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A Literature Review of Pharmacotherapy Treatment Outcomes for Comorbid Post-Traumatic Stress Disorder and Stimulant Use Disorder: Methamphetamine Type

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A Literature Review of Pharmacotherapy Treatment Outcomes for Comorbid Post-Traumatic Stress Disorder and Stimulant Use Disorder: Methamphetamine Type

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Abstract

Expanding research has shown, exposure to traumatic events increases the likelihood of developing a medical illness, mental disorder, substance use disorder, or comorbid conditions (Halter, 2014; Center for Behavioral Health Statistics and Quality, 2016; Child Welfare Information Gateway, 2013; National Institute of Mental Health, 2017). The Federal Drug Administration has approved medications for the treatment of alcohol use disorder, opioid use disorder and post-traumatic stress disorder (PTSD) symptoms; a medication for the treatment of methamphetamine use disorder, has yet to emerge (Perese, 2012; Stahl, 2013). The focus of research and this paper is to review current evidence on pharmacotherapy alone or in combination with psychotherapy, in the treatment of co-occurring stimulant use disorder methamphetamine-type and PTSD. Conducive to identifying all relevant studies, multiple bibliographic databases were used to complete a comprehensive search of evidence, including: MEDLINE, Pubmed, CINAHL, and PsycINFO. Searched keyword phrases included: stimulant use disorder methamphetamine-type, PTSD, cooccurring disorder, pharmacotherapy, psychotherapy, and treatment outcomes. Databases' own controlled vocabulary were used, when available, in performing the most inclusive search; preventing the chance of missing pertinent evidence. Resulting in 27 relevant pieces of evidence for critical appraisal. After critically appraising each study using CATmaker, the results were narrowed down to 14 of the most reliable and valid pieces of evidence used for synthesis including: 1 systematic review, level A; and 13, level B, randomized control trials. Modafinil, methadone, buprenorphine, N-acetylcysteine (NAC), mirtazapine, dexamphetamine, and bupropion were associated with positive treatment outcomes for methamphetamine dependence. However, these studies were conducted in short time frames with small sample sizes. The research supports further investigation into these medications as the preliminary studies showed promising results. An

integrated treatment approach of psychotherapy in combination with pharmacotherapy, had the most significant results in adults with methamphetamine dependence (Shearer et al., 2009; Colfax et al., 2011). No evidence was identified for pharmacotherapy treatment of co-occurring stimulant use disorder methamphetamine-type and PTSD. Conducive to finding an effective treatment for this comorbidity, further research is required.

Keywords: stimulant use disorder methamphetamine-type, PTSD, cooccurring disorder, pharmacotherapy, psychotherapy, and treatment outcomes

Background

Exposure to traumatic events is common, ranging from 55% to 90% of adults in the United States, will experience at least one traumatic event in their lifetime (Halter, 2014; National Institute of Mental Health, 2017). However, among individuals with exposure to one or more traumatic events, only 8% develop PTSD (Halter, 2014; Center for Behavioral Health Statistics and Quality, 2016). Research has shown, exposure to traumatic events increases the likelihood of developing a medical illness, mental disorder, substance use disorder, or comorbid conditions (Halter, 2014; Center for Behavioral Health Statistics and Quality, 2016; Child Welfare Information Gateway, 2013; National Institute of Mental Health, 2017).

While medications have been approved for the treatment of alcohol use disorder, opioid use disorder, and PTSD symptoms; the FDA has not approved any medications for the treatment of methamphetamine use disorder (Perese, 2012; Stahl, 2013). In 2016, an estimated 1,391,000 or 0.5% of persons aged 12 and older in the United States, reported methamphetamine use in the past year (CDC, 2018). More than 10,721 Americans died from an overdose involving methamphetamine in 2017 (CDC, 2018). The rate of overdose deaths involving methamphetamine increased by 33.3% from 2015, with the highest rates found primarily in smaller towns and in midwestern and western states (CDC, 2018).

The Substance Abuse and Mental Health Services Administration's 2015 National Survey on Drug Use and Health reported, approximately 8.1 million adults (3.3 percent of all adults) in the United States had cooccurring mental health and substance use disorders in 2015 (Center for Behavioral Health Statistics and Quality, 2016). The increasing number of illicit drug overdoses, deaths, and poorer treatment outcomes associated with this comorbidity elicits a review of literature relevant to the treatment outcomes of pharmacologic interventions alone or

in combination with psychotherapy of individuals with co-occurring PTSD and stimulant use disorder: methamphetamine-type.

La Crosse County Health and Human Services' Outpatient Mental Health and Substance Use Clinic serves an increasing population of individuals diagnosed with cooccurring mental health and substance use disorders in Wisconsin (Integrated Support & Recovery Services, 2018). During clinical practicum with La Crosse County this fall, a common theme emerged among patients diagnosed with substance use disorders (SUDs). Several of the patients had been exposed to at least one traumatic event in their lifetime. Below, used as an example of the patient population that could benefit from this review, is a case report of a patient seeking treatment for opioid use, methamphetamine use, and PTSD symptoms.

Chief Complaint: “I’m a heroin and meth addict. I need help with my cravings.”

A 31-year-old female client presented for a psychiatric intake appointment seeking treatment for her addiction to methamphetamine and heroin. Information was obtained from patient and past medical records. Today, patient reported 30 days of sobriety. Patient was serving an alternative to revocation from probation sentence, tracked by GPS and tested for drug and alcohol use. Patient reported her mood, thinking, and ability to concentrate had improved since being sober. Patient reported feeling hopeful for her future and recovery. Patient’s energy level was appropriate, not feeling fatigued or hyper throughout the day. Patient was motivated for treatment.

Patient reported difficulty falling asleep and staying asleep, “I can’t shut my mind off, it just keeps running.” Patient endorsed restlessness in the evenings, “I have restlessness in my hands and legs at night.” Patient reported she used Gabapentin in the past to help with restlessness, sleep, methamphetamine and heroin cravings. Patient denied excessive anxiety or worry, “I’m nervous about the future but I would say it’s a normal level of anxiety.” Patient’s anxiety did not interfere with her ability to function. Patient denied mania and psychotic symptoms.

Patient had a history of sexual abuse, a miscarriage and witnessing a suicide. Patient reported she had frequent flash backs, relived the traumatic moments, had nightmares once every few weeks, and was afraid to go to sleep. Patient reported some hypervigilance, but believed it was related to her substance use.

Patient’s strengths included a good family support system, motivated and determined in her recovery. Patient reported she was working on trying to think more positively. Patient enjoyed creating art.

Patients goals were to: maintain sobriety, change mind set to think more positively, express herself with art, and learn more coping skills to manage PTSD symptoms and drug cravings.

Previous psychotropic medication trials included: Gabapentin, Prozac and Vivitrol injection. Patient had no previous inpatient psychiatric hospitalizations. Patient denied history of suicide attempts.

Patient had attended an intensive outpatient treatment program for heroin and methamphetamine use, in the past. Patient was currently receiving therapy services at a local program designed to help individuals with mental health issues and substance abuse.

Patient's past medical history included diagnoses of Opioid Use Disorder and Hepatitis C. Patient was having regular menstrual periods, was not taking birth control, but was not currently sexually active. Patient had been pregnant once, but miscarried at 6 weeks gestation. Last physical and set of labs had not been completed for a few years. Patient was going to see her primary care physician that day. Patient had no known drug allergies.

Patient was born in the Midwest, where she was raised, and had one brother. Patient's parents divorced when she was a teenager. Both parents were in serious relationships with someone new. Patient was an average student and graduated high school. Patient was married at age 19 and recently divorced her husband. They used to use methamphetamine and heroin together. Patient's brother-in-law committed suicide. Patient's father had alcoholism. Her brother was addicted to "K2" and had ADHD. Patient was unemployed but had been employed at various places previously.

Patient was alert, fully attentive, casually dressed and groomed. Appeared average weight and stated age. Attitude was cooperative and not guarded. Activity was calm, not restless, no abnormal movements, good eye contact. Patient was fully oriented, memory intact. Mood was "good, better." Affect was within normal range, not restricted, flat or labile. Normal expressive and receptive language function. Thought process was organized, goal directed, and did not require redirections. Thought content was free from delusions, suicidal and homicidal ideation. Patient was not attending to internal stimuli. Patient had good insight and judgment appeared to be improving with sobriety. Patient had a normal gait and station; no tics or tremors were observed.

Records and labs will be reviewed from primary care visit. A follow-up appointment was made for 6 weeks out. Preliminary psychiatric diagnoses given include: opioid use disorder, stimulant use disorder: methamphetamine-type, PTSD rule out acute stress disorder. Psychotropic medications prescribed were Vivitrol 380 mg intramuscular every 28 days and gabapentin 300 mg by mouth three times a day as needed for restlessness.

A Literature Review of Pharmacotherapy Treatment Outcomes for Comorbid Post-Traumatic Stress Disorder and Methamphetamine Use

What is the evidence that pharmacotherapy alone or in combination with psychotherapy, improves treatment outcomes in adults diagnosed with cooccurring stimulant use disorder methamphetamine-type and post-traumatic stress disorder?

Method

The strongest level of evidence, Level A, consists of a meta-analysis of multiple controlled studies or a meta-synthesis of qualitative studies with results that consistently support a specific action, intervention or treatment (Armola et al., 2009). The primary focus of the research would revolve around finding level A studies. However, if level A evidence was not available, the next level of evidence down the ANCC's hierarchy of evidence, level B, would be used. Level B evidence consists of well-designed controlled studies, both randomized and nonrandomized, with results that consistently support a specific action, intervention, or treatment (Armola et al., 2009). Continuation down the hierarchy would be utilized as needed.

Conducive to identifying all relevant studies, multiple bibliographic databases were used to complete a comprehensive search of evidence. The databases used include: MEDLINE, Pubmed, CINAHL, and PsycINFO. MEDLINE is the largest health database, covering over 5,000 journals and other publication types in all areas of health sciences; therefore, increasing the likelihood of identifying significant evidence (Foreman & Mateo, 2014). Cumulative Index to Nursing and Allied Health Literature, CINAHL, provides coverage of 5,000 journals as well as 80 other document types (Foreman & Mateo, 2014). PsycINFO, a large behavioral science and mental health database produced by the American Psychological Association and containing more than 3 million

records from 2,500 journals, books, book chapters and dissertation (Foreman & Mateo, 2014). In order to warrant the most thorough and relevant results, it was essential for the databases used in the literature review to cover both healthcare and mental health studies.

Searched keyword phrases included: stimulant use disorder methamphetamine-type, PTSD, cooccurring disorder, pharmacotherapy, therapy, and treatment outcomes. Databases' own controlled vocabulary was used, when available, in performing the most inclusive search; preventing the chance of missing pertinent evidence.

MEDLINE and Pubmed databases were searched using Medical Subject Headings or MeSH terms from the National Library of Medicine's controlled vocabulary for MEDLINE (Fink, 2014; Foreman & Mateo, 2014). Using MeSH, the keyword phrase, stimulant use disorder methamphetamine-type, was searched, producing no results. No results were found using Pubmed. Next, keyword phrase methamphetamine use disorder, was searched using MeSH, which produced the MeSH match term of "methamphetamine." A Pubmed database search of methamphetamine produced an overwhelming 8,942 articles. However, a Pubmed database search of MeSH terms methamphetamine and pharmacology with Boolean connector "AND," narrowed results down to 6,180 articles. Continuing with the same search method of one keyword phrase at a time, using the database-controlled vocabulary, MeSH, then combining the searches using the Boolean "AND." A Pubmed database search of MeSH terms, "methamphetamine" "pharmacology" "treatment outcomes" "mental disorders" connected with Boolean connector "AND" with limitations of English, humans, and published within the past 10 years; produced 46 articles. Additional combinations of the keyword phrases, "therapy" "post-traumatic stress disorder" produced no results.

Next, it was necessary to determine if any of the 46 articles discovered were meta-analysis, the highest level of evidence. Once the meta-analysis filter was applied to the results,

one article remained. In order to obtain more results, another filter of randomized controlled trials was applied and a total of 21 articles remained.

Cumulative Index to Nursing and Allied Health Literature, CINAHL, database uses a different controlled vocabulary, called CINAHL Subject Headings (Fink, 2014; Foreman & Mateo, 2014) Keyword phrases and matching terms from CINAHL Subject Headings were searched in a variety of combinations. Unfortunately, many of the searches produced zero results. However, the combination of "treatment outcome" "methamphetamine" and "pharmacological treatment" using the Boolean connector "AND" produced 4 articles with the limitations of full text, academic journals and peer reviewed. 3 of the 4 articles were applicable to answering the research question.

Next, using PsycINFO's thesaurus, each keyword phrase and matching key terms from the thesaurus were searched independently. Different combinations of keyword phrases were used in order to thoroughly search for most significant results. Ultimately, the combination of "methamphetamine" AND "dual diagnosis" AND "treatment outcomes" AND "pharmacological" yielded the most results. After applying filter limitations of peer reviewed, full text, academic journal and published within the last 8 years; 2 articles remained and were kept for analysis.

Total, 26 pieces of evidence were identified using Pubmed, MEDLINE, CINAHL, and PsycINFO's databases. As a final step in the identification process, using the ancestry method, a hand search of the reference lists of each remaining study was conducted; in search of relevant studies that might not have been found in the original search (Fink, 2014; Foreman & Mateo, 2014). One additional article was discovered, resulting in 27 relevant pieces of evidence used for critical appraisal. No duplicate articles were identified.

CATmaker, an online appraisal tool available through Centers for Evidence-Based Medicine, was used to critically appraise each article. After performing a rapid critical appraisal of each article, a total of 13 reliable and valid studies had met inclusion criteria. Consisting of one level A piece of evidence, a systematic review; and 13, level B pieces of evidence which were randomized control trials. All 14 pieces of evidence were used in this synthesis of literature.

Results

In a randomized, double-blind, placebo-controlled trial, Shearer et al., found modafinil 200/mg a day, associated with a reduction in methamphetamine use among methamphetamine dependent patients (2009). Those who participated in psychotherapy showed better outcomes, as well as, those who did not have comorbidities (Shearer et al., 2009).

Methadone and buprenorphine have been approved by the FDA for treatment of opioid use disorder (Stahl, 2017). In a randomized control study, the efficacy of methadone and buprenorphine in the treatment of methamphetamine withdrawal cravings were examined. Both medications were effective in reducing methamphetamine use cravings (Ahmadi & Jahromi, 2017). However, those treated with buprenorphine showed significantly more reduction in cravings compared to those treated with methadone (Ahmadi & Jahromi, 2017). Salehi, Emadossadat, Kheirabadi, Maracy, and Sharbafchi also found buprenorphine to be effective in significantly reducing methamphetamine use cravings among individuals addicted to methamphetamine in a randomized, double-blind, placebo-controlled trial (2015).

A randomized, double-blind, placebo-controlled clinical trial of the amino acid, N-acetylcysteine (NAC), showed good efficacy in suppressing methamphetamine use cravings, in methamphetamine use dependence (Seyed, Ghafur, Mousavi et al., 2015). A randomized controlled study showed the addition of mirtazapine to psychotherapy, decreased

methamphetamine uses among active methamphetamine users (Colfax et al., 2011). A reanalysis of a multisite, double-blind, placebo-controlled trial showed bupropion to be effective in facilitating the achievement of abstinence of methamphetamine use amongst methamphetamine dependent individuals (McCann & Li, 2012).

The pharmacotherapy treatment effects of once-daily dosing of dexamphetamine sustained release in individuals with methamphetamine use disorder were analyzed in a randomized controlled trial (Longo et al., 2010). The results were measured by self-report and hair analysis. Those treated with dexamphetamine, self-reported decrease in methamphetamine use; hair analysis was used to confirm this finding (Longo et al., 2010). The use of daily dexamphetamine showed increased treatment retention, decreased methamphetamine use, decreased dependence and decreased withdrawal symptom (Longo et al., 2010). However, there was not a significant difference between the placebo group and the dexamphetamine treated group (Longo et al., 2010). The study supports further research on pharmacotherapy as a treatment intervention for methamphetamine dependence. (Longo et al., 2010).

A systematic review and meta-analysis of randomized, placebo-controlled trials by Kishi, Matsuda, Iwata, and Correll showed no advantages of antipsychotics over the placebo in psychostimulant abstinence or cravings (2013). Antidepressants were found to be ineffective in the treatment of methamphetamine use disorder in a randomized controlled trial by Hellem, Lundberg, and Renshaw (2015). Briones et al., hypothesized in a randomized double-blind phase II clinical trial, that varenicline, a nicotine receptor partial agonist, would be effective treatment for methamphetamine dependence due to the dopaminergic effects (2018). However, the study showed varenicline to be ineffective in treating methamphetamine use (Briones et al., 2018).

A multisite randomized clinical trial showed improved patient outcomes using 12-step sponsors among individuals receiving treatment for stimulant use disorder. (Wendt, Hallgren, Daley, & Donovan, 2017). Neurofeedback plus pharmacotherapy was shown to be more effective then pharmacotherapy alone in the of treatment of crystal methamphetamine dependent patients (Rostami & Dehghani-Arani, 2015). Longer durations of contingency management in conjunction with psychosocial treatment was found to be effective in abstaining from methamphetamine use among methamphetamine dependent individuals in a randomized control trial by Roll, Chudzynski, Cameron, Howell, and McPherson (2013).

Discussion

Modafinil, methadone, buprenorphine, N-acetylcysteine (NAC), mirtazapine, dexamphetamine, and bupropion were associated with positive treatment outcomes amongst individuals with methamphetamine dependence as evidence by decreased cravings to use meth and longer periods of abstaining from methamphetamine use (Ahmadi & Jahromi, 2017; Salehi et al., 2015; Shearer et al., 2009; Seyed, Ghafur, & Mousavi et al., 2015; Colfax et al., 201; McCann & Li, 2012; Longo et al., 2010). An integrated treatment approach of psychotherapy in combination with pharmacotherapy, had the most significant results in adults with methamphetamine dependence (Shearer et al., 2009; Colfax et al., 2011). Neurofeedback, sponsorship, and longer durations of contingency management in conjunction with pharmacotherapy, showed improved treatment outcomes amongst adults seeking treatment for stimulant use disorder (Wendt et al., 2017; Rostami & Dehghani-Arani, 2015; Roll, Chudzynski, Cameron, Howell, & McPherson, 2013). Antipsychotics, antidepressants and varenicline, showed to be ineffective in treatment of methamphetamine use (Kishi et al., 2013; Hellem, Lundberg, & Renshaw, 2015; Briones et al., 2018).

Limitations of These Studies

Several of the randomized controlled trials studying the efficacy of pharmacotherapy in individuals with methamphetamine use disorder, analyzed in this literature review; were faced with many barriers and limitations. Sample sizes were too small, many participants dropped out of the studies related to their substance use, difficulty of monitoring medication compliance amongst the control groups and mediating factors such as severity or duration of use that could may influence results, were not controlled. Scarce literature on treatment of comorbidities was identified. Multiple searches yielded no results with the addition of keyword phrases of comorbidity, trauma, and post-traumatic stress disorders; showing a lacking amount of evidence pertaining to the treatment of cooccurring stimulant use disorder: methamphetamine-type and post-traumatic stress disorder.

Conclusions and Future Study

An insufficient amount of literature is available on the treatment of cooccurring stimulant use disorder: methamphetamine-type and post-traumatic stress disorder supports my recommendation for further research on the treatment of this comorbidity. Despite years of effort and several randomized controlled trials, an effective medication for the treatment of methamphetamine dependence, has yet to emerge. While modafinil, methadone, buprenorphine, N-acetylcysteine (NAC), mirtazapine, dexamphetamine, and bupropion have been associated with positive treatment outcomes amongst individuals with methamphetamine dependence as evidence by decreased cravings to use methamphetamine and longer periods of abstaining from methamphetamine use; these studies were conducted in short time frames with small sample sizes. The research supports further investigation into these medications as preliminary studies show promising results.

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