antidote, buprenorphine, at relieving the symptoms of the neurotoxicity, beginning with just a single dose. In the second article, we presented the DNA of the opioid naive and the opioid dependent to Artificial Intelligence and for analysis. The question before the machine was whether Artificial Intelligence saw the DNA as one or two genetic populations. If the DNA of the opioid naive and the opioid dependent were seen as one population of DNA, this would lend credibility to the concept of a mental health diagnosis. But if the machine saw the DNA of the opioid naïve and the opioid dependent as two populations, separate and distinct, this would lend credibility to the concept of a genotoxicity having occurred in response to the repetitive exposure to the opioids. The results were clear. Utilizing three common techniques of unsupervised machine learning, Principal Component Analysis, Non-metric Dimensional Scaling, and PERMANOVA Analysis, the machine clearly saw two separate and distinct genetic populations. This use of Artificial Intelligence supported the concept of two separate and distinct genetic populations. This is strong scientific evidence in support of the opioids as a genotoxic agent. It was noted that part of the motivation to engage with Artificial Intelligence came from what we sensed to be a reluctance by some in the mental health community to engage in a dialogue consistent with the long-held principles of Popperian Science. This was reflected in the articles by Nutt et al (2015) [17] and Volkow et al (2016). [18] In order to have a meaningful scientific dialogue, all parties must be willing to adhere to the accepted principles of science. Once one is relieved of the burden of the scientific process, one is able to make any claim imaginable and not be required to offer supporting scientific evidence. This was a motivation to turn to Artificial Intelligence for an analysis. The machine is without bias. The machine does not have a stake in the outcome of the inquiry. And the machine clearly saw two separate and distinct genetic populations demonstrating the genotoxicity of the opioids.

In this third and final article, we demonstrated the effectiveness of the antidote, buprenorphine, long-term and for the suppression of symptoms of the neurotoxicity due to repetitive opioid exposure. Specifically, we demonstrated that buprenorphine had an immediate, profound , and long lasting suppression of the symptoms of the neurotoxicity. Every symptom followed in the Neurotoxicity Scale was essentially resolved with the administration of the buprenorphine. These symptoms remained resolved for the entire 100,000 patient day review period. The average score in the Neurotoxicity Scale prior to the initiation of daily buprenorphine was 46.1. The average score in the Neurotoxicity Scale after initiation of daily buprenorphine fell to 0.1. This fall from an average score of 46.1 to an average score of 0.1 represented an improvement of over 99%. If our hypothesis is correct, then a marked fall in opioid craving, aberrant opioid usage, and opioid overdose events should follow the drop in the symptoms of the neurotoxicity.

As it is our hypothesis that the sheer agony of the primary neurotoxicity is the driving force behind a secondary opioid craving, it should be no surprise that a drop in the Neurotoxicity Scale score of over 99% corresponded with a comparable drop of over 99% in the Opioid Craving Scale scores. Opioid craving essentially disappeared when the neurotoxicity was appropriately treated with the antidote, buprenorphine. And again, the opioid craving remained resolved for the entire 100,000 patient day review period. The average score in the Opioid Craving Scale prior to the initiation of daily buprenorphine was 27.1. The average score in the Opioid Craving Scale after initiation of daily buprenorphine fell to 0.01. This fall from an average score of 27.1 to an average score of 0.01 represented an improvement of over 99%.

As it is our hypothesis that it is the severity of the secondary opioid craving that is the driving force behind a tertiary pathologic consumption of the opioids, it should be no surprise that a drop in the Opioid Craving score of over 99% corresponded with a comparable drop of over 99% in the aberrant usage of the opioids. Aberrant opioid usage essentially disappeared when the neurotoxicity was appropriately treated with the antidote, buprenorphine. And again, aberrant opioid usage remained resolved for the entire 100,000 patient day review period. Aberrant opioid usage was reported at 100% in the study population prior to the initiation of daily buprenorphine. The aberrant opioid usage fell to 0.6% after the initiation of daily buprenorphine. Of note is a small subset of the study population of approximately 0.6% who still reported a craving for the opioids and were willing to stop the buprenorphine in order to "get high" on the opioids. This is a previously unknown subset of the population that has yet to be described in the literature. More study of the parameters of this subset is indicated.

As it is our hypothesis that it is the severity of the tertiary pathologic consumption of the opioids that is the driving force behind a quaternary opioid overdose event, it should be no surprise that a drop in aberrant opioid usage of over 99% corresponded with a comparable drop in opioid overdose events. There was not one single opioid overdose event that was discerned during the entire 100,000 patient day study period. The challenges of utilizing a Retrospective Chart Review are noted. It is believed preferable to utilize a Prospective Clinical Trial format for a more accurate assessment of opioid overdose events in the opioid dependent population stabilized on buprenorphine. As zero incidents were detected in the 100,000 patient study days, it is clear that a large population of the opioid dependent stabilized on buprenorphine will need to be studied and for a significant time period.

5). CONCLUSION

In the first article, we demonstrated how the antidote, buprenorphine, was effective at rapidly suppressing both the primary neurotoxicity due to the genetic damage resulting from repetitive opioid exposure, and the secondary opioid craving. This resolution of the symptoms occurred in under two hours and in every participant. In this article we further demonstrated how this suppression of the primary neurotoxicity and the secondary opioid craving remained suppressed for the duration of the treatment and over 100,000 patient days. Furthermore, and in keeping with our hypothesis, once the primary neurotoxicity and secondary opioid craving was suppressed, the aberrant opioid usage and opioid overdose events dropped by over 99%. In fact, not a single opioid overdose event was detected in the retrospective chart review of 100,000 patient days of data. This data is strongly supportive of our hypothesis. This data is further refutive of the previously debunked Brain Disease Theory of Addiction as it pertains to the opioids. At this point we call for continued research and to include the use of a large prospective study to further understand both the rare abuse of the opioids in a fractional subset of the population and the true incidence of opioid overdose events in the opioid dependent population stabilized on buprenorphine.