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Learning and Memory Performance After Withdrawal of Agent Abuse: A Review

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Abstract

Context: Agent abuse is a dire predicament worldwide. Learning and memory deficits stemming from the withdrawal of such agents is an increasingly burning issue for researchers.
Evidence Acquisition: The present review revisits the literature generated by far pertaining to the research on memory and cognition deficiencies after withdrawal of agent abuse and corresponding mechanisms.
Results: Deficiency on spatial memory, episodic memory and working memory are common after withdrawal of agent abuse.
Conclusions: The present review suggests that memory dysfunction may result from withdrawal of agent abuse.

Keywords: Cognition Deficit, Learning, Memory, Withdrawal of Agent Abuse

1. Context

Memory is the natural counterpart of learning, a necessary condition for the behavior change for being permanent (1). Agent abuse has been demonstrated to exert detrimental impact upon learning and memory. Over the past epoch, the number of drug consumers has unfortunately increased and concerns have been articulated pertaining to abused agents in various societies (2, 3). Memory dysfunction and its underlying mechanisms following chronic intake of abused agents have recently been a subject of interest for scientists. There is a growing body of literature both in experimental and clinical studies demonstrating the chronic use of some drugs either medically (legally) or recreationally (illegally). After cessation, brain plasticity and progressive structural alterations in the neural pathways appear in short and long periods, which are responsible for dysfunction of memory performance. In many studies, memory dysfunction observed after cessation is persistent after a long period of regressing withdrawal syndrome.

2. Evidence Acquisition

The present review summarizes the literature with respect to clinical and experimental studies on various abused drugs including depressants (ethanol, morphine), psychostimulants (cocaine, amphetamine, and MDMA) and psychoactive agents (marijuana) and possible mechanisms involved in memory impairment following a withdrawal.

3. Results

3.1. Ethanol

Ethanol or alcohol abuse is a common health problem. Cohort studies have shown an abrupt increase in a rate of current drinking from early (approximately 3% aged 12 - 13) to late adolescence (roughly 50% aged 18 - 20) (4). Over 17 million people have been diagnosed with ethanol abuse in USA (5). Approximately 76 million people suffer from adverse effects of alcohol abuse worldwide (6). In addition, the fetal alcohol syndrome is nowadays considered as the most common known cause of mental retardation, which influences from 1 to 7 per 1000 live-born infants (7). Alcohol is rapidly absorbed, readily penetrates into the central nervous system (CNS) and creates high potential neurotoxicity (8). Although studies of cognition effects of alcohol go back to a century ago, its mechanisms of action are still a less divulged topic.

It is said that after withdrawal, neuronal damage, neurochemical and morphological changes in certain brain regions can exert deleterious effects upon cognitive performance. Several preclinical and clinical studies revealed

dysfunction in learning and memory performance after a long period of alcohol abstinence (9, 10). In a Morris water maze test, spatial memory dysfunction in reference memory process was observed in withdrawn animals, as compared to alcohol consuming-non-withdrawn and control groups (11). It was shown that the time and distance spent to approach former position were significantly longer in withdrawn animals (12). Farr et al. (13) demonstrated that chronic ethanol consumption for 8 weeks by a 3 week withdrawal in mice resulted in significant learning and memory deficits. The authors showed that it impaired acquisition and long-term retention in T-maze, foot shock avoidance, shuttle box active avoidance and step-down passive avoidance (tests for assessing spatial learning and memory (14) applied in multiple studies (15, 16)) . These deficits were alleviated after 12 weeks and did not return to normal condition (13). In another study, after subsiding hyperexcitability symptoms in withdrawn mice with 34 weeks alcohol treatment, test of memory performance in object recognition task, odor habituation/discrimination and elevated plus maze showed significant deficits, compared to the control group (17). In a clinical study, alcoholic patients showed an estimate of 50% - 75% deficit in learning and memory after abstinence, which was independent of withdrawal hyperexcitability symptoms (18). In a comparative study among recently detoxified subjects, long-term abstinence subjects and intoxicated subjects, it was shown that deficits in visuospatial learning were significantly better in the intoxicated group (19). Meanwhile, there was no significant difference between recently detoxified and long-term abstinence individuals. The withdrawal may exert a deleterious effect upon learning performance, and time interval could not eliminate this type of memory dysfunction (19). Fein et al. (20) showed that most cognitive deficits in memory performance were recovered after long term abstinence (approximately about 7 years), except deficits in spatial memory performance. Due to the fact that spatial memory gradually declines with aging in normal subjects, devoting more attention to this aspect of memory in abstinent middle aged and elderly people was mentioned to be of value (20).

In some studies, the number of withdrawals also is an important contributing factor in cognition function. On another reading, the higher number of withdrawals showed the higher impairment of memory function. Duka et al. (21) showed that alcoholic patients with more than 2 times detoxification were significantly worse in memory tasks sensitive to frontal lobe damage such as porteus maze, the vigilance task and the delay task than those with less than 2 times. It was demonstrated that with an increase in the number of withdrawals, subjects become significantly weaker in memory testing during 24 hours of abstinence following ethanol intake in two groups of men and women; meanwhile, women showed more vulnerability than men (22). However, a conflicting result claimed that frequency of withdrawals brought about negligible effects upon the cognitive abilities in detoxified alcoholics (23). These discrepancies may be as a consequence of differences in samples or the measures for evaluating memory performance.

Pattern of memory deficits with respect to time course after withdrawal, is divided into three periods, that is to say, acute detoxification period, intermediate-term abstinence, and long-term abstinence (22). It is said that an acute detoxification period takes until 2 weeks, intermediate-term period lasts weeks to 2 months and long-term phase is greater than 2 months after abstinence. Hence, nonverbal abstract reasoning, visuospatial abilities, mental flexibility and nonverbal short-term memory last over 2 months of cessation that could disturb quality of life in abstinent patients and need more attention (24).

3.2. Morphine

Morphine, a member of narcotics family, is one of the most powerful analgesic agents widely used. Meanwhile, it produces many psychological effects, namely, relieving fear, anxiety and euphoria (25). Abuse of different derivatives of morphine is a crucial issue in various populations. By way of illustration, west European countries were reported to be the largest market for heroin, that is, N-acetylmorphine (26). Chronic use of opioids in different pain conditions and abuse of high dose of these agents were seen with reduced attention and working and episodic memory dysfunction in several experimental and clinical studies (27, 28). Understanding of memory dysfunction after narcotic stopping was also a subject of interest for researchers.

In the Y-maze task, acquisition of spatial recognition memory was impaired after withdrawal of chronic administration of morphine (repeated for 4 days), in a dose dependent manner. Such an impairment, which was observed in the 3rd but not 1st following withdrawal, supported independency to the withdrawn syndrome (29). Discontinuation of morphine in dependent mice after 14 hours showed cognition dysfunction, with spending more time to explore the objects in an object recognition task (30). Such a test can be used for assessing working and episodic-like memory in animals (31).

Early abstinence in individuals with opioid dependence produced some deficiency in complex working memory, executive function and fluid intelligence (32). In another study, patients on methadone showed memory deficit after withdrawal; nevertheless, they were normal after nine months except in visual attention and flexibility

(33). The finding was in line with that obtained from abstinent heroin users showing deficiency in executive function after eight mounts (34).

3.3. Amphetamine

Amphetamine, an indirect sympathomimetic agent with good penetration into the CNS, is prescribed for several disorders such as attention deficit hyperactivity disorder (ADHD), narcolepsy and weight loss (25). Its abuse has increased amongst the young during the past decade (35). It was also demonstrated that methamphetamine abuse could lead to cognitive deficits (36). There are, howbeit, some findings claiming that chronic use of amphetamine as well as its withdrawal can cause learning and memory dysfunction.

In a study, visual memory function and executive function were evaluated in five different groups including current amphetamine users and current opioid users for at least 3 years, abstinent ones from opioids and/or amphetamine for at least 1 year (some of them were abstinent for an average of 8.2 years) and non-user individuals. Four earlier groups showed impairment on memory tasks, compared to the control group. More to the point, memory dysfunction was not recovered in several years after withdrawal in abstinent subjects for both abused substances (37). Simon et al. (38) assessed current users of methamphetamine, individuals who were abstained from methamphetamine and a relapse group. The authors found that some aspects of cognitive performance such as selective learning and also all four measures of episodic memory (word recognition, picture recognition, word recall and picture recall) were significantly lower in the abstinent and relapse persons, as compared to current users. However, there was no significant difference among the groups with respect to working memory and executive function (temporary storage and manipulation of information). Generally, current users performed better than relapse subjects in the majority of tests and abstinent individuals experienced the least memory performance (38). These findings showed an alteration in different aspects of memory performance after withdrawal of amphetamine.

3.4. MDMA

(+/-)-3, 4-Methylenedioxymethamphetamine (MDMA) is an amphetamine derivative with complex effects on neurotransmitters including 5-Hydroxytriptamine (5-HT), noradrenaline (NA) and dopamine (DA) that inhibits uptake of 5-HT, NA and DA and also releases 5-HT. Such effects result in a large increase in 5-HT levels followed by depletion of neurons. This illegal drug, known as club drug, is very popular among the young (39). Abuse of MDMA can result in a variety of psychological, social and cognitive problems. There are also some reports on induced memory dysfunction by this agent remaining after abstinence. In an object recognition task, memory was significantly impaired after withdrawal of repeated, but not single administration of MDMA on 1st and especially 7th day of withdrawal period in mice (40). In a comparison among abstinent rats after chronic use of MDMA, current cannabinoid and control groups showed that abstinent MDMA animals were the worst group in memory tests (41). McCardle et al. (42) indicated that some measures of cognitive performance such as delayed recall and verbal learning were significantly poorer in individuals with a history of MDMA abuse than in control non-users.

3.5. Cocaine

Cocaine, one of the most important recreational stimulants, is consumed especially by young people. A recent estimation indicates that half a million Americans use this agent weekly. Nowadays, there are also concerns on the cocaine withdrawal induced memory impairment after its chronic use (43). In a Y-Maze and two-lever operant paradigm, rats showed a decrease in memory performance during a week withdrawal following a 7-day regimen of cocaine (44). Briand et al. (45) observed that recognition and memory functions were disturbed after withdrawal of chronic exposure to cocaine by an object recognition task in 2-week abstinent rats.

Chronic users of cocaine showed significant impairment on verbal memory and fluency as well as deficits in cognitive flexibility, but not in spatial memory after acute withdrawal (46). This defect continued up to 10 days after the assessment (46). Recent cessation (acute phase, within 72 hours of last use) and 2-week abstinent subjects beyond chronic use of cocaine showed impairment in memory, visuospatial and concentration tasks independent of depression induced by withdrawal (47).

3.6. Marijuana

Marijuana (dried leaves and flowers) and cannabis (extracted resin) derived from cannabis sativa contain Δ9-tetrahydrocannabinol (THC), a cannabinoid 1 receptor (CB1) agonist. These agents are the most popular illicit psychoactive substances used among teenagers; albeit, it is postulated to be relatively safe (48). The literature has flooded by animal and human studies revealing disruptive effects of cannabinoids in different aspects of memory and cognition after acute and chronic uses; however, there are a few studies on learning and memory changes after withdrawal of marijuana.

Bolla et al. (49) found that decision making was disturbed 28 days after abstinence of chronic use of marijuana in the studied subjects. Spatial working memory deficiency was also observed in adolescent marijuana users after 8 days of abstinence persisting even after 1 month observation (50).

3.7. Mechanisms Underlying Memory Impairment After Withdrawal

Chronic intake of abused drugs is associated with neurochemical and morphological alterations, neuronal plasticity and changes in the levels of neurotransmitters in the CNS, especially neocortex, basal forebrain and hippocampus, which are involved in cognition and memory processes (51). According to preceding studies, it appears that such alterations may occur in withdrawal period that might aggravate existing situation and contribute to memory deficit. To date, roles of contributing factors including neurotransmitters and neuropeptides such as dopamine, glutamate, glucocorticoids and cannabinoids have been demonstrated.

3.8. Glutamate

The amino acid "glutamate" is an important excitatory neurotransmitter in the CNS. Dys-regulation and high concentration of glutamate content in synaptic clefts serves a crucial role in the pathogenesis of many neurodegenerative disorders such as cognitive impairment (52).

The levels of excitatory amino acid, glutamate, are increased immediately after withdrawal of ethanol and further elevated in subsequent days (53). It was demonstrated that chronic abused ethanol leaded to inhibition of N-methyl D-aspartate (NMDA) receptors and also an increase in glutamate release as well as an increased expression of NMDA receptors (54, 55). Omission of this inhibition, in addition to increased glutamate levels after withdrawal, results in an exaggerated flux of Ca^{2+} through cells, an increase in function of glutamatergic system and thus induction of glutamate excitotoxicity, with a serious damage on the frontal lobe (ei, one of the critical regions for memory function) (56-58). It was demonstrated that an increase in expression of ionotropic channels, NMDA and AMPA receptors during alcohol withdrawal synergistically contributed to glutamate excitotoxicity (59). It was shown that administration of nimodipine, a ca2+ channel blocker, with high penetration into the CNS for 2 weeks to 1-2-month abstinent mice from 8 months intake of ethanol completely reversed cognition deficit observed in object recognition task (60).

Prolonged administration of morphine was shown to up-regulate brain L-type Ca^{2+} channels (61). It was reported that single and repeated administrations of nimodipine in morphine- dependent mice improved memory deficit during withdrawal of morphine in an object recognition test (62).

Moreover, memantine, an antagonist of NMDA receptors, improved the cognition impairment in abstinent rats from chronic intake of ethanol in a Morris water maze test (63).

It was observed that chronic use of opioids resulted in elevating expression of GluR1 and GluR2/3 subunits of AMPA receptors in hippocampus, an important location in learning and memory processing. Administration of the NMDA receptor antagonist (AP-5) or the antagonist of NR2B-containing NMDA receptors (Ro25-6981) prevented the increase in GluR2 subunits of hippocampus (64).

An increase in NMDA receptor expression was shown after 21 days but not 1 day following cocaine withdrawal in rats (65). This can be explained by excitotoxicity observed after withdrawal of cocaine (65).

3.9. Glucocorticoids

The role of glucocorticoids in memory processing has been pronounced in the literature. Another hypothesis for cognitive impairment after withdrawal of agent abuse is based on increase in glucocorticoid levels in regions of brain responsible for memory processing including hippocampus and prefrontal cortex. Following chronic intake of ethanol for about 3 weeks to 8 months, prolonged increase in glucocorticoids concentration occurred in brain of animals while their concentration did not change in plasma (66). Activation of hypothalamic-pituitary-adrenal axis pathway (HPA) was reported after withdrawal of morphine (67). It was previously found that brain and blood corticosterone increased following morphine withdrawal in morphine- dependent mice. Administration of mifepristone (glucocorticoid receptor blocker) and metyrapone (corticosterone synthesis inhibitor) improved memory deficit after withdrawal of morphine in an object recognition task in mice (68). Mifepristone also decreased memory deficits after withdrawal of chronic ethanol consumption in object recognition task, elevated plus maze and odor habituation/discrimination tests in rats (17). Spironolactone (a mineralocorticoid receptors or MR antagonist) also improved memory deficits in withdrawn mice (69).

3.10. Cannabinoids

Endogenous cannabinoids (anandamide and 2-arachydonyl glycerol) and their CB1 subtype receptor, abundant in hippocampus were implicated in learning and memory (70). In a study on rats, up-regulation of CB1 receptors and endogenous cannabinoids in hippocampus

appeared 40 days, but not 2 days after withdrawal of chronic alcohol consumption (71). Thus, the cannabinoid system is activated during withdrawal of ethanol. The levels of cannabinoid CB1 receptor mRNA and CB1 receptor binding in the brain increased after chronic exposure to morphine (72). In an object recognition memory task, chronic intake of AM281, a cannabinoid antagonist/inverse agonist, significantly improved the memory impairment following naloxone-precipitated morphine withdrawal in mice (73). Nawata et al. (40) showed that levels of cannabinoid CB1 receptor protein increased on the 7th day of withdrawal, but not on the first day after chronic use of MDMA. Prescribing a CB1 antagonist with MDMA and AM251, for mice prevented memory deficits observed in withdrawn animals by using an objective recognition task. Nevertheless, mice devoid of the CB1 receptor subtype showed no impairment in memory cognition after withdrawal of MDMA (40). Gonzalez et al. (74) found that cocaine exerted minor impacts on cannabinoid system in different regions of brain.

4. Conclusions

learning is the process of acquiring new information (75) and memory is natural compartment of learning (1). Abuse of recreational drugs is common throughout the word. Cocaine (47), Marijuana (48), Morphine (76) and other abused agents cause physiological dependence.Despite extensive research on the effects of chronic abuse of such agents on learning and memory, cognitive impairment occurred on the grounds of the withdrawal is a less divulged topic. An important question is to whether abstinence itself affects the learning and memory abilities in people who abuse these agents. Cognitive decline observed in withdrawn individuals resulting from drug abuse is not a simple subject to overlook. Most existent studies concerning chronic effects of abused drugs have performed after discontinuation of these agents and there are few studies comparing abstinent individuals with current users. Moreover, it has not yet been characterized whether memory dysfunction is a consequence of drug, residues and metabolites during abuse or neurochemical alterations engendering after withdrawal. The present review summarized the literature regarding the harmful effects of withdrawal of abused drugs on several cognitive aspects. Most studies showed deficiency on spatial memory, episodic memory and working memory. However, it is postulated that spatial memory deficiency persists longer than others. Although the precise underlying mechanism of cognitive impairment after withdrawal is not fully understood, multiple mechanisms are likely to be involved. Furthermore, the negative role of neurotransmitters and neuropeptides such as glutamate, glucocorticoids and cannabinoids has by far been elucidated. It appears that activation of one pathway may activate other pathways, which all contributes to memory dysfunction after withdrawal. Prolonged excessive glucocorticoid levels give rise to cognitive deficit. This may be due to excitatory amino acids rising rather than a direct neurotoxic effect of glucocorticoids (77, 78). Further investigations are, howbeit, required to converge understanding of neurochemical alterations, cellular, and molecular mechanisms in brain after withdrawal into a common conclusion. In the future, with applying appropriate pharmacological treatments that correct neurotransmitter irregularities and cover all putative involved mechanisms, cognitive impairing effects of abused drugs may be prevented or attenuated. Some other benefits may be obtained by increase in compliance of patients in some treatment strategies, preventing drug-seeking behavior and improving social relationship.

Footnotes

Authors' Contribution: Bahareh Amin performed data search and contributed to preparation of the text of the article. Sasan Andalib contributed to the writing of the first draft of the whole paper, editing and modifying the final version. Golnaz Vaseghi collected the related articles and contributed to preparation of the draft. Azadeh Mesripour commented and edited the paper. All the authors read and approved the final manuscript.

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