Research Article

DEMOGRAPHIC PROFILE, SUBSTANCE USE TRENDS AND ASSOCIATED PSYCHOTIC DISORDERS AMONG VETERANS WITH MENTAL HEALTH CONDITIONS: A RETROSPECTIVE COHORT STUDY OF US VETERANS

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Abstract

Background: Amphetamine and other substances induced psychotic disorder and associated suicidal risk among hospitalized US veterans is not clear.

Aims: To understand the demographic profile, substance use trends, psychotic disorders and suicide attempts in veterans hospitalized with acute Mental Health Conditions (MHC).

Methods: Veterans Affairs Informatics and Computing Infrastructure Database (ICD) and codes were used to identify veterans hospitalized with MHC diagnosis between 1999 and 2022. Laboratory records used to determine types of substances used hospitalization frequency, all-cause mortality, suicide attempts and suicide outcomes. SAS was used for statistical analysis.

Results: Among veterans with MHC, psychosis, manic-bipolar and PTSD were common diagnosis. Psychosis was comparatively less among males above 50 years of age, but prevalent among Hispanics. In general, substances use was significantly higher, and amphetamines were most used, followed by cannabis codeine, morphine, cocaine, barbiturates, fentanyl, and PCP among veterans with MHC. Amphetamine induced psychotic disorder persisted in 22.28% and other substance induced psychotic disorder persisted in 77.72% of veterans hospitalized with MHC. Psychosis was associated with higher rates of hospitalization, suicide attempts, and suicide death.

Conclusions: Among US Veterans with MHC, amphetamine was most used substance associated with higher rates of psychotic disorders, hospitalization, suicide attempts, and death. ***ASEAN Journal of Psychiatry, Vol. 25 (7) July, 2024; 1-11.***

Keywords: Psychotic Disorders; Hospitalization; Suicide Attempts; Depression; Anxiety

Introduction

Substance use is a common condition and often presents with psychotic symptoms. In fact, 7%-25% of first episode psychosis is precipitated by substance use [1]. Conversion rates from Substance-Induced Psychotic Disorders (SIPD) to a Primary Psychotic Disorder (PPD) such as schizophrenia vary with type of substance used. Rates are highest (34%-50%) among cannabis-induced psychotic disorder and lowest (5%) among alcohol-induced psychotic disorder [2-6]. Methamphetamine use can induce a psychotic state known as Amphetamine-Induced

Psychotic Disorder (AIPD) as defined by the Diagnostic criteria in the fifth edition (DSM-5) of the diagnostic and statistical manual of mental disorders. There are an estimated 27 million amphetamine users worldwide and approximately 2.3% of the North American population between the ages of 15-64 have used amphetamines in the past year [7]. It is estimated that as many as 40% of amphetamine users experience AIPD [2].

Established risk factors for AIPD include a history of a PPD, schizotypal and antisocial personality disorders, family history of mental illness, and methamphetamine dependence [8]. Conversion rates from AIPD to a primary psychotic disorder are in the range of 19%-40% [2,3,6,9,10]. There are many Subjects (or is it Subjects-level) factors that contribute in conversion from a SIPD to a PPD (schizophrenia or schizoaffective disorder) including a family history of schizophrenia in a first degree relative, male gender, subjects living in urban areas, an extended duration of untreated psychosis, continued substance abuse after index psychotic episode, younger age at the time of the first episode of substance induced psychosis, and having a preexisting diagnosis of either a substance use disorder, personality disorder (specifically schizotypal and antisocial), or an eating disorder prior to the index psychotic episode [2,6,11]. Moreover, conversions may occur rapidly. In one study, it has been shown that 50% of conversions from SIPD to schizophrenia occur within 3.1 years of the index substance induced psychotic episode [6].

Treatment of Substance Use Psychotic Disorders (SIPD) is evolving [12]. It is a recent diagnostic addition in the DSM-IV and has fallen under significant scrutiny [13]. Subjects presenting psychotic in the context of substance abuse are often diagnosed with AIPD and providers may neglect to consider the presence of an underlying primary psychotic disorder. Confirmation bias is an issue may delay in antipsychotic treatment or inaccurate Subjects advice that the symptoms will resolve with cessation of drugs alone. This may lead to suboptimal treatment of Subjects with SIPD [12]. Additionally, the SIPD Subjects population is often excluded from clinical trials resulting in a paucity of data to guide clinicians for subjects' management [14,15]. This is alarming because AIPD Subjects suffer from severe symptoms, higher rates of hospitalization, and are more likely to attempt suicide than methamphetamine users without psychotic features [16]. Furthermore, younger AIPD Subjects with an average age of 30.4 years and a history of requiring hospitalization have unusually high mortality rates (>8%) within 6 years of hospitalization [9]. This is of particular concern within the veteran population given that the suicide rate is higher among veterans as compared to the general population and suicide rate is doubled among veterans with a diagnosis of a substance use disorder [17,18]. Despite alarmingly high rates of mortality within the AIPD subjects population, treatment is often delayed resulting in prolonged periods of psychosis and a poor prognosis [5]. To date there are only few studies conducted in the in the veteran population. Given the elevated risk of suicide within the veteran population this study was undertaken to understand the demographic profile, incidence of mental disorders, substance use trends and associated psychotic disorders among subjects with mental illness admitted to a National VA Medical Center (VAMC).

Materials and Methods

Data base and study design

Veterans' Health Administration's Corporate Data Warehouse (VHA-CDW) uses a unique identifier to identify veterans across treatment episodes at more than 1,400 VHA centers organized under 21 Veterans Integrated Service Networks (VISNs). The VHA-CDW database contains veteran health care information comprised of diagnostic, laboratory, pharmacy, and other procedure related data from various sources in the electronic health record. VHA-CDW data and the VA Informatics and Computing Infrastructure (VINCI) workspace have been used widely for numerous studies of clinical importance. Since we used VHA-CDW and VINCI to extract data, consent has not been necessary for this retrospective cohort study [19].

Study population

Mental health conditions, a composite measure that included Psychosis, Manic-bipolar disorders, PTSD, schizophrenia, depression and TBI all defined by ICD-9 and ICD-10 according to International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth Revision (ICD-9, ICD-10) codes, between October 1, 1999, and February 27, 2022. The study population consisted of 156,435 veterans with MHC diagnosis (Group 2). We randomly selected a total of 156,189 cases of admissions of

similar gender, race, and age without any MHC diagnosis (Group 1) during that period, balanced for confounding factors such as age, race, sex, smoking and Type 2 diabetes. The final study groups comprise cases admitted to hospital with and without various mental illnesses.

Data analysis

We used the date of first admission (first occurrence in the data set) in the sample period 10/1/1999 through 02/27/2022 as the index time point to differentiate pre-existing and new events data and used a combination of standard SQL accessible files such as ICD, lab, or drugs and free text medical and administrative record searches to collect information on conditions, medications, and procedures.

Data were mainly used as categorical variables and was analyzed by standard frequency tables (chi sq and Odds ratios) using SAS (Guide 8.2) was used for statistical analysis. Continuous variables such as age are shown as Means (± SD). Odds ratios (OR) were also calculated. A Logistics procedure was used to initially evaluate associations of multiple variables with the various outcome variables. A greedy neighbor (nearest neighbor) procedure was used as given by SAS for the evaluation of all-cause mortality (death).

Principal outcomes were designated as number of hospital admissions (1-9 or >10), suicide rate (attempts/demise) and all-cause mortality among two groups. Frequencies, means, and Odds ratios were calculated and are reported in the tables and a p-value of <0.01 was deemed significant.

Ethics approval

This study (IRBNet #1663414) was approved by the Kansas City VA Medical Center (FWA 00001481) Institutional Review Board (IORG 0000081) on March 17, 2022, and complies with the declaration of Helsinki.

Results

Demographic characteristics of study population

We categorized principal demographics age groups (18-25, 26-35, 36-50, 51-65 and >65 years), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, white, White Not of Hispanic origin and declined to answer/ unknown), ethnicity (Hispanic/Latino, non-Hispanic/Latino and unknown/declined to answer) and marital status (single/never married, married, separated/divorced, widow/widower/widowed and unknown/missing).

As shown in Table 1, age had a measurable effect on prevalence of mental illness. The proportion of subjects with a diagnosis of mental illness increased up to the 50 years and declined in >50 years old subjects. Age groups (18-25, 26-35, 36-50, 51-65 and >65 years) are shown. In general, older subjects did better (OR=0.81, p<0.001).

Table 1. Demographic characteristics of study population.

	Group 1, subjects with no Mental Health Conditions (MHC) diagnosis N=156,189	**Group 2 subjects with MHC diagnosis N=156,435**	**p-value Group 2 *vs* Group 1**
AGE groups, number (%)			
18-25 years	125 (0.08%)	172 (0.11%)	-
26-35 years	6,388 (4.09%)	9,730 (6.22%)	-
36-50 years	24,537 (15.71%)	33,555 (21.45%)	-
51-65 years	80,422 (51.49%)	74,760 (47.79%)	-
Above 65 years	44,701 (28.62%)	38,201 (24.42%)	-
≥ 50 years	44707 (28.62%)	38,178 (24.42%)	-
<50 years	111,483 (71.38%)	118257 (75.58%)	<0.001
Gender (sex), number (%)			
Male	147,769 (94.61%)	146572 (93.7%)	

Female	8,421 (5.39%)	9,855 (6.3%)	<0.001
Race characteristics-number (%)			
American Indian/Alaska native	1327 (0.85%)	1455 (0.93%)	-
Asian	500 (0.32%)	720 (0.46%)	-
Black/African American	63,788 (40.84%)	62,089 (39.69%)	-
Native Hawaiian/other pacific islanders	984 (0.63%)	1001 (0.64%)	-
White	82,218 (52.64%)	84006 (53.7%)	-
White not of Hispanic origin	594 (0.38%)	469 (0.3%)	-
Unknown or declined to answer	6,779 (4.34%)	6695 (4.28%)	-
White	80,037 (51.24%)	83,431 (53.33%)	<0.001
Others	76,153 (48.76%)	73,012 (46.67%)	
Ethnicity characteristics, number (%)			
Not Hispanic/Latino	144,209 (92.33%)	143482 (91.72%)	-
Hispanic/Latino	7403 (4.74%)	9057 (5.79%)	<0.001
Unknown or declined to answer	4576 (2.93%)	3614 (2.31%)	-
Marital status, number (%)			
Single/never married	38,204 (24.46%)	41,721 (26.67%)	-
Married	28,176 (18.04%)	27157 (17.36%)	-
Separated/divorced	83,483 (53.45%)	81,925 (52.37%)	-
Widow/widower/widowed	5592 (3.58%)	5350 (3.42%)	-
Unknown/missing	734 (0.47%)	282 (0.18%)	-
All-cause mortality, number (10%)			
Alive	1,02,380	1,12,023	<0.001
Dead	53,810	44,412	-
Note: Numbers (%); Total subjects (percent).			

Males were less frequently associated with mental diagnosis than females (OR=0.85, p<0.001). There was a difference in the prevalence of mental illness based on race (White *vs* other OR=0.92 p<0.001). Race and ethnicity were grouped (American Indian or Alaska native, Asian, black, or African American, native Hawaiian or other Pacific Islander, white, white not of Hispanic origin and declined to answer/unknown), ethnicity (Hispanic/Latino, Non-Hispanic/Latino and unknown/declined to answer) of interest, Hispanic were more likely to carry a diagnosis of mental illness (OR=1.28, p<0.001).

Marital status was examined (single/never married, married, separated/divorced, widow/widower/widowed and unknown/missing). A great majority of subjects in the study were divorced or separated. About 18% were married and about 25% had never been married of interest, death during study period was less common (OR=0.740, p<0.001) in mental illness group compared to control group.

Distribution of various MHC diagnoses

As shown in Figure 1, psychosis, manic-bipolar and PTSD were most common diagnosis at 28% each followed by schizophrenia (9.83%) and depression (6.66%). TBI was uncommon at 2.4% of cases. Our analysis did not exclude any cases from any category where there was overlap as the primary condition could not always be identified.

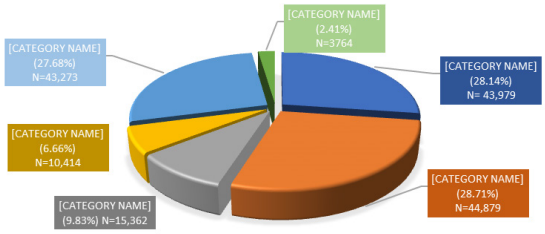

Figure 1. Prevalence represented by subjects' number (N) and percent (%) of various diagnoses among total numbers of veterans hospitalized with MHC between 1999 and 2022.

Frequency and types of substances used

Overall drugs use was very frequent in Group 2-MHC diagnosis (OR 11.1). There were notable differences for the types of drugs used. Barbiturates (OR 4.9), PCP (OR 5.0), and Cocaine (OR 5.2) use increased to a similar degree. Amphetamines (OR 9.4), Cannabis (OR 10.5) and Codeine (OR 13.9) were all increased even more strongly and a monumental increase in use of Morphine (OR 38.6) and Fentanyl (OR 57.9) was found in subjects with MHC.

As shown in Table 2, subjects with MHC diagnosis (Group 2) were significantly associated with an overall increase in substance use as compared to Group 1-no-MHC (11.98% *vs* 1.37%). The most abused substance was amphetamines (2.67% *vs* 0.29%) followed by cannabis (2.3% *vs* 0.23%), codeine, morphine, and cocaine. These were all at least two times as common as barbiturates or fentanyl. PCP use was uncommon among these subjects.

Primary and drug-induced psychosis among veterans with mental health conditions

As shown in Table 3, about 28% (N=43,979) of 156,435 subjects with mental illness in this study carried a psychosis diagnosis of which majority were non-substance users (88.1%, N=38,710). Among 11.9% substance users (N=5269) with psychosis, only 1,174 subjects used amphetamine resulting in an Amphetamine Induced Psychotic Disorder (AIPD) rate of 22.28%. Psychosis among other substance users including cannabis, codeine, morphine, cocaine, barbiturates, fentanyl, and PCP persisted in 4,095 subjects resulting in Substance abuse related Psychosis Disorder (SIPD) rate of 77.72%.

Frequency of hospitalization, suicide attempts and suicide death

Principle outcome examined included >10 hospitalization, suicide, attempts and suicide death. As shown in Table 4, frequency of hospitalization (>10 admissions) was significantly higher (p-value <0.001) in population with mental illness, Group 2 (52.95%) as compared to no mental illness Group 1 (47.11%) with an OR=1.22. Similarly, rate of suicide rate, attempts and death was also significantly higher (p<0.0001) in mental illness Group 2 as compared to no mental illness Group 1.

Table 2. Substances use frequency among subjects with and without Mental Health Conditions (MHC) diagnosis.

	Group 1 no MHC 156189	**Group 2 MHC 156435**	**Odds ratio Group 2 *vs* Group 1**	**p-value Group 2 *vs* Group 1**
Drug users N (%)	2134 (1.37%)	18,744 (11.98%)	11.1	<0.0001
Amphetamine	453 (0.29%)	4179 (2.67%)	9.4	<0.0001
Barbiturates	406 (0.26%)	1927 (1.23%)	4.9	<0.0001
Cannabis	359 (0.23%)	3617 (2.31%)	10.5	<0.0001
Cocaine	513 (0.33%)	2650 (1.69%)	5.2	<0.0001
Codeine	222 (0.14%)	3051 (1.95%)	13.9	<0.0001
Fentanyl	13 (0.01%)	750 (0.48%)	57.5	<0.0001
Morphine	52 (0.03%)	1987 (1.27%)	38.6	<0.0001
PCP	116 (0.07%)	583 (0.37%)	5	<0.0001

Note: Numbers as (percent) of total subjects in Group1 (control) and Group 2 (MHC); p-value represents significance when compared Group 2 *vs* Group 1.

Table 3. Amphetamine-Induced Psychosis Disorder (AIPD) *vs* other Substances-Induced Psychosis Disorder (SIPD) among subjects diagnosed with psychosis.

Total veterans with MHC N=156,435		
Veterans with Psychosis DX N=43,979 (28.14%)		
Substance users, N=5,269 (11.98%)		Non-substance users N=38,710 (88.01%)
Amphetamine users, N=1,174	Other substance users N=4095	
AIPD rate 22.28%	SIPD rate 77.72%	
Note: Numbers as (percent) of total subjects in the category; AIPD and SIPD rate in % is calculated by dividing numbers of amphetamine and other substances users by the number of substance users with psychosis diagnosis.		

Table 4. Comparison of outcomes among subjects with and without MHC.

Measured outcome	**Group 1 control (no-MHC)**	**Group 2 MHC diagnosis 156,435**	**Odds ratio Group 2 *vs* Group 1**	**p-value Group 2 *vs* group 1**
>10 admissions	73,581 (47.11%)	81,419 (52.05%)	1.22	<0.0001
Suicide	3,972 (2.54%)	58,012 (37.08%)	23.32	<0.0001
Attempt	2,644 (1.69%)	43,035 (27.51%)	57.5	<0.0001
Suicide	1,328 (0.85%)	14,698 (9.40%)	38.6	<0.0001
Note: Numbers as (percent) of total subjects in Group 1 (control) and Group 2 (MHC); p-value represents significance when compared Group 2 *vs* Group 1.				

Discussion

Demographic characteristics of our study population demonstrated that mental illness diagnosis was less frequently associated with males than females (OR=0.85, p<0.001). These findings parallel global statistics. The age-standardized disability-adjusted life-years rate for mental disorders, prevalence and incidence rates of common mental disorders, specifically affective disorders, such as anxiety and depression, is greater in females than males [20,21]. We found that overall mortality was less common (OR=0.740, p<0.001) in mental illness group compared to control group. This correlates with the findings of the systematic analysis for the Global Burden of Disease Study 2019, which concluded that estimated years of life lost for mental disorders were low and do not reflect premature mortality in individuals with mental illness [20]. Veterans of Hispanic origins were more likely to carry a diagnosis of mental illness (OR=1.28, p<0.001). Our data and published reports suggest a need to do additional epigenetic and sociocultural research in the Hispanic population [22].

We found that substance abuse was significantly higher in the mental illness group (11.98%) compared to the control group (1.37%, (OR=11.1). Co-occurring Substance Use Disorders (SUD) with Mental Disorders is a well-known phenomenon, frequently referred as a dual diagnosis, which is highly prevalent and represents a serious national health problem. Unfortunately, it is often under-diagnosed and therefore, poorly treated. In a nationally representative U.S sample, dually diagnosed adults are estimated to represent 17.8% of the 75.6 million adults diagnosed with SUD and Mental disorder [23].

We observed a monumental increase in abuse of morphine (OR=38.6) and fentanyl (OR-57.9) by 48 and 42 times, respectively, among subjects with mental illness when compared with hospitalized adults without concurring mental illness. It is well known that a dual diagnosis is especially prevalent among adults with the Opioid Use Disorder (OUD) and that it increases the risk for morbidity and mortality. For instance, 24.5% of adults with OUD and recent mental illness in the past year and 29.6% of adults with OUD and serious mental

illness reported receiving services for both mental health and substance use treatment [24]. This is alarming because opioid abuse in the US has reached an epidemic status. The alarming increase in fentanyl abuse found in our study corresponds with the current course of the US opioid crisis. Three main causes for the opioid epidemic are:

- Increase in prescription of opioids,
- Drug use, and
- Access to illicitly manufactured fentanyl. Centers for disease control and prevention statistics estimated 500,000 opioid associated deaths between 1996 and 2019.

While death related to the opioid drug overdose started to decline in 2017, Fentanyl use associate deaths continue to increase [25].

Use of amphetamine among veterans with mental illness is higher than estimated use among 15-64 years old North American population. We detected that amphetamines (OR=9.4), cannabis (OR=10.5) and codeine (OR=13.9) abuse was 9.2 to 13.92 times more frequently noted in the MHC group. Moreover, amphetamine was the most frequently used substance (2.67%), followed by cannabis (2.3%), codeine, morphine, cocaine, barbiturates, fentanyl, and PCP in the mental illness group. Our findings correlate with both nation and worldwide trends, showing that synthetic drugs, represented by methamphetamine, have become the most abused drugs in the world and have surpassed traditional drugs of abuse (including opioids). The rates of stimulant use disorders, including methamphetamine, and stimulant-related overdose and mortality is steadily increasing in the USA [26-29].

We observed that Amphetamine Induced Psychotic Disorder (AIPD) presented in 22.28% whereas other Substance (cannabis, codeine, morphine, cocaine, barbiturates, fentanyl, and PCP) Induced Psychotic Disorder (SIPD) presented in 77.72%. Psychosis has been described in the medical literature as a well-known complication of long-term methamphetamine use since after the Word War II. Epidemiologic studies provide different opinions regarding the prevalence of AIPD [30]. One meta-analysis of seventeen studies showed a composite event rate of 36.5%. Overall, difference in prevalence of AIPD varies from 13% in the USA to 50% in Asia that can be explained by the potency and purity of methamphetamines used in different geographic locations [31].

The time elapsed from the initial substance use to developing AIPD varies from a few weeks to years. It is influenced by the frequency of consumption, dose of the substance, route of administration (intravenous, oral, inhalation), and individual vulnerability to psychosis. Early consumption of amphetamines initially induces psychotomimetic effects, to include euphoria, feelings of increased concentration and stimulation. Continuous use of methamphetamines induces pre-psychotic delusional moods followed by overt psychotic state manifesting with delusions and hallucinations [32].

In our study 11.98% of veteran-subjects with psychosis diagnosis used substance. Psychosis among amphetamine and other substance users presented at higher rate among subjects with mental illness. The most prevalent AIPD symptoms are persecutory delusion (82%), auditory hallucination (70.3%), and delusion of reference (57.7%), visual hallucination (44.1%), grandiosity delusion (39.6%) and jealousy delusion (26.1%). AIPD may be accompanied by severe violent behavior warranting clinical intervention to prevent harm to subjects and society. Tactile hallucinations are more so frequent among subjects using higher daily doses of the drug and frequently described as parasites crawling under subject's skin (formication, "meth mites").

Chronic methamphetamine use induces neuroinflammation, ischemia, oxidative stress, and direct neurotoxicity leading to degeneration processes. It may unmask or expedite the development of schizophrenia in first-degree relatives of subjects with schizophrenia, emphasizing the importance of differentiating AIPD from schizophrenia. Higher prevalence of visual and tactile hallucinations was reported among subjects with AIPD *vs* schizophrenia, while delusion patterns were similar in both groups. Subjects with AIPD have less "negative" psychotic symptoms (i.e., social withdrawal, blunted affect, disorganization, etc.,) and similar levels of "positive" symptoms (i.e., hallucinations, paranoid delusions) compared with schizophrenic subjects [32,33].

The large number of drug reactions and side effects would be expected to lead to increased use of medical services and complications. Indeed, we found that a diagnosis of mental illness was significantly associated with higher

(>10) admission rates (OR=1.22), suicide rate (OR=23.3), suicide attempts (OR=57.5), and suicide death (OR=38.6). Suicide is more prevalent among veterans compared with the general US population. Data published by the US department of Veterans affairs in 2016 showed that veteran suicide rates were 1.5 times higher than among non-veterans. Our data coincide with the findings that mental illness significantly increases the risk of suicide in veterans, in addition to other risk factors, such as older age, male gender, substantial medical comorbidities, substance abuse etc., [34-36]. Female veterans with substance use disorders are at particularly elevated risk for suicide [37]. Moreover, approximately 30% of completed suicides and 20% of deaths resulting from high-risk behavior were attributed to substance use, according to the study conducted on military personnel [38,39].

Both suicide rates (37.08%) and substance use (11.98%) were significantly higher in the mental illness group compared to control group (2.54% and 1.37% correspondingly). Substance use has been identified as a strong risk factor for suicidal behavior among US Veterans [38]. Amphetamine was the most used substance followed by cannabis in the studied mental illness group. The incidence of overdose-induced deaths due to psycho-stimulants other than cocaine (largely methamphetamine) is on significant rise. Cannabis use has also been indicated as a risk factor for suicide in veterans. Logistic regression models indicated that cannabis use was associated with past year suicidal ideation and elevated risk for suicidal behavior. These findings included a concerning association between cannabis use and suicide risk in Gulf War veterans [40].

Increasingly common use of stimulants with synthetic opioids, such as fentanyl and its analogies and surge in amphetamine use and AIPD among veterans with mental illness in the light of documented high rates of mortality associated with amphetamine use and substance-induced psychosis is underestimated and warrants immediate attention to this mental health emergency. Keeping in mind the deadly risks associated with it, methamphetamine has become "America's most dangerous drug". Stimulant-related deaths involving psycho-stimulants other than cocaine (largely methamphetamine) are on the rise in the United States. Psycho-stimulant-related mortality has progressively increased 5-fold from 2012 to 2018 [29,36].

Unfortunately, there are no FDA-approved medications for treating either AIPD or methamphetamine use disorder. Most medications evaluated for methamphetamine/amphetamine use disorder have not shown a statistically significant benefit. However, there is low-strength evidence that Methylphenidate may reduce amphetamine/methamphetamine use.

Numerous Randomized Controlled Trials (RCTs) investigated over 20 potential pharmacotherapies. Methylphenidate, Bupropion, Modafinil, and Naltrexone demonstrated limited evidence of benefit for reducing amphetamine use. Dexamphetamine has benefit on treatment retention, but not for reducing amphetamine use. Based on moderate strength evidence, antidepressants as a class, to include SSRIs, have not shown statistically significant effect on either abstinence or treatment retention [41,42].

Methamphetamine triggers neurotoxicity, oxidative change, neuroinflammation, induces cell death cascade, and degenerative loss of dopaminergic neurons in the brain, which contributes to the higher risks of developing Parkinsonism syndrome and Parkinson's disease itself among methamphetamine users [43]. Therefore, when treating AIPD, clinicians should keep in mind that these subjects are at increased risks of extrapyramidal movement complications, if treated with the first-generation antipsychotics, such as Haloperidol. Consequently, second-generation antipsychotics maybe a preferable class to address psychotic symptoms of AIPD. Subjects diagnosed with substance induced psychotic disorder require close follow up and treatment with psychotropic medications.

Conclusion

In conclusion, our results call for action to increase awareness among VHAs and general practicing clinicians to address the surge in amphetamine use and related mortality, seek evidence-based prevention strategies, and treatment interventions for the amphetamine use associated disorder including AIPD. Further research is urgently needed to identify successful public health approaches targeting Methamphetamine abuse epidemic and to develop effective clinical interventions and relapse prevention strategies.

Our findings underscore the importance of considering demographic factors such as age, gender, race, and service-related characteristics in

understanding the complex landscape of mental health among veterans. Furthermore, the link between substance use and psychotic disorders among this population highlights the need for integrated screening, prevention, and treatment approaches that address both mental health and substance use disorders concurrently.

Limitations of our study include

- False-positive or false-negative Urine Drug Screens (UDS) for amphetamine might have occurred in small number of subjects.
- UDS amphetamines detection could have included prescription stimulants for ADHD, narcolepsy, off-label treatment for major depressive disorder, weight-loss medication, etc., and
- Initial diagnosis of AIPD could have overlapped with unmasked symptoms of first onset of psychosis, schizophrenia, or schizophrenia-like presentation secondary to poly substance use, including highly potent synthetic cannabinoids.

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Disclosures

The contents of this article are those of authors and do not necessarily reflect the position and policy of the Department of Veterans Affairs. All authors' participants have given consent for their data to be used in the research. The data that support the findings of this study are available from the corresponding author, (RS), upon reasonable request.

References

1. Regier DA, Kuhl EA, Kupfer DJ. The DSM-5: Classification and criteria changes. World Psychiatry. 2013;12(2):92-98.
2. Murrie B, Lappin J, Large M, Sara G. Transition of substance-induced, brief, and atypical psychoses to schizophrenia: A systematic review and meta-analysis. Schizophr Bull. 2020;46(3):505-516.
3. Niemi-Pynttäri JA, Sund R, Putkonen H, Vorma H, Wahlbeck K, et al. Substance-induced psychoses converting into schizophrenia: A register-based study of 18,478 Finnish inpatient cases. J Clin Psychiatry. 2013;74(1):20155.
4. Shah D, Chand P, Bandawar M, Benegal V, Murthy P. Cannabis induced psychosis and subsequent psychiatric disorders. Asian J Psychiatr. 2017;30:180-184.
5. Jeppesen P, Petersen L, Thorup A, Abel MB, Øhlenschlaeger J, et al. The association between pre-morbid adjustment, duration of untreated psychosis and outcome in first-episode psychosis. Psychol Med. 2008;38(8):1157-1166.
6. Starzer MS, Nordentoft M, Hjorthøj C. Rates and predictors of conversion to schizophrenia or bipolar disorder following substance-induced psychosis. Am J Psychiatry. 2018;175(4):343-350.
7. Substance abuse and mental health services administration. 2021.
8. Glasner-Edwards S, Mooney LJ. Methamphetamine psychosis: Epidemiology and management. CNS Drugs. 2014;28:1115-1126.
9. Kittirattanapaiboon P, Mahatnirunkul S, Booncharoen H, Thummawomg P, Dumrongchai U, et al. Long-term outcomes in methamphetamine psychosis patients after first hospitalisation. Drug Alcohol Rev. 2010;29(4):456-461.
10. Alderson HL, Semple DM, Blayney C, Queirazza F, Chekuri V, et al. Risk of transition to schizophrenia following first admission with substance-induced psychotic disorder: A population-based longitudinal cohort study. Psychol Med. 2017;47(14):2548-2555.
11. Björkenstam E, Björkenstam C, Hjern A, Reutfors J, Bodén R. A five year diagnostic follow-up of 1840 patients after a first episode non-schizophrenia and non-affective psychosis. Schizophr Res. 2013;150(1):205-210.
12. Van Boekel LC, Brouwers EP, Van Weeghel J, Garretsen HF. Stigma among health professionals towards patients with substance use disorders and its consequences for healthcare delivery: Systematic review. Drug Alcohol Depend. 2013;131(1-2):23-35.
13. Mathias S, Lubman DI, Hides L. Substance-induced psychosis: A diagnostic conundrum. J Clin Psychiatry. 2008;69(3):358-367.
14. Weibell MA, ten Velden Hegelstad W, Johannessen JO. Substance-induced psychosis:

Conceptual and diagnostic challenges in clinical practice. InNeuropathology of Drug Addictions and Substance Misuse 2016:50-57.

15. Fusar-Poli P, Cappucciati M, Bonoldi I, Hui LC, Rutigliano G, et al. Prognosis of brief psychotic episodes: A meta-analysis. JAMA psychiatry. 2016 Mar 1;73(3):211-20.
16. Glasner-Edwards S, Mooney LJ, Marinelli-Casey P, Hillhouse M, Ang A, et al. Clinical course and outcomes of methamphetamine-dependent adults with psychosis. J Subst Abuse Treat. 2008;35(4):445-450.
17. Blow FC, Bohnert AS, Ilgen MA, Ignacio R, McCarthy JF, et al. Suicide mortality among patients treated by the veterans health administration from 2000 to 2007. Am J Public Health. 2012;102(S1):S98-104.
18. Ilgen MA, Bohnert AS, Ignacio RV, McCarthy JF, Valenstein MM, et al. Psychiatric diagnoses and risk of suicide in veterans. Arch Gen Psychiatry. 2010;67(11):1152-1158.
19. VA Informatics and Computing Infrastructure (VINCI). 2024.
20. GBD. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: A systematic analysis for the global burden of disease study 2019. Lancet Psychiatry. 2022;9(2):137-150.
21. Shimamoto A, Rappeneau V. Sex-dependent mental illnesses and mitochondria. Schizophr Res. 2017;187:38-46.
22. Alarcón RD, Parekh A, Wainberg ML, Duarte CS, Araya R, et al. Hispanic immigrants in the USA: Social and mental health perspectives. Lancet Psychiatry. 2016;3(9):860-870.
23. Jegede O, Rhee TG, Stefanovics EA, Zhou B, Rosenheck RA. Rates and correlates of dual diagnosis among adults with psychiatric and substance use disorders in a nationally representative US sample. Psychiatry Res. 2022;315:114720.
24. Jones CM, McCance-Katz EF. Co-occurring substance use and mental disorders among adults with opioid use disorder. Drug Alcohol Depend. 2019;197:78-82.
25. Gardner EA, McGrath SA, Dowling D, Bai D. The opioid crisis: Prevalence and markets of opioids. Forensic Sci Rev. 2022;34(1):43-70.
26. Courtney KE, Ray LA. Methamphetamine: An update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. Drug Alcohol Depend. 2014;143:11-21.
27. Fogger SA. Methamphetamine use: A new wave in the opioid crisis? J Addict Nurs. 2019;30(3):219-223.
28. Ciccarone D, Shoptaw S. Understanding stimulant use and use disorders in a new era. Med Cli North Am. 2022;106(1):81-97.
29. Ciccarone D. The rise of illicit fentanyls, stimulants and the fourth wave of the opioid overdose crisis. Curr Opin Psychiatry. 2021;34(4):344-350.
30. Lecomte T, Dumais A, Dugre JR, Potvin S. The prevalence of substance-induced psychotic disorder in methamphetamine misusers: A meta-analysis. Psychiatry Res. 2018;268:189-192.
31. Ujike H, Sato M. Clinical features of sensitization to methamphetamine observed in patients with methamphetamine dependence and psychosis. Anna N Y Acad Sci. 2004;1025(1):279-287.
32. Fasihpour B, Molavi S, Shariat SV. Clinical features of inpatients with methamphetamine-induced psychosis. J Ment Health. 2013;22(4):341-349.
33. Edinoff AN, Kaufman SE, Green KM, Provenzano DA, Lawson J, et al. Methamphetamine use: A narrative review of adverse effects and related toxicities. Health Psychol Res. 2022;10(3).
34. Inoue C, Shawler E, Jordan CH, Moore MJ, Jackson CA. Veteran and military mental health issues. 2023.
35. Barbic D, Whyte M, Sidhu G, Luongo A, Chakraborty TA, et al. One-year mortality of emergency department patients with substance-induced psychosis. PLoS One. 2022;17(6):e0270307.
36. Han B, Compton WM, Jones CM, Einstein EB, Volkow ND. Methamphetamine use, methamphetamine use disorder, and associated overdose deaths among US adults. JAMA Psychiatry. 2021;78(12):1329-1342.
37. Chapman SL, Wu LT. Suicide and substance use among female veterans: A need for research.

Drug and Alcohol Dependence. 2014;136:1-0.

38. Na PJ, Nichter B, Hill ML, Kim B, Norman SB, et al. Severity of substance use as an indicator of suicide risk among US military veterans. Addict Behav. 2021;122:107035.
39. Bohnert KM, Ilgen MA, Louzon S, McCarthy JF, Katz IR. Substance use disorders and the risk of suicide mortality among men and women in the US Veterans health administration. Addiction. 2017;112(7):1193-1201.
40. Grove JL, Kimbrel NA, Griffin SC, Halverson T, White MA, et al. Cannabis use and suicide risk among gulf war veterans. Death Stud. 2023;47(5):618-623.
41. Lee NK, Jenner L, Harney A, Cameron J. Pharmacotherapy for amphetamine dependence: A systematic review. Drug Alcohol Depend. 2018;191:309-37.
42. Chan B, Freeman M, Kondo K, Ayers C, Montgomery J, et al. Pharmacotherapy for methamphetamine/amphetamine use disorder-a systematic review and meta-analysis. Addiction. 2019;114(12):2122-2136.
43. Jayanthi S, Daiwile AP, Cadet JL. Neurotoxicity of methamphetamine: Main effects and mechanisms. Expe Neurol. 2021;344:113795.

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