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Methamphetamine: Potential Risk Factor for Neurodegenerative Conditions

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Abstract

- Methamphetamine use is a relevant problems in many communities. While it has many adverse health effects, it may also contribute to the development of the neurodegenerative conditions such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and Parkinson's disease (PD).
- A literature review was conducted using PubMed, EMBASE, Clinical Key, and DynaMed. Literature found included high quality systematic reviews, randomized controlled trials, and meta-analysis.
- Literature supports that METH use has several major neurotoxic effects resulting in physical and cognitive deficits. There is minimal available evidence evaluating METH use as a risk factor for ALS although, they do share a common pathway for neurotoxicity. METH use does not appear to be a risk factor for developing MS but can be a mimicker. METH is a risk factor for developing PD.
- **Keywords:** *methamphetamine, neurodegeneration, neurotoxicity, MRI, multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis, attenuation, structural changes.*

Intro

- 1.6 million people per year use METH in the US (CDC, 2020)
- The Midwest is a leader in METH use (DEA, 2019)
- Purity and potency is improving while cost is declining (NDTA, 2018)
- Prevalence of neurodegenerative conditions steadily increasing
  - The prevalence of MS has increased by 27% in the last 40 years while PD has increased more than 100% in just 30 years (Wallin et al. 2019, Marras et al. 2018)
  - Higher prevalence rates in the Midwest regions
  - Idiopathic in nature no obvious cause known, thought to be related to environmental exposures

Statement of the problem

- METH continues to be a relevant drug problem within communities and is projected to worsen due to increased affordability, purity, and potency.
- Providers are faced with managing the wide scope of health problems associated with METH use including neurodegenerative changes which are not widely recognized.
- Providers should be informed on the potential ramifications of METH and its neurodegenerative consequences to allow for early recognition and better health care/education

Research Questions

- Are those who use methamphetamine at an increased risk for developing amyotrophic lateral sclerosis vs those who do not use methamphetamine?
- Are those who use methamphetamine at an increased risk for developing multiple sclerosis vs those who do not use methamphetamine?
- Are those who use methamphetamine at an increased risk for developing Parkinson's disease vs those who do not use methamphetamine?

Literature Review

Structural Brain Changes Related to METH

- Brain structures changes
  - Brain structures most affected include prefrontal cortex, anterior cingulate cortex, and those associated with the reward pathway; striatum, cerebral cortex, thalamus, basal ganglia. (May et al. 2013; Thompson et al. 2004; Sabrini et al. 2019)
  - Increased occurrences of white matter hyperintensities (WMH) in METH users vs. healthy comparisons ($p<0.001$). (Bae et al. 2006)
  - Significant cognitive decline in learning abilities, decision making, and speech. (Thompson et al. 2004; Sabrini et al. 2019)
  - All studies showed improvement in cognition and recession of WMH with protracted abstinence (approximately 2 years)
- Nerve structures and microglia
  - METH has neurotoxic effects to myelin sheath resulting in reduced nerve impulses. This leads to motor disorder such as choreoathetoid movements, punding, and ataxia. (Flavel et al. 2012; Huang et al. 2017)
  - Elevated levels of microglia with repeated METH use in both animal and human studies (Bowyer et al. 2016;Sekine et al. 2008)
  - Most concentrated areas of microglia in reward pathway structures (Sekine et al. 2008)
  - Limited nerve regeneration and reduced microglia associated with 2 years of abstinence. (Sekine et al. 2008; Grandado et al. 2018)

Chemical Brain Changes Related to METH

- Dopamine
  - METH causes decreased dopaminergic terminals, decreased dopamine transporters, and reduced dopamine production in the striatum/reward pathway structures, like that of individuals with PD (Huang et al. 2017; Ashok et al. 2017; Volkow et al. 2001)
  - Reduced tyrosine hydroxylase (rate limiting enzyme needed for dopamine production) in those using METH (Ares-Santoes et al. 2013. Volkow et al. 2001).

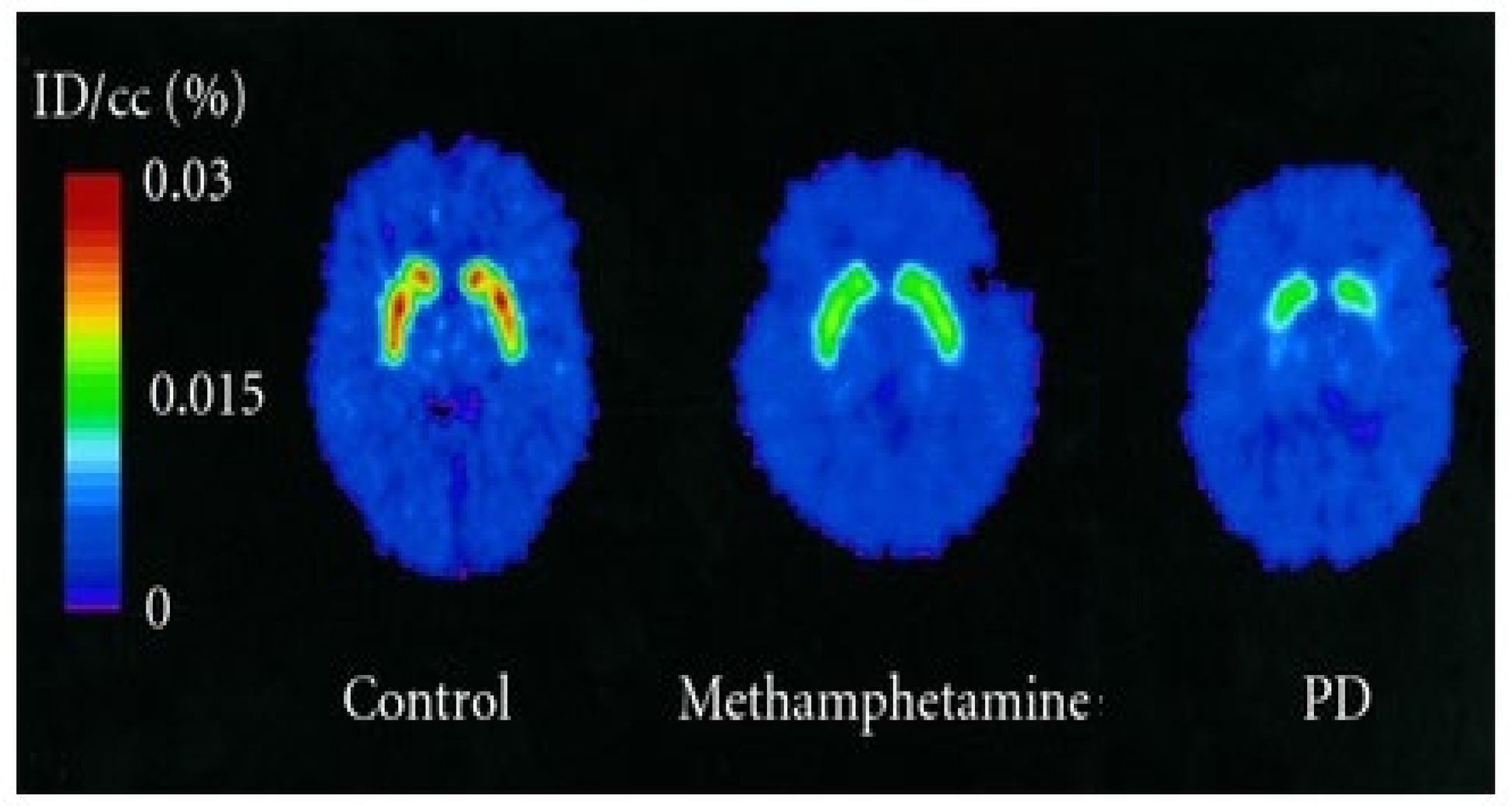

Figure 1: Image depicting reduced dopamine transporters in the striatum of control, abstinent METH, and PD individual. Adapted from Mccann, U. D., Wong, D. F., Yokoi, F., Villemagne, V., Dannals, R. F., & Ricaurte, G. A. (1998). Reduced Striatal Dopamine Transporter Density in Abstinent Methamphetamine and Methcathinone Users: Evidence fromwith [11C]WIN-35,428. *The Journal of Neuroscience*, *18*(20), 8417–8422. doi: 10.1523/jneurosci.18-20-08417.1998 Positron Emission Tomography Studies

- Reactive oxygen species
  - METH use causes large amounts of dopamine to be released which in turn, causes increase in ROS and neurodegeneration.
  - Animal studies show increased ROS correlated with motor impairment and increased addictive behavior (Jang et al. 2016)
- N-acetyl-aspartate
  - Metabolite marker that is used to identify neuronal viability in the brain, low levels of NAA associated with neurodegeneration
  - Individuals using METH had reduced NAA in select brain areas. Reductions remained in prolonged abstinence. (Sung et al. 2007)

METH and Neurodegenerative conditions

- METH vs ALS
  - Familial ALS has a SOD1 gene mutation resulting in increased ROS levels and severe motor problems.
  - There appears to be a common mechanism for neurotoxicity between individuals with a SOD1 gene mutation and those who use METH. Damage occurs through increased ROS, specifically peroxynitriate. (Ferrante et al. 2002 & 2008)
- METH vs MS
  - Similar demyelination patterns and clinical motor presentations (Neva at al. 2016; Giffroy et al. 2016)
  - Patterns of microglial activation similar between METH users and MS patients (Granado et al. 2012)

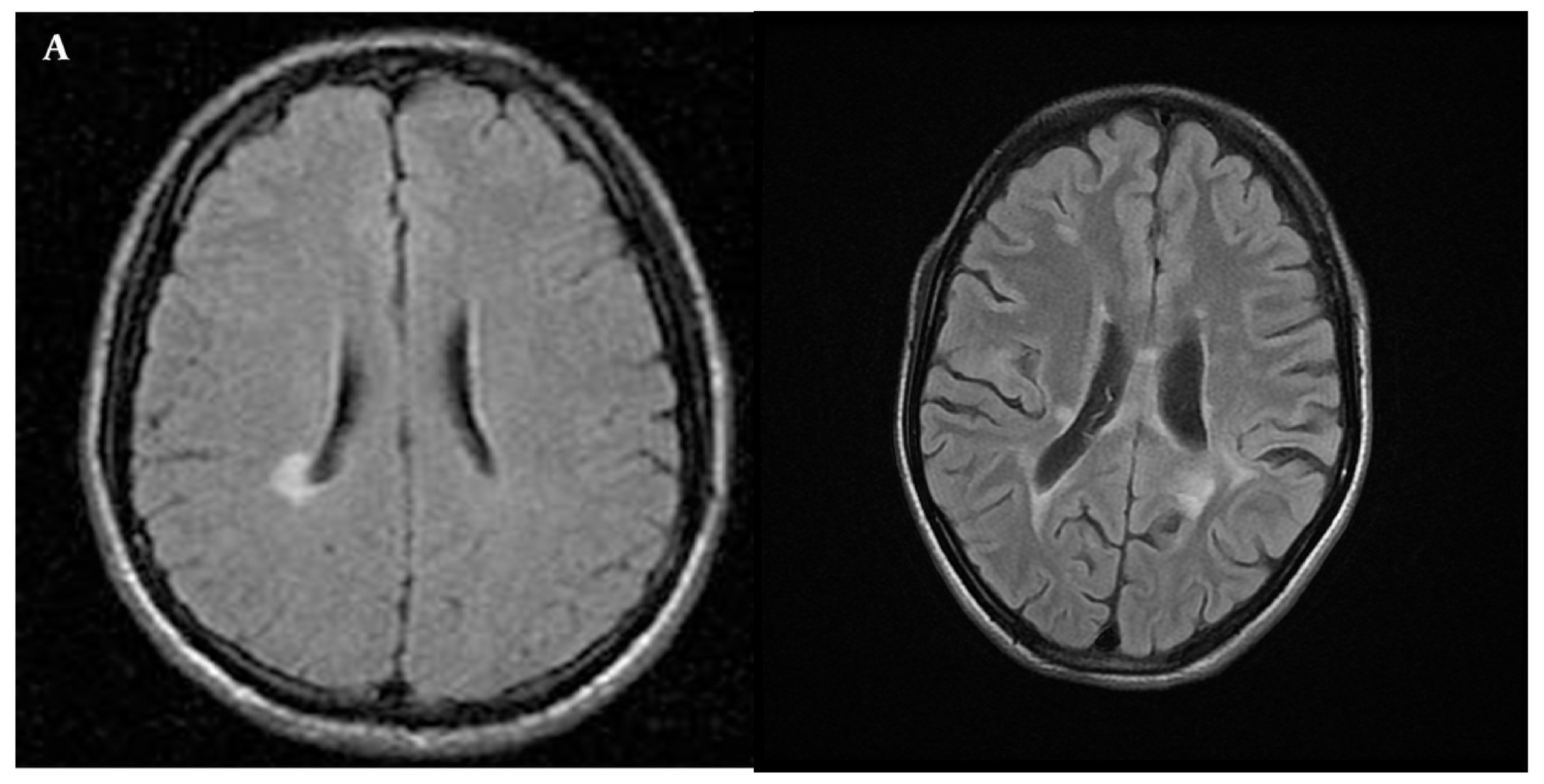

Figure 2: Image depicting two individuals in their mid 20's. Picture on the left is an abstinent METH user. Picture on the right is a patient with MS. Adapted from Radiopedia.

- METH vs PD
  - In two independent retrospective studies, it was concluded that individuals with a history of METH use had significantly higher rates of developing PD later in life
    - Callaghan et al. 2010: Study conducted over 10 years showed METH users had increased diagnosis of PD ($p = 0.019$) vs controls
    - Curtin et al. 2015: Study based on the population of Utah showed METH users had increased diagnosis of PD ($P = 0.001$) vs controls
  - Postmortem evaluation and live imaging of human brains of METH users had decreased dopamine structures in the caudate and putamen, however; at a lesser degree than those with PD. (Kish et al. 2016;Volkow et al. 2001)
  - Animal studies showed METH had negative impact on dopamine terminals and had reduced TH-ir (marker of active dopamine neurons). The brains of fetal and older animals were more affected vs young (Morrow et al. 2001)
  - METH users had neurodegeneration secondary to ROS however; total neuronal cell death only occurred when increased levels of iron were present. (Lotharius et al. 2009)
  - Multiple studies found ROS from METH use led to conformational protein changes which increased levels of alpha-syncuclin (protein contributing to development of Lewy body formation). (Lotharius et al. 2009; Jiang et al. 2014; Tavassoly et al. 2012)

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Discussion

- **METH vs ALS**
  - Share common properties for neurodegeneration. There is really very limited information available. No specific research linking METH use and ALS at this time.
  - Conclusion: More research needed
- **METH vs MS**
  - A diagnosis of exclusion
    - McDonald criteria
      - Evidence of CNS damage in two or more parts with dissemination in time
      - No mimickers present
      - Can use supportive tests but not definitive if they result negative (CSF oligoclonal bands)
  - WMH are indifferent between METH and MS
  - WMH, microglial activation, and motor disturbances present in protracted abstinence
  - Research lacking regarding METH use and occurrence of MS
  - Conclusion: METH is a mimicker of MS. Unless CSF oligoclonal bands present, cannot give diagnosis of MS until sufficient abstinence from METH. Does not appear to contribute to the development of the disease.
- **METH vs PD**
  - METH use has significant impact on the caudate nucleus, putamen, striatum and other brain structures like PD.
  - Reduced levels of Dopamine transporters, dopamine terminals, and tyrosine hydroxylase resulting in decreased overall dopamine production, although not to the degree of PD.
  - Increase in microglial activation
  - In protracted abstinence there is limited recovery of dopamine structures and nerve components
  - METH contributes to increased levels of alpha-syncuclein, complete cell death did not occur unless increased levels of iron present
  - Documented increased rates of PD amongst METH users. Suggested individuals are 5x more likely to develop PD.
  - Conclusion: METH use does not cause PD independently but does contribute to and acts as a risk factor for the future development of the disease.

Applicability to Clinical Practice

- Providers should be aware that METH does create significant changes to brain structure and its chemical components
- These changes have long lasting results even with protracted abstinence
- METH use can contribute to the development of PD
- METH can mimic MS

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