

## State of the art treatment options for Pakistan's opioid, alcohol and methamphetamine crisis

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### Abstract

The literature review was planned to discuss the extent of opioid, alcohol and methamphetamine use disorder in Pakistan, the neurobiology of opioids, alcohol and methamphetamine, the importance of medication-assisted treatment and recommendations for Pakistan. A PubMed literature search was conducted and newspaper articles were also reviewed. In per capita terms, Pakistan is reported to be the most heroin-addicted country in the world. Pakistan has a significant alcohol abuse issue as well. The newest epidemic is that of crystal methamphetamine or "ice" which is consuming the youth and urban elite. There are long-term structural and functional changes in the opioid-addicted brain and factors that influence the vulnerability to addiction. The genesis of Pakistan's opioid epidemic is critical to understand as the country became victim to the proximity to, and politics of, Iran and Afghanistan. There is poor resource allocation for the treatment of substance use disorder, especially in comparison to what is spent on counter-terrorism. Addiction has had a devastating effect on children and the youth of Pakistan. It is vital to recognise addiction as a chronic disease comparable to diabetes, hypertension and asthma; and not a personal weakness. Medication-assisted treatment includes using buprenorphine-naloxone and naltrexone for opioid use disorder, injectable naltrexone for alcohol use disorder, and mirtazapine and bupropion for amphetamine use disorder. Coordination between the healthcare system, the Anti-Narcotics Force, the pharmaceutical industry and parliament is important. A university-affiliated addiction centre should be developed so it can provide guidance with research and treatment. Buprenorphine-naloxone and injectable naltrexone are urgently needed at an institutional level for the treatment of opioid and alcohol use disorder.

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### Introduction

In per capita terms, Pakistan is reported to be the most heroin-addicted country in the world.<sup>1</sup> "Pakistan's illegal drug trade is believed to generate \$2 billion a year [making] Pakistan the most heroin-addicted country, per capita, in the world," wrote David Browne in 2014 in an expose for The Telegraph<sup>2</sup>.

This review article was planned to present the statistics of the addiction crisis in Pakistan, the neurobiology of addiction, medication-assisted treatment as well as specific recommendations for Pakistan.

### Statistics

There is a paucity of statistics related to alcohol and drug use in Pakistan, and since the situation has reached a critical level, greater efforts need to be directed to gathering statistics so that treatment plans are more effective, targeted and comprehensive.

### Opioids

The United Nations Office on Drugs and Crime (UNODC) issued a report in 2013 and the current situation is most likely a great deal worse than it was back then. As 8.9 million used drugs in Pakistan, according to this report and 6.7 million used drugs the previous year. Thus, 6% of the population used controlled substances and prescription drugs. Cannabis was the most common and opioids were a close second. The majority of users were in the 25-39 age group.<sup>3</sup>

A confluence of factors has caused Pakistan's opioid crisis. In February, 1979, the Iranian Revolution brought Ayatollah Khomeini to power, and drug dealers were ordered to be punished with the death penalty. Iranian heroin chemists fled to Afghanistan. In December, 1979, the Soviets invaded Afghanistan and two million refugees fled to Pakistan and brought heroin with them.<sup>4</sup>

Kabul remains the opium capital of the world and Afghanistan is the source for 75% of the world's heroin. Most of it is trafficked through Pakistan on its way to lucrative foreign markets. In 2013, 150 tons entered Pakistan and 44 tons of it were consumed in Pakistan.

Student hostels across the country are becoming hubs of drug abuse and this includes male and female users. The statistics get even more daunting when drug-related deaths are reviewed. According to the Anti-Narcotics Force (ANF), about 700 people die of drug-related complications every day, which translates to 250,000 deaths each year. This is in contrast to the 77,000 people who died of opioid overdose in 2018 in the United States and which has led to this issue being labelled as an opioid epidemic.<sup>5</sup>

Both terrorism and drug-addiction in Pakistan are not home-grown, but imported. Pakistan spent Rs800 billion per year on the war on terror over the past 15 years largely from its own resources. The federal budget 2017-18 allocated a mere Rs70 million as the 'National Fund for Control of Drug Use' as laid out in Section 54 of the Control of Narcotic Substances Act (CNSA), 1997. This translates to the federal government wanting to spend Rs11 on each addicted patient in 2018.<sup>6</sup>

Injection drug users in 2007 were 90,000 and in 2014 the number quintupled to 500,000. According to the 2013 UNODC report, regular heroin users totalled 860,000, opium users numbered 320,000 and inhalant abuse was common in street children.

Men favoured cannabis and opioids, while women abused sedatives and amphetamines. Methamphetamine, which was not common in Pakistan, is now being reported at alarming rates.

One packet of grey-coloured heroin, also known as powderi, the size of a large pinch of salt, is worth Rs100 and obtaining it is as easy as buying a cup of green tea. One quarter of Pakistan's population lives on less than Rs125/day so heroin is a very expensive habit for the poor.<sup>2</sup>

Charas, or marijuana, is known as the gateway drug and smoking hashish has been socially acceptable in Muslim societies for hundreds of years. In Pakistan, the transition from smoking charas to smoking powderi is seamless.

Children, as young as four, have been noted to indulge in glue and solvent sniffing, as well as charas and powderi. According to the UNODC Drug Use in Pakistan 2013 Survey Report, Khyber Pakhtunkhwa (KP) has the highest number of drug users in the country, with 10.9% of its residents having used an illicit substance during the preceding year.

## Alcohol

According to a 2013 BBC report, alcohol-related diseases

in Pakistan were up by 10% in the preceding five years. In 2007, the drinkers were in their 20s, and in 2013, the drinkers were as young as 14.<sup>8</sup>

In 1977, alcohol shops and bars were banned and thus the elite buy imported alcohol from bootleggers and the poor use moonshine, which results in blindness and death. A New York Times article of 2016 said, "It's true that most people in Pakistan don't drink because they are Muslim. But many more do not drink because they are Muslim and poor. Nobody abstains from drinking because it's prohibited by law."<sup>8</sup>

Its 10 million users illustrate the growing problem of alcohol in Pakistan. One million have alcohol use disorder. A 2009 cross-sectional study revealed alcohol-drinking among final year medical students across six different medical colleges of Pakistan.<sup>9</sup>

## Crystal-methamphetamine or stimulant use disorder

Over the last two years or so, Pakistan's youth is being overtaken by crystal methamphetamine or "ice" or "glass" use.<sup>10</sup>

One kilogram of ice costs Rs650,000 to Rs1.1 million and, thus, it has become a drug for the higher socio-economic classes. The purer form in Peshawar sells for Rs8,000 per gram and "Lahori Ice" goes for Rs1500-2500 per gram. In Pakistan, crystal meth is mostly imported but local labs are also present. News reports suggest that ice addiction is slowly taking over the urban elite of Pakistan. Parliamentarians need to enact legislation to clearly define crystal meth as an illegal drug.<sup>11</sup>

## Neurobiology of Addiction

Extensive evidence reveals that opioid dependence is a chronic, relapsing disease of the central nervous system (CNS) as evidenced by changes in drug reward circuits as well as changes at the neurochemical, molecular, and cellular levels.<sup>12</sup>

It is important to recognise that addiction is a chronic brain disease. Opioid addiction can cause long-term structural functional and behavioural changes in the brain. Reduced mu receptor density, a blunted response to dopamine and enhanced dopamine catabolism has been noted.<sup>12</sup>

The risk factors influencing vulnerability to addiction are divided into environmental and biological factors and drug properties. Environmental factors include home stressors, parental use and attitudes, peer influences, community attitudes, education and drug availability. Biological factors include genetics, gender, age of first use

and psychiatric disorders. Drug properties govern use as well, especially the effects of the drugs and the route of administration.

The route of administration is key in that the rapidity with which the drug reaches the brain governs the euphoria from the drug. The fastest route is intravenous (IV), followed by intranasal, then sublingual and the slowest is oral.

A landmark set of studies was done from 2000 to 2006 which illustrated that addiction was a chronic disease, much like diabetes mellitus (DM), hypertension (HTN) and asthma. It was effectively shown that, like DM, asthma and HTN, addiction was heritable, influenced by behaviour, was predictable, had effective treatments and required continued care. Most importantly there is no known cure for all these chronic diseases and relapse rates in DM, asthma and HTN were 30-70% and addiction had a relapse rate of 40-60%.<sup>13</sup>

Some definitions are important so that substance use disorder can be best understood. With use, an opioid is used as prescribed for an appropriate indication. With misuse, there is overuse, getting high, sharing or selling, multiple prescribers or non-prescribed sources or concurrent use of alcohol and illicit substances. In abuse there is a maladaptive pattern of using drugs that is not condoned or supervised by a physician. In addiction or opioid use disorder, there is compulsive use despite negative consequences.<sup>14</sup>

Opioids activate specific neurotransmitter receptors, mu, kappa and delta. Opioids have a profound analgesic effect at the mu receptors, which are found in the midbrain and the spinal cord. Opioids cause sedation, respiratory depression, euphoria, bradycardia, dependence and constipation, among other effects.

The various effects of opioids on the mu receptor are caused by several classes of opioids and antagonists. Opioid agonists with full effect on the mu receptor have no ceiling effect for analgesia and there is an increased effect with increased dose. Some examples are methadone, morphine, heroin, codeine, hydrocodone and fentanyl.

Partial opioid agonists have partial activity at the mu receptor, resulting in a ceiling effect for analgesia. The advantage of partial opioid agonists is that they help with opioid craving and withdrawal, but due to their lower potency and ceiling effect, their abuse potential is lower. A good example of a partial opioid agonist is buprenorphine.<sup>15</sup>

Naloxone and naltrexone are mu receptor antagonists. The primary use of naloxone is to reverse an opioid overdose. It is used with buprenorphine as a combination product, buprenorphine-naloxone, in the treatment of opioid use disorder, because the naloxone in this product is not active when taken sublingually. It is only when buprenorphine-naloxone is injected that it becomes bio-available and places the opioid-using patient in withdrawal. These properties of buprenorphine-naloxone make it a very unique and a very useful product for the treatment of opioid use disorder.<sup>16</sup>

Naltrexone is a long-acting mu receptor antagonist. A 2005 study showed that naltrexone attenuates the rewarding properties of ethanol by interfering with the ethanol-induced stimulation of the mesolimbic dopaminergic pathway.<sup>17</sup>

Oral naltrexone is not as successful as injectable naltrexone in the treatment of opioid use disorder.<sup>18</sup>

Monthly injectable naltrexone is effective in opioid use disorder in the more motivated patient. It is also useful in the criminal justice system<sup>19</sup> and in patients that refuse opioids in the course of their treatment for opioid use disorder.

Methamphetamine has profound and multi-level effects on the dopamine system in the brain. Clinical manifestations of methamphetamine use include intense euphoria, energy, increased libido, and excessive talkativeness. Some patients experience psychotic symptoms. The course of methamphetamine addiction is prolonged and often characterised by repeated episodes of intense use, sobriety and relapse. Individuals who inject the drug have been found to experience a worse course compared with those with other routes of administration. Current evidence indicates that exposure to methamphetamine is neurotoxic, and neuroimaging studies confirm that long-term use in humans may lead to extensive neural damage. These physiological changes are commonly associated with persistent forms of cognitive impairment, including deficits in attention, memory and executive function. Cardiovascular complications are the leading causes of increased mortality in methamphetamine users, including malignant HTN, arrhythmias, aortic dissection, and myocardial infarction (MI) secondary to vasospasm, stroke, and cardiomyopathy.<sup>20</sup>

## Medication-Assisted Treatment Opioid Use Disorder

The modes of treatment for opioid use disorder are abstinence, methadone maintenance, buprenorphine-

naloxone and naltrexone.

Abstinence-based therapy was the first mode of treatment offered to patients, and it still has validity in the appropriate clinical situation. Sudden cessation of opioid use, or quitting cold-turkey, results in the classic opioid withdrawal syndrome with restlessness, piloerection, muscle and bone pain, insomnia, nausea and emesis and of course intense craving. This syndrome resolves in two to five days. In abstinence-based therapy, symptomatic treatment for the withdrawal symptomatology can be given such as ondansetron for nausea and emesis, ibuprofen for bone pain, muscle relaxants for myalgia and trazodone or hydroxyzine for insomnia. Anxiety accompanies this withdrawal syndrome, but benzodiazepines should be avoided and, if used, should be for the shortest time possible.

Abstinence-based therapy works best for patients with greater motivation for treatment, have had a shorter duration of addiction, have used smaller amounts of opioids, have had prior treatment experience and have few co-morbid medical and psychiatric conditions.

Abstinence-based therapy involves multimodal interventions which include addiction counselling, mutual help groups, and typically include interventions such as structured groups focussed on skills training, group focussed employment support ("job club"), pro-social recreational activities, and regular urine testing.<sup>21</sup>

### **Methadone maintenance**

Methadone maintenance in the United States occurs in a tightly regulated system with federal oversight. Methadone is a high-potency, full mu agonist and must be handled with care due to the ease with which opioid overdoses can occur, especially in association with alcohol, benzodiazepine and other concurrent respiratory depressant use. A meta-analysis of 1969 participants in 11 randomised trials compared methadone maintenance therapy with placebo or non-medication treatment for Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) opioid dependence. Patients receiving methadone were more likely to remain under treatment and to reduce opioid use compared with placebo or non-medication treatment.<sup>22</sup>

### **Buprenorphine-naloxone**

Buprenorphine is a partial mu-opioid agonist and reduces illicit opioid use when used in the long-term treatment of patients with opioid use disorder. With over 25 years of research and over 5000 patients exposed during clinical trials, it has been proven safe and effective for the treatment of opioid addiction.

Three characteristics of buprenorphine make it ideal for use in opioid use disorder. It is a partial agonist, and, thus, is safer, with less of an abuse potential. It has high affinity for opioid receptors and blocks the effect of other opioids. It is also long-acting and, thus, does not require frequent monitoring.

Naloxone is an opioid antagonist and has poor sublingual bioavailability and, thus, has little to no activity when administered sublingually. When combined with buprenorphine, it discourages IV buprenorphine abuse since the naloxone can precipitate withdrawal when given parenterally to individuals with physiologic dependence on opioids.

It is vital that the patient should present in opioid withdrawal when they come in for treatment because buprenorphine has a high mu receptor affinity and will displace the full agonist and place patient in opioid withdrawal.

The phases of office-based opioid treatment with buprenorphine are induction, stabilisation, maintenance and weaning. In induction, buprenorphine-naloxone is titrated according to opioid use, avoiding blanket doses of 16mg. During stabilisation, the task is to ensure that the Clinical Opioid Withdrawal Scale (COWS)<sup>23</sup> is close to zero and, especially, there is no craving, lab tests are done and the patient starts counselling and 12-step meetings. In the phase of maintenance, attention is paid to psychosocial rehabilitation and employment and education. In the weaning phase, it is important to ensure that weaning is a mutual decision and not forced upon the patient. Discussions should be gentle and non-threatening and sometimes indefinite treatment has to be accepted by both the patient and the clinician.<sup>24</sup>

### **Naltrexone**

This is used either orally or in a depot injectable formulation 380mg/injection, injected every 4 weeks in the gluteus. When compared to placebo, those receiving extended release naltrexone had fewer opioid-positive urine status, stayed in treatment longer, had less craving, and showed greater improvement in overall health status.<sup>25</sup>

Strong scientific evidence unequivocally shows that for opioid use disorder, medication is overwhelmingly the essential component of treatment.<sup>26</sup>

### **Alcohol Use Disorder**

Abstinence and naltrexone remain the mainstays of treatment for alcohol use disorder. Injectable naltrexone reduces relapse. Other treatment options are



acamprosate, topiramate, disulfiram and gabapentin.<sup>27</sup>

### Stimulant Use Disorder

No medications have shown consistent evidence of efficacy in the treatment of stimulant use disorder in clinical trials. Only psychosocial interventions have proven efficacy in reducing stimulant use in patients with stimulant use disorder, but these treatments alone are insufficient for many patients. Some medications have shown promise in trials of patients using methamphetamine. A clinical trial suggested that mirtazapine may be efficacious in the treatment of methamphetamine use disorder. A secondary clinical trial showed that bupropion may be useful for less severe methamphetamine use disorder.<sup>28,29</sup>

### Recommendations for Pakistan

#### University-affiliated addiction centre

Creating a university-affiliated addiction centre is important so that it can be a repository for statistics, develop an addiction curriculum for medical colleges in Pakistan, work on policy development and coordinate treatment in the Pakistan paradigm.

#### Recognising addiction as a disease

A comprehensive plan needs to be developed to educate the public and physicians about the scope of the alcohol and substance abuse problem as well as the availability of treatment options.

Concerted and coordinated actions by ANF, parliamentarians, physicians and the pharmaceutical industry are necessary. And a rapid action plan needs to be developed to cope with this scourge, and parliamentarians should work to pass laws that make crystal methamphetamine illegal.

#### Making buprenorphine-naloxone available

It is recommended that buprenorphine-naloxone be made immediately available to established treatment facilities with physicians trained in its use. It should not be available to the general public. Until local pharmaceuticals are able to manufacture buprenorphine-naloxone, it should be imported.

#### Making injectable naltrexone available

Oral naltrexone has not shown promise in clinical trials and it is recommended that injectable naltrexone, which has been shown to be effective in opioid and alcohol use disorder should be made available in Pakistan. Due to the need for training and experience in its use, this too should be available only to certified treatment facilities.

#### Using bupropion and mirtazapine for crystal

### methamphetamine use

The use of crystal meth is destroying the college-going youth of Pakistan. Education of the public regarding the dangers of this drug, admission of stimulant use disorder patients to treatment facilities, and the use of bupropion and mirtazapine to augment behavioural therapy are recommended.

### Conclusion

Pakistan is in the throes of a heroin epidemic, most of which is imported from Afghanistan on its way to lucrative foreign markets. Even young children in Peshawar are addicted to heroin. About 700 people die of drug-related complications in Pakistan every day, which translates to 250,000 deaths every year. Alcohol use disorder also needs to be addressed and the newest crisis is that of crystal-methamphetamine or "ice" which is consuming the youth of Pakistan. It is very important to understand that addiction is a chronic disease and not a moral weakness or character flaw. It has characteristics very similar to DM, HTN and asthma. Abstinence-based therapy is not as effective as medication-assisted treatment for both opioid and alcohol use disorder. Buprenorphine-naloxone and injectable naltrexone are very useful in opioid use disorder, and injectable naltrexone in alcohol use disorder. Mirtazapine and bupropion have been shown to be helpful in some patients with methamphetamine use disorder and their use is encouraged. Buprenorphine-naloxone and injectable naltrexone should be made available on an urgent basis and supplied to certified drug treatment facilities.

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