Drug and Alcohol Dependence 120 (2012) 35–40

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Increased risk of Parkinson's disease in individuals hospitalized with conditions related to the use of methamphetamine or other amphetamine-type drugs

Russell C. Callaghan[a,b,*], James K. Cunningham[c], Jenna Sykes[a], Stephen J. Kish[a,d]

[a] Centre for Addiction and Mental Health, 33 Russell St., Toronto, ON M5S 2S1, Canada
[b] Dalla Lana School of Public Health, University of Toronto, Toronto, ON M5T 3M7, Canada
[c] Department of Family and Community Medicine, The University of Arizona, Tucson, AZ 85719, United States
[d] Departments of Psychiatry and Pharmacology, University of Toronto, Toronto, ON M5A 2N4, Canada

ARTICLE INFO

Article history:
Received 13 May 2011
Received in revised form 13 June 2011
Accepted 15 June 2011
Available online 26 July 2011

Keywords:
Parkinson's disease
Incidence
Methamphetamine
Amphetamine
Dopamine
Cocaine
Cohort studies
Movement disorders

ABSTRACT

Background: Since methamphetamine and other amphetamine-type stimulants (meth/amphetamine) can damage dopaminergic neurons, researchers have long speculated that these drugs may predispose users to develop Parkinson's disease (PD), a dopamine deficiency neurological disorder.
Methods: We employed a retrospective population-based cohort study using all linked statewide California inpatient hospital episodes and death records from January 1, 1990 through December 31, 2005. Patients at least 30 years of age were followed for up to 16 years. Competing risks analysis was used to determine whether the meth/amphetamine cohort had elevated risk of developing PD (ICD-9 332.0; ICD-10 G20) in comparison to a matched population-proxy appendicitis group and a matched cocaine drug control group. Individuals admitted to hospital with meth/amphetamine-related conditions ($n = 40{,}472$; ICD-9 codes 304.4, 305.7, 969.7, E854.2) were matched on age, race, sex, date of index admission, and patterns of hospital admission with patients with appendicitis conditions ($n = 207{,}831$; ICD-9 codes 540–542) and also individuals with cocaine-use disorders ($n = 35{,}335$; ICD-9 codes 304.2, 305.6, 968.5).
Results: The meth/amphetamine cohort showed increased risk of PD compared to both that of the matched appendicitis group [hazard ratio (HR) = 1.76, 95% CI: 1.12–2.75, $p = 0.017$] and the matched cocaine group [HR = 2.44, 95% CI: 1.32–4.41, $p = 0.004$]. The cocaine group did not show elevated hazard of PD compared to the matched appendicitis group [HR = 1.04, 95% CI: 0.56–1.93, $p = 0.80$].
Conclusion: These data provide evidence that meth/amphetamine users have above-normal risk for developing PD.

1. Introduction

Methamphetamine and other amphetamine-type stimulants (meth/amphetamine) comprise the second most widely used class of illicit drugs in the world (United Nations Office on Drugs and Crime, 2008). Such consumption patterns, along with serious concerns specifically about methamphetamine toxicity (Thrash et al., 2009), have had a major influence on drug policy legislation (e.g., U.S. Combat Methamphetamine Epidemic Act of 2005) (Sununu, 2005) and health service utilization in the United States (e.g., one-third of all recent publicly funded substance-abuse treatment episodes in California were due primarily to methamphetamine) (Substance Abuse and Mental Health Services Administration, 2010a,b). In addition, humans are exposed to licit amphetamine to promote wakefulness in narcoleptic patients, maintain alertness in armed forces personnel, facilitate weight reduction in the obese, and treat the symptoms of attention deficit hyperactivity disorder (ADHD) in children (Kish, 2008). Currently, the absence of powerful longitudinal studies in this area is a major critical barrier to understanding and anticipating the full, long-term impact of meth/amphetamine consumption.

It has been more than 30 years since the discovery that methamphetamine and its metabolite amphetamine can harm brain dopamine neurons in experimental animals (Fibiger and McGeer, 1971; Seiden et al., 1976; Ricaurte et al., 1984; Ryan et al., 1990). Because of the animal findings, there is concern that use of meth/amphetamine might damage dopamine neurons in humans and thereby increase the risk of developing Parkinson's disease (PD), a dopamine deficiency brain disorder (Guilarte, 2001; Caligiuri and Buitenhuys, 2005; Thrash et al., 2009).

Biochemical brain studies of young methamphetamine users (who do not show the symptoms of PD) have disclosed changes in levels of some dopamine markers (Wilson et al., 1996a; McCann

* Corresponding author at: Centre for Addiction and Mental Health, 33 Russell St., Toronto, ON M5S 2S1, Canada. Tel.: +1 416 535 8501x6599; fax: +1 416 595 6899.
E-mail address: Russell_Callaghan@camh.net (R.C. Callaghan).

0376-8716/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.drugalcdep.2011.06.013

et al., 1998). However, the findings have yet to (and may never) confirm actual structural damage to or loss of dopamine neurons, because of the likelihood that such markers are not stable measures of dopamine neuron integrity (Boileau et al., 2008).

Significant and enduring dopamine toxicity caused by meth/amphetamine might only become clinically evident in susceptible users who have advanced to middle or older age—a time characterized by some age-related loss of dopamine neurons—and, as a result, longitudinal cohort designs offer a rigorous way to test this possibility. Given the high cost and common obstacles (e.g., participant loss to follow-up) associated with long-term longitudinal studies of illicit drug users, especially in regards to the estimation of low-incidence (but quite debilitating) conditions such as PD, a large-scale record-linkage approach may be one of the only feasible and effective designs available to assess the potential link between meth/amphetamine use and incidence of PD. In a previous epidemiological investigation of a small sample of older hospitalized meth/amphetamine users (≥50 years old) in California, we introduced a record-linkage approach which provided preliminary data suggesting that use of meth/amphetamine, sufficient to warrant a hospital diagnosis, might be associated with developing PD (Callaghan et al., 2010). Our present study adds significantly to this preliminary work by including: (1) a much larger and age-diversified group of meth/amphetamine users from California; (2) a sufficiently sized cocaine drug-control cohort; (3) a longer follow-up time (up to 16 years); and (4) the use of a more sophisticated statistical technique (i.e., competing risks analysis), along with the addition of death-record information, to account for potential differences in mortality across cohort groups. Here, we assess the risk of developing Parkinson's disease among meth/amphetamine users in comparison to that of population-proxy and stimulant-drug controls.

2. Materials and methods

2.1. Data sources

2.1.1. California Patient Discharge Database (PDD) and Vital Statistics Database (VSD): 1990–2005. The current study utilized California Office of Statewide Health Planning and Development (OSHPD) inpatient hospital admission data from January 01, 1990 until December 31, 2005 from the Patient Discharge Database (PDD). The dataset consists of a record containing demographic information and diagnoses (up to 25) for each inpatient discharged from a California licensed hospital. Licensed hospitals include general acute care, acute psychiatric care, chemical dependency recovery, and psychiatric health facilities. Death records from the California Vital Statistics Database (VSD; which captures all death records for the state) were linked to the PDD inpatient data. The probabilistic matching algorithm linking California inpatient records to state death records has a linkage sensitivity and specificity of 0.9524 and 0.9998, respectively, and positive and negative predictive values of 0.994 and 0.998 (Zingmond et al., 2004).

2.2. Measurement of outcome

The primary outcome variable in the study was time to: (1) subsequent inpatient admission with a diagnosis, in any position in the diagnostic record, of Parkinson's disease [ICD-9 code: 332.0 (Parkinson's disease, Paralysis Agitans)]; or (2) death with an underlying cause of death listed on the death certificate as ICD-9 code 332.0 or ICD-10 code G20 (Parkinson's disease).

2.3. Patient group assignment

2.3.1. Appendicitis cohort assignment. Individuals at least 30 years old were included in the appendicitis group if they had: (1) a diagnosis of an appendicitis-related condition (ICD-9 codes 540–542), which indicated their index admission; (2) no prior or concurrent indication (in relation to their index appendicitis admission) of Parkinson's disease (ICD-9 332.0) or parkinsonism [ICD-9 332.1 (secondary parkinsonism); 333.0 (other degenerative diseases of the basal ganglia), 333.1 (essential and other specified forms of tremor)]; (3) no indication, at any time, of any ICD-9 alcohol- or drug-use diagnoses [303 (alcohol dependence), 305.0 (alcohol abuse), 980.0 (alcohol poisoning); 304.4 (amphetamine and other psychostimulant dependence), 305.7 (amphetamine or related acting sympathomimetic abuse), 969.7 (psychostimulant poisoning) and E854.2 (accidental/unintentional psychostimulant poisoning); 304.2 (cocaine dependence), 305.6 (cocaine abuse), 968.5 (cocaine poisoning); 304.0 (opioid dependence), 304.7 (combination of opioid dependence with any other drug), 305.5 (opioid abuse), 965.0 (poisoning by opioids and related narcotics); 304.3 (cannabis dependence), 305.2 (cannabis abuse), 969.6 (poisoning by hallucinogens, such as cannabis); other drug abuse or dependence conditions (ICD-9 304.1, 304.5–304.9, 305.3, 305.4, 305.9)]; and (4) given that HIV can facilitate the development of parkinsonism (Tse et al., 2004), no indication of HIV [ICD-9 042 (human immunodeficiency virus) or V08 (asymptomatic human immunodeficiency virus)] in their diagnostic records prior to or concurrent with their PD diagnosis, if any.

2.3.2. Meth/amphetamine cohort assignment. Individuals at least 30 years old were assigned to the meth/amphetamine group only if they had the following characteristics: (1) an ICD-9 diagnosis, in any diagnostic position, of 304.4 (amphetamine and other psychostimulant dependence), 305.7 (amphetamine or related acting sympathomimetic abuse), 969.7 (psychostimulant poisoning) or E854.2 (accidental/unintentional psychostimulant poisoning), with the earliest ICD-9 meth/amphetamine diagnosis indicating the index admission; (2) no prior or concurrent indication (in relation to their index admission) of PD or parkinsonism (as defined previously using ICD-9 codes); (3) no indication, at any time, of any alcohol or drug use other than meth/amphetamine (using the ICD-9 codes previously outlined); and (4) no indications of HIV (as listed above).

Even though the ICD-9 coding framework does not distinguish between methamphetamine and other amphetamine-type stimulants, it is likely that the ICD-9 amphetamine-related codes serve as reasonable proxies for methamphetamine-related conditions in our study of California hospital admission records. From 1992 to 2005, there were 514,625 primary amphetamine-related inpatient and outpatient treatment admissions to publicly funded substance abuse treatment programs in California, and methamphetamine accounted for 97.8% of all of these primary amphetamine-related episodes (Substance Abuse and Mental Health Services Administration, 2010b). Also, in California, Arizona, and Nevada, U.S. methamphetamine-precursor legislation, which was designed to reduce the manufacture and supply of methamphetamine, was associated with statistically significant reductions in inpatient hospital admissions with the same ICD-9 amphetamine-related codes as used in our study (Cunningham and Liu, 2003). Consistent with these observations, we previously reported much higher blood and brain levels of methamphetamine than those of its metabolite amphetamine in an autopsied brain study of recreational drug users from California (Wilson et al., 1996a). Based on these lines of evidence, we argue that it is reasonable to expect that the bulk of the admissions in our study are specific to methamphetamine; however, in order to account for the full range of methamphetamine and other amphetamine-type stimulant conditions captured in the ICD-9 classification system, we use the term "meth/amphetamine" throughout the paper.

2.3.3. Cocaine cohort assignment. Patients at least 30 years old were assigned to the cocaine group only if they had the following characteristics: (1) an ICD-9 diagnosis, in any diagnostic position, of 304.2 (cocaine dependence), 305.6 (cocaine abuse), or 968.5 (cocaine poisoning), with the earliest ICD-9 cocaine diagnosis indicating the index admission; (2) no prior or concurrent indication (in relation to their index admission) of PD or parkinsonism (as listed above); (3) no indication, at any time, of ICD-9 indication of any alcohol or drug use other than cocaine (using the ICD-9 codes previously outlined); and (4) no indications of HIV (as listed above).

2.4. Analytic plan

2.4.1. Propensity-score matching of case and control subjects. To account for possible confounding across variables captured in the medical records, we used a greedy nearest-neighbor propensity-score matching approach (Austin, 2009) to match case and control cohorts on the following variables: age, race, sex, date of index admission and total number of an individual's inpatient admissions which occurred after the index episode until the PD outcome (or the end of the study). To ensure that this method produced matched samples, balance between the variables in all of the propensity-score matched cohorts was assessed using standardized differences (Austin and Mamdani, 2006).

2.4.2. Competing risks analyses. We used a competing risks analysis (Pintilie, 2006) with a robust variance estimator (Austin, 2008) to compare the hazard of developing PD across matched groups, while accounting for the higher rate of mortality in the drug cohorts (Singleton et al., 2009; Degenhardt et al., 2011). All competing risks analyses were computed using the "crrSC package" for the R statistical software program (Zhou and Latouche, 2011).

3. Results

A description of the baseline and matched features of all eligible individuals assigned to the appendicitis (n = 207,831), meth/amphetamine (n = 40,472), and cocaine (n = 35,335) groups can be found in Tables 1–3. Approximately 96% of individuals in the unmatched meth/amphetamine group (n = 40,472) received a