Review

The Neurobiology of Methamphetamine Addiction and Ways to Reduce Misuse through Vaccines

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The Neurobiology of Methamphetamine Addiction and Ways to Reduce Misuse through Vaccines

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Abstract: The methamphetamine epidemic continues to worsen each year and has contributed to more overdose deaths than opioids. Methamphetamine was listed in the top ten lethal drugs in 2021 in the United States. The drug has been shown to cause many health problems. One solution to this crisis is through vaccinations. Although still early in the development phase, vaccinations have been found to improve withdrawal symptoms and decrease drug seeking behavior with minimal health side effects compared to medications.

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1. Introduction

Methamphetamine is a derivative of amphetamine that was synthesized in 1893 for the intended use for depression, narcolepsy, weight loss, and an over-the-counter nasal decongestant (1,2). The stimulant played an extensive role in keeping troops awake in World War II (2). With this drug having a high potential for physical dependence, recreational use of the crystalline white powder was outlawed in the US in 1970 (1). Despite this, misuse dramatically increased in the 1990s (3). Long term methamphetamine misuse puts individuals at risk for Parkinson's Disease, HIV/AIDs, and other opportunistic infections (4,5).

Methamphetamine use disorder is a global concern, impacting users' organ systems, particularly the neurological and cardiovascular systems (6). Approximately 35 million people worldwide and 10 million people in the US used methamphetamine in 2020 (7). There are several recreational routes of administration whether it be oral, snorted, smoked, or injected (8). This small lipophilic agent rapidly crosses the blood-brain barrier, allowing the drug to have an increased absorption in the central nervous system (CNS) and having lasting effects (9). Reports from the Research and Development Corporation in 2009 show the economic burden of methamphetamine use in the US was $23.4 billion (10). These costs include treatment and rehabilitation, premature death, criminal justice, and child endangerment (10).

There are limited efficacious pharmacotherapeutic options available to combat this highly addictive substance (11). Immunopharmacotherapy has shown promise as a treatment strategy for drug addiction in recent years (12). Evidence supporting the use of vaccines for addiction included significant self-administration of cocaine and nicotine using rodent models (13). Given the findings for these studies, the development of a vaccine for methamphetamine has the potential to treat methamphetamine misuse.

The studies showed significant decrease in drug self-administration can be achieved via higher levels of a drug-specific antibody (13). A sufficient antibody response is required for the immunotherapeutic strategy to be efficacious (11). Effective processing and recognition of the antibody-drug complexes by leukocytes produced long lasting antibody responses (14). As a result, methamphetamine misuse and the possibility of future relapses and overdoses can be reduced. A Phase II trial (NCT03336866) examining monoclonal antibodies has been shown to be safe, tolerable,

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and highly efficacious binding to methamphetamine in healthy humans with a history of methamphetamine use (15).

The advantage of using vaccines includes expectations of high patient adherence rates given treatment consists of a few injections over a brief period of time compared to taking pharmaceutical treatments daily or on a weekly basis to produce active immunization, prevent relapses during recovery, reduction of adverse effects and drug reinforcement (16).

Herein, we reviewed the literature on the clinical presentation of methamphetamine misuse, the neuropsychiatric drug-seeking behavior, the anti-methamphetamine vaccine responses and its adverse effects in rodents.

2. Methods

Literature review on vaccine treatments for drug misuse as well as effects of methamphetamine were conducted using a variety of sources and credible databases such as PubMed and Google Scholar using search terms: "methamphetamine", "methamphetamine addiction", "neurological methamphetamine effects", "clinical methamphetamine effects" and "methamphetamine vaccine". Articles evaluating preclinical and clinical trials were examined.

2.1. Clinical Presentation of Methamphetamine Addiction

Methamphetamine targets the CNS via sympathomimetic action. After ingestion, physiological changes such as increased blood pressure, increased temperature, and pupil dilation occur by reverse transport to redistribute catecholamines (17,18). Methamphetamine has a high lipid solubility that leads to rapid transfer of the drug across the blood brain-barrier (19). Methamphetamine affects the CNS and produces adverse effects that include flight or fight symptoms such as increased heart rate, blood pressure, vasoconstriction, bronchodilation and hyperglycemia, euphoria, increased energy, alertness, emotion and a decrease in anxiety (8). A common symptom associated with chronic methamphetamine misuse is methamphetamine-associated psychosis and hallucinations (20,21, 22).

Methamphetamine has a severe effect on the cardiovascular system such as vasoconstriction, pulmonary hypertension and atherosclerotic plaque formation, arrhythmias and heart failure (6). A common illness seen in chronic misuse of methamphetamine can be associated with ventricular hypertrophy which predisposes users to methamphetamine-induced myocardial ischemia (23). The cardiovascular system has complications due to the increase and decrease of certain receptors. For example, an increase in free radicals damages cardiac tissues. If methamphetamine is taken intravenously, an internalized accumulation in the lungs leads to increased reactive oxygen species production (6). Increased reactive oxygen species levels lead to lung damage. Regardless of the route of administration, there are cardiovascular and complications with methamphetamine misuse (23).

Other effects seen with methamphetamine addiction are in the gastrointestinal (GI) and immune system. A common side effect seen in individuals with addiction or withdrawal is weight loss and insomnia (24). Methamphetamine affects the sympathetic and parasympathetic nervous system that regulates the immune system (25). The effects are seen in the mesenteric vessels within the gut that can lead to acute existential ischemia (25). GI and gut pain can also increase irritability in misusers. Other health problems induced by methamphetamine use include vasoconstriction, bowel ischemia, stomach cramping, constipation, and tissue dehydration (25). Often observed are stress-induced symptoms. For example, due to dopamine and norepinephrine release, increased neural activity in the brain stimulates a stress response in the body (25). There is growing evidence methamphetamine causes suppression of the immune system (26).

Substance misuse results in psychological and behavioral changes. Such changes include feeling irritable, feeling like you need the substance every day, changing the high of the drug and being unable to do certain activities without the drug. With methamphetamine addiction, physiological changes take place. An investigation looked at the effects of face asymmetry with methamphetamine addiction and found addiction increased poor performance on face recognition and changes to the individual's face (27). Another study looked at facial appearance changes in methamphetamine users

 doi:10.20944/preprints202305.0045.v1

and found there was accelerated biological aging (27). The following were changes seen to the face with methamphetamine effects: teeth decay, dark circles under the eyes, runny nose or swelling, skin showed sores and itching and loss of soft tissue and weight loss (27).

The social impacts of misusing methamphetamine have been examined. If used when young, school attendance decreased in children. The Ontario Student Drug Use Survey 2005 found that in grades 7-12, there were 2.2% of students who admitted to using methamphetamine (24). This study was followed for 8 years where social side effects include sexual promiscuity, weight loss, poor nutrition and decreased coping strategies (24).

After a single dose, methamphetamine stays in the human body for almost seven days (28). The half life for methamphetamine is 9-24 hours while amphetamine has a half life of 46 hours (40). Side effects of methamphetamine can be short or long term (29). When young adults use methamphetamine, the exposure leads to damaged monoaminergic neurons (30). A study investigating young mice and their level of glial cell line derived neurotrophic factor found there was a decrease in motor activity, nervous system activity and increased behavior problems (30).

Addiction and methamphetamine misuse have behavioral effects on the individual. Not only is there an increase in irritability, but other behavioral patterns are seen. These behaviors are noted in different age groups as well as overall addiction to the drug**.** Common behavior changes are violent behavior and violent criminal behaviors (31). The increase in usage and dependence is seen in drug abuse which can increase addictive behavior. There were social behavior changes seen in those who use methamphetamine as people adapting to smoking the substance instead of injection when around those who do not inject (33). Due to the statistics of increases in crime involvement with methamphetamine use, it was determined there is a likelihood of poor life quality due to decrease in health and social cost (33). Other effects are an increase in sex drive and increased self-confidence (34). The increase in sex drive and the effect of the drug also contributes to HIV rates in misusers (34). Overall, the impact from drug abuse and methamphetamine addiction is seen in individual changes in behavior as well as social behavioral changes.

2.2. The Neuropsychiatric Substrates of Drug-Seeking Behavior

The brain plays a key role in drug-seeking behavior and is the control center for positive and negative feedback which influences drug-seeking behaviors. Nearly one-third of methamphetamine users develop psychotic symptoms such as paranoia, auditory and visual hallucinations, persecutory delusions as well as an increased risk of suicide and violence (33). This is important to understand because the brain can increase drug-seeking behavior and induce lasting effects on itself and the body. The information presented here may help shape therapy programs through acknowledging drug-seeking behaviors may sometimes be outside of one's control.

Some people may be more vulnerable to the effects of drugs due to genes, environmental factors, and lifestyle. Genes contribute to a person's vulnerability to drug addiction, including environmental impact on gene function and expression (36). Environmental factors can create lasting epigenetic changes (36). Conditions such as increased stress and anxiety along with drug usage can result in long-term changes to the brain (36).

2.2.1. A. Mesolimbic Dopamine (DA) System

The mesolimbic dopamine (DA) system is also known as the reward center. It is responsible for the euphoric feelings due to the release of neurotransmitters such as norepinephrine and dopamine in the brain (37). The DA system acts as positive feedback for drug-seeking behaviors which motivates drug use. Rats that were administered a dopamine (D_3) receptor antagonist, VK4-116, showed reduced drug-seeking behaviors after drug reinstatement following withdrawal (35). In another study, rats repeatedly exposed to cocaine (stimulating dopamine release in the brain like methamphetamine) for 24-hour intervals showed an escalation in self-administration and drug intake than when drugs were administered between ten-day intervals (38). With prolonged and frequent drug usage, both D_1 and D_2 dopamine receptors in the brain began to decrease. This indicates more

 doi:10.20944/preprints202305.0045.v1

dopamine must be released and bind to dopamine receptors in order to achieve prior levels of euphoria.

Subsequently, other activities that produce enjoyment such as eating and socializing with family cannot supply enough dopamine as drugs which makes these activities feel flat. This further encourages drug intake for emotional stimulation. Additionally, prolonged drug usage leads to decrease in dopamine transporters (39). Dopamine transporters are specialized cells in the CNS that remove dopamine from the synaptic cleft (40). A decrease in dopamine transporters increases dopamine in the synaptic cleft, allowing more dopamine to bind to receptors on the postsynaptic neuron to prolong euphoric effects. Additionally, prolonged drug use has been linked to dopaminergic axon degeneration where severe degeneration has been linked to the development of Parkinson's disease (40). There are three core regions in the brain that largely affect drug usage: basal ganglia, extended amygdala, and prefrontal cortex (41).

2.2.2. B. Basal Ganglia

The basal ganglia is part of the nigrostriatal dopamine pathway that works together with the DA system to produce euphoric effects and increased addiction behaviors. Specifically, it is responsible for coordinated movements and motivating behavior. It is essential to encourage prolonged drug-usage. There are two sub-regions in the basal ganglia that particularly contribute to drug-seeking behaviors. The first region is the nucleus accumbens which is involved in the euphoric experience and positive feedback (37). The second region is the dorsal striatum, which is involved in habituation and other drug-seeking behaviors including compulsive drug use (37). In methamphetamine users, the basal ganglia have been linked to structural changes and metabolite alterations which are associated with the production and persistence of psychiatric symptoms in abstinent users (70). Rats treated with a neurotoxic regimen of methamphetamine exhibited long-term changes to the striatonigral region when tested three weeks following methamphetamine administration (72). Thus data indicates altered basal ganglia function. Increased iron levels, which is typically observed in aging, were found in the basal ganglia after methamphetamine use which makes the area vulnerable to oxidative stress (71).

2.2.3. C. Extended Amygdala

The extended amygdala controls feelings of stress, anxiety and unease (42). It is responsible for the withdrawal effects, also known as the "dark side" of addiction, and is the main reason for drug relapse. With prolonged drug use, addicts transition from seeking rewarding effects to avoiding the emotional distress and physical discomfort that comes with withdrawal (42). Additionally, the extended amygdala increases sensitivity. This causes "drug hunger" which contributes to compulsive drug-seeking behaviors and leads to habituation to decrease stress. With increased withdrawal effects, the brain sends corticotropin-releasing factor, norepinephrine, and dynorphins into the extended amygdala which contributes to the negative emotional states (43). Patients who have obsessive-compulsive disorder were more motivated by the desire to avoid stress and negative emotional states compared to controls (44). This indicates negative reinforcement avoidance plays a role in compulsive behaviors.

2.2.4. D. Prefrontal Cortex

The prefrontal cortex (PFC) is located in the frontal lobe of the brain and is responsible for executive functions such as planning, solving problems, and making decisions. It plays a role in executing compulsive activities as well as impulse control (37). With prolonged drug use, the PFC becomes more dysfunctional (37). Functional magnetic resonance imaging identified numerous metabolic differences in the PFC among methamphetamine users during cognitive and socioemotional tasks (45). This lowered the ability to make decisions and exert control over their actions in the user which increased risk-taking and lower self-control.

2.2.5. E. What PET Imaging Has Shown Us

 doi:10.20944/preprints202305.0045.v1

Positron emission tomography (PET) is most widely used to image the brain in adults with addiction (44). This technique is minimally invasive and yields information on acute and long-term drug-induced structural and functional changes in the brain over time, making it favorable to study drug addiction (46). In a study that tracked methamphetamine users through PET imaging, dopamine transporters decreased after repeated methamphetamine use but could be restored after fourteen months of abstinence (35). This report confirmed structural abnormalities in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and prefrontal cortex (PFC) with hypoactivity in ACC and PFC which supports the diminished control of an addict's drug usage, make decisions, execute abstinence, and carry out other executive functions (47,48).

Neuroimaging also revealed changes to the extended amygdala. Prolonged use of drugs increased activation of the amygdala and decreased control of the PFC over the amygdala (37). This decreased control over one's emotions and stress which increased negative reinforcements. Imaging also showed changes in the metabolic activity in other brain regions involved in drug hunger craving including the thalamus, cerebellum, and striatal complex (37). Prior to craving sensations, neuroimaging revealed the activation of the ACC which corresponds to the mood states involved in drug need (37). Through imaging and brain measures, a positive correlation was found between cognitive performance and brain regional volume/density, blood flow, glucose metabolism, creativity, and activation in methamphetamine users (49).

Lastly, drug abuse can harm the neurodevelopment of fetuses. Fetal brain structures, in particular the frontal cortex and subcortical areas were found to be highly susceptible to functional and structural change due to intrauterine drug exposure (50).

Sections of the brain work together to stimulate drug-seeking behaviors. While the brain exhibits neuroplasticity and other mechanisms to restore itself, certain brain transformations can increase drug-seeking behaviors while other areas of the brain suffer irreversible damage (2).

2.3. Treatment Vaccine Response In Rodents

Currently, the US FDA does not have approved medications for the treatment of methamphetamine addiction. Addressing methamphetamine drug-seeking behaviors is hard to apply given the limitations of human studies. Exploring options such as IXTv-100 (addresses the the relationship between the CNS and dopamine signaling after methamphetamine administration), toll-like receptor-4 (TLR-4) agonists such as E6020 (boosts anti-addiction immunity with methamphetamine) conjugate vaccine and immunity treatments, are all previously explored treatments in rodents (12, 54, 11). By exploring these previously tested rodent treatments, we can assess whether these options may be better suited for human treatment with methamphetamine misuse.

2.3.1. A. IXTv-100 Rodent Related Studies

As of March 2023, there are limited studies on the effects of methamphetamine reduction related vaccines in humans. However, the reduction of methamphetamine misuse and its relationship to specific vaccines are well researched among rodents (12). Such studies are utilized as a way to obtain data as it also relates to humans. In 2019, a study was conducted to increase antibodies to reduce methamphetamine related addictive behavior by administering the methamphetamine vaccine IXTv-100 to rodents (12). These mice were able to self-administer methamphetamine over an eight-week period through a reinforcement lever of various dosages before administering repeated injections of IXT-v100. There were decreased levels of methamphetamine-seeking behavior in rodents exposed to IXT-v100 (12). IXT-V100 can work in combination with glucopyranosyl lipid to decrease drug seeking behavior (5). Vaccination reduced meth-self administration by 50% (51). This investigation show psychostimulants can control the CNS. The need for drug seeking excitation affects both active and passive forms of conjugate vaccines and monoclonal antibodies (mAbs) (52). The anti-methamphetamine antibodies found in vaccine treatment lead to reduced drug seeking behaviors and the increase of methamphetamine bound in the bloodstream (12). These studies show the presence of mAbs decreased methamphetamine levels in the brain. IXT-v100 related vaccines

 doi:10.20944/preprints202305.0045.v1

increased that resulted in decreased neurotransmitter release. This treatment reduces methamphetamine in the bloodstream to prevent the crossing of the blood-brain barrier (12). Methamphetamine usage is known to affect multiple neurotransmitters including dopamine, norepinephrine and serotonin (16). By altering the neuropsychological effects caused by methamphetamine misuse, drug seeking behavior can be reduced (16). These studies show the benefit of utilizing IXT-v100 as a future vaccine alternative for humans for the reduction of methamphetamine (12, 16).

2.3.2. B. E6020 Rodent Studies

Other studies utilized rodents to investigate reduction of methamphetamine substance use disorder by receptor agonists such as E6020. E6020 is a toll-like receptor agonist which enhances other vaccines such as succinyl-methamphetamine absorbed on aluminum oxide. In one study, methamphetamine hydrochloride was injected into mice. A control group of mice that did not receive methamphetamine hydrochloride was compared to rodents treated with the E6020 vaccine. The vaccinated rodents had higher rates of antibodies and decreased levels of methamphetamine in the brain (53). Using receptor agonists such as E6020 in anti-addiction vaccines produced a high level of specific antibodies so methamphetamine will not be able to pass the blood-brain barriers (54). This mouse study provides further clarity on generating human related vaccines (54).

While E6020 was used in vaccines to increase immunizations of antigen-specific antibodies, there was a reduction of drug hunger (55). More research is needed to uncover the relationship between methamphetamine and drug hunger and the compulsive need for more methamphetamine (55). Vaccines using E6020 reduce the side effects associated with substances like methamphetamine in the human body (54). Using rodent studies to investigate the relationship between blood brain barrier related vaccines and methamphetamine misuse can be helpful for humans in the future.

2.3.3. C. Methamphetamine Conjugate Vaccine

Reducing addiction related behaviors was studied using methamphetamine conjugate vaccine (ICKLH-SMO9). Rodents were trained to use a lever to attain food. Assessments were made in relation to food behavior. After four months of training, rodents received a dose of methamphetamine. A group of rodents injected with high levels of methamphetamine had reduced food intake compared to the rodents given a dose of the vaccine after methamphetamine administration. Food habits were not altered in the vaccinated group. This indicated the antibodies of the methamphetamine conjugate vaccine reduced methamphetamine related behaviors in rodents, showing its usefulness in future pharmacovigilance in humans (11). Other rodent studies examined the relationship between ICKLH-SMO9 and antibody response by studying blood samples post injection. Radioimmunoassay analysis showed higher antibody response in rodents injected intramuscularly with the vaccine (69). Methamphetamine conjugate vaccines consist of drug-based haptens conjugated to immunogenic carrier proteins (54). . Generating vaccines to alter the behavioral effects, such as the feelings of euphoria, will reduce misuse.

2.3.4. D. Active and Passive Immunity on the Reward System

The effects of methamphetamine on active and passive immunity is not fully understood in humans. Past rodent studies investigating immunity provide insight to immunity and methamphetamine misuse in humans. Rodent studies show more research is needed to create active and passive immunity related vaccines (57,61). Methamphetamine increases dopamine, serotonin, and epinephrine (56). When methamphetamine is misused, rapid release of these neurotransmitters affects the reward system (57). Human methamphetamine misuse affects not only the CNS but various cell and tissue types (61). It engages the reward system, specifically euphoria and self-confidence, which leads to addiction (58). Increasing antibodies within the bloodstream reduces the effects of methamphetamine and thus decreases the effects on the reward system (56). Methamphetamine activates the reward system after crossing the blood brain barrier to increase

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dopamine in the mesolimbic and mesocortical pathways (61). This builds tolerance in the reward system and misusers need higher doses of methamphetamine to attain the euphoric feeling (61). By regulating the neurotransmission of methamphetamine within the CNS through vaccines, there might be a reduction in methamphetamine misuse behaviors (61).

Further research on human vaccine clinical trials need to be considered for methamphetamine (23). The CNS and immune systems contribute to these variations. The CNS inflammatory response in humans has different triggers that are hidden in by the blood brain barrier. More research is needed in finding those hidden triggers (60). Further study is is also needed to create a vaccine to help assist the immune system to mitigate the effects of methamphetamine misuse (60). Past research indicates T cells, natural killer cells, macrophage dendritic cells and B cells are affected in humans misusing methamphetamine (60). A decrease in addiction leads to a decrease in dendritic cells (26). Knowing more of the signals in the immune system will aid in creating more effective vaccines (60).

2.4. Adverse Effects of Current Vaccines

Past research in rodents showed active vaccination can reduce the physiological and behavioral effects of methamphetamine (3,4,5,9,11,12,13,16,61). Active vaccination attenuated methamphetamine induced disruptions of thermoregulation, wheel activity and stereotype after methamphetamine was administered in high doses (61). Methamphetamine increased rectal temperature in rodents at 27^{o}C and decreased body temperature at 23^{o}C in unvaccinated control groups (61,56). In the vaccinated groups, these disruptions were attenuated (61). The efficacy of this approach depended on the antibody concentration responses and the affinity and specificity of antibodies to methamphetamine (61). Vaccinated groups also showed increased >6,600% methamphetamine levels in serum and >60% decreased methamphetamine levels in the brain after injection with the drug (56, 61). This indicates the vaccine offers neuroprotection in the CNS against the effects of the drug (56, 61).

Behavioral effects were also attenuated in vaccination groups as well. Behavior was measured using wheel activity. Given methamphetamine is a stimulant, there was a significant increase in physical activity induced by meth (1). In vaccinated rodents, there was a 50-70% decrease in meth induced wheel activity (61,62, 63). This is consistent with previous stimulant studies with cocaine and nicotine vaccine (44).

Prior preclinical studies using rodents suggest vaccine administration is safe as there were no adverse effects (11,61,63). Vaccination strategies against methamphetamines are still under investigation by researchers and clinicians (15). Strategies utilizing either active or passive immunization have shown potential (15). Not only can the vaccine efficacy be drastically different in human patients compared to animal models, the quantity of antibodies produced and the safety profile including side effects could also be significantly different (15). Progression to clinical trials using human subjects will provide further information on the safety profile of the vaccine (15).

Future clinical trials using human subjects need to be able to control the level of antibodies since there is variability amongst individuals (65). Measuring the effectiveness of the vaccine using antibodies titers is also not certain (65). Human subjects should also have a strong motivation to end their drug dependency as there is a risk of overdose to compensate for the vaccine (65). Because the vaccine limits methamphetamine from crossing the blood-brain barrier, the positive reinforcement of feeling euphoric will not be achieved (65). However, patients who are addicted may take higher doses of the drug to achieve a high, putting their lives at risk (65).

3. Conclusions

Originally created to address narcolepsy, attention deficit disorder, obesity, and fatigue, methamphetamine has now become one of the misused drugs of choice not only in America but around the world (64, 66). Methamphetamine was the second most popular drug in 2019 and is now the most dangerous drug in 2022 according to Harvard School of Medicine (67,68). Longitudinally in the US, drug overdose death rates have increased 300% from 2013 to 2019 and increased significantly during COVID-19 (64). From January 2020 to December 2020, it was reported an estimate of over

93,000 overdosed deaths were due to psychostimulants including methamphetamine (64). Methamphetamine deaths are the highest in the US and affect all age groups (68). The rates also increased in other countries such as Australia and Canada (64). The overdose epidemic poses a challenge to resolving this public health issue in the community and healthcare system (64). One solution is conducting research in reducing overdose risks and patterns and using vaccines as a preventative treatment (64).

The need for treatment is dire as the substance use disorder rates continue to rise (51). Methamphetamine use disorder is challenging to treat since the long-acting effects contribute to the increase in rates of misuse (66). Treatment using methamphetamine vaccines reduce drug side effects and rates of mortality and morbidity (16). Associated long term side effects include vascular complications, neurological impairments, physical injuries and physiological impairments (66). Other reported side effects include shortness of breath, agitation, anxiety, delusions, hallucinations and seizures (68).

People misusing methamphetamine often combine multiple opioid substances, contributing to the increased rates of mortality and morbidity (51). Hawai'i High Intensity Drug Trafficking Area reports methamphetamine is often taken with heroin to reduce withdrawal symptoms (66). This is one concern where preclinical trials using rodents are limited as results may not translate in humans (51).

The lack of clinical trials using human subjects fails to paint an accurate response of the vaccine's safety and efficacy (51). Clinical trials evaluating the immunological response of vaccines on methamphetamine usage are needed to provide insight of key players in the pathway in the peripheral and CNS (60). Prevention and early intervention studies tackling drug misuse using vaccines is also needed. Further research on vaccine treatments is one step closer to reducing misuse of the most dangerous drug in America.

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