Managing the Patient With Pulmonary Arterial Hypertension and Methamphetamine Use: A Practical Perspective for the Clinician

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Pulmonary arterial hypertension (PAH) is a serious, chronic, progressive cardio-pulmonary disease. PAH is associated with several concomitant conditions, as well as drugs and toxins.\(^1,2\) Methamphetamine abuse is likely associated with the development of PAH.\(^3\) Methamphetamine abuse is epidemic in the United States and abroad, with rates of new users escalating since 2012. There are over 100,000 new users annually as young as 12 years old. Treating a patient with a history of methamphetamine abuse poses many challenges for a clinician, including nonadherence, therapeutic treatment selection, complex psychosocial issues, and relapse or continued drug abuse. Patients with methamphetamine-associated PAH (Meth-APAH) have higher mortality rates when compared to idiopathic PAH.\(^3\)

Having a better understanding of the complexities of addiction and working with a multidisciplinary team that includes a social worker to provide care and counseling to these patients can improve their trajectory. In this article, we will offer insight and background into methamphetamine abuse and addiction, as well as discuss a practical approach for clinicians in treating a patient with Meth-APAH, based on the literature, as well as our personal experiences at University of California, San Francisco Medical Center.

STIMULANT-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION, PAST AND PRESENT

The association between anorexigenic and pulmonary arterial hypertension (PAH) was first reported in the 1960s, after an epidemic of PAH was seen in association with the use of the diet pill (and stimulant) aminorex. Since then, aminorex as well as the diet pills fenfluramine and desfenfluramine have been classified as “definitely” associated in expert consensus documents, while amphetamine and methamphetamine have been classified as likely associated (Table 1). Given the increasing evidence of an association between methamphetamine and PAH from numerous studies,\(^3,4\) and the fact that the molecular structure of methamphetamine is similar to that of aminorex and fenfluramine,\(^5\) it is thought that we may soon be able to place methamphetamine into the “definite” category of risk factor for PAH.\(^4\) Adding methamphetamine to the “definitely causal” category in the World Health Organization’s (WHO) PAH classification list would be an important and significant addition, as it would increase screening for methamphetamine use by clinicians in the field, and it would also increase public awareness of additional serious health consequences related to methamphetamine use.

Methamphetamine is a highly addictive stimulant that is cheap and easily accessible. Use is not confined to any specific geographic region. The National Institute on Drug Abuse reports the highest rates of use in the United States can be found on the West Coast and Midwest, with Hawaii, San Diego, and San Francisco having the highest drug-related hospital admissions, followed by Denver and Phoenix.\(^7\)


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Key Words—addiction, methamphetamine, parenteral therapy, pulmonary arterial hypertension, stimulant

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UNDERSTANDING METHAMPHETAMINE ADDICTION

In treating the patient with a current or former methamphetamine addiction, it is important to understand the effects of methamphetamine on an individual and how it differs from other illicit substances. These differences contribute to the highly addictive nature of methamphetamines and the difficulty in ceasing use. Methamphetamine is a psychostimulant that causes the release and blocks the reuptake of monoamine neurotransmitters, including dopamine, norepinephrine, and serotonin. Clinical manifestations of methamphetamine use include increased energy and alertness, euphoria, sympathetic nervous system activation, decreased need for sleep, increased sexuality, and weight loss. It is metabolized more slowly than other stimulants, with a 9- to 13-hour half-life. Cocaine, on the other hand, has a half-life of approximately 30 minutes, thereby making methamphetamine a potentially more desirable drug, given the longer results it offers. Given the many seemingly pleasurable effects of methamphetamines, one could imagine how this might easily become addictive. However, there are also negative side effects to methamphetamine use, including dry mouth that can lead to tooth decay, and chronic adverse mood and cognitive changes, including irritability, anxiety, aggression, panic, suspiciousness and/or paranoia, hallucinations, executive dysfunction, and memory impairment. Methamphetamine can also exacerbate existing psychiatric symptoms.

When patients attempt to cease use, they experience an “early abstinence syndrome” causing one or more of the following symptoms: depression, anhedonia, irritability, poor concentration/poor cognitive performance, increased hunger and food consumption, insomnia or hypersomnia, and psychomotor agitation or retardation. It is often these many negative symptoms associated with cessation that drive methamphetamine users to pick up again. It becomes a vicious cycle. This may be why a US survey of persons who used unprescribed stimulants found that methamphetamine users were more likely to become dependent soon after onset of use, compared with users of other stimulants. Furthermore, unlike other illicit substances such as heroin that have a prescription treatment available (ie, methadone) to help with addiction, there is currently no prescription therapy available to aid in cessation of methamphetamine addiction.

SCREENING FOR METHAMPHETAMINE USE

Every new patient who is being evaluated for pulmonary hypertension (PH) goes through multiple diagnostic tests to elucidate a diagnosis. At our University of California, San Francisco (UCSF) Pulmonary Hypertension Center, it is also our policy to perform a urine toxicology screen on every new patient as part of their diagnostic evaluation, whether or not a patient is suspected of current or former drug use. The only exception to this is when patients disclose current use, rendering the lab unnecessary. It is important to note that not all patients will disclose a history of prior use. If a patient has used in the past but is no longer using, their drug screen will be negative. As clinicians, we can work to establish therapeutic rapport with our patients, particularly by conveying a nonjudgmental and supportive stance, and hope that eventually they may feel comfortable enough to disclose their drug use history. In the interest of having a more productive clinician-patient relationship, we also feel it is best practice to be fully transparent with patients about the inclusion of the drug screen in their medical evaluation. There are many benefits to making this a universal part of a patient intake. Individual provider discomfort around approaching this sensitive topic is often diminished since it is built into the evaluation protocol. The possibility of acting on false assumptions about patients’ substance use history is reduced, if not altogether eliminated. Moreover, interventions—with regard to both the type of PAH therapies that are offered, as well as interventions targeted toward patients’ substance abuse—can be effectively tailored to patients’ needs.

Our experiences with this strategy have challenged us to look beyond the stereotypes frequently ascribed to a methamphetamine user. Indeed, some real-life patients for whom we have uncovered current methamphetamine use have included: a geriatric couple who put methamphetamines in their morning cup of coffee as an added “pick-me-up”; a very meticulous, well-groomed gentleman who has a high-profile career in finance; a middle-class, married, working mother who is juggling work-life balance; and a high-achieving, highly driven graduate student; among many others who may not match the stereotypes most frequently portrayed in media.

Before a patient’s methamphetamine use is revealed, either by drug screens or disclosure, there are often several physical and behavioral indicators suggestive of use. Patients may complain of having an extremely dry mouth (“cotton mouth”), appear to have poor dentition, complain about frequent sores that are not healing well (often being picked to the point of bleeding), and/or describe a sensation of bugs crawling on their skin. Moreover, they may demonstrate increased paranoia symptoms or cognitive impairment, including impaired word recall, difficulty ignoring irrelevant information, and difficulty organizing information from multiple sources. It is important to note that if a urine drug screen tests positive for the presence of amphetamines, the provider should request a “confirmatory test” using gas chromatography-mass spectrometry (GC-MS) tests. GC-MS separates samples into fragments that are specific to each individual compound. GC-MS is much more specific than immunoassays and can detect the presence and amount of each drug screened. A urine drug screen that tests positive for amphetamines can be a result of ingestion of drugs that are structurally similar to the amphetamine. These include decongestants such as pseudoephedrine or phenylephrine, the weight-loss supplement dimethylamphetamine (DMAA), and the antidepressant and smoking cessation aid bupropion, among many others. Ensuring accurate results of the urine toxicology screen helps to guide future treatment choices. Providers should also hold a high level of suspicion for active drug use in patients who fail to submit a...
TREATMENT CONSIDERATIONS

Treatment selection for the methamphetamine-associated PAH (Meth-APAH) patient depends on many factors. This includes whether the patient is still actively using, severity of disease at the time of presentation, (based on Registry to Evaluate Early and Long-Term PAH Disease Management [REVEAL] registry risk score calculator), social support, and level of engagement with the health care team, among other things. The REVEAL risk score was derived from the REVEAL registry, a large multicenter observational, United States-based registry of patients with PAH. This score assigns a probability of 1-year survival based on clinical data. The risk score calculator has demonstrated good discriminatory ability to stratify risk based on the score. Moreover, the REVEAL risk score was further validated by Cogswell and colleagues in a UCSF Medical Center cohort of patients. This cohort included a higher percentage of WHO Group 1 PAH patients with methamphetamine use (19.3% vs 4.9%, P=0.0001). This is critically important when assessing these patients’ risk and considering therapies.

In our center, therapy options for patients who are actively using methamphetamines are limited to oral and inhaled therapies, as the risk and complexities of parenteral therapies are felt to outweigh the benefits in patients with active methamphetamine use. The therapies offered in our center include phosphodiesterase-5 (PDE-5) inhibitors, endothelin receptor antagonists (ERA), inhaled prostacyclins, oral prostacyclin/prostacyclin IP receptor agonist, and soluble guanylate cyclase (sGC) stimulators. Acute management of these patients may also necessitate inhaled nitric oxide as temporary inpatient treatment until stabilized.

Prior to initiating any of the therapies, insurance authorization is required. This process can take 24 hours to more than 2 weeks. If there is a delay and a patient is too unstable to wait for insurance approval, some pharmacies offer a temporary “bridge” and can provide the drug while awaiting authorization. For stable patients, during this time waiting for insurance approval, the clinician can assess compliance with follow-up and with laboratory and other testing. Laboratory evaluation is conducted to assess blood count, hepatic function, among many other things. Both hepatic function and blood count can be affected by ERA therapy. Concomitant alcohol abuse or right heart failure may be present in the Meth-APAH patient, leading to elevated transaminases, a potential contraindication to initiation of ERA therapy. In some instances, the patients do not complete laboratory testing. In either case, further ERA therapy may not be appropriate.

Furthermore, initiation of oral prostacyclin IP receptor agonists require uptitration of the dose (based on tolerance), adherence to the twice daily (BID) dosing schedule, and adherence to the dosing schedule to prevent increased side effects associated with erratic/missed dosing. Likewise, oral treprostinil requires similar considerations. These are complex regimens, and some patients may find this too difficult, especially if they are not used to BID or TID dosing or have unusual sleep/wake patterns, both of which are common among methamphetamine users. These medication regimens also require regular communication with the PH center to assess tolerability/side effects, etc. At our center, we have asked the specialty pharmacy registered nurses (RNs) to visit a patient’s home every week for the first 4 weeks upon initiating an oral prostacyclin IP receptor agonist. This frequent communication and assessment with the patient has resulted in better adherence in all patients, but especially among patients with substance abuse issues. All of these factors must be considered by the clinician when choosing therapies.

Initiation of advanced parenteral therapy (intravenous or subcutaneous) requires thoughtful and careful consideration. Our practice is to perform a comprehensive psychosocial evaluation from a licensed clinical social worker prior to initiation to fully assess risk of the treatment and address patient safety concerns.

PSYCHOSOCIAL EVALUATION FOR PARENTERAL THERAPY

As a team, our group has decided that psychosocial contraindications for initiating parenteral PH therapies include the following: active or recent drug abuse that could impact adherence (including assessment of recidivism risk based on a number of factors, including length of abstinence and engagement in a recovery program); lack of available or appropriate caregiver (may include active substance abuse on the part of caregiver); history of very poor medical adherence; low motivation for advanced treatment (including patient’s own emotional readiness to pursue treatment); unstable mental health (eg, high risk of harm to self/others, severe untreated anxiety; evidence of significant or worsening cognitive impairment); unstable housing; and lack of insurance coverage.

The social work assessment addresses domains such as social history (including family composition, education, work, and legal history), mental health history, substance use history, history of abuse/violence/trauma, history of adherence with medical regimens, social support, patient’s perception of his/her quality of life, motivation for treatment, financial and insurance considerations, and advance directives. Once the psychosocial information is synthesized, the social worker stratifies patient risk into low, moderate, or high categories, while also...
acknowledging that some risk factors may carry more weight than others. Our experience has taught us that some decisions about how we proceed with a specific patient's treatment course are much clearer than others, and there are certainly many instances that are far “grayer” rather than strictly “black and white” decisions. In some cases, we may elect to make treatment decisions that simply mitigate the perceived risk, such as initiating subcutaneous therapy rather than catheter-based therapy, though with the latter we also take into consideration our plan for managing pain in the setting of preexisting addiction issues—an additional challenge.

Ultimately it is optimal that decision-making be done as a multidisciplinary team rather than by any single provider, not only to draw on the expertise of different disciplines and providers, but also to account for any individual provider biases we have. A clinician who has amassed a number of challenging patients is going to have a more skewed perspective than one who has a very different kind of patient load. Moreover, it is evident that we each bring our own biases that are influenced by patient similarity or other personal compelling circumstances, such as a patient’s age or the fact that he or she has young children.

**WORSE OUTCOMES WITH METH-APAH PATIENTS VS IDIOPATHIC PAH**

Barnett and colleagues performed a retrospective chart review from 2008-2011, at UCSF and San Francisco General Hospital to assess demographic differences in patients with Meth-APAH vs idiopathic PAH (IPAH). In contrast to data from Barnett and colleagues, this group found that Meth-APAH patients had more advanced heart failure symptoms, had higher right atrial pressure, and a lower stroke volume index. Their study also found that patients with Meth-APAH had more than double the risk of clinical worsening or death than patients with IPAH.1

**INTERVENTIONS AND COUNSELING**

In working with patients with methamphetamine and other drug use, it is undeniably helpful to have a familiarity with some of the parlance associated with methamphetamines, including the terms used for the drug itself, as well as the various ways of describing the act of getting high. While it should be noted that that the slang terms vary by region and are constantly evolving, some com-

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**Figure 1:** Survival in IPAH vs Meth-PAH. Reprinted with permission from Barnett CF, Wiley BM, Oveson L. et al. Abstract 13817: Methamphetamine Use is Common Among Patients with Pulmonary Arterial Hypertension (PAH) in California and is Associated with Worse Long Term Survival Compared with Idiopathic PAH. *Circulation*. 2018;126:A13817 [https://doi.org/10.1161/circ.126.suppl_21.A13817].
mon and pervasive euphemisms for methamphetamines include crank, crystal, crystal meth, speed, Tina, Christina, ice, and glass. The act of using methamphetamines may also be described as “tweaking,” “getting spun out,” “getting geared up,” “getting fried,” or “zooming,” among other phrases. Methamphetamines can also be ingested by swallowing, snorting, smoking, and injecting. Smoking is the most common form of ingestion, wherein the crystals are smoked in a glass pipe, similar to crack cocaine.

Consistent with the literature that suggests a high correlation of early substance abuse in individuals with a history of adverse childhood experiences, including abuse/neglect, substance abuse in the household, household mental illness, or an incarcerated household member, we have also observed methamphetamine use among countless individuals with a history of abuse or trauma in their lives. Many of the individuals who are using are seemingly high-functioning addicts—able to maintain some stability in their lives, whether in relation to their social or occupational functional status—and from the social work perspective, can sometimes be the most difficult to engage. Denial, grandiose egos, a high sense of invincibility, and a strong need to “perform” at work or in other social settings certainly pose major challenges to pursuing treatment and can often be difficult to overcome.

Interestingly, despite the potential perceived discomfort around probing into more intimate details of patient’s lives, most patients are very open to discussing their substance use in order to improve their health. Indeed, patients actually expect it to be addressed by health care professionals in the clinical setting and are generally not annoyed or embarrassed by such discussion; instead, they frequently express relief at not having to carry the burden of hiding secret use. Moreover, it is clear in our practice that patients benefit from gaining a clearer understanding of the association between methamphetamine use and PAH, which often increases motivation to discontinue current use.

THE SBIRT MODEL
One simple but effective framework that can be used by health care providers in any setting for approaching harmful patterns of substance use is the SBIRT Model: Screening, Brief Intervention, and Referral to Treatment. The model starts with universal screening for quickly assessing use and severity of alcohol, illicit drug, and prescription drug abuse, followed by a brief intervention phase using motivational interviewing techniques and increasing awareness of risk. Evidence demonstrates that even a brief conversation and intervention with a health care provider can change behaviors (Table 2).

If the provider determines that a patient meets criteria for a substance use disorder, referral to a specialty treatment program may be undertaken.

The universal screening part of the model involves single-question screeners that are rapid, sensitive, and specific. For example, in relation to drug use, the question is, “How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?” If the response is one or more, then the screen is considered positive. This simple question has been found to be 100% sensitive and 73.5% specific for a drug use disorder. It should be noted how such a screening question is framed: “How many times have you used?” vs “Do you use?” Such an approach can certainly take away some of the stigma or sense of shame patients who use may feel. This approach also applies to situations in which you already have a positive drug test result. In other words, it is often much more productive to jump to exploration of substance use (eg, “How often do you use?”) vs making a statement, “I see from your labs that you use,” which can just invite defensiveness.

It is imperative to convey nonjudgmental, empathic verbal and nonverbal behaviors during screening (Table 3). Furthermore, it is highly important to respect patients’ autonomy and rights to privacy and confidentiality, especially if you wish to be effective in assessing patients for substance use disorders and persuading them to decrease use or enter treatment. Providers must remain mind-
ful about engaging patients in discussion about substance use only when they are alone. The majority of patients at our center keep methamphetamine use hidden from loved ones and would never make a disclosure in front of others. In this vein it is also important not to make any “accidental disclosures” in front of others at future visits, as this will likely heavily compromise the integrity of the patient-provider relationship.

The “meat” of the model is the brief intervention, which should occur regardless of the stage of readiness or original reason for the medical visit. Brief interventions, by presenting factual information in a straightforward manner, can help patients realize that their drug use is putting them at risk for negative health and social consequences. Again, it is important to keep in mind that the mere act of educating patients about the association between methamphetamine use and PAH is an intervention and one that is often very much needed. The specific elements of an intervention start with raising the subject itself. It is particularly effective to empower patients to have some sense of control, particularly in the early stages of establishing rapport with a new patient. This may involve asking the patient’s permission to raise the subject (e.g., “May I talk with you more about this lab result?”), as well as accepting and honoring a patient’s decision not to talk about their substance use if they so desire.

Another element of the brief intervention phase involves providing feedback regarding that individual’s use, whether it results in helping make the connection to their health or giving a clear recommendation about the need to discontinue use. For example, a clinician might directly state, “It is highly probable that your methamphetamine use has caused your PAH and continuing to use will significantly worsen your condition.” It can also be highly effective to let the patient know that you are genuinely concerned about them when giving your recommendation to discontinue use, perhaps stating something like, “I
am really worried that if you do not stop using, you are at high risk for dying of heart failure.” The next element involves enhancing motivation for change, which includes assessing readiness for change, helping to identify discrepancies between present behavior and self-identified concerns, asking thoughtful, open-ended questions, and listening and responding reflectively. Individuals will often drop “clues” about elements of change they have already been considering, and the provider can use these tips to guide further conversation. Once this is done, the provider can secure an agreement regarding the changes the patient is willing to undertake, making sure that the plan is specific, concrete, measurable, and realistic, matches the patient’s level of readiness for change (which may lean more toward harm reduction rather than abstinence), and schedule an appropriate follow-up to provide accountability.

Finally, if the patient is ready, contemplate making a referral to treatment, considering such factors as the appropriate level of care needed; unfortunately, many residential treatment programs will not accommodate an individual with significant medical needs.

**PITFALLS AND TIPS FOR PROVIDERS**

Common pitfalls of intervening with this patient population include rushing into “rescue mode” regardless of the patient’s readiness for change: Often there are other psychological conditions, such as depression or anxiety, which also need appropriate treatment to reduce patient suffering and minimize barriers to positive outcomes. Providers may also become frustrated and view the patient as “resistant” or “self-sabotaging” instead of viewing the patient through the lens of having an overlay of another complex chronic illness in addition to their PAH. As a result of this lack of recognition that addiction is a chronic relapsing illness, providers may not fully appreciate the need for ongoing assessment or monitoring even after a patient has reportedly quit using or has completed a formal treatment program. It is certainly possible—if not likely—that a provider may have to reassess, intervene, and refer a patient for substance abuse treatment more than once.

It is important to be mindful that the difficulties in managing multiple chronic illnesses, along with a host of other related psychosocial issues, undoubt edly heighten the risk of “compassion fatigue” among providers working with this patient population. Participation in self-care for the provider is important in dealing with these patients and can prevent burnout. Maintaining healthy professional boundaries and taking time off from work are 2 important ways to prevent burnout.

**CONCLUSION**

In summary, methamphetamine use is associated with development of PAH in at-risk individuals; as such, screening for methamphetamine use should be included in every new evaluation of PAH. Methamphetamines are highly addictive, making cessation difficult. Understanding this can assist providers in compassionately and effectively caring for this population and enhance the provider–patient relationship. The multidisciplinary team, including a clinical social worker, is critical in providing optimal and holistic care for these patients. Meth-APAH patients have more advanced heart failure symptoms, worse hemodynamics, and have more than double the risk of clinical worsening or death compared to IPAH patients. Providers can consider adapting the tool SBIRT (Screening, Brief Intervention, Referral to Treatment), or adapt it to meet the needs of their practice to help patients with efforts to quit using, as it has been shown to be highly effective in treating patients with substance abuse problems. As a medical professional, working with patients with substance abuse can be challenging and exhausting work. There is a risk of “compassion fatigue” and burnout. Taking care of one’s personal well-being is paramount in maintaining a healthy, continued dedication to a demanding professional practice.

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