Testimony and Statement for the Record of

Edythe D. London, Ph.D.
Thomas and Katherine Pike Professor of Addiction Studies
Director of the Laboratory of Molecular Neuroimaging

David Geffen School of Medicine, UCLA

Hearing: “Methamphetamine Addiction: Using Science to Explore Solutions”

Before the

Subcommittee on Research and Technology,
Committee on Science, Space, and Technology
House of Representatives

September 18, 2013
2321 Rayburn House Office Building
Washington, D.C.
Chairman Bucshon, Ranking Member Lipinski and Members of the Subcommittee, thank you for the opportunity to testify today concerning the use of science to address the problem of methamphetamine addiction in the United States. My name is Edythe London, and I am Director of the Laboratory of Molecular Neuroimaging of the David Geffen School of Medicine at the University of California at Los Angeles (UCLA).

Our program of research at UCLA began in 1999 with the generous support from the Office of National Drug Control Policy (ONDCP) and was one of the first major research efforts in the nation to address the growing problem of methamphetamine addiction. Here I would like to note at the outset that the strong support from the Congress to the National Institutes of Health and its research recipients over the past two decades have enabled both basic research as well as the development of new medications and treatment modalities. This critical area continues to be important, affects many lives in our nation, and needs your continued support.

Why is methamphetamine such a critical problem? Unlike other drugs of abuse, methamphetamine is relatively easy to manufacture; the street cost to the use is low compared to other drugs; and it produces a “high” that is long-lasting. At the same time there are very significant mental and physical effects from its use, and in far too many cases, it is a cause of early death.

1. Methamphetamine Abuse and the Scope of the Problem in the U.S.

Methamphetamine use disorders (classified as methamphetamine abuse and dependence in DSM-V) are major public health problems [1-3], with >14.3 million adults estimated to be using amphetamine-type stimulants for non-medical purposes worldwide. Among illicit substances, amphetamines are second only to marijuana in prevalence of use, exceeding heroin and cocaine combined [4]. In the United States, admissions to publicly funded drug treatment programs for amphetamine-related problems peaked at 8.1% in 2005 and increased from 3.7% to 5.7% between 2000 and 2010 [3]. The cost of MA abuse in the US in 2005 was estimated at $23.4 billion [5], and was associated with crime, premature mortality, lost productivity, and medical conditions, such as infectious disease and cardiovascular insults [6-8].

The illegal use of methamphetamine in our country is not as widespread as it was in the early to mid-2000s [9], now reduced to 50% of the levels of 2006; however, the problem is still severe in the communities where there still are established cores of users and supply connections set up with the Mexican cartels. In California, for example, admissions to treatment for methamphetamine use disorders in 2009 and 2010 exceeded admission rates for all other substances, including alcohol [10, 11].

2. How is Methamphetamine Different from Other Stimulants?

Among stimulants, methamphetamine is unique in its pharmacokinetic and pharmacodynamic properties, which render it more effective as a stimulant, more addictive, and more toxic. Methamphetamine is structurally very similar to amphetamine and related agents, such as MDMA (3,4-methylenedioxy-N-methylamphetamine), which is widely known as “ecstasy”, and
designer drugs, such as cathinone derivatives (including “bath salts”). The amphetamines, including methamphetamine, are similar to cocaine in causing an increase of dopamine and other neurotransmitter levels in the synapse, augmenting their actions. Along with cocaine, the amphetamines have similar stimulant and euphoric properties. The amphetamines, however, have long durations of action (half-life of 9-12 hours for methamphetamine) [12] and, therefore, longer stimulant effects than cocaine, which has a half-life of 1 hour and behavioral effects that last up to an hour, depending on the dose and route of administration [13]. Methamphetamine also is well absorbed following administration by various routes, including inhalation; and it is highly lipophilic, entering the brain faster than other stimulants (including amphetamine), and is more stable to enzymatic degradation in the brain [14]. Finally, methamphetamine is more potent than other stimulants [15], leading to much higher concentrations of synaptic dopamine than cocaine, producing toxic effects on nerve terminals. These pharmacokinetic considerations, along with the lower cost as compared with cocaine, likely contribute to a more chronic and continuous use pattern of methamphetamine as compared with cocaine, which is used more in binges. They also may contribute to differences in addiction potential, with only 16-20% of cocaine abusers progressing from regular use to dependence [16, 17]. A corresponding figure for methamphetamine is not available.

Methamphetamine users stay under the influence for longer stretches of days and weeks, with extensive sleep deprivation, possibly contributing to the greater incidence of associated psychosis than with cocaine, along with poor health maintenance and hence more medical consequences (e.g., cardiovascular, neurological) than with cocaine. One notable problem involves dental problems, referred to as “meth mouth”, due to diminished saliva production and other putative mechanisms; this problem is most commonly seen in intravenous users of the drug [18]. Other problems are the potential for prolonged psychosis [19, 20] and high rates of suicide attempts [21].

Finally, methamphetamine is used heavily in the community of men who have sex with men worldwide, and its use is connected to risky sexual behavior among these individuals more than cocaine abuse. Methamphetamine use is highly associated with HIV infection in gay men [22], and is the only drug whose use has shown significant correlation with the incidence of HIV infection among gay and bisexual men who are methamphetamine users [23]. No other drug has shown consistent and significant correlations with HIV transmission. Moreover, metabolic abnormalities in the brain due to HIV and chronic methamphetamine use are additive [24].

3. How have Basic Science Studies Advanced Knowledge about Addiction to Methamphetamine?

Building on a large body of preclinical research, controlled laboratory studies of human volunteers have provided critical insights into the factors that influence methamphetamine use, and the maladaptive consequences of chronic exposure. Noninvasive brain imaging techniques, such as positron emission tomography (PET) and magnetic resonance imaging (MRI), have proven to be particularly valuable for this purpose, clarifying the effects of methamphetamine use on brain chemistry, structure, and function. In related studies, neuroimaging procedures have assisted in the elucidation of the neural mechanisms underlying key behavioral abnormalities thought to promote compulsive drug use and predict poor treatment response. A
synthesis of the findings indicate that chronic use of methamphetamine is associated with deficits in the cerebral cortex and striatum, which accompany and appear to contribute to cognitive deficits, including impaired inhibitory control [25 review].

Molecular Neuroimaging. Human molecular neuroimaging studies suggest that, in addition to effects on other neurotransmitter systems [e.g., 26-28, 29 review], chronic methamphetamine use causes a down-regulation of dopamine neurotransmission in the striatum, which can disrupt cognitive processes in ways that may undermine the user’s ability to remain abstinent. Dopamine signaling in the brain is critically involved in reward processing and motivation [30 review], and is linked to activity in the prefrontal cortex, with bi-directional influences guiding reward-related behavior and decision-making [31]. Dopamine signaling in the brain is influenced by the integrity of receptors for the neurotransmitter (D1 and D2 subtypes), by activity-dependent release of the transmitter from the neuronal terminals into to the synapse, by its reuptake to the presynaptic terminal, and by metabolic enzymes.

These studies have revealed that chronic methamphetamine abuse is associated with deficits in several markers of dopamine signaling in the striatum, including dopamine D2-type receptor availability [32-35], dopamine transporter availability [36-40], and activity of the presynaptic dopaminergic terminal, indexed by dopamine release [34]. These deficits may contribute to a “Reward Deficiency Syndrome”, characterized by anhedonia and a dysfunctional “impulsive-addictive-compulsive” trajectory of behaviors, in which one rewarding substance or activity is substituted for another. During early abstinence, methamphetamine addicts exhibit unusually high caloric intake, presumably reflecting the substitution of food for methamphetamine, and caloric intake is negatively correlated with striatal D2-type dopamine receptor availability [35]. Moreover, low striatal D2-type receptor availability has been linked with greater self-reported impulsivity in abstinent methamphetamine users [33], and along with reduced striatal dopamine release, with greater likelihood of relapse during treatment [34]. Although there is evidence for recovery of the dopamine transporter protracted abstinence [39], this is not true for D2-type dopamine receptors. A direct relationship between the recovery of dopamine transporters and duration of abstinence from methamphetamine [37] suggests that reductions in the striatal dopamine transporter associated with methamphetamine dependence may reflect short-term, drug-induced neuroadaptations.

Studies of the vesicular monoamine transporter (VMAT2), which is present in all monoaminergic neurons, also have pointed to a transient neuroadaptation in response to methamphetamine exposure. Lower striatal VMAT2 was seen in postmortem brain tissue from former methamphetamine abusers [41], and PET studies of striatal VMAT2 in vivo showed lower levels in methamphetamine users even after 3 months of abstinence [40]. In another study, however, recently abstinent methamphetamine-dependent individuals had greater VMAT2 binding availability than controls [42], but increases relative to control subjects were seen only in those who had most recently used methamphetamine (<12 days) [42]. Collectively, these findings suggest that increased VMAT2 may be a transient response to drug exposure and the reduction in VMAT2 binding observed after longer abstinence may indicate lasting damage to neuronal terminals as a consequence of drug use.

With respect to D2-type dopamine receptor deficits, methamphetamine abusers are not unique, as chronic users of cocaine [43], alcohol [44], opiates [45], or nicotine [46, 47] all
display below normal levels of striatal D2-type receptor availability. This commonality across several addictive disorders raises questions regarding the extent to which low D2/D3 receptor availability predates drug abuse, or is an effect of chronic drug exposure. For ethical reasons, this question could be answered only by measuring D2-type receptor availability before any drug use and performing a longitudinal study in which individuals naturally self-administer the drug, or by animal studies in which the agent is administered under controlled conditions. In this regard, Vervet monkeys exposed to a methamphetamine dosing regimen designed to mimic human consumption of the drug showed significant decreases in striatal D2-type receptor availability after 2 weeks of methamphetamine exposure. These deficits persisted for at least 7 weeks following cessation of treatment [48], indicating deleterious effects that are long lasting. Taken together, these findings indicate that while D2-type receptor deficiencies in methamphetamine users may, to some extent reflect a vulnerability to drug abuse, chronic methamphetamine abuse negatively impacts the dopamine system in the brain.

Other relevant data center on the D3 receptor, a member of the D2-type receptor family. The PET studies showing low striatal D2-type receptor availability in methamphetamine users employed radiotracers that do not distinguish between D2 and D3 receptors (both in the D2-type family). Development of a D3-preferring radiotracer, [11C]-(+)-propyl-hexahydro-naphtho-oxazin [49], now allows assessment of D3 receptors in the living human brain. D2 dopamine receptors are distributed uniformly throughout the striatum [50], but D3 receptors are localized primarily to the ventral striatum, which functions in reward processing and motivation [50, 51], making them of special interest with respect to addiction. A recent study has shown higher binding of the D3-preferring tracer in D3-rich regions of the brain in methamphetamine users than in healthy controls, with D3 receptor binding in the midbrain (substantia nigra) related to self-reports of “drug wanting” [52]. Therefore, unlike the D2 receptor, the D3 receptor may be upregulated in those who use methamphetamine chronically.

In addition to the dopamine system, another subject of interest with respect to the effects of methamphetamine in the human brain is the serotonin system. For example, PET was used to show that compared with healthy controls, methamphetamine users had lower density of the serotonin transporter in the midbrain, thalamus, caudate, putamen, cerebral cortex, and cerebellum [28]. This reduction was inversely correlated with the duration of methamphetamine use; and the density in the orbitofrontal, temporal, and anterior cingulate areas was associated with aggression in the methamphetamine abusers.

Microglial cells are activated in association with neurodegenerative processes, and there is evidence that reactive microgliosis accompanies methamphetamine toxicity in animals [53-55]. Using PET, and a radiotracer for activated microglia, [11C](R)-(1-[2-chlorophenyl]-N-methyl-N-[1-methylpropyl]-3-isoquinoline carboxamide) ([11C](R)-PK11195), an elevation in activated microglia was shown in methamphetamine users, suggesting that chronic self-administration of methamphetamine can cause reactive microgliosis in the human brain [56].

**Functional Brain Imaging.** Brain function can be evaluated using PET imaging and the radiotracer [18F]fluorodeoxyglucose, which can provide maps of how fast glucose is utilized throughout the brain. PET studies of cerebral glucose metabolism in meth-amphetamine users, who had remained abstinent for periods varying from weeks to over 2 years, showed elevated
activity relative to control in cortical areas but apparently reduced glucose metabolism in subcortical regions [57]. When participants were studied in early abstinence (4-7 days) corresponding to the time that many clients would approach a treatment episode, there was clear evidence for corticolimbic dysregulation, with reduced activity in prefrontal and limbic cortex, but elevated activity in ventral striatum and amygdala (Figure 1); hyperactivity in the amygdala was associated with depression and anxiety [58]. Among a variety of cognitive deficits [59], the early-abstinent methamphetamine users had higher error rates than control subjects on a vigilance task and abnormal relationships between task performance and activity in the cingulate cortex and the insula, brain regions important for cognitive control, error-monitoring and decision-making [60]. Over the course of a month of abstinence, cortical activity, especially in parietal cortex, increased [61], consistent with an umasking of reactive gliosis [56]. With protracted abstinence (12-17 months), glucose metabolism in thalamus but not the striatum recovered to control levels [62].

In addition to PET, functional MRI (fMRI) provides valuable information about brain function. With substantially greater time resolution than available with functional studies that use PET, fMRI allows measurement of brain activation while participants perform tasks that invoke cognitive and/or emotional processing. Such studies have shown that when abstinent, methamphetamine users exhibit less activation in prefrontal cortex than healthy controls during learning, attention, and emotion processing, consistent with deficits in cortical information processing [63-65]. Functional MRI studies also have also indicated that methamphetamine abusers have abnormalities in cortical activation when abstinent methamphetamine users choose between smaller, more immediate monetary rewards (which they favor) over larger, more delayed rewards [66]. While performing a task to test their temporal discounting of rewards, methamphetamine users exhibit as much recruitment in prefrontal and parietal areas of cortex when making an easy choice as when making a hard choice, suggesting an inefficiency of cortical function [66]. Defective prefrontal cortical control may also contribute to heightened aggression, a common feature of methamphetamine abuse [67], by limiting emotional insight. Functional MRI data have suggested that emotional insight relies on activity of the ventral inferior frontal gyrus, but that in methamphetamine-dependent participants exposed to an emotional probe, activity is low bilaterally in this area [68].

Broadly consistent with these findings and the view that a deficit in “top-down” cortical control is an important feature of methamphetamine abuse is the observation that cortical activation during a simple decision-making task can predict relapse risk in methamphetamine-dependent individuals [69]. The regions involved include components of the prefrontal cortex and the insula. These and other studies have shown the usefulness of fMRI for determining which brain regions under specific behavioral conditions are affected by prolonged methamphetamine use. They also point to fMRI as a valuable technique to evaluate the effects
of potential treatments for methamphetamine dependence. For example, medications, such as modafinil, which improve cognition, in part by promoting greater dopamine function, enhance brain function in the prefrontal cortical regions affected by methamphetamine abuse (Figure 2) [63].

Figure 2. fMRI brain activation maps showing response to Modafinil in prefrontal cortex during learning in methamphetamine users that corresponded with improvements in learning. Prefrontal regions include the anterior cingulate cortex and bilateral anterior insula/ventrolateral prefrontal cortex, orbitofrontal cortex. No difference in activation was observed in healthy individuals (from Ghahremani et al., 2011 [63]).

Structural Brain Imaging. In keeping with the observations of brain function and biochemistry as related to methamphetamine abuse, abnormalities in components of frontostriatal circuitry have been demonstrated by structural brain imaging as well. Structural MRI studies have generally yielded the unexpected finding that methamphetamine abuse is associated with greater gray-matter volume in the basal ganglia (including the striatum) than in healthy control subjects [70, 71]. Until recently, however, it was unknown whether these differences in gray matter were caused by methamphetamine or if they reflected vulnerability factors that predated substance abuse. One study revealed that stimulant abusers and their unaffected siblings have greater volume in the putamen than healthy control participants, suggesting that the difference reflects familial risk for drug dependence [72]. Animal studies, however, have also shown that monkeys exposed to methamphetamine, using a regimen that simulates human patterns of drug use, have increases in putamen gray matter [73] (Figure 3). The structural change is correlated with impaired performance on a three-choice visual discrimination task that evaluates inhibitory control/cognitive flexibility.

Figure 3. Exposure to methamphetamine is associated with structural differences in the brain. Warmer values (reds) indicate increases in gray matter in the putamen. Cooler values (blues) indicate trends toward losses of gray matter in the prefrontal cortex (from Groman et al., 2013 [73]).

With respect to the cerebral cortex, it was unexpectedly found that in addition to larger striatal volumes, research participants who had used methamphetamine but had maintained abstinence for an average of three months, exhibited larger volumes of the parietal cortex [70]. This effect was not seen in a study of participants who had used methamphetamine for most of the 30 days before enrolling in a brain imaging study and then maintaining abstinence for about 1-2 weeks [74]. Cortical maps of the MRI data revealed severe gray-matter deficits in medial aspects of the brain, including the cingulate, limbic, and paralimbic cortices as compared to control values, deficits in hippocampal volumes, which were related to verbal memory
performance, and an unexpected observation of white-matter hypertrophy. The findings suggested that chronic methamphetamine abuse causes a selective pattern of deterioration that contributes to impaired cognitive performance, and white-matter hypertrophy that may reflect adaptive glial changes, including gliosis secondary to neuronal damage. Although not as dramatic, the same study found a gray-matter deficit in lateral prefrontal cortex [74], including a region (right inferior frontal gyrus) that is important for several forms of self-control [75].

Given the prominence of self-control deficiencies in methamphetamine addiction as well as other substance use disorders, it is important to understand the etiology of this structural abnormality and the extent to which it may be reversed with abstinence from drug of abuse. Therefore, methamphetamine-dependent subjects underwent structural MRI before and after approximately 3 weeks of abstinence from the drug [76]. Gray matter volume increased over time in the prefrontal cortex and other brain regions in methamphetamine-dependent participants, but not in members of a healthy control group that were scanned at a similar time interval (Figure 4, from Morales et al., 2012 [76]). Lack of full recovery may indicate the need for prolonged abstinence, some permanent damage, or the influence of a factor other than methamphetamine use. For example, approximately 87-92% of individuals who abuse methamphetamine also smoke cigarettes [77], and research suggests that some of the of the gray matter deficits in prefrontal cortex detected in MA-dependent individuals may be attributable to cigarette smoking or premorbid factors that promote it [76]. More research is necessary to determine how smoking and other factors may interact to influence gray matter in stimulant abusers as these interactions may have important implications for treatment.

4. What Promising Treatments have been Developed as a Result of Basic Science Research?

At this time, behavioral treatments are the most effective ones for methamphetamine dependence [78-81]. These include cognitive behavioral therapy and contingency management, but both are associated with high dropout rates early in treatment [82] and more than 50% relapse in the first 6-19 months after treatment ends [83, 84]. After more than two decades of concerted effort to develop a broadly effective medication for MA dependence, clinical trials have yielded no such agent [85 review]. One potentially very important consideration is the heterogeneity among methamphetamine users and the need to personalize treatment. In this
regard, promising findings have been observed with a handful of agents that reduce stimulant use in subgroups of patients. The approaches include opiate receptor antagonism, augmentation of dopamine action with medications that have relatively low abuse potential, antagonism of dopamine D3 receptors, and reducing glial cell activation.

Naltrexone, an opiate receptor antagonist drug has been considered as a medication for stimulant abuse, in part, because of its potential to antagonize stimulant-induced augmentation of dopaminergic neurotransmission indirectly [86]. To date, clinical trials with naltrexone for treatment of amphetamine dependence have shown stronger effects than those of placebo on drug abstinence [86, 87] and retention in treatment [87]. These findings suggest that naltrexone may be useful for the treatment of methamphetamine dependence.

The “agonist medication” approach, used successfully for treatment of opiate and nicotine use disorders, involves using a medication that mimics some of the actions of the abused drug without the same high addiction potential. In this regard, methylphenidate reduced amphetamine-positive urines in intravenous amphetamine users [88]. A phase II clinical trial involving methamphetamine users is now underway at UCLA, directed by Walter Ling.

Some positive findings were obtained with modafinil, a non-amphetamine stimulant that has cognitive enhancing properties, and augments synaptic dopamine and norepinephrine [89, 90]. In a randomised, double-blind, placebo-controlled trial with methamphetamine users, the medication was no more effective than placebo in improving retention in the trial or in reducing methamphetamine use in the full sample, but there was an indication of reduced stimulant use among participants who were compliant with their medication [91]. Negative findings were obtained in subsequent trials [92, 93], but compliance in one of these trials was cited as a problem [93]. Nonetheless, preliminary findings from the human laboratory indicate that modafinil reduces the rewarding effects of intravenous methamphetamine [94], and further studies are warranted, especially with the active enantiomer, R-modafinil [95].

Another medication that augments dopamine transmission is bupropion, which inhibits the dopamine transporter [96] and shows promise as a medication in subgroups of methamphetamine abusers. One placebo-controlled double-blind trial indicated that sustained-release bupropion did not outperform placebo in enhancing retention in the trial or in increasing methamphetamine-free urine samples, but participants who used methamphetamine 18 or fewer days in the month before randomisation exhibited a positive response to bupropion [97]. This finding was supported in a subsequent trial [98]. Finally, a small, randomised, placebo-controlled trial with high-risk men who have sex with men lacked the statistical power to detect differences in treatment outcome, but the findings were in the direction of efficacy of bupropion [99].

Another promising pharmacotherapy is buspirone, which has antagonist properties at the dopamine D3 and D4 receptor subtypes [100 review]. Buspirone (Buspar®) is approved by the US Food and Drug Administration for treating anxiety, and its anxiolytic effect is thought to be mediated by a partial agonist action at a serotonin receptor (5HT_{1A}) subtype [101-103]. Buspirone also exhibits antagonist properties at dopamine D3 and D4 receptors [100, 104-106]. The affinities of buspirone for D3 and D4 receptors are an order of magnitude higher than for D2 receptors, but are similar to the affinity for 5HT_{1A} receptors [100]. Thus, any behavioral effects of buspirone are attributable to activity at D3, D4 or 5HT_{1A} receptors.
D₃ receptor antagonists reduce the reinforcing and reward-facilitating properties of methamphetamine in rats. For example, administration of the D₃ receptor antagonist SB-277011A [107] or PG01097 [108, 109] attenuate methamphetamine self-administration under a progressive ratio schedule of reinforcement, suggesting that the reinforcing efficacy or the incentive motivational properties of methamphetamine are counteracted. Notably, D₃ receptor blockade appears to diminish reinstatement of extinguished MA-seeking behavior [107, 108, 110]. Combined with the demonstration of D₃ receptor upregulation in methamphetamine users [52], these findings from animal studies identify buspirone as a potential medication for methamphetamine use disorders.

Finally, given substantial evidence from studies of animal models of methamphetamine toxicity [53-55] and PET studies of human methamphetamine users [56], it is reasonable to believe that reactive gliosis and inflammation may contribute to the neuropathology of methamphetamine dependence. For this reason, there is interest in the potential for medications that reduce microglial activation as medications for methamphetamine use disorders. One candidate is ibudilast, which is approved for treatment of bronchial asthma, post-stroke dizziness and ocular allergies in Asia. Ibudilast reduced methamphetamine self-administration in the rat [111] as well as methamphetamine prime-induced reinstatement of methamphetamine-seeking behavior in rats [112]. A phase Ib clinical trial of ibudilast for the treatment of methamphetamine dependence is now being conducted by Steven Shoptaw at UCLA.

5. How Can the Scientific Disciplines Complement Ongoing Research Efforts in Methamphetamine Addiction?

An interdisciplinary approach is needed for basic science to facilitate rapid progress in treatment for methamphetamine addiction. We have made great progress in understanding how methamphetamine alters brain function and behavior through the use of noninvasive brain imaging. This effort has required the collaborative effort of physicists and mathematicians to develop and improve the instrumentation for data collection as well as the algorithms for data analysis. Moreover, this research was linked to the efforts of cognitive neuroscientists to develop appropriate behavioral probes and clinicians to integrate this work in a way that targeted the problems of the addict.

Certainly, the field would be advanced with the development of new probes and more sensitive instruments. For example, there is still a substantive need for new radiotracers that can be used in molecular imaging to assess the complexities of brain chemistry, how it changes with the progression of addiction and how it responds to treatment. However, the greatest advances require a strong collaboration involving a multi-disciplinary team.

Such collaboration has been undertaken using cutting-edge neurotechnology in other areas of mental health, and can be used as models of success for addiction. For example, deep brain stimulation of neurocircuitry for the treatment of depressive illness has proven to be effective in mitigating relapse [113]. The work leading to this development comprised the confluence of several fields, including bioengineering, electrical engineering, materials science, neurosurgery, MRI physics, psychology, and neuroscience, to determine the optimal methods
and procedures for successful outcomes. Discussions of applying this technology to addiction have begun [114], yet much more interdisciplinary effort is required to adapt the technology to the context of addiction and to verify its efficacy.

**References**


