ASSESSMENT OF NEUROCOGNITIVE FUNCTIONS IN PATIENTS DEPENDENT ON NATURAL OPIUM

Thesis

Submitted to

All India Institute of Medical Sciences, Jodhpur

In partial fulfilment of the requirement for the degree of

DOCTOR OF MEDICINE (MD)

(PSYCHIATRY)

JAN, 2020 **DR. RAGHVENDRA S. SINGH**

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DECLARATION

I hereby declare that the thesis titled "**Assessment of neurocognitive functions in patients dependent on natural opium**" embodies the original work carried out by the undersigned in All India Institute of Medical Sciences, Jodhpur.

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CERTIFICATE

This is to certify that the thesis titled **"Assessment of neurocognitive functions in patients dependent on natural opium"** is bonafide work of **Dr. Raghvendra S. Singh** carried out under guidance and supervision, in the Department of Psychiatry, All India Institute of Medical Sciences, Jodhpur, Rajasthan.

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ABBREVIATIONS

WHO	World Health Organization
NMHS	National Mental Health Survey
ICD	International Classification of Diseases
DSM	Diagnostic and Statistical Manual for Mental Disorders
UNODC	United Nations Office on Drugs and Crime
OUD	Opioid Use Disorder
ELISA	Enzyme Linked Immuno Sorbent Assay
COWS	Clinical Opioid Withdrawal Scale
SODQ	Severity of Opioid Dependence Questionnaire
FTND	Fagerstrom Test for Nicotine Dependence
FTND-ST	Fagerstrom Test for Nicotine Dependence – Smokeless Tobacco
IQ	Intelligence Quotient
VAIS	Verbal Adult Intelligence Scale
WAIS	Wechsler Adult Intelligence Scale
DSST	Digit Symbol Substitution Test
DST	Digit Span Test
TMT	Trail Making Test
RAVLT	Rey Auditory Verbal Learning Test

SUMMARY

Background: The understanding of patients about substance use, adherence to treatment, and relapse have all been found to be affected by cognitive deficiencies. These cognitive deficiencies might be retrainable, which would affect the prognosis in general. In order to effectively treat people who are dependent on opioids, it is essential to have a thorough understanding of cognitive dysfunction. This is because people who experience cognitive alterations, that appear to be suggestible of patients' denial, may continue to act in ways that feed their addictions. More sessions are required to help these individuals adopt abstinence-sustaining techniques in their life since these cognitive deficiencies may make it more difficult for the afflicted person to benefit from counselling.

Opioid use has been linked to cognitive impairments such executive dysfunction and memory loss. These deficiencies play a key role in perpetuating addictive behaviours and impeding the effectiveness of cognitive treatments, which are frequently used in combination to pharmacotherapies. The findings of studies conducted in western nations, however, might not apply here due to the distinct sociocultural environment of the Indian subcontinent. Additionally, research on the cognitive effects of natural opium use, which are relatively prevalent in Western Rajasthan, is quite limited.

Aim: To assess the cognitive functions in patient's dependent on natural opium.

Methodology: All the participants who fulfilled the selection criteria were explained about the study in detail, and a written informed consent was taken from them. On the first day, after ruling out the other psychiatric disorders by clinical interview, socio-demographic and clinical profile sheet were filled. Urine quantitative analysis for opium was done at the baseline with enzyme-linked immunosorbent assay (ELISA) technique by using the commercially available ELISA kit. The severity of opioid dependence was assessed by the Severity of Opioid Dependence Questionnaire (SODQ). Thereafter baseline cognitive assessment was carried out, if patient had withdrawal score <5, based on assessment on clinical opiate withdrawal scale (COWS), cognitive performances was assessed by battery of tests to probe different aspect of cognitive functions such as attention, working memory, verbal memory, processing speed and executive functioning. Participants were provided treatment as usual (detoxification/substitution) as per standard protocol for the opioid dependence syndrome. Similarly, for controls, socio-demographic

profile sheet was filled and cognitive performances were assessed by the same cognitive tools.

Results: All the study partcipants were males belonging to Hindu religion. Mean age of cases and control were 36.07± 8.38 and 32.96±7.20 years respectively. Mean years of education were 12.80±2.33 and 13.46±2.08 years respectively. Mean income in both groups were around INR 20000. Among the cases 13 cases used Amal (resinous form) and other 13 used Doda (dry husk form). Among cases, 20 used tobacco (19 dependent) while same number was 18 in controls. Nearly 80% individuals in both groups had family history of substance use. There was no significant difference between the groups in Marital Status, Occupation, Family type or the Locality. Similar to socio-demographic variables, no significant was noted between the categorical variables like High risk behavior, Nicotine use and pattern, Past and Family substance history. In cognitive variables, significant difference was noted between the groups on Stroop Test, in Stroop Color-Word (CW) (p=0.000) and Stroop Interference scores (p=0.025), Digit Span Test (sequencing component) (p=0.005), Trail Making test Part B duration (p=0.001) and on RAVLT, in RAVLT hit (p=0.003) and omission (p=0.004) component, with cases performing poorly on these tests as compared to controls. In our study DSST coding was negatively correlated with age (p=0.004) and age of opioid initiation (p=0.041). Stroop Word (W) subtest was negatively correlated with Age (p=0.005) and duration of opioid dependence (p=0.026) and positively correlated with years of education (p=0.002). Stroop Color (C) was negatively correlated with Age (p=0.005), duration of opioid dependence (p=0.007) and positively correlated with years of education (p=0.009). Stroop Color-Word (CW) was negatively associated with Age (p=0.020), positively correlated with years of education (p=0.004) and partially correlated positively with Urine opioid ELISA levels (p=0.011). Stroop Interference was correlated negatively with Age (p=0.004), duration of opioid dependence (p=0.001) and partially correlated negatively with duration of opioid dependence (p=0.023) along with positive partial correlation close to significant with Age of opioid initiation (p=0.055). Regarding F-A-S Phonemic Fluency, no significant bivariate or partial correlation was found with any of the variables. DST Forward was negatively correlated with Age (p=0.005), positively correlated with years of education (p=0.012) and correlation was negatively close to significant with duration of opioid dependence (p=0.056). DST Backward was positively correlated with years of education (p=0.005). DST Sequence was negatively correlated with duration of opioid

dependence (p=0.023) and positively correlated with years of education (p=0.004) along with partially correlating negatively with duration of opioid dependence (p=0.030) and partial correlation close to significance with Age of opioid initiation (p=0.054). DST Total was negatively correlated with duration of opioid dependence (p=0.028) and positively correlated with years of education (p=0.001). TMT B duration is positively correlated with Age (p=0.031), age of opioid initiation (p=0.039) and negatively correlated with years of education (p=0.020)

Only RAVLT commission was positively correlated with Age (p=0.001).

Conclusion: In this comparative study, natural opium use was found to affect cognitive domains of response inhibition which refers to the suppression of actions that are inappropriate in a given context and that interfere with goal-driven behavior, suggesting cases have difficulty in controlling their response to different stimuli (proxy for impulsivity) along with poor processing speed as tested by Stroop Test. The sequencing component of DST suggest deficit in domains of working memory, sustained attention and encoding. Significant deficits were seen in domains of set shifting, cognitive flexibility and executive functioning as implied significant difference between groups in TMT Part B duration. Cases were also found to have deficit in verbal learning and recognition on RAVLT. Increased number of omission errors suggest poor retention, retrieval and recognition of verbal information presented on RAVLT. This may open the door to additional studies that analyse the effect sizes of (a) specific opioids like buprenorphine, tramadol, methadone, or tapentadol, which are frequently used to treat natural opioid dependence, and (b) assess residual psychophysiological effects using longitudinal studies, in abstinent patients or patients using multiple substances. By doing so, we will be better able to understand how the key phenotypes of addiction may represent and contribute to neuropsychological deficits in several domains.

INTRODUCTION

In Indian communities, natural opium (opiate) is frequently served as a ceremonial beverage at social gatherings like weddings and festivals. (1) Opium use is woven into the local community's sociocultural fabric. Opium is used for self-medication to treat a variety of health issues, as well as to ease emotional discomfort. In addition to these applications for the alleviation of misery, the substance is also used recreationally and in environments that promote social interaction. (2)

In the western Rajasthan region, opium is also referred to as amal or afeem. It comes in two different forms: the resinous form (Amal), which yields 9.5–14.2% morphine, and the dry husk (Doda), which is processed into powder form and yields 0.1-0.3% morphine. Doda is primarily consumed by those in the lower socioeconomic strata of society since it is affordable, however, consuming Doda also involves eating highly contaminated substance, which is frequently combined with non-opium husk and dust. (2)

In addition to codeine, papaverine, thebaine, and other naturally occurring opiates, the drug morphine, which is generated from the natural juice of the opium poppy, is thought to be the most effective analgesic painkiller on the market. It is also known to cause relaxation and euphoria. All opioids, including morphine, heroin, and prescription analgesics, have a very high potential for abuse because of these characteristics. (3)

The group of medications known as opioids interact with the opioid receptors in our bodies. They can also have euphoric effects in addition to dulling the senses and numbing pain. Opiates, a subclass of opioids, are produced by the opium poppy plant. The opioid receptors in the central nervous system are affected by a class of drugs known as opioids. They include illegal narcotics like heroin as well as medications recommended for pain, including morphine, buprenorphine, oxycodone, codeine, and fentanyl.

The **World Drug Report 2022** has claimed India to be having most number of opiate users in the world. The trend is anticipated to rise with an increase in illegal trade. The information provided by the United Nations Office on Drugs and Crime (UNODC) has provided data regarding seizure or various form of opioids in India:

- 5200 kg opium (4^{th} highest globally)
- 700 kg morphine (3^{rd} highest)

- 3750 kg heroin (5th highest)

The report, which was released on June 27, 2022, did not provide specific information about the number of opioid users in India but did note that the country is one of the biggest markets on the planet for the drug and is particularly vulnerable to supply growth given its geographic location between the Golden Triangle and Golden Crescent. Additionally, there are indications that illegal trades coming from Afghanistan may be intensifying, possibly moving eastward in addition to southwards and westward along the traditional route. (4)

The National Mental Health Survey (NMHS) of India, 2015-16 revealed that 0.6 % of the population with age more than 18 years were recognized with illicit substance use disorder which included opioids, cannabis, stimulants, inhalants, and prescription drugs. A huge treatment gap in India was also revealed by the survey, which refers to the number of people who require treatment but are unable to access it for a number of different reasons. According to NMHS statistics, there was a greater difference between the treatment gaps for alcohol use disorders (86%) than for other drug use disorders (73%). (5)

Nearly 2.1% of the nation's population (2.26 billion people) take opioids, of which 77 lakhs (0.70%) are problem users and 28 lakhs (0.26%) dependent users, including Heroin (or its impure form, smack or brown sugar), Opium (in various forms, such as poppy husk/phukki), and a number of prescription opioids. In the country, heroin is the most often used opioid (1.14%), followed by prescription opioids (0.96%), and opium (0.52%). Rajasthan is home to 3.1 lakh of the 77 lakh problem opioid users (those who use in an unhealthy or addicted manner). (6)

The International Classification of Diseases and Health Problems Eleventh Revision (ICD-11), defines substance abuse as, "*a disorder of regulation of the use of a psychoactive substance arising from repeated or continuous use of the substance. Its central feature is a strong internal drive to use the substance, manifested by impaired ability to control use, increasing priority given to use of the substance over other activities, and persistence of use despite harm and adverse consequences*." If an opioid is used continuously for at least three months, opioid dependency can be diagnosed. (7)

Numerous adverse consequences have been reported with opioid dependence. The development of antibodies and immunological responses, NK cell activity, cytokine expression, and phagocytic activity are all known to be inhibited by it. (8) An enhanced sensitivity to pain is commonly referred to as hyperalgesia or hyperalgia, and it is a relatively recent side effect linked to opioid usage. (9) Numerous hormones are affected by opium use, but testosterone in particular has received the most attention due to its association with the development of numerous adverse sexual effects. (10) Constipation is a typical issue that affects 40% to 90% of patients using opioids and can develop even after taking just one dose of morphine. (11) Along with lower contraction force, diminished feelings of fullness and the urge to urinate, and suppression of the voiding reflex, opioids also result in decreased detrusor muscle tone. (12)

Opioids do not frequently have cardiac side effects. Due to how it works, morphine has been linked to histamine release causing vasodilation and hypotension. Even with prolonged opioid medication, cardiovascular adverse effects are uncommon, especially when using methadone and buprenorphine, where QTc prolongation is a concern. (13)

The sedating effect of opioids is a fairly well known fact. The anticholinergic activity is thought to be what causes sedation and sleepiness. Although tolerance to this side effect may develop, dose commencement and rapid dose titration may also cause sedation, which can cause non-compliance and a lower quality of life as a result. (14) The widespread notion among opioid users is that they improve sleep, however there is little data to back up this assertion. Opioids change the delta and REM sleep patterns and increase the frequency of sleep-waking transitions. They also shorten sleep length and sleep efficiency. (15)

Though not associated with the use of natural opium, which is taken by oral route, possible contamination and concomitant use with benzodiazepines and antihistamines via the intravenous route, associated with spread of the human immunodeficiency virus (HIV), hepatitis (especially hepatitis C), and other sexually transmitted diseases. (16)

Apart from all these, social issues like crime, unemployment, legal issues, interpersonal breakdown, and disturbance of family dynamics are also quite common. Opioids, including medications used in clinical settings for pain management, have the potential to produce long-lasting neuropsychological and cognitive side effects.

The mental activity or process of learning and comprehending through reason, experience, and the senses is known as cognition. (17) The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines six key domains of cognitive function: executive function, learning and memory, perceptual-motor function, language, complex attention, and social cognition. (18)

When one needs to focus and pay attention, one needs to use their executive functions (EFs), also known as executive control or cognitive control. This is because using automatic processes or relying solely on instinct or intuition could have unfavourable effects. (19)

The persistent concentration of cognitive resources while filtering or ignoring external information is best characterised as attention. One of the most fundamental neurological/cognitive processes, attention frequently comes before all other processes. The Sohlberg and Mateer model, which divided attention into the following categories, is one of the most popular ones used to assess attention:

- **Focused attention:** The capacity to react distinctly to a particular sensory stimuli.
- **Sustained attention (vigilance and concentration):** The aptitude for maintaining attentional activity over a period of time.
- **Selective attention:** The ability to foreground 1 or 2 important stimuli while suppressing awareness of competing distractions
- **Alternating attention:** the capacity to change one's attentional focus and switch between tasks requiring various cognitive skills.
- **Divided attention:** This refers to the ability to respond to more than one task at a given time. (20)

Memory and learning are the abilities to store and recall information such as events or facts. Working, procedural, semantic, episodic, and prospective memory are only a few of the many subdomains that make up one of the most complex and sophisticated domains: memory functioning. (21)

The ability to communicate via writing, reading, or speaking is closely related to language.

Language skills include a wide range of behaviours, such as naming objects, selecting the right words for descriptions, and preserving the flow and fluency of different speech styles, grammar, and syntactic structures. (21)

The ability to coordinate one's body's movements in response to external stimuli is referred to as perceptual-motor control. With its assistance, one can engage with the environment by using a variety of senses, particularly vision, touch, and motor abilities. (21).

In order to benefit from belonging to a social group, social cognition is concerned with using information in social contexts to explain and anticipate behaviour.

This involves the capacity to restrain urges, display empathy, recognise social cues, comprehend facial emotions, and be motivated. (21)

While assessing patients with opioid dependence, gross impairment in cognitive functions is usually not present and hence neurocognitive tests are required to assess the cognitive dysfunctions. Tests like the Trail Making Tests (TMT-A & B), Digit Vigilance Test (DVT), Verbal and Visual N-Back Test (NBT), Rey's Auditory Verbal Learning Test (RAVLT), Wisconsin Card Sorting Test (WCST), Controlled Oral Word Association Test (COWA), Wechsler Adult Intelligence Scale (WAIS), Logical Memory, Construction Praxis, etc. are frequently used to measure different domains of cognition.

Patients have various beliefs regarding natural opium use: it provides them with energy to do the farm work, relieves pain, enhances their attention as well as sexual performance and also treats common sexual disorders, makes them stronger when it comes to handling stress, not as deteriorating or intoxicating as other substance like alcohol or cannabis, not causing any serious illness like cancer, increases appetite, particularly in elderlies.

In general, benefits are perceived more than the ill effects and further clarifications regarding the neurocognition impairments can be helpful in the prevention part as well as to motivate patients to quit.

All of the aforementioned cognitive domains play important roles in treatment and are thought to have an impact on patients' mental states, treatment compliance, and the course of their illnesses. Learning new skills to prevent relapse, control impulsive impulses and

automatic thoughts, and create problem-solving strategies are all necessary for adopting a new lifestyle and maintaining abstinence. (22)

Cognitive dysfunctions are known for leading to poor treatment adherence and lower self-efficacy, which ensues in poor outcome with remaining sober for lesser duration than expected. And all these results are not uncommon in opioid users even with mild cognitive impairments. (23) The individual's capacity to benefit from therapy may be hampered by such cognitive deficiencies, requiring extensive additional efforts in order to assimilate strategies for sustaining abstinence into daily lives. (24)

There is a tonne of data to support memory impairment, and short-term abstinence has also been linked to impairments in executive functioning, including verbal fluency, inhibition, and decision-making. These negative effects have been shown up to a year after quitting, but it is debatable whether or not full recovery takes place. (25)

Cognitive ability may have an impact on treatment adherence and participation. There is growing research that proposes tailoring therapy for substance addiction based on these distinct cognitive features. This encourages the highest therapeutic outcomes possible in turn. As a result, researching individuals' neurocognitive profiles may be crucial in influencing therapeutic decisions made during the course of treatment. (26)

Particularly in adolescents with weak cognitive control, substance use may affect brain development to be skewed toward unfavorable decision-making. Additionally, research highlights that given its moderating role in the neuroadaptive consequences of substance use on brain development, cognitive control may be a primary target in the prevention and treatment of adolescent substance use. (27) Opioids also affect cognitive control by affecting the cost-benefit balance, which in turn influences how cognitive control is distributed, in a manner similar to how they affect decision-making. (28)

Natural opium use is common in this region and there is limited data among this population regarding its effect on cognitive functions. Such information can be used to emphasize appropriate treatment and in the future to target specific cognitive domains which can hinder the progress of substance use disorder treatment and to start specific cognitive interventions for the comprehensive and successful treatment of these disorders. However, the existing literature regarding this topic is scarce, Moreover, the evidence gained from western studies might not apply to Indian patients dependent on natural

opium, which differ significantly in socio-cultural aspect. This study will contribute to the body of knowledge in the area and open the door to similar research in the future.

REVIEW OF LITERATURE

Literature search about the cognitive profile of patients of opioids along with their comparison has revealed limited data from both western countries as well as India. There is a dearth of data, especially in the Indian setting regarding the assessment of cognitive profiles in substance use disorders. Neuropsychological dysfunctions associated with opiate use are well studied and documented but assessment studies in patients with opioid dependence who are consuming natural opioids are sparse, especially from our country.

Opioid medicines have the potential to significantly affect cognitive control and reward-based judgments even after only one usage through altering motivational processing and/or learning. In fact, studies on rodents show that certain measures of sustained attention and response inhibition are impaired by opiate use. Despite this, it has generally been assumed that opioid medications will impair focus, and studies of human drug subjects collecting measures of cognitive control and executive function have typically lacked a compelling theoretical justification for task inclusion. (29)

In a study, **Wollman et al., (2018)** used meta-analysis to assess the results from earlier studies in order to examine the neuropsychological impairments connected to opioid usage across 14 different neurocognitive domains. In total, 2580 patients with opioid dependence and 2102 healthy control participants from 61 trials were included in the analysis. The largest effect size variation was seen in complex psychomotor abilities when compared to neuropsychological performance. The motor and processing speed domains, which showed no group differences, were the only two neurocognitive domains that did not have small-to-medium effect sizes. In the complex psychomotor domain, meta-regression revealed a relationship between longer periods of abstinence and smaller effect sizes. Additionally, executive functioning and verbal memory impact sizes differ, and attentional ability predicts these variations. Opioid Use Disorder (OUD) patients' overall raw scores frequently fell below the normal range in these investigations, despite the majority of meta-analysed research demonstrating significant differences between OUD patients and controls. (30)

Baldacchino et al., (2012), carried a meta-analysis which linked chronic opioid usage to abnormalities in a variety of cognitive domains. But only three areas—cognitive impulsivity (risk-taking), verbal working memory, and cognitive flexibility—show a substantial reduction, according to a meta-analysis. Using Cohen's benchmark standards, the size of the outcome across various cognitive domains was average. This analysis drew attention to methodological flaws in the studies done so far and the significance of employing meta-analytic methods to assist further explain how long-term opioid use affects the neuropsychological characteristics of "core" addiction phenotypes. In limitations, authors reported that it was difficult to distinguish drug usage directly from more subtly occurring causes of deleterious cognitive effects in chronic opioid takers. (31)

Cross-sectional study by **Saroj et al., (2020)** compared 4 groups: patients on buprenorphine maintenance (n = 20), patients using naltrexone (n = 20), patients undergoing early detoxification (n = 20), and a control group (n = 30). The following tests were administered to all four groups: WCST, DVT, COWAT, the Verbal and Visual NBT, and RAVLT. When compared to the control group, the buprenorphine maintenance group (Index Group; IG) fared worse on the TMT-B, DVT, verbal NBT, and WCST (CG). Patient performance during early detoxification was noticeably worse in TMT-A and B than in IG. In TMT-B, IG were poor in performance than the naltrexone group (NG), and NG did worse in the RAVLT than CG. The patients receiving medication-assisted treatment were shown to have significant cognitive impairment that was restricted to less significant cognitive domains; however, in the group of people who were actively misusing opioids, the degree and severity were highest. It is the only study on this subject to have been conducted in India (32).

In the rural villages in districts of Barmer, Jaisalmer, and Bikaner, **Lakshminarayana and Singh (2009)** conducted a house-to-house survey. They discovered that the rate of addiction increased with age and that consumption had significantly increased ($P<0.05$), meaning that a larger population was becoming addicted to opium (Doda). Substance use was higher among people aged 40 to 50 in comparison to other age groups. Illiteracy and low socioeconomic status are two of the primary risk factors for addiction ($P<0.05$), which is significant because they had

inadequate awareness of its harmful consequences over a longer period of time. The usage of it is done to increase labour in the fields and to treat minor illnesses, but over time, it leads to dependence. (33)

Soyka et al., (2008) looked for the cognitive functioning of 46 subjects on Buprenorphine (n=22) and Methadone maintenance (n=24) and 24 controls, comparing their baseline cognitive (t1) functions at the start of therapy with stable substitution levels after 8-10 weeks (t2) when a successful treatment outcome may be predicted. Following cognitive tests were used - d2 test of Attention, Regensburger Word Fluency Test (RWT), Trier Inventory for the Assessment of Chronic Stress (TICS–2-K, German version), Verbal Learning and Memory Test (VLMT) and Trail Making Test (TMT). The outcomes delineated almost identical effects on cognitive functions with both therapies. Concentration and executive function improved in both subgroups. Patients on methadone reported noticeably increased perceived social performance stress. There were no cognitive function changes between the groups with high and low stress levels. Regarding the restrictions, a somewhat smaller sample size and corresponding loss of statistical power can be used to explain the results, as can the high number of cannabis or other substance positive tests in both groups. (34)

Using the Multiple-Choice Vocabulary Test, Block Design Test, Rey Complex Figure Test, VLMT, Letter-Digit-Ordering, TMT-A and B, and "Alertness," "Divided Attention," and "Go/No go" sub-tests from the Test Battery for Attentional Functions, **Soyka et al., (2010)** conducted a cross-sectional study to examine the differences in cognitive function between 35 patients on short-term (30 days) However, there were no differences between the groups in terms of learning, memory, or attention. Cannabis use, which has been found to have an effect on cognition, was not controlled in this study. (35)

Charles-Walsh et al., (2016) used the Monetary Incentive Control Task (MICT) in a cross-sectional study of 32 patients dependent on opioids and 29 matched controls to examine the link between cognitive control and reward sensitivity. They discovered that dependents had a generalised decline in cognitive control due to a poor ability to modulate their behaviour in accordance with external cues. The connection between cognitive control and reward didn't differ between the two

groups, though. Key demographics were essentially similar between the two groups, but the drug-dependent group was significantly aged, had less years of education, had a lower estimated premorbid intellect, had a greater present depression and anxious symptoms, and had less positive affect than controls. (36)

According to cross-sectional study of 39 participants by **Arias et al., (2016),** there was a higher likelihood of both general and domain-specific neurocognitive impairment, with a worsening of learning and memory. The WAIS-III Digit Symbol and Symbol Search, COWAT, Semantic (Animal) Fluency, Hopkins Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised, Grooved Pegboard Time, and WAIS-III Letter Number Sequencing were all part of the cognitive test battery. Long-term dependency on alcohol and cocaine was linked to higher neurocognitive impairment, particularly in executive functioning. These results suggest that opioid-dependent people may require additional support for medical decision-making because executive functioning is a critical component of decision-making and learning/memory dysfunction may prevent information from being encoded. (37)

A study by **Shmygalev et al., (2011)** on 30 patients with 90 matched controls on the influence of long-term buprenorphine maintenance therapy on complex psychomotor and cognitive functions using a test battery for evaluating motor coordination and vigilance, didn't find substantial decline in cognitive function with stable sublingual dose. Because the matching statistics for the control group were not available, the controls were not matched for socioeconomic class and educational attainment, which could be a potential weakness of the study. (38)

A study conducted by **Rapeli et al., (2006)** on 15 patients dependent on opioids and 15 controls matched for sex, age, and verbal intelligence, aimed at inspecting cognitive functions with Wechsler Memory Scale-Revised (WMSR), PASAT, modified Stroop task, Ruff Figural Fluency Test and Culture Fair Intelligence Test (CFIT) during the first week of abstinence, concluded that subject performed inferior to controls in domains of working memory, executive function, and fluid intelligence, corresponding statistically with duration of withdrawal pointing out general neurocognitive decline. However, in this study, prior benzodiazepine or cannabis use was common among the patients which could have affected the results.

Also, the majority of patients had a personality disorder, especially the Antisocial type. In addition, cognitive testing was done on any day chosen at random anywhere between 5 to 15 days after the last opioid dose was taken. (39)

Prosser et al., (2006) conducted a study on 56 subjects and 29 controls to examine the cognitive impairment in long-term Methadone Maintenance Therapy (MMT) (n=29) and abstinent subjects (n=27) following methadone detox in the erstwhile heroin users in contrast to controls. WAIS-Revised Vocabulary Test, the Stroop Color-Word Test, the COWAT, and the Benton Visual Retention Test were used for testing cognitive functions. Both maintained and abstinent subjects performed poorly in comparison to controls in verbal function, visual-spatial analysis, memory, and resistance against distractibility. In comparison to the MMT group, absent participants underperformed in visual memory and construct construction. They came to the conclusion that the cognitive impairment displayed by both categories of patients was almost identical. Cigarette use was not controlled in this study. (40)

A study on the variables affecting cognitive skills in individuals with opioid dependence was undertaken by **Loeber et al., (2012)** with 54 patients who were dependent on opioids. To minimise confusing withdrawal effects, the cognitive testing (lasting for 2 hours), was carried out 30 minutes after the daily dose of methadone or buprenorphine was consumed. The California Verbal Learning Exam, the TMT, the Continuous Performance Test, the D2, the Determination Test, the VIGIL, and a vocabulary test were then delivered as part of a neuropsychological test battery that measures memory, executive function, and attention. According to the study, other substance use and the length of opioid dependency and maintenance therapy were the significant contributors to attention and executive function impairment. However, no evidence was found for the role of demographic variables like age and educational status. (41)

In 93 heroin users, **Guerra et al., (1987)** examined cognitive performance before and after 1 week of detoxification. The performance of the addicts and a sample of 30 controls with comparable IQs showed substantial differences. The Toulouse-Pieron (TP) cancellation test was used to assess perception and attention, as well as the F factor of PMA (PMA-F), verbal fluency, immediate auditory memory, short-term and long-term memory tasks, and the elicitation of events. To assess

intelligence, Raven's Progressive Matrices were also used. Addicts responded more strongly to most variables at the time of re-evaluation, including overall clinical state. Additionally, no variations in the group of sober addicts and controls were found on tests of neuropsychological performance. There was no relationship between psychological symptoms and cognitive functions after drug detoxification in users. The duration of addiction or drug usage in the group of heroin users did not indicate cognitive decline. (42)

Using the Medical Outcomes Study Mental Health Inventory (MOS-MHI) cognitive functioning scale, a study of 889 (m=277, f=612) chronic opioid users by **Randall et al ., (2006)** examined the adverse effects and cognitive function. The study's overall study sample appeared to have more cognitive dysfunction than the general population, but there was no statistically significant difference. (43)

Pujol et al., (2018) examined 34 articles on the treatment of opioid dependence for their study, "Cognitive effects of labelled addictolytic medicines." In comparison to healthy people, this study indicated that both buprenorphine and methadone appeared to be the source of disorders of executive functions and general cognition, however methadone appeared to have more negative effects. Both result in improved cognitive function after several months of therapy, albeit opioid abstinence can also be blamed for this. Additionally, buprenorphine seems to be more appropriate for people who must drive. (44)

With the help of the Game of Dice Task, **Brand et al., (2008)** looked at 18 people who were opiate addicted (OD) and 18 healthy control (CG) subjects who had the same age, sex, and educational profile. The Gambling Decision Assignment (GDT) is a gambling task with specific rules for losses and wins and predetermined winning odds. All participants also finished a battery of tests that mainly focused on executive functioning and a personality assessment. On the GDT, patients more frequently selected the riskier options than the control group. Other cognitive features, personality qualities, or dependence-specific criteria were not associated with patients' performance on the GDT, with the exception of days of abstinence. Therefore, individuals with opiate dependence display abnormal decision-making that could be cognitively linked to dysfunctional behaviour in daily life. In the management of opiate dependence, cognitive functioning, including decision-

making, is intended to be taken into account. The study's generalizability to various subgroups of opioid-dependent patients living in different environments was hampered, as stated by the authors, because all members of the OD group were admitted to psychiatric facilities with a focus on the treatment of substance use, where psychotherapy was also provided. (45)

According to **Messinis et al., (2009),** 34 non-drug dependent controls and 32 heroin addicts who are currently abstinent on naltrexone hydrochloride therapy were used to compare the cognitive performance of 18 patients who were maintained on buprenorphine. Demographic equilibrium existed among the three groups. The 15-item Boston Naming Test, the Verbal Fluency Test: Phonemic and Semantic Fluency, the RAVLT, the Repeatable Battery for the Assessment of Neuropsychological Status, the Color Trails Test, the Symbol Digits Modalities Test, and the Ruff 2 & 7 Selective Attention Test were all included in the cognitive test battery. According to the results, naltrexone treatment may cause abstinent heroin addicts to experience less cognitive damage than Buprenorphine treatment. These results are pertinent to more accurate forecasting and updated treatment strategies for patients who are opioid-dependent. (46)

Iowa gambling task was used by **Pirastu et al., (2006)** compared the decision-making abilities of methadone-maintained (n=18) and buprenorphine-maintained (n=30) participants to non-opiate-dependent drug-free controls (n=21). The findings imply that buprenorphine improves decision-making compared to methadone and may therefore be more helpful in opiate-dependent individuals' rehabilitation programmes. This benefit may be related to buprenorphine's unique kappa antagonist pharmacological effect. (47)

Twenty buprenorphine/naloxone-treated adults with OUD (mean age = 45.2 years [SD=8.1]; 25% female) were recruited by **Scott et al., (2017)** to participate in baseline reference and 6-month visits using a neuropsychological test battery consisting of COWAT, Semantic (Animal) Fluency, WAIS-III Digit Symbol, WAIS-III Symbol Search, WAIS-III Letter Number Sequencing. Study reported increased adherence to the Buprenorphine/Naloxone combination in some way relates to longer-term cognitive improvement in OUD patients. However, there is no long-term link between cognitive function and depressive symptomatology. In OUD

patients, continued adherence to the Buprenorphine/Naloxone combination may enhance and/or sustain memory and learning capacities. (48)

In their review article, **Ramey and Reiger (2018)** came to the conclusion that cognitive dysfunction is a transdiagnostic domain and that improvements in the diagnosis, treatment, and improvisation of cognitive impairment in substance use disorder could be applied to other numerous psychiatric disorders. (49)

In their cross-sectional study, **Shakeri et al., (2020)** compared the MMSE scores of opium users (n = 52), Methamphetamine users (n = 50), and healthy controls (n = 100), and discovered that differences were significant between the normal and substance user groups in terms of mean scores for orientations, attention, and mental status ($p>0.05$).The difference between methamphetamine and opioid addicts, who made up the substance use group, however, was statistically insignificant ($p>0.05$). Additionally, only the controls and methamphetamine users had scientifically significant mean language test scores ($P<0.05$.). In this study, instead of using psychological test specific to individual cognitive domains, MMSE was used as used which might not be as sensitive in detecting the subtle cognitive impairments in patients with substance use. (50)

A descriptive, causal-comparative study by **Ghanbari et al., (2016),** addressing males, dependent (n=35) and abstinent (n=32) on natural opium and healthy control (n=35) found a major difference in long-term memory performance among these 3 groups but no significant difference was reported when it comes to short term memory performances. For data collecting Prospective and Retrospective Memory Questionnaires (PRMQ) were used and data was analyzed using MANOVA and Tukey test. (51)

In a causative-comparative study by **Nejati et al., (2012),** 30 opium-dependent patients were compared with 30 healthy controls who were matched for gender and education, and the results showed that opium addicts had considerably lower mind-reading skill. Additionally, opium users performed noticeably worse when it came to identifying the emotions shown by joyful, sad, and angry expressions, which suggests that social cognition testing be used as a benchmark when assessing and evaluating drug users. (52)

Using WCST and the Letters-Digits Sequence Test, conducted by **Sadeghi et al., (2021)**, it was discovered that opiate users (n=25) had lower executive function scores compared to the normal group (n=25), but better functioning compared to in-abstinence groups (n=25). However, opiate users significantly outperformed the in-abstinence group. This study also discovered a link between long-term substance use and poor executive function. (53)

Using a test battery including the WAIS-R Digit Symbol Substitution Test (DSST), the Auditory Verbal Learning Test-Revised (AVLT-R), the Brief Visuospatial Memory Test-Revised (BVMT-R), the Digit Forward and Backward Tests (DFT and DBT), and other measures, **Moghaddam et al., (2021)** conducted a cross-sectional study to examine the effects of OUD. The study found DBT (r = 0:483) and DSST (r = 0:542) scores were correlated with the length of usage. DBT score was correlated with opium use quantity (OUQ) (r = 0:385). Based on these results, the authors propose that DBT and DSST could be utilised as techniques for quick clinical examinations to check for cognitive abnormalities in OUD patients. (54)

The cognitive performance of OUD patients receiving OT or methadone treatment was examined by **Wong et al., (2021).** Participants with OUD were assigned arbitrarily to either the methadone (n=38) or the opium tincture group (OT, n=26) in a randomised controlled experiment. The Montreal Cognitive Assessment (MoCA) was applied to measure cognitive functions. The MoCA was finished by participants at baseline, weeks 4, 8, and 12. Participants' cognitive abilities significantly improved. From the beginning of opioid agonist treatment until week 4, there was an improvement, but from week 4 to week 12, this improvement stalled. Participants undergoing OT and methadone did not significantly differ in their cognitive performance. Their findings support the contribution of OT and methadone in improving OUD patients' cognitive function. (55)

Using various test batteries, multiple neuropsychological investigations have examined cognitive impairments in OUD patients in the past few decades. However, multitude of issues have limited or confounded the findings of earlier research such as: (a) only a handful of studies evaluated pure opium users, per se; as the majority of opium users consume other substances; (b) using a restricted battery of neuropsychological tests; (c) the length, quantity, and method of opium intake in

patients, which were frequently overlooked in earlier studies and may have had an impact on the severity of cognitive dysfunctions in OUD patients; (d) socio-demographic variables in most of the studies were not adequately controlled; (e) variable period when tests were applied during the withdrawal phase; (f) non-availability of measure to accurately quantify the dosage of opioids.

The results of earlier research on opioid users generally hint to cognitive impairments across a variety of categories, but their findings are complicated by the use of substances other than opioids.

From the review, it is obvious that opioid dependence is associated with cognitive impairment in various domains. However, studies on natural opium users with a battery of tests are lacking, especially in the Indian setting. With this background, the current study design was planned.

AIMS AND OBJECTIVES

AIM:

To assess the cognitive functions in patients dependent on natural opium.

OBJECTIVES:

1. To assess the cognitive functions in patient's dependent on natural opium.
2. To compare the cognitive functions of patient's dependent on natural opium with matched healthy control.
3. To find association of cognitive functions with clinical covariates in patient's dependent on natural opium.

MATERIALS AND METHODS

Study setting:

Patients who attended the OPD and IPD services of Department of Psychiatry of All India Institute of Medical Sciences, Jodhpur, Rajasthan and healthy controls from the care givers/ attendants of patients or from community.

Study design: Comparative Study

Study participants:

Study consisted of 2 groups: Equal number of cases (patients with natural opium dependence) and controls were taken as study participants.

CASES:

Inclusion criteria:

1. Treatment naïve patients' dependent on natural opium who fulfilled the criteria of opioid dependence as per International Classification of Diseases, Eleventh Revision (ICD-11)
2. Age between 20 to 50 years of either gender
3. Patient who gave written informed consent for participation in study
4. Able to read, write and understand Hindi or English

Exclusion criteria:

1. Presence of co-morbid psychiatric disorders
2. Presence of other substance dependence except nicotine
3. Presence of dependence on synthetic opioids
4. History of chronic medical disorder, epilepsy, head injury and neurological disorder
5. Patient with IQ less than 80
6. Patient with color blindness

CONTROLS:

Inclusion criteria:

1. Age and gender matched healthy subjects
2. Healthy subjects who gave written informed consent for participation in study
3. Healthy subjects who were able to read, write and understand Hindi or English

Exclusion criteria:

1. Presence of any substance dependence except nicotine
2. Individuals with any psychiatric disorders
3. History of chronic medical disorder, head injury and neurological disorder
4. Healthy subjects with color blindness or IQ less than 80

Sampling and sampling size:

Non probability convenience sampling methods was used for the selection of the study participants.The sample size was calculated from study titled "Neurocognitive functions in patients on Buprenorphine maintenance for opioid dependence: a comparative study with three matched control groups" (Saroj et al., 2020). (14) Available literature reported that verbal memory and executive functions were consistently impaired in patients with OUD. (12, 13) Therefore, the results from the TMT-A & TMT-B and RAVLT (mean and standard deviation) were taken into account for determining the sample size. In a research by Saroj et al., the mean (SD) RAVLT assessment scores for active opioid dependency and control groups were 9.05 (1.47) and 10.17 (1.39), respectively. In this study, the mean (SD) score on TMT assessment were 45.65 (16.86) and 28.23 (7.39) on TMT-A & 104.65 (27.06) and 70.83 (34.28) on TMT-B for active opioid dependence and control groups respectively. The threshold of significance (two-sided) was remained at 0.05 and the power was maintained at 80%. With the aid of the following software, the sample size was estimated: (http://statulator.com/SampleSize/ss2M.html). Highest sample size found was 26 in each group, calculated from above software on the basis of RAVLT. So, 26 participants were recruited in each group.

Study duration:

From February 2021 to February 2022.

Procedure for the study:

All the participants who satisfied the criterion for selection were explained about the study in detail (Appendix 1 or 3), and a written informed consent (Appendix 2 or 4) were taken from them. On the first day, after ruling out the other psychiatric disorders, socio-demographic and clinical profile sheet (Appendix 5 and 6) were filled. Urine quantitative analysis for opium were done at the baseline with enzyme-linked immunosorbent assay (ELISA) technique by using the commercially available ELISA kit. The opioid dependence severity was assessed by the Severity of Opioid Dependence Questionnaire (SODQ). Thereafter baseline cognitive assessment was carried out if patient had withdrawal score <5, based on assessment on clinical opiate withdrawal scale (COWS). Cognitive performances were assessed by battery of tests to probe different aspect of cognitive functions such as attention, working memory, verbal memory, executive functioning and processing speed. Participants were provided treatment as usual (detoxification/substitution) as per standard protocol for the opioid dependence syndrome. Similarly, for controls, socio-demographic profile sheet were filled and cognitive performances were assessed by the same cognitive tools.

Flow Chart 1: Methodology

Patients dependent on natural opium attending the OPD and IPD services of Department of Psychiatry of All India Institute of Medical Sciences, Jodhpur

↓

Patients dependent on natural opium fulfilling the selection criteria after explaining study detail and taking informed written consent

↓

Screening using clinical interview screen to rule out the other psychiatric disorders (on Day-1)

↓

IQ Assessment by VAIS

↓

SOD-Q and FTND (to assess severity of opioid and nicotine dependence respectively)

↓

Urine quantitative analysis for opium by ELISA (on Day 1)

↓

Socio-demographic details and clinical profile(on Day 1)

↓

Cognitive assessment were done when COWS score < 5

↓

Data collection and statistical analysis

Measures and Tools of Assessments:

1. **Socio-demographic variables:** Name, age, sex, religion, marital status, educational background, employment and socio-economic status.

2. **Clinical variables:** Age of onset, duration of use, duration of dependence pattern, form and amount of opioid use, previous abstinent attempt, family history of psychiatric illness and substance abuse, withdrawal scores at the baseline and before cognitive assessment, and level of motivation to quit the substance.

3. **Verbal Adult Intelligence Scale (VAIS):** The verbal component of IQ is tested using the four subtests that make up the VAIS: information, comprehension, arithmetic, and digit span. These two assessments are part of the PGI Battery of Brain Dysfunction (PGIBBD). Applicable to anyone aged 20 to 59 years old. (56)

4. **Severity of Opioid Dependence Questionnaire (SOD-Q):** This 9-item instrument was developed to quantify the opiate dependence severity. It is an self-administered questionnaire which consists of 5 sections of questions corresponding to: (1) Quantity and pattern of opiate use (usual route of administration, e.g.); (2) Physical symptoms of withdrawal (symptoms upon awakening prior to taking the first dosage); (3) Mood symptoms related to withdrawal, including craving, mood states after waking up before taking first dose); (4) Withdrawal-relief drug taking; and (5) Reinstatement timeframe of withdrawal symptoms after a period of abstinence. An additional sixth related section, the "Opiate Subjective Dependence Questionnaire," can also be used; containing five questions evaluating the subjects' impression of their own dependence. (57)

5. **Fagerström Test for Nicotine Dependence (FTND& FTND-ST):** This is a commonly used tool for determining the degree of physical nicotine addiction. Multiple-choice questions are marked from 0 to 3, whereas yes/no questions are rated either 0 or 1. The items are added up to create a final score between 0 and 10. The patient's physical reliance on nicotine is more severe, the higher their overall Fagerström score is. (58)

6. **Clinical Opioid Withdrawal Scale (COWS):** 11 item scale administered by clinician, helps in evaluating the degree of opioid dependence and the opioid withdrawal severity. (59)

7. **The WAIS-IV Digit Symbol Substitution Test/Coding (DSST)**: Response time, sustained focus, visual spatial abilities, and set shifting are all needed for this test. Within 90 seconds, the participant completes a series of correctly coded symbols. Higher the score, better the performance. Test items in WAIS-IV^{INDIA} have been adapted to India for cultural appropriateness. India norms for WAIS-IV^{INDIA} are the most recent set of norms and representative of the Indian population across the country (60, 61)

8. **The Stroop Color-Word Test**: A measurement of distraction resistance and sustained attention. The individuals are asked to identify the presented color-words' printed hues as well as control stimuli. The score is based on how many correct answers were provided in the allocated period. The only Stroop scores used were the Color-Word (CW) and Interference scores. Regardless of the word stimuli that are given, the Stroop CW score is the total number of colours that are correctly named. The increase in reaction time when the stimulus is a color-word printed in an unrelated colour is known as the Stroop Interference score. Future experimental psychomotor evaluation investigations may benefit from the simplicity, sensitivity to drug acting on CNS, and potential of the Stroop color-word recording and analysis system. (62, 63)

9. **The F-A-S Test**: An evaluation of verbal fluency. Within a 60 second time limit, subjects are instructed to list as many words as they can that start with the letters F, A, and S. The total number of accurate responses is kept track of. This test evaluates cognitive abilities such as self-monitoring, internal response generation, mental set changing, and selective attention. Tests with Indian norms are available to measure particular cognitive categories. (64, 65)

10. **The Digit Span Test**: A subset of WAIS-IV, this test measures working memory, attention, encoding and auditory processing. This test has 3 components, Digit Span Forward, Digit Span Backward and Digit Span Sequencing. Test items in WAIS-IV^{INDIA} have been adapted to India for cultural appropriateness. India norms for WAIS-IV^{INDIA} are the most recent set of norms and representative of the Indian population across the country (60, 61)

11. **The Trail Making Test (TMT) Part A and B**: This test evaluates cognitive and perceptual speed, requiring the ability to quickly recognise a number's symbolic significance and order them under time constraints. Part A measures information processing and psychomotor speed, by connecting numbers 1-25 which are randomly distributed over a page. Part B evaluate cognitive flexibility and ability to switch between amounts by alternately connecting number and letter in sequential order. Test is available with Indian norms for testing specific cognitive domains. (66, 67)

12. **Rey Auditory Verbal Learning Test (RAVLT):** This neuropsychological test is used to assess verbal memory individuals who are 16 years of age or above. The RAVLT is a tool that can be used to assess the type and severity of memory impairment and monitor changes in memory function over time. (68)

Statistical Analysis:

Data was entered and analyzed using SPSS (Statistical Package for the Social Science) version 21. Descriptive analysis was applied in terms of frequency and percentages for categorical socio-demographic and clinical variables. Contingency tables were made for categorical clinical and socio-demographic variables among subjects of both groups to determine the statistically significant difference using Chi-square test and Fisher's exact test for contingency tables with smaller sample size (less than 5). Continuous socio-demographic and clinical (cognitive) variables were compared using paired T-test or Mann-Whitney U test depending on whether the continuous variables were parametrically or non-parametrically distributed respectively. Bivariate correlation was used to obtain correlation coefficients and partial correlation was used to obtain correlation coefficients after controlling for Age, Education years, FTND, FTND-ST to look for association of cognitive functions with level of exposure to natural opium which are indirectly indicated by age of opioid initiation, duration of opioid dependence, urine opioid ELISA level and SOD-Q.

Ethical Consideration: Data collection was started after obtaining ethical clearance (AIIMS/IEC/2020/3138) from institute's Ethics Committee. Study participants were recruited after seeking written consent.

All of the cases were given proper treatment as per standard guidelines followed in routine care of patients.

RESULTS

Descriptive Statistics:

Cases

Table 1: Socio-demographic variables of cases (n=26)

Socio-demographic variable	**n (%)**
Marital Status	
• Single	5 (19.2)
• Married	21 (80.8)
Occupation	
• Cleric/farmer/shop owner	10 (38.5)
• Skilled	3 (11.5)
• Semi/unskilled	10 (38.5)
• Unemployed	3 (11.5)
Family type:	
• Nuclear	6 (23.1)
• Extended	11 (42.3)
• Joint	9 (34.6)
Locality:	
• Urban	12 (46.2)
• Rural	4 (15.4)
• Town	10 (38.5)
	Mean± SD
Age	36.07± 8.38
Education (years)	12.80±2.33
Income	19916.53±10607.47

n = number of participants; % = percentage; SD = Standard Deviation

Table 1 shows that majority of the cases were married and were equally occupied in Cleric/farmer/shop owning or doing occupations in which they were semi/unskilled. Nearly half of the cases belonged to extended family. Cases mostly resided in urban locality followed by towns. Mean age of cases was around 36 years, with average

education of nearly 13 years and income averaging to approximately Rs. 20000 per month.

Table 2 (a): Clinical variables (categorical) of cases (n=26)

Clinical variable	**n (%)**
High risk behavior: • No • Yes	 25 (96.2) 1 (3.8)
Nicotine use: • No • Yes	 6 (23.1) 20 (76.9)
Nicotine use pattern: • Occasional • Dependent • Abstinent	20 0 (0) 19 (95.0) 1 (5.0)
Past substance history: • No • Yes	 17 (65.4) 9 (34.6)
Family substance history: • No • Yes	 5 (19.2) 21 (80.8)

n = number of participants; % = percentage of participants of a particular variable in a particular group

As shown in Table 2 (a), High risk behavior was not found in majority of cases. Most of the cases had nicotine use in one form or other, mainly in dependent pattern. For majority of the patients, natural opium or tobacco were the first substances to be used and nearly 80% had family history of substance use.

Table 2 (b): Clinical variables (continuous) of cases (n=26)

Variable	Mean± SD
Age of opioid initiation (years)	28.23±7.00
Duration of opioid use (years)	7.84±5.40
Duration of opioid dependence (years)	7.61±5.15
Usual opioid dose (grams)	908.65±962.71
Urine opioid ELISA level (ng/L)	.306±.178
SODQ Total score	38.5±5.46
FTND score (n=7)	4.14±2.67
FTND ST score (n=14)	4.07±1.68
COWS score	2.23±1.50

ELISA = Enzyme Linked Immuno Sorbent Assay; SODQ = Severity of Opioid Dependence Questionnaire; FTND = Fagerstrom Test for Nicotine Dependence; FTND-ST = Fagerstrom Test for Nicotine Dependence – Smokeless Tobacco; COWS = Clinical Opioid Withdrawal Scale; SD = Standard Deviation

Table 2 (b) shows mean age of opioid initiation in cases was 28 years with average duration of opioid use and dependence being nearly same, just more than 7.5 years, indicating becoming dependent very early in the course of opioid use. Average dose of Doda users was around 1750 grams while the same for Amal users was around 67 grams in a month. Mean FTND or FTND-ST score was around 4 indicating an overall low to moderate nicotine dependence in the case group. Average COWS score in case group was around 2 indicating no withdrawal.

Table 2 (c): Clinical variables (cognition) of cases (n=26)

Variable	Mean± SD
Digit Symbol Substitution Test	
• Coding	40.42±6.48
• Error	0.500±1.03
Stroop Color-Word Test	
• Word	71.03±14.13
• Color	45.23±11.09
• Color-Word	24.31±6.49
• Interference	21.04±5.77
F-A-S Phonemic Fluency Test	
• Phonemic F	7.92±1.69
• Phonemic A	6.85±1.87
• Phonemic S	7.07±1.38
Digit Span Test	
• Forward	7.31±1.22
• Backward	6.50±1.10
• Sequence	4.96±0.77
• Total	18.77±2.66
Trail Making Test Part A and B (TMT A & TMT B)	
• TMT A duration	30.69±6.28
• TMT A error	0±0
• TMT B duration	77.53±26.07
• TMT B error	0.96±1.95
Rey Auditory Verbal Learning Test (RAVLT)	
• RAVLT DR	9.27±2.14
• RAVLT hit	10.58±1.39
• RAVLT omission	4.38±1.41
• RAVLT commission	2.77±1.27

SD = Standard Deviation

Table 2 (c) shows the mean score and standard deviation of the various sub sections of the neuropsychological tests applied to test the different cognitive parameters in cases.

Control

Table 3: Socio-demographic variables (categorical) of controls (n=26)

Socio-demographic variable	**n (%)**
Marital Status: • Single • Married	 4 (15.4) 22 (84.6)
Occupation: • Cleric/farmer/shop owner • Skilled • Semi/unskilled • Unemployed	 15 (57.7) 1 (3.8) 7 (26.9) 3 (11.5)
Family type: • Nuclear • Extended • Joint	 5 (19.2) 9 (34.6) 12 (46.2)
Locality: • Urban • Rural • Town	 11 (42.3) 5 (19.2) 10 (38.5)
	Mean± SD
Age	32.96±7.20
Income (years)	13.46±2.08
Income	20538.46±11218.66

n = number of participants; % = percentage; SD = Standard Deviation

As shown in table 3, majority of the controls were married and did mostly occupied in Cleric/farmer/shop owning. Nearly half of the cases belonged to joint family. Controls mostly resided in urban locality followed towns. Mean age of cases was around 33 years, 3 years younger than cases, with average education of nearly 13.5 years and income averaging to approximately Rs.20500 per month.

Table 4 (a): Clinical variables (categorical) of controls (n=26)

Clinical variable	**n (%)**
High risk behavior: • No • Yes	 26 (100) 0 (0)
Nicotine use: • No • Yes	 8 (30.8) 18 (69.2)
Nicotine use pattern: • Occasional • Dependent • Abstinent	18 1 (5.6) 17 (94.4) 0 (0)
Past substance history: • No • Yes	 18 (69.2) 8 (30.8)
Family substance history: • No • Yes	 6 (23.1) 20 (76.9)

n = number of participants; % = percentage of participants of a particular variable in a particular group

Table 4 (a) shows that none of the control ever engaged in High risk behavior. Most of the cases did use tobacco, mostly in dependent pattern. For majority of the patients, natural opium or tobacco were the first substances to be used and nearly 75% of cases had family history of substance use.

Table 4 (b): Clinical variables (continuous) of controls (n=26)

Variable	**Mean± SD**
FTND score (n=6)	2.66±1.97
FTND ST score (n=13)	3.23±1.36

SD = Standard Deviation; FTND = Fagerstrom Test for Nicotine Dependence; FTND-ST = Fagerstrom Test for Nicotine Dependence – Smokeless Tobacco

As in Table 4 (b), mean FTND or FTND-ST score of controls was slightly more than 3 indicating an overall low to moderate nicotine dependence.

Table 4 (c): Clinical variables (cognition) of controls (n=26)

Variable	Mean± SD
Digit Symbol Substitution Test	
• Coding	43.07±4.50
• Error	0.50±0.81
Stroop Color-Word Test	
• Word	74.96±9.13
• Color	50.23±7.45
• Color-Word	32.11±5.83
• Interference	18.04±3.28
F-A-S Phonemic Fluency Test	
• Phonemic F	8.69±2.03
• Phonemic A	7.54±2.48
• Phonemic S	7.27±1.61
Digit Span Test	
• Forward	7.50±1.10
• Backward	6.61±.89
• Sequence	5.73±1.00
• Total	19.84±2.18
Trail Making Test Part A and B (TMT A & TMT B)	
• TMT A duration	28.77±5.51
• TMT A error	0±0
• TMT B duration	57.16±11.76
• TMT B error	0.84±1.56
Rey Auditory Verbal Learning Test (RAVLT)	
• RAVLT DR	10.04±1.63
• RAVLT hit	11.77±1.36
• RAVLT omission	3.23±1.36
• RAVLT commission	2.77±1.27

SD = Standard Deviation

Table 4 (c) shows the mean score and standard deviation of the various sub sections of the neuropsychological tests applied to test the different cognitive parameters in controls.

Analytic Statistics:

Table 5: Comparison of socio-demographic variables (categorical) of cases and controls

Socio-demographic variable	**Cases (%)**	**Control (%)**	**Chi square/ Fischer exact (#)**	**(*p*)**
Marital Status: • Single • Married	 5 (19.2) 21 (80.8)	 4 (15.4) 22 (84.6)	-	1.000
Occupation: • Cleric/farmer/shop owner • Skilled • Semi/unskilled • Unemployed	 10 (38.5) 3 (11.5) 10 (38.5) 3 (11.5)	 15 (57.7) 1 (3.8) 7 (26.9) 3 (11.5)	2.526#	0.490
Family type: • Nuclear • Extended • Joint	 6 (23.1) 11 (42.3) 9 (34.6)	 5 (19.2) 9 (34.6) 12 (46.2)	0.719	0.698
Locality: • Urban • Rural • Town	 12 (46.2) 4 (15.4) 10 (38.5)	 11 (42.3) 5 (19.2) 10 (38.5)	0.234#	1.000

 # = Mark for Fischer exact; % = percentage; p = level of significance

The findings of Table 5 shows no significant difference between the groups in Marital Status, Occupation, Family type and the Locality.

Table 6 (a): Comparison of clinical variables (categorical) of cases and controls

Clinical variable	**Case (%)**	**Control (%)**	**Chi square/ Fischer exact (#)**	**(*p*)**
High risk behavior • No • Yes	 25 (96.2) 1 (3.8)	 26 (100) 0 (0)	 1.020#	 1.000
Nicotine use: • No • Yes	 6 (23.1) 20 (76.9)	 8 (30.8) 18 (69.2)	 0.391	 0.532
Nicotine use pattern: • Occasional • Dependent • Abstinent	20 0 (0) 19 (95) 1 (5)	18 1 (5.6) 17 (94.4) 0 (0)	 1.881#	 0.730
Past substance history: • No • Yes	 17 (65.4) 9 (34.6)	 18 (69.2) 8 (30.8)	 0.087	 0.768
Family substance history: • No • Yes	 5 (19.2) 21 (80.8)	 6 (23.1) 20 (76.9)	 0.115	 0.734

 # = Mark for Fischer exact; % = percentage; *p* = level of significance

In Table 6 (a), similar to socio-demographic variables, no significant between the categorical variables like High risk behavior, Nicotine use and pattern, past and family substance history was noted.

Table 6 (b): Comparison of clinical and cognitive variables (continuous) of cases and controls

Variable	Case (Mean±SD)	Control (Mean±SD)	t Value/ U(#)	(*p*)
Age	36.07± 8.38	32.96±7.20	1.437	0.157
Education (years)	12.80±2.33	13.46±2.08	-1.066	0.292
Income	19916.53±10607.47	20538.46±11218.66	-0.191	0.850
FTND	4.14±2.67 (7)	2.66±1.97 (6)	1.116	0.288
FTND ST	4.07±1.68 (14)	3.23±1.36 (13)	1.418	0.169
DSST coding	40.42±6.48	43.07±4.50	-1.714	0.093
DSST error	0.500±1.03	0.50±0.81	359#	0.636
Stroop Word	71.03±14.13	74.96±9.13	-1.189	0.240
Stroop Color	45.23±11.09	50.23±7.45	422#	0.123
Stroop Color-Word	24.31±6.49	32.11±5.83	-4.564	<0.001*
Stroop interference	21.04±5.77	18.04±3.28	2.304	0.025*
Phonemic F	7.92±1.69	8.69±2.03	-1.481	0.145
Phonemic A	6.85±1.87	7.54±2.48	-1.135	0.262
Phonemic S	7.07±1.38	7.27±1.61	342#	0.933
DST forward	7.31±1.22	7.50±1.10	371#	0.531
DST backward	6.50±1.10	6.61±.89	355#	0.744
DST sequence	4.96±0.77	5.73±1.00	479#	0.005*
DST total	18.77±2.66	19.84±2.18	-1.596	0.117
TMT A duration	30.69±6.28	28.77±5.51	1.172	0.247
TMT A error	0±0	0±0		
TMT B duration	77.53±26.07	57.16±11.76	3.631	0.001*
TMT B error	0.96±1.95	.84±1.56	345#	0.873
RAVLT DR	9.27±2.14	10.04±1.63	-1.453	0.152
RAVLT hit	10.58±1.39	11.77±1.36	-3.119	0.003*
RAVLT omission	4.38±1.41	3.23±1.36	2.990	0.004*
RAVLT commission	2.77±1.27	2.77±1.27	338#	1.000

FTND = Fagerstrom Test for Nicotine Dependence; FTND-ST = Fagerstrom Test for Nicotine Dependence – Smokeless Tobacco; DSST = Digit Symbol Substitution Test; DST =

Digit Span Test; TMT = Trail Making Test; RAVLT = Rey Auditory Verbal Learning Test; SD = Standard Deviation; t = Paired t-test; # = Mann–Whitney U test; *p* = level of significance; * = level of significance less than 0.05

As shown in Table 6 (a), the difference was significant between the groups on Stroop Test, in Stroop Color-word (p=0.00), with cases scoring less indicating decrease in processing speed and Stroop Interference scores (p=0.025) that suggests poor response inhibition in the case group.

There was significant difference between the groups on Digit Span Test (sequencing component) (p=0.005), where cases scored less indicating a negative impact on working memory, attention, encoding and auditory processing along with deterioration of focus in increasingly complex task.

Significant difference was there between the groups on Trail Making test Part B duration (p=0.001), with cases taking more time indicating impaired cognitive flexibility, and poor executive functioning.

Though there was no difference found on the delayed recall trial of RAVLT however the performance of cases were poor considering the significant difference between the scores on Hit (p=0.003) which suggest poor verbal learning and recognition of the given words. Significant difference was observed on the errors score of Omission (p=0.004) between cases and controls which indicate poor retention, retrieval and recognition of information.

Table 7: Comparison of clinical (continuous) variables of cases [Doda (dry husk form, n=13) versus Amal users (resinous form, n=13)]

Variable	**Doda users (Mean±SD)**	**Amal users (Mean±SD)**	**t Value**	**(*p*)**
Duration of opioid dependence	9.54±5.71	5.70±3.84	2.016	0.055
Age (Years)	38.54±7.97	33.62±8.35	1.537	0.137
Education (Years)	12.84±1.99	12.77±2.71	0.082	0.935
Age of opioid initiation (Years)	28.77±7.33	27.69±6.90	0.385	0.703
Duration of opioid use (Years)	9.77±6.08	5.92±3.98	1.906	0.069
Usual monthly dose (gram)	1750±629.15	67.30±36.66	9.627	<0.001*****
Urine opioid by ELISA	0.293±0.168	0.319±0.193	-0.368	0.716

SD = Standard Deviation; t = Paired t-test; p = level of significance; * = level of significance less than 0.05

In Table 7, no significant difference was noted among the various socio-demographic and clinical parameters, though significant difference was there in monthly dose.

Table 8 (a): Bivariate Correlation of socio-demographic and clinical variables with cognitive variables

Variables	Age	Education years	Income	Age of opioid initiation	Duration of opioid dependence	Urine opioid ELISA analysis	SODQ total
Education Years	-0.095						
Income	0.423*	0.317					
Duration opioid dependence	0.564*	-0.060	0.126	-0.091			
Urine opioid ELISA	0.091	-0.152	0.156	-0.049	0.173		
SODQ total	-0.165	0.039	-0.025	-0.269	0.126	0.248	
FTND	0.304	0.079	-0.046	0.311	0.096	-0.231	0.197
FTND ST	0.122	-0.150	0.027	0.007	0.158	0.041	0.084
DSST coding	-0.547*	0.172	-0.107	-0.404*	-0.364	-0.207	-0.144
DSST coding error	-0.079	0.241	-0.097	-0.072	-0.038	-0.170	-0.288
Stroop W	-0.536*	0.588*	0.125	-0.328	-0.435*	0.118	-0.013
Stroop C	-0.531*	0.517*	-0.033	-0.275	-0.504*	0.128	0.149
Stroop CW	-0.452*	0.551*	0.073	-0.298	-0.346	0.283	0.185
Stroop interference	-0.541*	0.357	-0.184	-0.220	-0.595*	-0.029	0.081
Phonemic F	-0.211	0.107	-0.234	-0.130	-0.177	-0.047	0.082
Phonemic A	0.139	0.167	0.246	0.272	-0.164	0.187	-0.074
Phonemic S	0.082	0.290	0.256	0.283	-0.198	-0.194	0.032

Variables	Age	Education years	Income	Age of opioid initiation	Duration of opioid dependence	Urine opioid ELISA analysis	SODQ total
DST Forward	-0.536*	0.483*	-0.122	-0.358	-0.380^{+}	0.054	-0.036
DST Backward	-0.095	0.536*	0.254	0.119	-0.302	-0.007	-0.156
DST Sequence	-0.215	0.550*	0.088	0.076	-0.445*	-0.175	-0.109
DST Total	-0.349	0.605*	0.075	-0.094	-0.430*	-0.029	-0.113
TMT A duration	0.361	-0.368	-0.011	0.263	0.218	-0.072	-0.339
TMT B duration	0.482*	-0.454*	0.101	0.406*	0.235	0.076	-0.071
TMT B error	0.311	-0.222	-0.029	0.279	0.150	0.132	0.238
RAVLT DR	-0.155	0.219	0.032	-0.068	-0.171	-0.268	-0.268
RAVLT hit	-0.121	0.196	0.186	0.035	-0.275	-0.094	0.050
RAVLT ommission	0.112	-0.183	-0.167	-0.013	0.235	0.103	-0.021
RAVLT commission	0.593*	-0.190	0.121	0.441*	0.370	0.064	-0.178

SODQ = Severity of Opioid Dependence Questionnaire ;FTND = Fagerstrom Test for Nicotine Dependence; FTND-ST = Fagerstrom Test for Nicotine Dependence – Smokeless Tobacco; DSST = Digit Symbol Substitution Test; DST = Digit Span Test; TMT = Trail Making Test; RAVLT = Rey Auditory Verbal Learning Test; $^{+}$ = *p* value between 0.05 and 0.06, * = *p* value less than 0.05

Table 8 (b): Partial Correlation of cognitive variables with Income, Age of opioid initiation, Duration of opioid dependence, Urine opioid ELISA level and SODQ total

Partial correlation: controlled variables – Age, Education years, FTND, FTND-ST

Variables	Income	Age of opioid initiation	Duration of opioid dependence	Urine opioid ELISA analysis	SODQ total
SODQ total	0.148	-0.255	0.298	0.404	1.000
DSST coding	0.079	0.084	-0.132	-0.233	-0.322
DSST coding error	-0.196	0.008	-0.018	-0.137	-0.405
Stroop W	0.265	0.210	-0.274	0.361	-0.160
Stroop C	0.024	0.294	-0.363	0.348	0.088
Stroop CW	0.090	0.087	-0.150	0.533*	0.226
Stroop interference	-0.088	0.414^{+}	-0.481*	0.111	-0.079
Phonemic F	-0.195	0.068	-0.091	0.028	-0.032
Phonemic A	0.137	0.272	-0.310	0.198	-0.041
Phonemic S	0.213	0.352	-0.310	-0.121	-0.033
DST Forward	-0.050	0.067	-0.103	0.283	-0.229
DST Backward	0.206	0.306	-0.334	0.135	-0.242
DST Sequence	0.023	0.417^{+}	-0.464*	-0.074	-0.217
DST Total	0.082	0.312	-0.358	0.174	-0.294
TMT A duration	-0.175	0.011	0.000	-0.306	-0.224

Variables	Income	Age of opioid initiation	Duration of opioid dependence	Urine opioid ELISA analysis	SODQ total
TMT B duration	0.057	0.088	-0.058	-0.052	0.052
TMT B error	-0.032	0.024	0.007	0.186	0.284
RAVLT DR	0.031	0.095	-0.121	-0.245	-0.359
RAVLT hit	0.225	0.247	-0.299	-0.061	-0.013
RAVLT ommission	-0.199	-0.205	0.258	0.075	0.047
RAVLT commission	-0.212	-0.016	0.049	-0.092	0.000

SODQ = Severity of Opioid Dependence Questionnaire ;FTND = Fagerstrom Test for Nicotine Dependence; FTND-ST = Fagerstrom Test for Nicotine Dependence – Smokeless Tobacco; DSST = Digit Symbol Substitution Test; DST = Digit Span Test; TMT = Trail Making Test; RAVLT = Rey Auditory Verbal Learning Test; $^{+}$ = *p* value between 0.05 and 0.06, * = *p* value less than 0.05

Bivariate correlation:

Age is correlated significantly with Income (.031), Duration of opioid dependence (.003), DSST coding (.004), Stroop W (.005), Stroop C (.005), Stroop CW (.020), Stroop interference (.004), DST Forward (.005), TMT B duration (.013), RAVLT commission (.001). **Years of education** is correlated significantly with Stroop W (.002), Stroop C (.007), Stroop CW (.004), DST Forward (.012), DST Backward (.005), DST Sequence (.004), DST Total (.001), TMT B duration (.020). **Income** is not correlated with any of the variable. **Age of opioid initiation** is correlated significantly with DSST coding (.041), TMT B duration (.039), RAVLT commission (.024). **Duration of opioid dependence** is correlated significantly with Stroop W (.026), Stroop C (.009), Stroop interference (.001), DST Sequence (.023), DST Total (.028) **correlation was close to significant with** DST Forward (.056). **Urine opioid ELISA and SODQ** are not correlated significantly with any of the variable

Partial correlation:

Income is not correlated significantly with any variable**. Age of opioid initiation** is not correlated significantly with any of the variable; however **correlation was close to significant with** Stroop interference (.055), DST sequence (.054)**. Duration of opioid dependence** is correlated significantly with Stroop interference (.023), DST sequence (0.30)**. Urine opioid ELISA** is correlated significantly with Stroop CW (.011)**. SODQ** is not correlated with any of the variable.

DISCUSSION

The purpose of this study was to assess and compare the cognitive functions of patients dependent on natural opium with matched healthy controls and to find association of cognitive functions with socio-demographic and clinical covariates like Age, Education years, Income, Age of opioid initiation, Urine opioid ELISA analysis and SODQ in patient's dependent on natural opium (Amal and Doda).

As Doda (dry husk form) and Amal (resinous form) come in varying different qualities and standard dose conversion has not been defined for such forms of opioids, urine quantitative analysis can provide uniform data regarding the dose of opioids and be an important variable while comparing the cognitive performances which has been used in this study.

Socio-demographic and clinical factors of patients dependent on natural opium:

No statistically significant difference was found between the cases and control in this study concerning any of the socio-demographic variable. Although lower literacy and lower socioeconomic status have been some of the main factors for the initiation of opium use (33, 69-72), no consistent association of other socio-demographic variables like marital status, family type, occupation or locality was found in existing literature, which can be explained by the varied social, cultural, economic or religious background of the clinical population.

Characteristics of patients dependent on natural opium:

The socio-demographic characteristic of patients in our study is more or less similar to the findings in natural opioid related epidemiological studies conducted in India. Opioids were by far the most often used illicit narcotics in the state, according to an epidemiological research conducted in Punjab that included all 22 districts. Natural opioid users made up the majority share (1.7%) of the population and 0.4% and 0.2%, respectively, of the population used prescription and injectable opioids respectively. Majority (98.14%) comprised of males and their mean Years of Education was 7.66 years with user nearly equally distributed between urban and rural locality. (73) First-degree relatives (FDRs) of males with opioid dependence were compared to healthy controls in a case-controlled study conducted in 2006 to determine the prevalence of substance use and other psychiatric disorders. The results showed a significant ($p<0.05$) 3.62 times higher risk of

alcohol use disorder in FDRs. Opioid use was also significant in FDRs of opioid dependent group. In the above mentioned study, mean age of patients was around 27 years and mean year of education was nearly 12 years but only 23% of cases were using natural opium in this study. (74) In our study, nearly 80% of both cases and controls had family history of substance use which can be attributed to the fact that opium in natural form is culturally accepted.

Though high-risk behaviour is prevalent among opioid users (75), similar finding was not found in this study. This is because natural opium is taken via oral route and hence injection related complications are also rare. (1, 2, 33)

In Rajasthan, tobacco is currently smoked by 13.2% of individuals overall, 22.2% of males, and 3.7% of women. Currently, 14.1% of all individuals, 5.8% of women, and 22.0% of men use smokeless tobacco. Men make up 39.6% of smokers, while women make up 9.0% and 24.7% of all individuals using tobacco in any form. The two most popular tobacco products in Rajasthan are bidi and gutkha, with 11.4% of adults smoking bidi and 9.0% using gutkha. (76) No significant difference was found between the nicotine use pattern between cases and control, with majority being dependent on nicotine, especially the smokeless form.

Majority of the patients (80.8%) had positive family history of substance use, which is consistent with the findings of previous studies. (77-79) Drug use in families tends to cluster, which may be due to shared genetic or environmental variables that affect the emergence of drug diseases. Individual differences in the effects of medications, such as metabolism, sensitivity, tolerance, side effects, cognitive or psychological impacts, or alteration of affective, emotional, or cognitive states, such as decrease of stress, depression, or anxiety, could be influenced by genetic variables. (77)

No statistically significant differences in IQ scores were detected across the groups in the current investigation, which could have been a confounding factor when examining the relationship between opium use and subsequent cognitive impairment. (32) Premorbid IQ has also been assessed retrospectively in some investigations, however this clinical indicator is not thought to be highly sensitive in research. (42) Though many of the studies have used IQ score as an inclusion criterion, significant differences existed between the cases and control groups which could have led to consequent higher non-perseverative

error. (32) Across the board, IQ predicts contemporaneous neuropsychological performance, but it does so more so for people with average or lower IQs than for those with higher IQs. (80)

Similarly, no significant difference was noted in FTND or FTND-ST score and both of them were not correlated significantly with any of the variable. This result differed from that of the study by Rotheram-Fuller et al., 2006 (81), whose groups varied considerably on the gambling task despite the authors' inability to determine a link between tobacco use among the methadone-maintained patients and subpar performance on the GT. One possible explanation could be that in our study nicotine dependence was equally distributed in cases and control, apart from being nearly similar in other socio-demographic variables.

Cognitive functions among patients dependent on natural opium:

The existing literature regarding studies on cognitive functions among natural opium users is very scarce. Therefore we are comparing our study findings with the available literature (synthetic or medicinal opioids etc.) worldwide.

In the present study, no statistically significant difference was evident in WAIS-IV DSST (both coding and error) which requires response speed, sustained attention, visual-spatial skills and set-shifting. (61) Arias et al., 2016 (37) used the test to evaluate the processing speed and have reported a negative relation with opioid use but the difference was not statistically significant. A similar finding was noted in a study done by Scott et al., 2017. (48) The finding in both these studies were consistent with our findings. However a recent study has reported significantly lower score in DSST ($p< 0.0001$) in patients with OUD. Authors have even suggested DSST for brief assessment of cognitive deficits in opioid-dependent patients in outpatient settings. (54) It has been proposed that fronto-subcortical circuitry plays a crucial role in DSST performance. Numerous studies showing cognitive and psychomotor impairments in long-term opioid users, including declines in working memory, less cognitive flexibility, and increased impulsivity, are consistent with disrupted neural circuitry function in cognitive control networks. (82-84)

There was significant difference between the groups on Stroop Test, in Stroop Color-Word (cases scored less indicating poor processing speed) and Stroop Interference scores that suggest poor response inhibition in the case group). This was in contrast with result of

previous studies (39, 40) which didn't find any difference in Stroop Interference score. In a longitudinal study conducted in Tehran, the cognitive rehabilitation treatment (CRT) group outperformed the control group on the Stroop but the difference was not statistically significant. The study examined the effectiveness of CRT for individuals with opioid use disorder who were enrolled in a methadone maintenance treatment (MMT) programme. (85) Though apart from these many other studies have utilized Stroop test in cognitive assessment but the patients enrolled in these were either terminally ill, cancer patients or patients suffering from chronic pain conditions especially in elderly population, whether this can be extrapolated to the clinical population with opioid dependence is a matter of debate. Based on the results of an animal study by Befort et al., (2010) (86), authors suggested that delta opioid receptors are involved in cognitive processes like response inhibition; however, impulsivity is a poorly defined cognitive function that involves a variety of different processes, as multiple neural systems are implicated. Given the likelihood that none of these operate independently, a thorough description of the neural mechanisms that control impulsivity must be based on interactions between diverse neuropharmacological systems. There are no published studies examining how opiates affect motor impulsivity in humans, and also there is conflicting evidence that opiate addicts have impaired inhibitory control. (87, 88)

In the present study, a statistically significant difference was not found in the F-A-S Phonemic verbal fluency test between the cases and the controls. In addition no significant correlation was found with any of the variables.The reported findings are partially in line with someprior studies. Similar findings were reported in an Indian study by Saroj et al., (2020) (32) and Messinis et al., (2009) (46) where no significant difference was found in verbal fluency parameter in Methadone, Buprenorphine or control group. Prosser et al., 2006 (40) also reported similar finding. These findings are in line with early reports suggesting that opiate users and controls do not differ in verbal fluency. (89) However, several recent studies have found a significant association of verbal fluency deterioration with chronic opioid use (30, 31, 37, 42). However all these studies involved patients dependent on synthetic opioids or treatments with agents like Buprenorphine or Methadone. Also studies on effect of natural opioids on cognitoive functions have not explored its effect on verbal fluency and this can be considered as a strength of this study.

There was a significant difference between the groups on the Digit Span Test (sequencing component) with cases scoring less indicating a negative impact on working memory, attention, encoding, and auditory processing along with deterioration of focus in an increasingly complex task. The finding in current study is in line with the existing literature. In study by Moghaddam et al., (2021) (54), the significant difference was found in Digit Backward test (DBT). Numerous studies pointing to cognitive and psychomotor impairments in long-term opioid users, including declines in working memory and decreased cognitive flexibility, show disorganised neuronal connections and functioning in cognitive control networks. In one study, early abstinent opioid dependent people performed worse than average controls in complex working memory, executive function, and fluid intelligence, according to a study evaluating cognitive functions during early abstinence and comparing with controls who were age, gender, and verbal intelligence matched. (39) In many areas, the impact sizes of the group differences are comparable to or greater than those observed in investigations of current substance use. The concept of a temporary cognitive loss is supported by the strong positive associations between fluid intelligence performance or complicated working memory performance and withdrawal days (as seen patients of Transient Ischemic Attack, suggesting a form of neuronal injury during opioid withdrawal). Correlations may provide future direction for further in-depth investigations even while they may not establish causality.

There was significant difference between the groups on Trail Making test Part B duration, with cases taking more time indicating impaired cognitive speed and flexibility, sustained attention and poor executive functioning. The finding is consistent with the existing literature. This affected domain was similar to those reported in the meta-analyses (30, 31). It has been discovered that the length of opioid dependence is a predictor of a greater impairment with regard to the executive function element, which makes up the two portions of the Trail Making Test. Although, prior studies have frequently been unable to show a favourable link between substance use duration and cognitive impairment (41, 84, 90). In addition, post-mortem analyses have shown non-specific ventricular and cortical volume loss (91) and a down-regulation of *mu* opioid receptors in long-term opioid use. Opioid dependence has also been associated with reduction in densities of noradrenaline and dopamine receptors. (92) Some studies have found that opioid-dependent patients perform worse than controls on a variety of cognitive tasks, particularly with regard to cognitive abilities like sustained attention and cognitive flexibility. These anatomical

abnormalities and functions may be the cause of these findings. As ceiling effects may obscure the relationship between dependency duration and cognitive dysfunction in individuals who are chronically dependent, it is plausible that sample differences (particularly with regard to dependence duration) account for the divergent findings of different research.

Though there was no significant difference found on the delayed recall trial of RAVLT however the performance of cases were poor considering the significant difference between the scores on Hit which suggest poor verbal learning and recognition of the given words. Significant difference was observed on the errors score of omission between cases and controls which indicate poor retention, retrieval and recognition of information. Our study's findings match those of the current literature. A significant deficit in verbal working memory is suggested by Baldacchino's meta-analysis. (31) Long-term (>6 months) heroin users experience "core" neuropsychological negative effects in verbal fluency and working memory as well as opioid-specific neuropsychological negative effects in divided attention, reasoning, and decision making. Effective retrieval of verbal and visual information from memory storage requires executive processes, which were also shown to be impaired in a relatively high proportion of the clinical groups. (93) The results are similar to previous studies done by authors who formulated the hypothesis about the existence of verbal memory damage in cases chronic Heroine use. (94, 95) Under the influence of drugs, Rapeli et al., (2006) (39) highlighted the damage to the multicomponent working memory system, highlighting the fact that the damage is inextricably linked to the damage to attention systems. In addition, they find a strong link between short-term memory impairment, the overall duration of heroin addiction, and the overall duration of abuse of psychoactive substances. The findings of this study show a link between the early onset of any psychoactive substance usage, including heroin abuse, and the impairment of short-term verbal memory. Patients who experience their addiction more intermittently may have more severe short-term verbal memory loss, which highlights the potential link between the withdrawal syndrome and cognitive damage due to the dysregulation of the neural cortex that it causes. The hypothesis that the frontal brain regions are the most sensitive to opioid use is supported by the observation that opioid dependence causes damage to learning function while preserving recognition, which suggests that verbal memory deficiencies in heroin addicts are likely of the frontal type. (96)

Association of cognitive functions with level of exposure to natural opium and other variables:

DSST coding was negatively correlated with age (p=0.004) and age of opioid initiation (p=0.041).

Stroop Word (W) subtest was negatively correlated with Age (p=0.005) and duration of opioid dependence (p=0.026) and positively correlated with years of education (p=0.002). Stroop Color (C) was negatively correlated with Age (p=0.005), duration of opioid dependence (p=0.007) and positively correlated with years of education (p=0.009). Stroop Color-Word (CW) was negatively associated with Age (p=0.020), positively correlated with years of education (p=0.004) and partially correlated positively with Urine ELISA opioid levels (p=0.011). Stroop Interference was correlated negatively with Age (p=0.004), duration of opioid dependence (p=0.001) and partially correlated negatively with duration of opioid dependence (p=0.023) along with positive partial correlation close to significant with Age of opioid initiation (p=0.055).

Regarding F-A-S Phonemic Fluency, no significant normal or partial correlation was found with any of the variables.

DST Forward was negatively correlated with Age (p=0.005), positively correlated with years of education (p=0.012) and correlation was negatively close to significant with duration of opioid dependence (p=0.056). DST Backward was positively correlated with years of education (p=0.005). DST Sequence was negatively correlated with duration of opioid dependence (p=0.023) and positively correlated with years of education (p=0.004) along with partially correlating negatively with duration of opioid dependence (p=0.030) and partial correlation close to significance with Age of opioid initiation (p=0.054). DST Total was negatively correlated with duration of opioid dependence (p=0.028) and positively correlated with years of education (p=0.001).

TMT B duration is positively correlated with Age (p=0.031), age of opioid initiation (p=0.039) and negatively correlated with years of education (p=0.020).

Only RAVLT commission was positively correlated with Age (p=0.001).

One methodological challenge when researching the neuropsychological impairments linked to chronic opioid use is how the chronicity (total duration of use) and severity (which is not a static phenomenon, varying with important milestone in user's life) of the opioid dependence will affect the findings. Some investigations found a direct relationship between both factors and the degree of cognitive decline in opioid users (97) while others have drawn attention to the inconsistent connections between the degree and duration of drug use and the results of the neuropsychological tests (40). Rounsaville et al. (1982) (88) examined the impact of the following variables on cognitive functioning: the variety of abused substance categories, the frequency of opiate use over the previous 30 days, the number of years of regular opiate use, and the amplitude of opiate usage (product of years used by frequency of use). There were no differences in the capacity of these traits to predict the level of consumption. Future study should focus on drug use more specifically to discover whether moderate to heavy substance use is the sole type of substance use that can lead to cognitive impairment. (98) It is strongly urged that future study evaluate substance usage in more detail with special emphasis on quantifying substance exposure in order to ascertain whether any use, regular consumption, or only excessive drug usage contribute to cognitive impairment.

Another strategy is toxicological analyses of the urine, however these results are also inconclusive. Despite the fact that these measurements might not be exhaustive, these analyses allow us to establish the existence of a given drug in the individual at a particular time. The analysis's results indicate weak correlations between urine opioid levels and measures of substance use, which depend on a number of factors including frequency of use, amount consumed, when the consumption happened, or a pattern of use that has been seen over a long period of time. (99) This might be decreased by carrying out repeated drug metabolite analyses or by utilising more sophisticated technologies, like a hair analysis, which has been shown to provide more accurate data regarding usage patterns. (100) However, these techniques frequently are either impractical or extremely expensive.

CONCLUSION

In this comparative study, natural opium use was found to affect cognitive domains of response inhibition which refers to the suppression of actions that are inappropriate in a given context and that interfere with goal-driven behavior, suggesting cases have difficulty in controlling their response to different stimuli (proxy for impulsivity) along with poor processing speed. Deficit in domains of working memory, sustained attention and encoding were also significant. Significant deficits were seen in domains of set shifting, cognitive flexibility and executive functioning as implied significant difference between groups. Cases were also found to have deficit in verbal learning and recognition along with poor retention, retrieval and recognition of verbal information. This study's findings are consistent with earlier meta-analyses that objectively demonstrated impulsivity, verbal fluency, and verbal working memory deficits in groups that use opioids.

Strengths of the study:

- The present study is the first Indian study which assessed the neurocognitive functions in patients dependent on natural opium
- Use of extensive battery of cognitive tests for specific domains
- No significant difference between cases and controls in term of socio-demographic and clinical variables
- Though not included in analysis, mean IQ scores (one of the inclusion criteria) of cases (87.92±5.77) and control (89.97±7.21) didn't differ significantly (p=0.615), which can be a confounder while assessing neurocognitive functions as highlighted in previous studies

Limitations of the study:

- Small sample size limiting the generalizability of the result to whole of the clinical population
- It was a cross-sectional study, hence does not comment upon the course of cognitive functioning with time and treatment.
- All individuals were males
- Sample drawn from a tertiary care center , so can not be generalized on community sample

Future directions:

Since the majority of the data under evaluation were collected as part of cross-sectional research, it is impossible to say whether the neuropsychological impairments that were noticed came about as a result of opioid usage or if they were caused by it. A increasing amount of data from human studies suggests that preexisting executive dysfunction, especially in cognitive impulsivity, may have been present before the onset of drug use and act as vulnerability markers for susceptibility to addiction.

In order to more fully describe the time course and long-lasting characteristics of neurocognitive deficits among the natural opium users and to more clearly establish the relationship between opioid use and such deterioration, future studies should include natural opioid users participating in drug-free programmes as controls to subjects receiving substitution treatments and assess the neurocognitive functions longitudinally. In any case, it is critical from a clinical standpoint to acknowledge these results because they may have implications for the prognosis and management of opioid dependence in patients and have an impact on their recovery and social functioning.

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ETHICAL CLEARANCE CERTIFICATE

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2020/3273 **Date: 23/09/2020**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2020/** 3138

Project title: **"Assessment of neurocognitive functions in patients dependent on natural opium"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**M.D. Dissertation**
Student Name:	**Dr. Raghvendra S Singh**
Guide:	**Dr. Navratan Suthar**
Co-Guide:	**Dr. Naresh Nebhinani, Dr. Mukesh Swami, Dr. Tanu Gupta & Dr. Prasenjit Mitra**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary

Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

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अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
अनुसंधान अनुभाग
Research Section

No.: AIIMS/RES/2021/6636

Dated: 23/10/21

To
Dr. Navratan Suthar
Assistant Professor,
Department of Psychiatry,
AIIMS, Jodhpur.

Subject: Request to change thesis Co-Guide: Reg.

Dear Dr. Suthar,

This is in reference to your letter no. AIIMS/JDH/PSY/2021/472&473 dated 18/10/2021. I am directed to inform you that Dean (Research) accorded his permission to appoint Dr. Dharmveer Yadav as a co-guide in place of Dr. Prasenjit Mitra for following students as per your request, if he is eligible for co-guideship as per institutional guidelines. Details as follows:

Sr. No.	Name of Student	Session	Thesis Title
1.	Dr. Dinesh Kumar	July-2020	Assessment of sexual dysfunction and its association among male patients dependent on natural opium seeking treatment from a tertiary care Centre
2.	Dr. Raghvendra S. Singh	Jan-2020	Assessment of Neurocognitive Functions in Patients Dependent on Natural Opium

Dr. Jaykaran Charan
Sub Dean (Research)
Sub Dean (Research)
All India Institute of Medical Sciences
Jodhpur (Raj.)-342005 India

Copy for Information to: -

1. Dr. Naresh Nebhinani, Additional Professor & Head, Dept. of Psychiatry Biochemistry, AIIMS, Jodhpur
2. Dr. Dharmveer Yadav, Associate Professor, Dept. of Biochemistry, AIIMS, Jodhpur
3. Concerned PG Student
4. Member Secretary, IEC, AIIMS. Jodhpur

PATIENT INFORMATION SHEET (ENGLISH)

Name of the patient: **Patient ID.:**

ASSESSMENT OF NEUROCOGNITIVE FUNCTIONS IN PATIENTS DEPENDENT ON NATURAL OPIUM

1. **Aim of the study:** To assess cognitive functions of patients with dependence on natural opiumatbaselineby battery of tests to probe different aspect of cognitive functions such as attention, working memory, verbal memory, executive functioning, processing speedand to compare with suitable matched control
2. **Study site:** OPD and IPD services of Department of Psychiatry, All India Institute of Medical Sciences, Jodhpur, Rajasthan.
3. **Study procedure:** All the participants who will fulfill the selection criteria's will be explained about the study in detail, and a written informed consent will be taken from them. On the first day, Socio-demographic and clinical profile sheet will be filled. Thereafter, each participant will be screened to rule out the other psychiatric disorders.After screening IQ will be assessed. SOD-Q and FTND will be used to assess severity of opioid and nicotine dependence respectively. Thereafter baseline cognitive assessment will be carried out if patient had withdrawal score <5, based on assessment on clinical opiate withdrawal scale (COWS). Participants will be provided treatment as usual (detoxification/substitution) as per standard protocol for the opioid dependence syndrome. Similarly, for controls, socio-demographic profile sheet will be filled and cognitive performances will be assessed by the same cognitive tools.
4. **Likely benefit:** Study will help in identifying patient-specific characteristic which can be used to tailor treatment for opioid dependence. This, in turn, help to maximize treatment outcomes. Explicitly, examining patient's neurocognitive profile may serve as an important role in informing clinical decision making throughout the treatment process.
5. **Confidentiality:** All the data collected from each study participant will be kept highly confidential.
6. **Risk:** Enrollment in above study poses no substantial risk to any of the study participant and if any point of time participant wants to withdraw himself/ herself, he/she can do so voluntarily at any point of time during the study.

For further information, / questions, the following personnel can be contacted:

Dr. Raghvendra S. Singh, Junior Resident, Department of Psychiatry, All India Institute of Medical Sciences, Jodhpur, Rajasthan. Ph: 9024942115

INFORMANT CONSENT FORM (ENGLISH)

Title of Thesis/Dissertation: ASSESSMENT OF NEUROCOGNITIVE FUNCTIONS IN PATIENTS DEPENDENT ON NATURAL OPIUM
Name of PG Student: Dr. Raghvendra S. Singh Tel. No.: 9024942115

Patient/Volunteer Identification No. : _____

I, _____ S/o or D/o _____

R/o _____

give my full, free, voluntary consent to be a part of "ASSESSMENT OF NEUROCOGNITIVE FUNCTIONS IN PATIENTS DEPENDENT ON NATURAL OPIUM", the procedure and nature of which has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions.

I understand that my participation is voluntary and am aware of my right to opt out of the study at any time without giving any reason.

I understand that the information collected about me and any of my medical records may be looked at by responsible individual from All India Institute of Medical Sciences, Jodhpur. I give permission for these individuals to have access to my records.

Date: _____ _____

Place: _____ Signature/Left thumb impression

This to certify that the above consent has been obtained in my presence.

Date: _____ _____

Place: _____ Signature of PG Student

1. Witness 1

Signature
Name: _____
Address: _____

2. Witness 2

Signature
Name: _____
Address:_____

PATIENT INFORMATION SHEET (HINDI)

- अध्ययन का उद्देश्य: प्राकृतिक अफ़ीम लत के मरीजों में संज्ञानात्मक क्रिया के मूल्यांकन हेतु अध्ययन|
- अध्ययन की जगह: मनोचिकित्सा विभाग की OPD और IPD, AIIMS, जोधपुर |
- अध्ययन प्रक्रिया: सभी प्रतिभागी जो चयन मानदंडों को पूरा करेंगे, उन्हें विस्तार से अध्ययन के बारे में समझाया जाएगा,और उनसे लिखित सहमति ली जाएगी। पहले दिन सोशियो-डेमोग्राफिक और क्लिनिकल प्रोफाइल शीट भरी जाएगी। इसके बाद, प्रत्येक प्रतिभागी की अन्य मनोचिकित्सा विकारों के लिए जांच की जाएगी। स्क्रीनिंग के बाद **IQ** का आकलन किया जाएगा। **SODQ** और **FTND** क्रमशः अमल और निकोटीन निर्भरता की गंभीरता का आकलन करने के लिए उपयोग किया जाएगा।इस के बाद बेसलाइन संज्ञानात्मक मूल्यांकन किया जाएगा यदि रोगी का निकासी स्कोर<5 है, जो नैदानिक अफीम निकासी पैमाने (**COWS)** पर मूल्यांकन के आधार पर होगा। प्रतिभागियों को ओपिओइड निर्भरता सिंड्रोम के लिए मानक प्रोटोकॉल के अनुसार सामान्य (विषहरण/प्रतिस्थापन) के रूप में उपचार प्रदान किया जाएगा। इसी तरह, नियंत्रण के लिए, सामाजिक जनसांख्यिकीय प्रोफ़ाइल शीट भरी जाएगी और संज्ञानात्मक प्रदर्शनों काआकलन उसी संज्ञानात्मक उपकरण द्वारा किया जाएगा।
- अध्ययन के संभावित लाभ: यह शोध उपचार में सहायक विभिन्न कारकों की पहचान में उपयोगी होगी एवं इस से मरीज़ के लिए बेहतर उपचार के चुनाव में सहायता मिलेगी|
- गोपनीयता: मरीज़ से एकत्रित समस्तजानकारी गोपनीय रखी जायेगी |
- जोखिम: इस अध्ययन में भाग लेने से कोई विशेष हानि नहीं है और यदि किसी समय भागीदार मरीज़ अध्ययन को बीच में छोड़ना चाहता है उसके लिए वह पूर्ण रूप से स्वतंत्र है|
- अध्ययन के बारे में कोई और जानकारी या सवालों के लिए सम्पर्क् कीजिये: डॉ.राघवेंद्र सिंह, मनोचिकित्सा विभाग, अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर, राजस्थान | दूरभाष न. 9024942115

<u>अन्वेषक के बयान</u>

मैंने मरीज/उसकेरिश्तेदारों को अध्ययन के उद्देश्य कार्यविधि लाभहानि के बारे में उसकी भाषा में विस्तृत रूप से समझा दिया है।मैंने मरीज/उसके रिश्तेदारों की संतुष्टि के लिए सवाल-जवाब पूछने का पूरा मौका दिया है।मैंने अध्ययन के किसी भी तथ्य को मरीज/उसके रिश्तेदारों से छिपाया नहीं है।

अन्वेषक के हस्ताक्षर　　गवाह के हस्ताक्षर

अन्वेषक का नाम　　गवाह का नाम

दिनांक

INFORMED CONSENT FORM (HINDI)

सूचित सहमति पत्र

प्रोटोकॉल /अध्ययन सं_____

इस अध्ययन लिए रोगी आयीडी_____

- अध्ययन का शीर्षक: प्राकृतिक अफ़ीम लत के मरीजों में संज्ञानात्मक क्रिया के मूल्यांकन हेतु अध्ययन|

अन्वेषक: डॉ राघवेंद्र सिंह , मोबाइल नंबर: 9024942115

इस सूचना पत्र की सामग्री दिनांक को प्रदान की गयी थी। मैंने सावधानी पूर्वक पढ़ लियाहै, मुझे मेरी भाषा में विस्तार से समझा दिए गया है और मैंने पूरी जानकारी को अच्छी तरह समझ लिया है। मैं पुष्टि करता हूँ की मुझे प्रश्न पूछने का अवसर दिया गया है। अध्ययन का प्रकार और प्रयोजन तथा इसके संभावित जोखिम/ लाभ और अध्ययन पूरा होने की अनुमानित अवधि तथा अध्ययन के अन्य सम्बंधित विवरण मुझे विस्तार से समझा दिए गए है। मुझे बताया गया है की मेरी भागीदारी स्वेच्छानुसार है और मैं कोई कारण बताये बिना किसी भी समय अध्ययन से बाहर होने के लिए पूरी तरह स्वतंत्र हूँ और इसका मेरीचिकित्सा देखभाल या कानूनी अधिकारों पर कोई प्रभाव नहीं पड़ेगा।

मुझे पता है की इस अनुसन्धान में मेरी भागीदारी के बारे में जमा की गयी जानकारी और मेरे चिकित्सा नोट्स एम्स के जिम्मेदार व्यक्तियों द्वारा देखे जायेंगे। उपरोक्त अध्ययन में भाग लेने के लिए सहमत हूँ।

दिनांक_____

स्थान_____ हस्ताक्षर/अंगूठे का निशान_____

रोगीकानाम_____ पुत्र/ पुत्री/ जीवनसाथी_____

पूरा पता_____

यह प्रमाणित किया जाता है की उपरोक्त स्वीकृति मेरी उपस्थिति में प्राप्त की गयी है।

प्रधान अन्वेषक के हस्ताक्षर

दिनांक_____ स्थान_____

गवाह १ गवाह २

गवाह का नाम_____ गवाह का नाम_____

डाक का पूरा पता_____ डाक का पूरा पता_____

SOCIO-DEMOGRAPHIC DATA SHEET

1. **OPD No.:**
2. **Age:**
3. **Sex:**
4. **Education years:**
5. **Marital status:** 0) single 1) married
6. **Occupation:** 0) professional 1) clerical, shop owner/farm 3) skill worker 4) semi-skilled / unskilled worker 5) unemployed 6) house wife/house hold 7) retired 8) student 9) not known
7. **Income:**
8. **Religion:** 0) Hindu 1) Muslim 2) Sikh 3) Christian 4) others 5) not known
9. **Family type:** 0) nuclear 1) extended 2) joint 3) others 4) not known
10. **Locality:** 0) urban 1) rural 2) town/suburban
11. **Intelligence Quotient (IQ)**

CLINICAL HISTORY SHEET

1. **Patient id: Name of patient:**
2. **Psychiatric diagnosis:**
3. **Physical diagnosis:**
4. **Age of initiation of opioid use:_____**years
5. **Duration of opioid use:_____**years
6. **Duration of opioid dependence:_____**years
7. **Usual dose:**
8. **Last intake of opioids:**
9. **Abstinent attempts:**
10. **High riskbehavior:**
11. **Injecting drug use:**
12. **Urine quantitative analysis for opium by ELISA:**
13. **Nicotine use and pattern:**
14. **Past history of substance use:**
15. **Family history of substance use:**
16. **Premorbid Personality:**
17. **Mental status examination:**
18. **Level of motivation to quit:**
19. **Current treatment:**

VERBAL ADULT INTELLIGENCE SCALE (VAIS)

(6)

Sub-Test III. Verbal Adult Intelligence Scale (V A I S)

1. INFORMATIONS
Discontinue after 7 consecutive failures response.

1. Ball
2. Year
3. Thermometer
4. Sun
5. Prime Minister
6. Guru Nanak
7. Flag
8. Lohri
9. Ramayana
10. Kuran/Bible
11. Women Ht
12. Independence
13. Birbal
14. Gandhi
15. Rubber
16. Taj Mahal
17. Population
18. Triveni
19. Bombay
20. Direction-Delhi-Madras
21. Curd
22. Dark coloured clothes
23. Year-Weeks
24. Temperature
25. Ceylone
26. England
27. Geeta
28. Meghdoot
29. Mahabharata
30. Vedas
31. Delhi-Bombay Distance
32. Lok Sabha
33. Veins

TOTAL SCORE —

2. DIGIT SPAN
Discontinue after failure on BOTH TRIALS of any item.

DIGITS FORWARD SCORE =

DIGITS BACKWARD SCORE =

TOTAL SCORE =

3. ARITHMETIC
Discontinue after 5 consecutive failures.

Problem	Score 1 or 0
1.	
2.	
3.	
4.	
5.	
6.	
7.	
8.	
9.	
10.	
11.	
12.	
13.	
14.	
15.	

TOTAL SCORE =

4. COMPREHENSION Discontinue after 6 failures Response	Score
1. Engine 2. Clothes * 3. Health 4. Bad habbits 5. Movie (Cinema Hall) 6. City land * 7. Eatables 8. Credit 9. Envelope *10. Cheque 11. Tax 12. Unity 13. Empty Vessel 14. Forest *15. Child law 16. Driving Licence 17. Deaf man 18. Strike-iron	
TOTAL SCORE (Max. 36)	

* If the subject replies with only one idea, ask for a second response. Rephrase the test item appropriately, saying, Tell me another reason why (another thing people can do).

SUMMARY OF V A I S

Sub-tests	Information	Digit Span	Arithmetic	Comprehension
Raw Scores				
Test Quotients				

Verbal I. Q.--

SEVERITYOF OPIOID DEPENDENCE QUESTIONNARE (SOD-Q)

APPENDIX 1

1. *Which opiate(s) do you usually take?* (please circle as appropriate)

	Amount per day
Heroin	_____
Morphine	_____
Methadone (Dolophine)	_____
Meperidine (Demerol)	_____
Dilaudid	_____
Paregoric	_____
Codeine	_____
Percodan	_____
Other	_____

Please answer each question by circling *one* response only

For the rest of the questions please think of a typical recent period of opiate use.

---

2. *Do you usually* inject/fix?

YES ↓ NO ↓ → Go straight to Q.3

(a) *How many times do you fix during a typical day?*
0 1 2 3 4 5 6 7 8 9 10 or more

(b) *What would be the* fewest *injections you would have during a typical day?*
0 1 2 3 4 5 6 7 8 9 10 or more

(c) *What would be the* greatest *number of injections you would have during a typical day?*
0 1 2 3 4 5 6 7 8 9 10 or more

---

3. *Do you usually* smoke *opiates?*

YES ↓ NO ↓ → Go straight to Q.4

(a) *How many times do you smoke during a typical day?*
0 1–2 3–4 5–6 7–8 9–10 11–12 13–14 15–16 17 or more

(b) *What would be the* fewest *smokes you would have during a typical day?*
0 1–2 3–4 5–6 7–8 9–10 11–12 13–14 15–16 17 or more

(c) *What would the* greatest *number of smokes you would have during a typical day?*
0 1–2 3–4 5–6 7–8 9–10 11–12 13–14 15–16 17 or more

---

4. *Do you usually take* liquid *or* pills?

YES ↓ NO ↓ → Go straight to Q.5

→(a) *How many times do you take it/them during a typical day?*
0 1 2 3 4 5 6 7 8 9 10 or more

→(b) *What would be the* fewest *times you would take it/them during a typical day?*
0 1 2 3 4 5 6 7 8 9 10 or more

→(c) *What would be the* most *times you would take it/them during a typical day?*
0 1 2 3 4 5 6 7 8 9 10 or more

---

5. *Does the amount of opiate you take vary from day to day?*
Not at all Varies a little Varies a lot

---

6. *Do you find you need higher doses than you did 6 months ago for the same effect?*
No Slightly Higher Much Higher

---

7. *On waking, and* before *my first dose of opiates:*

(a) *My body aches or feels stiff:*
Never or almost never Sometimes Often Always or nearly always

(b) *I get stomach cramps:*
Never or almost never Sometimes Often Always or nearly always

(c) *I feel sick:*
Never or almost never Sometimes Often Always or nearly always

(d) *I notice my heart pounding:*
Never or almost never Sometimes Often Always or nearly always

(e) *I have hot and cold flushes:*
Never or almost never Sometimes Often Always or nearly always

(f) *I feel miserable or depressed:*
Never or almost never Sometimes Often Always or nearly always

(g) *I feel tense:*
Never or almost never Sometimes Often Always or nearly always

(h) *I feel irritable or angry:*
Never or almost never Sometimes Often Always or nearly always

(i) *I feel restless and unable to relax:*
Never or almost never Sometimes Often Always or nearly always

(j) *I have a strong craving:*
Never or almost never Sometimes Often Always or nearly always

---

8. (a) *I try to save some opiates to use on waking:*
Never or almost never Sometimes Often Always or nearly always

(b) *I like to take my first dose of opiates within 2 hours of waking up:*
Never or almost never Sometimes Often Always or nearly always

(c) *In the morning, I use opiates to stop myself feeling sick:*
Never or almost never Sometimes Often Always or nearly always

(d) *The first thing I think of doing when I wake up is to take some opiates:*
Never or almost never | Sometimes | Often | Always or nearly always

(e) *When I wake up I take opiates to stop myself aching or feeling stiff:*
Never or almost never | Sometimes | Often | Always or nearly always

(f) *The first thing I do after I wake up is to take some opiates:*
Never or almost never | Sometimes | Often | Always or nearly always

---

9. *Have you ever stopped using opiates* completely *for at least 2 weeks?*
YES ↓ NO ↓ → Go straight to Q.10

(a) *How long after the first time you used again were you using every day?*
Within 24 hrs | Within a week | Within 2 weeks | Within 4 weeks | More than 4 weeks

(b) *How long after you started using every day did you first feel sick when you woke up?*
1 day | 2 or 3 days | 4, 5 or 6 days | 7 or more days

(c) *How long after you started using every day were you using first thing in the morning?*
1 day | 2 or 3 days | 4, 5 or 6 days | 7 or more days

APPENDIX 2

Please answer each question by circling *one* response only
Please think of your opiate use during a typical recent period of drug taking for these questions:

(a) *Did you think your opiate use was out of control?*
Never or almost never | Sometimes | Often | Always or nearly always

(b) *Did the prospect of missing a fix (or dose) make you very anxious or worried?*
Never or almost never | Sometimes | Often | Always or nearly always

(c) *Did you worry about your opiate use?*
Not at all | A little | Quite a lot | A great deal

(d) *Did you wish you could stop?*
Never or almost never | Sometimes | Often | Always or nearly always

(e) *How difficult would you find it to stop or go without?*
Impossible | Very difficult | Quite difficult | Not difficult

Thank you very much for your help

FAGERSTROM TEST FOR NICOTINE DEPENDENCE (FTND)

Fagerstrom Nicotine Dependence Scale

Questions	Answers	Points
How soon after you wake up do smoke your first cigarette?	Within 5 min	3
	6 - 30 min	2
	31 – 60 min	1
	After 60 min	0
Do you find it difficult to refrain from smoking in places where it is forbidden, e.g. in church, at the library, in a cinema, etc.?	Yes	1
	No	0
Which cigarette would you hate to give up most?	The first one in the morning	1
	All others	0
How many cigarettes do you smoke per day?	10 or less	0
	11 - 20	1
	21 – 30	2
	31 or more	3
Do you smoke more frequently during the first hours after awakening than during the rest of the day?	Yes	1
	No	0
Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0
		Total =

Scoring Instructions: Add up responses to all items. A score of 5 or more indicates a significant dependence, while a score of 4 or less shows a low to moderate dependence.

Fagerstrom Nicotine Dependence Scale-Smokeless Tobacco (FTND-ST)

Questions	Answers	Points
How soon after you wake up do you place your first dip?	Within 5 min	3
	6 - 30 min	2
	31 – 60 min	1
	After 60 min	0
How often do you intentionally swallow tobacco juice?	Always	2
	Sometimes	1
	Never	0
Which chew would you hate to give up most?	The first one in the morning	1
	All others	0
How many cans/pouches per week do you use?	More than 3	2
	2- 3	1
	1	0
Do you chew more frequently during the first hours after awakening than during the rest of the day?	Yes	1
	No	0
Do you chew if you are so ill that you are in bed most of the day?	Yes	1
	No	0
		Total =

CLINICAL OPIOID WITHDRAWAL SCORE (COWS)

APPENDIX 1
Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

Source: Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*, 35(2), 253–9.

WAIS-IV DIGIT SYMBOL SUBSTITUTION TEST (DSST)

Coding

1	2	3	4	5	6	7	8	9
⌟	ↄ	∧	—	‖	⊢	ᑕ	⅂	⊣

Demo Sample

6	8	3	9	5	4	1	7	2	1	4	8	2	7	6	9	3	5

8	3	1	9	2	5	6	4	3	7	2	9	8	1	4	7	6	5

9	1	2	4	7	2	5	6	9	5	8	6	4	3	1	7	8	3

1	3	9	6	3	9	7	5	1	4	2	8	7	2	8	5	6	4

7	6	4	1	3	2	8	1	7	9	2	5	3	4	8	6	5	9

8	1	9	5	1	4	2	6	9	8	7	3	5	6	4	7	2	3

3	6	8	9	1	8	4	7	5	2	9	6	7	1	5	2	3	4

6	4	1	9	5	7	3	6	8	3	2	7	5	8	4	2	9	1

(STROOP COLOR-WORD TEST)

STROOP

COLOR AND WORD TEST

ADULT VERSION

Name: _____

Age: _____ Sex: _____ Date: _____

FOR PROFESSIONAL USE ONLY

	Raw Score	Age/Ed. Predicted*	Residual	T-Scores**
Word Score (W)				
Color Score (C)				
Color-Word Score (CW)				
CW - Predicted = Interference (Table V) ____ - ____ = _____				

* This comes from Tables I - III.
** This should come from Table IV or VI.

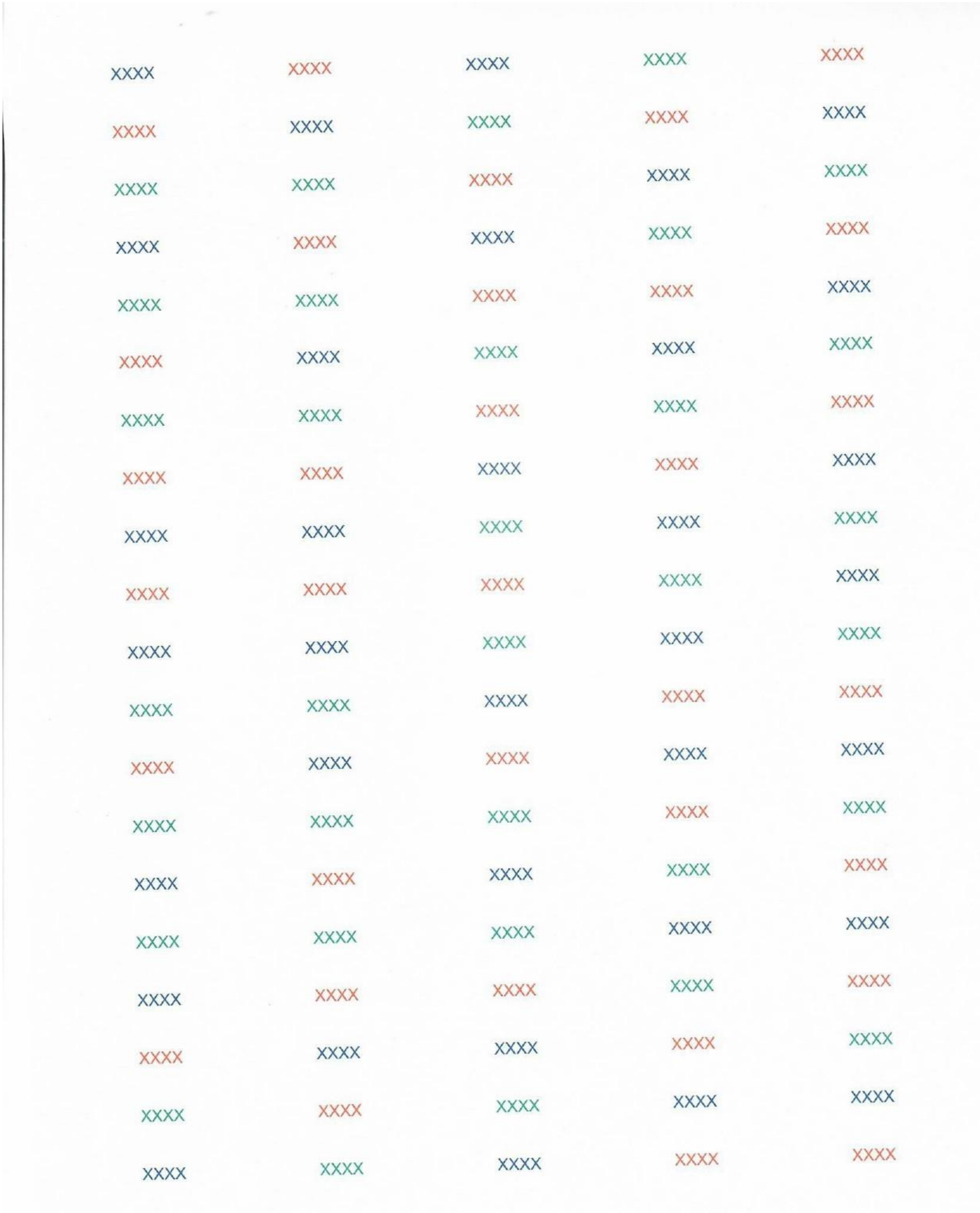
DO NOT OPEN THE BOOKLET UNTIL YOU ARE INSTRUCTED TO DO SO

#30150A REV. 01/07

Stroop Test – Word

RED	BLUE	GREEN	RED	BLUE
GREEN	GREEN	RED	BLUE	GREEN
BLUE	RED	BLUE	GREEN	RED
GREEN	BLUE	RED	RED	BLUE
RED	RED	GREEN	BLUE	GREEN
BLUE	GREEN	BLUE	GREEN	RED
RED	BLUE	GREEN	BLUE	GREEN
BLUE	GREEN	RED	GREEN	RED
GREEN	RED	BLUE	RED	BLUE
BLUE	GREEN	GREEN	BLUE	GREEN
GREEN	RED	BLUE	RED	RED
RED	BLUE	RED	GREEN	BLUE
GREEN	RED	BLUE	RED	GREEN
BLUE	BLUE	RED	GREEN	RED
RED	GREEN	GREEN	BLUE	BLUE
BLUE	BLUE	RED	GREEN	RED
RED	GREEN	BLUE	RED	GREEN
GREEN	RED	GREEN	BLUE	BLUE
RED	BLUE	RED	GREEN	RED
GREEN	RED	GREEN	BLUE	GREEN

Stroop Test – Color



Stroop Test – Color-Word

RED	BLUE	GREEN	RED	BLUE
GREEN	GREEN	RED	BLUE	GREEN
BLUE	RED	BLUE	GREEN	RED
GREEN	BLUE	RED	RED	BLUE
RED	RED	GREEN	BLUE	GREEN
BLUE	GREEN	BLUE	GREEN	RED
RED	BLUE	GREEN	BLUE	GREEN
BLUE	GREEN	RED	GREEN	RED
GREEN	RED	BLUE	RED	BLUE
BLUE	GREEN	GREEN	BLUE	GREEN
GREEN	RED	BLUE	RED	RED
RED	BLUE	RED	GREEN	BLUE
GREEN	RED	BLUE	RED	GREEN
BLUE	BLUE	RED	GREEN	RED
RED	GREEN	GREEN	BLUE	BLUE
BLUE	BLUE	RED	GREEN	RED
RED	GREEN	BLUE	RED	GREEN
GREEN	RED	GREEN	BLUE	BLUE
RED	BLUE	RED	GREEN	RED
GREEN	RED	GREEN	BLUE	GREEN

F-A-S PHONEMIC FLUENCY TEST

The F-A-S Test, a subtest of the *Neurosensory Center Comprehensive Examination for Aphasia* (NCCEA; Spreen& Benton, 1977), is a measure of phonemic word fluency, which is a type of verbal fluency. It assesses phonemic fluency by requesting an individual to orally produce as many words as possible that begin with the letters F, A, and S within a prescribed time frame, usually 1 min.

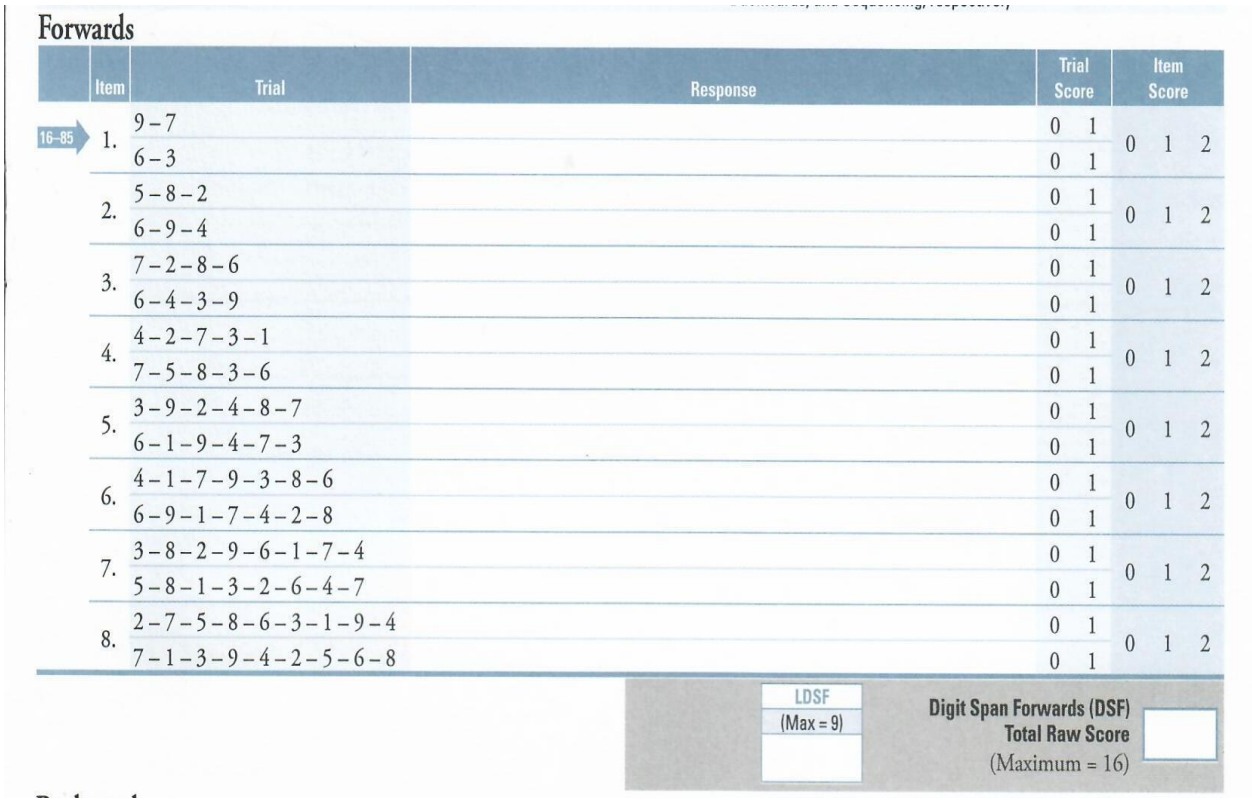
Verbal fluency is a cognitive function that facilitates information retrieval from memory. Successful retrieval requires executive control over cognitive process such as selective attention, mental set shifting, internal response generation, and self-monitoring

1. F – Ka (क)
2. A –Pa (प)
3. S – Ma (म)

DIGIT SPAN TEST (DST)

3 COMPONENTS - DIGIT SPAN FORWARD, DIGIT SPAN BACKWARD, DIGIT SPAN SEQUENCING

DIGIT SPAN FORWARD



Forwards

	Item	Trial	Response	Trial Score	Item Score
16–85	1.	9 – 7		0 1	0 1 2
		6 – 3		0 1	
	2.	5 – 8 – 2		0 1	0 1 2
		6 – 9 – 4		0 1	
	3.	7 – 2 – 8 – 6		0 1	0 1 2
		6 – 4 – 3 – 9		0 1	
	4.	4 – 2 – 7 – 3 – 1		0 1	0 1 2
		7 – 5 – 8 – 3 – 6		0 1	
	5.	3 – 9 – 2 – 4 – 8 – 7		0 1	0 1 2
		6 – 1 – 9 – 4 – 7 – 3		0 1	
	6.	4 – 1 – 7 – 9 – 3 – 8 – 6		0 1	0 1 2
		6 – 9 – 1 – 7 – 4 – 2 – 8		0 1	
	7.	3 – 8 – 2 – 9 – 6 – 1 – 7 – 4		0 1	0 1 2
		5 – 8 – 1 – 3 – 2 – 6 – 4 – 7		0 1	
	8.	2 – 7 – 5 – 8 – 6 – 3 – 1 – 9 – 4		0 1	0 1 2
		7 – 1 – 3 – 9 – 4 – 2 – 5 – 6 – 8		0 1	

LDSF (Max = 9)

Digit Span Forwards (DSF) Total Raw Score (Maximum = 16)

DIGIT SPAN BACKWARD

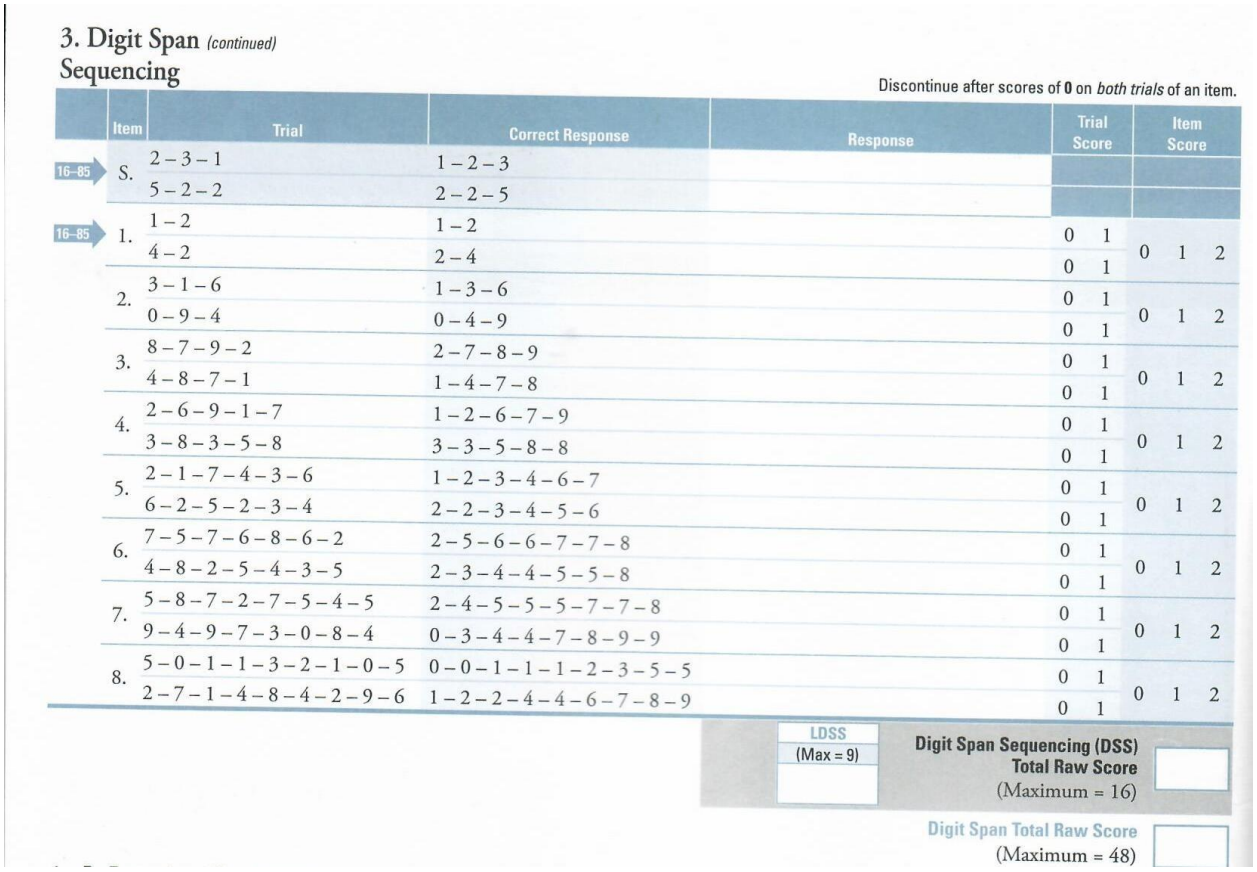
Backwards

	Item	Trial	Correct Response	Response	Trial Score	Item Score
16–85	S.	7 – 1	1 – 7			
		3 – 4	4 – 3			
16–85	1.	3 – 1	1 – 3		0 1	0 1 2
		2 – 4	4 – 2		0 1	
	2.	4 – 6	6 – 4		0 1	0 1 2
		5 – 7	7 – 5		0 1	
	3.	6 – 2 – 9	9 – 2 – 6		0 1	0 1 2
		4 – 7 – 5	5 – 7 – 4		0 1	
	4.	8 – 2 – 7 – 9	9 – 7 – 2 – 8		0 1	0 1 2
		4 – 9 – 6 – 8	8 – 6 – 9 – 4		0 1	
	5.	6 – 5 – 8 – 4 – 3	3 – 4 – 8 – 5 – 6		0 1	0 1 2
		1 – 5 – 4 – 8 – 6	6 – 8 – 4 – 5 – 1		0 1	
	6.	5 – 3 – 7 – 4 – 1 – 8	8 – 1 – 4 – 7 – 3 – 5		0 1	0 1 2
		7 – 2 – 4 – 8 – 5 – 6	6 – 5 – 8 – 4 – 2 – 7		0 1	
	7.	8 – 1 – 4 – 9 – 3 – 6 – 2	2 – 6 – 3 – 9 – 4 – 1 – 8		0 1	0 1 2
		4 – 7 – 3 – 9 – 6 – 2 – 8	8 – 2 – 6 – 9 – 3 – 7 – 4		0 1	
	8.	9 – 4 – 3 – 7 – 6 – 2 – 1 – 8	8 – 1 – 2 – 6 – 7 – 3 – 4 – 9		0 1	0 1 2
		7 – 2 – 8 – 1 – 5 – 6 – 4 – 3	3 – 4 – 6 – 5 – 1 – 8 – 2 – 7		0 1	

LDSB (Max = 8)	Digit Span Backwards (DSB) Total Raw Score (Maximum = 16)	

continue

DIGIT SPAN SEQUENCING



3. Digit Span *(continued)*

Sequencing

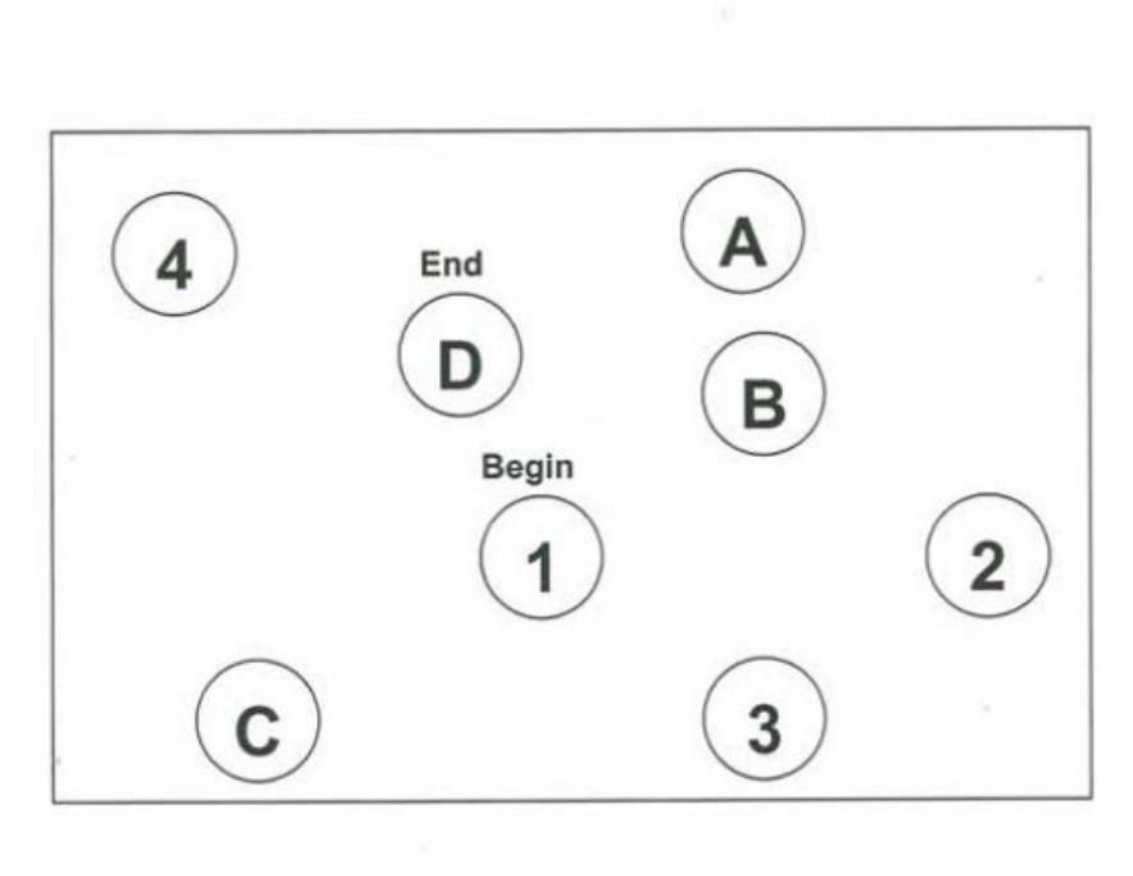
Discontinue after scores of **0** on *both trials* of an item.

	Item	Trial	Correct Response	Response	Trial Score	Item Score
16–85	S.	2 – 3 – 1	1 – 2 – 3			
		5 – 2 – 2	2 – 2 – 5			
16–85	1.	1 – 2	1 – 2		0 1	0 1 2
		4 – 2	2 – 4		0 1	
	2.	3 – 1 – 6	1 – 3 – 6		0 1	0 1 2
		0 – 9 – 4	0 – 4 – 9		0 1	
	3.	8 – 7 – 9 – 2	2 – 7 – 8 – 9		0 1	0 1 2
		4 – 8 – 7 – 1	1 – 4 – 7 – 8		0 1	
	4.	2 – 6 – 9 – 1 – 7	1 – 2 – 6 – 7 – 9		0 1	0 1 2
		3 – 8 – 3 – 5 – 8	3 – 3 – 5 – 8 – 8		0 1	
	5.	2 – 1 – 7 – 4 – 3 – 6	1 – 2 – 3 – 4 – 6 – 7		0 1	0 1 2
		6 – 2 – 5 – 2 – 3 – 4	2 – 2 – 3 – 4 – 5 – 6		0 1	
	6.	7 – 5 – 7 – 6 – 8 – 6 – 2	2 – 5 – 6 – 6 – 7 – 7 – 8		0 1	0 1 2
		4 – 8 – 2 – 5 – 4 – 3 – 5	2 – 3 – 4 – 4 – 5 – 5 – 8		0 1	
	7.	5 – 8 – 7 – 2 – 7 – 5 – 4 – 5	2 – 4 – 5 – 5 – 5 – 7 – 7 – 8		0 1	0 1 2
		9 – 4 – 9 – 7 – 3 – 0 – 8 – 4	0 – 3 – 4 – 4 – 7 – 8 – 9 – 9		0 1	
	8.	5 – 0 – 1 – 1 – 3 – 2 – 1 – 0 – 5	0 – 0 – 1 – 1 – 1 – 2 – 3 – 5 – 5		0 1	0 1 2
		2 – 7 – 1 – 4 – 8 – 4 – 2 – 9 – 6	1 – 2 – 2 – 4 – 4 – 6 – 7 – 8 – 9		0 1	

LDSS (Max = 9)	Digit Span Sequencing (DSS) Total Raw Score (Maximum = 16)	
	Digit Span Total Raw Score (Maximum = 48)	

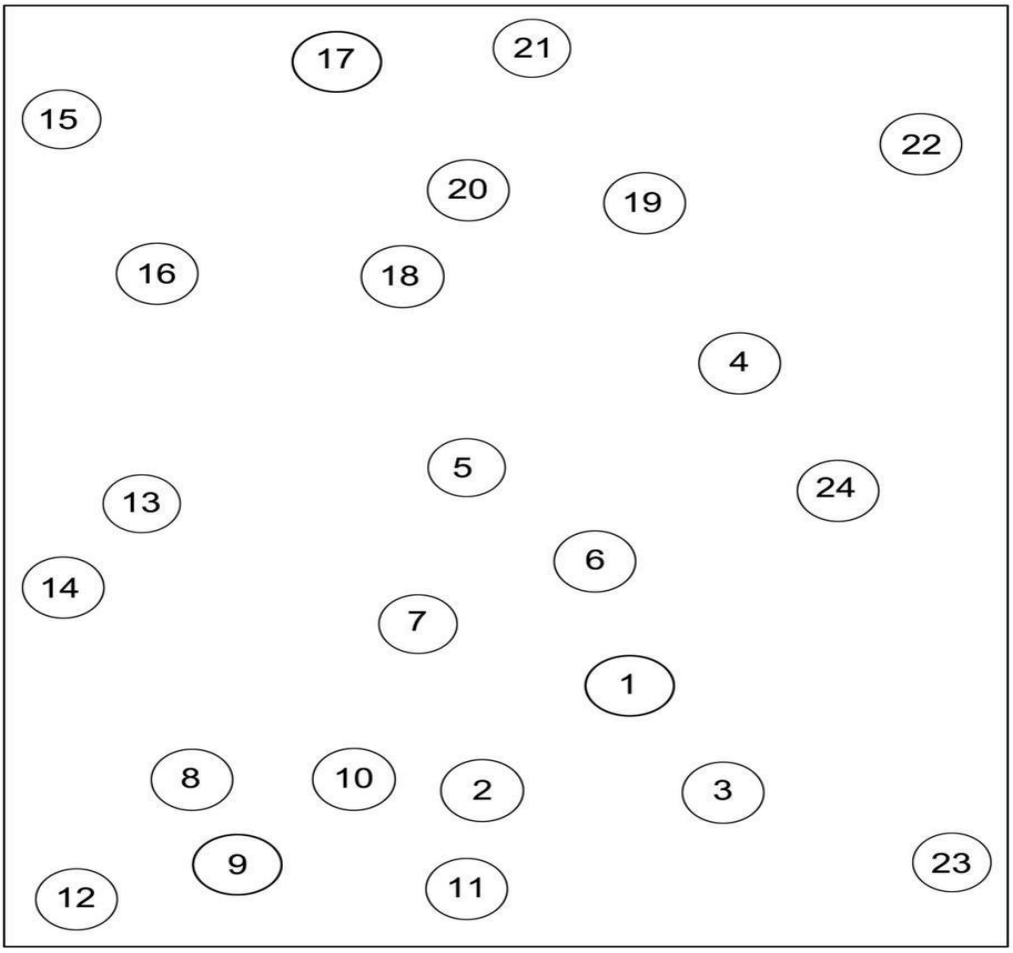
TRAIL MAKING TEST (TMT) – PART A AND B

SAMPLE



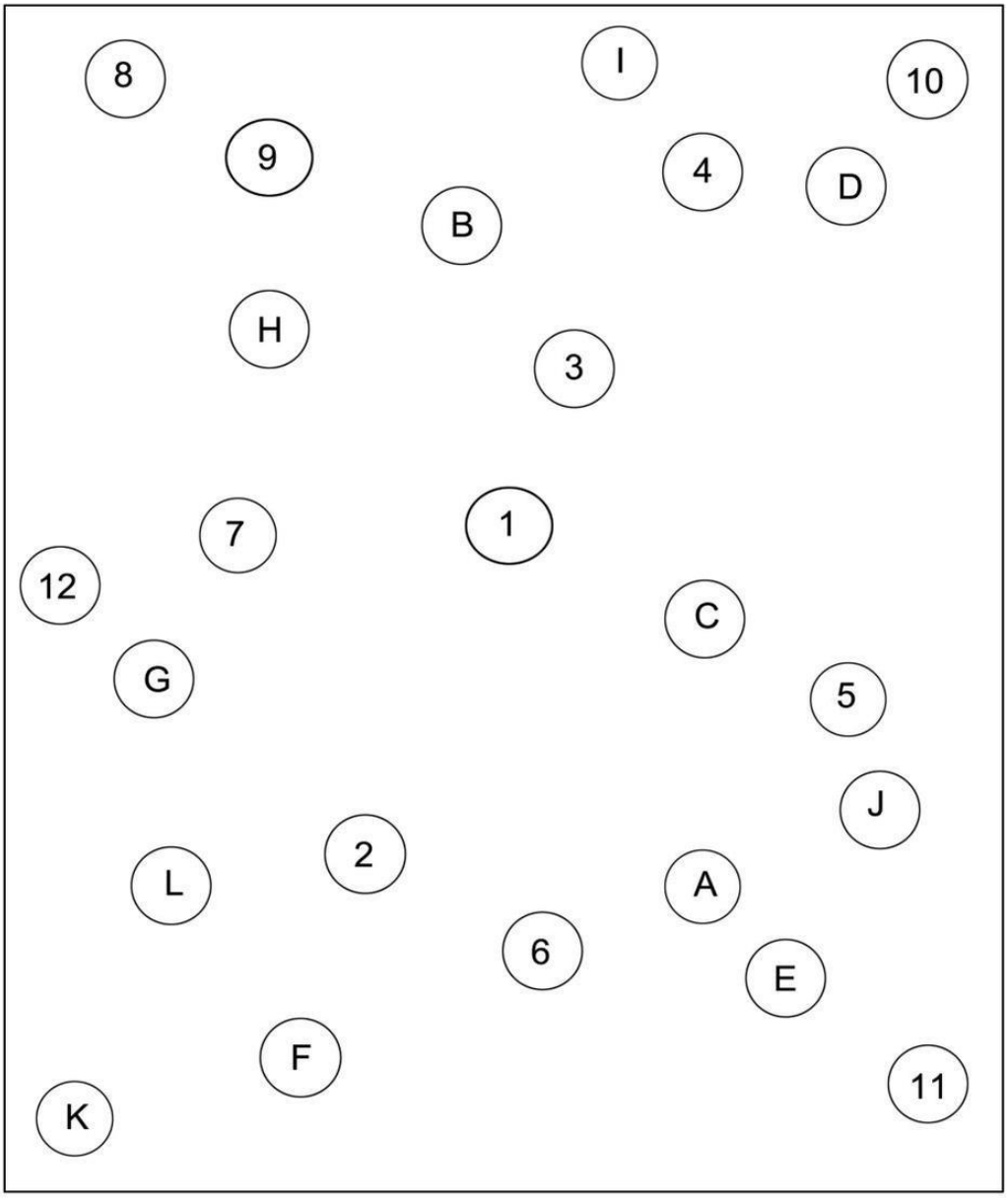
Trail making test A

Patientens namn: ..... Personnummer:..... Datum:.....



Trail making test B

Patientens namn: ..... Personnummer:..... Datum:.....



REY AUDITORY VERBAL LEARNING TEST (RAVLT)

Appendix

AUDITORY – VERBAL LEARNING TEST

DATE:

English Version

S.No	LIST - A	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	LIST B	IR-A	DR- A
1	Arm						Shoes		
2	Cat						Monkey		
3	Axe						Bowl		
4	Bed						Cow		
5	Plane						Finger		
6	Ear						Dress		
7	Dog						Spider		
8	Hammer						Cup		
9	Chair						Bee		
10	Car						Foot		
11	Eye						Hat		
12	Horse						Butterfly		
13	Knife						Kettle		
14	Clock						Mouse		
15	Bike						Hand		

Recognition
Hits
Mirror
Hammer
Knife
Candle
Motorcycle
Axe
Clock
Chair
Plane
Turtle
Leg
Dog
Table
Cat
Lips
Tree
Arm
Nose
Sun
Truck
Eye
Fish
Ear
Horse
Bike
Stool
Bus
Bed
Car

TOTAL SCORES

TRIAL 1	TRIAL 2	TRIAL 3	TRIAL 4	TRIAL 5	LIST B	IR- A	DR	RECOGNITION	
								HITS	
								OMMISSION	
								COMMISSION	

Appendix

AUDITORY – VERBAL LEARNING TEST

DATE:

Hindi Version

	LIST-A	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	LIST-B	IR - A	DR- A	Recognition
1	Haath						Joota			**Hits**
2	Billi						Bandar			Shisha
3	Kulhadi						Katori			**Hathoda**
4	Bistar						Gai			**Chaaku**
5	Plane						Ungli			Mombatthi
6	Kaan						Dress			Motorcycle
7	Kutta						Makhdi			**Kulhadi**
8	Hathoda						Cup			**Ghadi**
9	Kursi						Makkhi			**Kursi**
10	Car						Pair			**Plane**
11	Aankh						Topi			Taang
12	Ghoda						Tithli			**Ghoda**
13	Chaaku						Ketli			Pair
14	Ghadi						Chuha			**Kutta**
15	Bike						Haath			Table
										Billi
										Hont
										Ped
										Haath
										Naakh
										Suraj
										Truck
										Aankh
										Machali
										Kaan
										Sanp
										Stool
										Bus
										Bistar
										Car

TOTAL SCORES

TRIAL 1	TRIAL 2	TRIAL 3	TRIAL 4	TRIAL 5	LIST B	IR- A	DR	RECOGNITION	
								HITS	
								OMMISSION	
								COMMISSION	