HHS Public Access

Author manuscript

J Psychoactive Drugs. Author manuscript; available in PMC 2018 November 05.

Published in final edited form as:

J Psychoactive Drugs. 2017 ; 49(4): 326–332. doi:10.1080/02791072.2017.1342152.

Early initiation of amphetamine-type stimulants (ATS) use associated with lowered cognitive performance among individuals with co-occurring opioid and ATS use disorders in Malaysia.

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Abstract

Amphetamine-type stimulants (ATS) use is increasingly prevalent in Malaysia, including among individuals who also use opioids. We evaluated cognitive functioning profiles among individuals with co-occurring opioid and ATS dependence and their lifetime patterns of drug use. Participants (N=50) enrolling in a clinical trial of buprenorphine/naloxone treatment with or without atomoxetine completed the Raven's Standard Progressive Matrices, Rey-Osterrieth Complex Figure test, Digit Span, Trail Making and Symbol Digit Substitution tasks. Multidimensional scaling and a K-means cluster analyses were conducted to classify participants into lower versus higher cognitive performance groups. Subsequently, analyses of variance procedures were conducted to evaluate between group differences on drug use history and demographics. Two clusters of individuals with distinct profiles of cognitive performance were identified. The age of ATS use initiation, controlling for the overall duration of drug use, was significantly earlier in the lower than in the higher cognitive performance cluster: 20.9 (95% CI: 18.0 – 23.8) versus 25.2 (95% CI: 22.4 – 28.0, p = 0.038). While adverse effects of ATS use on cognitive functioning can

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Disclosure Statement: All authors declare no conflicts of interest.

be particularly pronounced with younger age, potentially related to greater vulnerability of the developing brain to stimulant and/or neurotoxic effects of these drugs, the current study findings cannot preclude lowered cognitive performance before initiation of ATS use.

Keywords

opioids; amphetamine-type stimulants; dual drug dependence; cognitive functioning

Introduction

Amphetamine-type stimulants (ATS) use is rising globally and its use has exceeded the use of heroin and cocaine (UNODC 2014). In Asia, individuals with ATS use disorders increasingly seek treatment for ATS use disorders and associated problems (UNODC 2015). In Malaysia, increasing rates of ATS use particularly among those under age 20 (NADA 2015) and among individuals who are also opioid dependent are observed (Chawarski 2012).

Chronic use of ATS has been consistently associated with learning and memory impairments (Ersche et al. 2006, Hoffman et al. 2006, Moon et al. 2007, Ornstein et al. 2000), and with response inhibition impairments (Ersche and Sahakian 2007, Salo et al. 2009, Clark et al. 2006). It is uncertain if cognitive deficits were present prior to the onset of drug use or are the result of drug use, but recent research has indicated potential recovery of some cognitive impairments following sustained abstinence from drug use (Schulte et al. 2014).

Thus far there are no studies of potential cognitive impairments among individuals with co-occurring (dual) opioid and stimulant dependence. Recent studies of drug using individuals in Malaysia found that concurrent use of ATS (primarily crystal methamphetamine and amphetamine/methamphetamine tablets) and opioids (primarily heroin) is prevalent and may be associated with increased behavioral risks and higher prevalence of HIV infection (Chawarski et al. 2012; Desrosiers et al., 2016). The reported behavioral risks may be related to cognitive impairments associated with chronic use of both ATS and opioids. In particular, cognitive functioning among individuals dependent on both ATS and opioids in Malaysia, where co-occurring ATS and opioid dependence has become increasingly prevalent over the past two decades (Singh et al. 2013), has not been evaluated extensively. Consequently, we evaluated cognitive performance profiles among individuals enrolling in a randomized, placebo-controlled, double-blind, pilot study (RCT) investigating medication assisted treatment for co-occurring ATS and opioid dependence in Kota Bharu, Malaysia. The cognitive assessments component of the RCT was conducted as an exploratory evaluation to characterize the sample baseline cognitive functioning levels prior to treatment initiation and to explore potential relationships between cognitive functioning and lifetime history and patterns of drug use. No hypotheses were stated in advance and the study findings were planned to guide future studies of cognitive impairments among dually dependent individuals in Malaysia and in other regions.

Methods and procedures

Participants

The RCT inclusion criteria were: age 18 years and above; meeting DSM-IV criteria for both opioid and ATS dependence; ATS use on two or more days per week in the month prior to study admission; and opioid- and ATS-positive urine toxicology test results at study enrollment. The exclusion criteria included current psychotic and/or mood disorder and current participation in treatment for a substance use disorder. Potential participants were recruited by outreach efforts in communities with a high prevalence of drug use in Kota Bharu, the capital city of Kelantan state, and the surrounding rural areas. The study was reviewed and approved by the Institutional Review Boards of Yale University and Universiti Sains Malaysia (USM). All study participants provided written informed consent.

A total of 90 participants were enrolled in the RCT; 63 of them were invited to take part in cognitive assessments: among 27 not invited to participate, 13 were training cases in the RCT, 10 withdrew early from the RCT, and 4 were enrolled before implementation of the cognitive assessment component. Twelve of the 63 invited declined to participate in the cognitive assessment component. One participant did not complete Raven's SPM and therefore is not included in all subsequent analyses. Data from 50 patients were analyzed and reported in the current study.

Setting and Procedures

The research was conducted at the Department of Psychiatry, Hospital USM (HUSM) in Kota Bharu, Malaysia between March 2013 and August 2014. In the RCT, all participants were admitted for 10 days to an inpatient unit for withdrawal from ATS, induction and stabilization on buprenorphine/naloxone, initiation of cognitive behavioral drug and HIV risk reduction counseling, and randomization to atomoxetine or placebo. Participants started buprenorphine/naloxone treatment on day one of their inpatient stay.

Buprenorphine/naloxone is a medication combining an opioid agonist (buprenorphine) and an opioid antagonist (naloxone) in a ratio 4:1 and it is approved and used for a maintenance treatment of opioid use disorder. On day seven of the inpatient stay, participants were also randomized in a 1:1 ratio to a double-blind atomoxetine or placebo. Atomoxetine is a non-stimulant medication approved for treatment of attention deficit/hyperactivity disorder (ADHD) and hypothesized to improve response inhibition among adults with ADHD who frequently display deficits in response inhibition. In the RCT, atomoxetine was evaluated for safety and potential efficacy to treat ATS use disorder. None of the study participants was diagnosed with ADHD. Cognitive assessments were administered between days 3 and 6 of the inpatient stay after all participants were stabilized on buprenorphine/naloxone and were receiving therapeutically appropriate doses (8 to 16 mg daily) and atomoxetine (or placebo) was initiated after participants completed cognitive assessments. Access to drugs and opportunities to use drugs were restricted in the locked, closely supervised inpatient unit, and all participants tested negative on urine tests conducted during their inpatient stay. The research assistant who conducted the cognitive assessments checked for physical signs of withdrawals, intoxication, or sedation and also asked participants how they felt and if they

wanted to postpone the assessment session for any reason. None of the participants had any signs of withdrawal, intoxication, or sedation at the time of cognitive assessments.

Cognitive Assessments & Outcome Measures

The cognitive tasks consisted of non-verbal paper-and-pencil and computerized tests and included Raven's Standard Progressive Matrices (SPM) (Raven 1981), Rey-Osterrieth Complex Figure (ROCF) test (Shin et al. 2006), computerized Digit Span Test (DST) (Wechsler 1997), Trail Making Test (TMT) version A and B (Bowie and Harvey 2006), and computerized Symbol Digit Substitutions Task (SDST) (Mattila et al. 1994).

The Raven's SPM is a nonverbal test of general cognitive ability that involves visual-perceptual abilities and logical reasoning (Raven and Raven 2003). The ROCF is a visual memory test that engages primarily visual-perceptual and visuo-constructional skills (Stern et al. 1994, Shin et al. 2006). The computerized DST (forward and backward) is a modification of the digit span test (Wechsler 1997) that measures the span of one's short-term or working memory (Woods et al. 2011). The TMT is a test of attention, perceptual motor speed and cognitive flexibility or task-set switching ability (Arbuthnott and Frank 2000). Part A measures primarily perceptual motor speed, attention and visual scanning. Part B involves selective attention, sequencing and shifting between two sets of stimuli simultaneously (Salthouse 2011). The computerized SDST, an adaptation of Symbol-Digit Modalities Test (Smith 1968), is an information-processing test for attention and visual scanning.

Additionally, a computerized version of The Stroop Test (Killikelly and Szücs 2010), the Continuous Performance Test (Riccio et al. 2002), the Test of Variables of Attention (TOVA) (Leark et al. 2007), and the Balloon Analogue Risk Test (BART) (Lejuez et al. 2002) were administered. Eighteen participants did not complete the CPT, 11 did not complete the Stroop, and 31 did not complete the TOVA. Participants who did not complete the TOVA complained of attentional fatigue from staring at the computer screen with blinking stimuli. Those who did not complete the Stroop reported inability to see clearly, color blindness, or difficulties navigating the keyboard. The main outcome measure of the BART, the adjusted average number of pumps for each balloon of 64 and higher that indicates potentially risk-disadvantageous choices (Lauriola et al. 2014), was reached by only two participants. Due to low completion rates these tests are not included in the data analyses.

The Raven's SPM test was administered without a time constraint, and the total number of correct responses (maximum of 60) was the measured outcome. Performance on ROCF task was evaluated based on the 20-minute delay recall. During the delay, BART, Stroop, DST and SDST were administered. The drawings of the recalled ROCF figures were coded using the Boston Qualitative Scoring System, BQSS (Stern et al. 1994). Performance on the TMT was measured by the ratio of time taken (seconds) to complete part B over time to complete part A. This performance measure is an indicator of executive functioning (Arbuthnott and Frank 2000) and has been found to be significantly related to information processing speed and fluid cognitive abilities (Salthouse 2011). Performance on the DST was measured by the number of digits recalled in each condition (forward and backward) and the total of number

of digits recalled in both conditions. Performance on the SDST was measured by the total number of errors during all 5 trials.

Baseline Assessments

Demographic information, self-reported lifetime history and patterns of drug use (frequency, amounts, and routes), urine toxicology tests (morphine and amphetamine/methamphetamine metabolites using rapid immunoassays) and self-reported drug use data using a timeline follow back method were collected at baseline during the RCT admission.

Statistical analyses

Data analysis consisted of three sequential steps. In the first step, a multidimensional scaling technique in SPSS (ALSCAL; (Moore 1990)) using outcomes of five cognitive tests with complete data was employed to identify cognitive performance tests that are most sensitive to individual differences within the study cohort. In the second step, a K-means cluster analysis (Hartigan and Wong 1979) was used to group participants into distinct separate clusters based on the results of assessments identified by the multidimensional scaling technique as best differentiating among the study sample. In the third step, a General Linear Model analysis of variance was conducted to evaluate differences in drug use indices (age of drug use initiation, years of use, frequency and routes of use) between the clusters identified by the K-means analysis. We also used chi-square and t-tests to evaluate differences in demographics, other patterns of drug use, and cognitive tests results between the identified clusters of participants.

Results

All participants were males (N=50) of the Malay ethnicity. Mean (SD) age was 34.3 (6.4) years (range: 23 to 48 years). The age of ATS use initiation ranged from 13 to 42, with 44% reporting the first ATS use at 20 or younger. Participants reported initiating heroin use between the ages of 12 and 28, with 50% reporting initiation of heroin use at the age of 20 or younger. At study admission, 36% reported using ATS every day and 98% of participants reported using heroin every day during the previous month. Demographic information of all participants are presented in Table 1. History and patterns of drug use are presented in Table 2. There were no significant differences on any of the evaluated variables between those who participated and did not participate in the cognitive assessments.

The multidimensional scaling technique revealed that Raven's SPM and ROCF were most sensitive to individual differences among the study sample and performance scores on these two tests differentiated study participants better than the performance on the other three tests (i.e., TMT, DST, and SDST). Consequently, we conducted a K-means cluster analysis using the Raven's SPM and ROCF scores to identify unique groups of participants. Two distinct clusters were identified by the K-means cluster analysis. Participants in the lower cognitive performance cluster (Lower CP, n_1=21) were characterized by significantly lower performance on the Raven's SPM ($t(48) = 6.22$, $p < 0.01$) and ROCF ($t(48) = 7.50$, $p < 0.01$) compared to those in the higher cognitive performance cluster (Higher CP, n_2=29). The two clusters also differed on the scores of the other three tests (see Table 3).

A multivariate analysis of variance evaluating between cluster differences on lifetime history of drug use, patterns of drug use, and other available characteristics showed that the age of ATS use initiation and the current age were the only two significantly different variables between the two clusters. In the Lower CP cluster, the mean (95% CI) age of ATS use initiation was 20.9 (18.0, 23.8), whereas in the Higher CP cluster it was 25.2 (22.4, 28.0). This difference was statistically significant with and without controlling for the overall duration of ATS use ($F(1, 48) = 4.57$, $p = 0.038$; $F(2, 48) = 7.40$, $p = 0.002$). Participants in the two clusters also differed significantly on current age – mean (95% CI) age was 32 (29.2, 34.7) in the Lower CP cluster and 36 (33.6, 38.4) in the Higher CP cluster ($t(48) = 2.28$; $p = 0.027$). The two clusters did not differ on other evaluated characteristics (see Table 4).

Discussion

Participants dually dependent on opioids and ATS who had a lower cognitive performance in tasks evaluating reasoning skills and general cognitive ability (Raven's SPM) and visual memory (ROCF) reported a significantly earlier age of ATS use initiation compared to those with a higher cognitive performance on these tasks. They also showed a lower level of cognitive performance on other tasks evaluating short term or working memory (DST), and attention and executive functioning (TMT B/A ratio). Participants in both groups in the current study shared similar patterns of opioid use: they reported consuming heroin multiple times a day and mostly every day; and ATS use: they reported consuming crystal methamphetamine or amphetamine/methamphetamine tablets on approximately half days in each month (see Table 4). Notably, age of heroin initiation and overall duration of ATS or heroin use among participants in the current study were not significantly different between the groups with lower versus higher cognitive performance.

The design of the current study does not preclude the possibility that pre-existing cognitive deficits (e.g., resulting in impaired judgment, diminished cognitive control) were responsible for an earlier ATS use initiation. Further research is needed to disentangle the direction of the potential relationship between cognitive impairments and initiation of psychoactive and stimulant substance use.

The mental processes engaged in the battery of the study cognitive assessments are subsets of higher order cognitive processes that govern goal-directed behaviors and involve decision making, planning and selecting goals, and monitoring of activities to facilitate attainment of the selected goals. Such abilities play important roles in decisions and behaviors related to drug use, drug discontinuation, treatment participation, and selection and attainment of recovery goals; hence lowered performance in these cognitive functions may pose a barrier to recovery from drugs. The findings that participants with lower cognitive performance who initiated ATS use at an earlier age were also significantly younger (mean age 32 years) than participants with higher cognitive functioning (mean age 36 years) at the time of testing further emphasize potentially negative consequences of the early initiation of ATS use since performance in memory and reasoning skills tests have been shown to decline with age (Schroeder and Salthouse 2004), therefore, strengthening the main finding.

Findings are consistent with other published studies on the relationships between the age of onset of substance use and cognitive functioning. In a recent study on poly-drug users, early onset of substance use (before age 16) was associated with greater cognitive impairments, including lower IQ, deficits in processing speed, visual perception and executive functioning (Capella, Benaiges, and Adan 2015). Poorer verbal memory, visuo-spatial functioning, executive functioning, deficits in attention and processing speed were observed among individuals with early onset alcohol use (before age 25) (Hanson et al. 2011, Thoma et al. 2011). There is growing evidence that adverse effects of cannabis use are more profound among chronic users who initiated cannabis use during adolescence (Volkow et al. 2016) – those who initiated use before age 18 had reduced verbal IQ (Pope Jr et al. 2003); those who initiated use before age 16 performed worse on tasks engaging executive functions (Meier et al. 2012); those who initiated use before age 15 exhibited poorer sustained attention, cognitive inhibition, and abstract reasoning (Fontes et al. 2011). A recent epidemiological survey also found that nonmedical stimulant use during adolescence may increase the likelihood of substance use and related problems (McCabe, Veliz, and Boyd 2016). These findings together with the proposed mechanism of how drugs disrupt critical brain development during adolescence (Lubman, Cheetham, and Yucel 2015) may suggest that initiating drug use at younger age affects cognitive performance more adversely than later drug use initiation.

Findings from our study of dually dependent individuals add to the accumulating observations that initiation of chronic substance use at early age may be associated with potentially long-term cognitive deficits and support health care policies and messages forewarning about harmful effects of substance use on the developing brain.

Findings should be interpreted in context of study limitation. Participants were not evaluated for other factors, including history of head injury, meningitis, encephalitis or septicemia, episodes of loss of consciousness and visual acuity which could have affected their cognitive performance. Acute effects of recent drug use may have affected cognitive performance but such effects were reduced because participants were in a closed inpatient unit, and all urine samples collected during the inpatient stay were negative for opioids and ATS. Participants were at an early stage of induction onto buprenorphine, but they participated in cognitive assessments after achieving a stable response to this medication, and before receiving atomoxetine or placebo. The study did not evaluate cognitive processes related to speed of information processing, response inhibition, or impulsivity because of low discriminability of obtained data. Finally, the study sample size was relatively small.

Conclusions

In the current study of people with co-occurring ATS and opioid dependence, individuals with lower cognitive performance on measures related to reasoning, short term or working memory, attention, and visual processing reported a younger age of ATS use initiation. These findings add to the growing evidence that the developing brain may be more vulnerable to chronic drug exposure, including ATS, and combined effects of ATS and opioids. However, the current study findings cannot preclude lowered cognitive performance before the ATS use onset. ATS substances are often initially taken as performance enhancing

drugs and while immediate, short term effects of these drugs may be perceived as beneficial, preventive interventions targeting adolescents and young adults should forewarn that early initiation and prolonged use of ATS has a potential to result in harmful effects including longer-term cognitive impairments. Individuals with early onset of ATS use may also have greater cognitive difficulties during the time of treatment initiation at the later age. Treatment providers should evaluate cognitive performance of patients initiating treatment and consider providing cognitive remediation strategies to patients with significant cognitive performance impediments.

Acknowledgements:

This work was supported by the National Institute on Drug Abuse (DA014718) and Universiti Sains Malaysia Grant 1001.CDADAH.852003.

References

Arbuthnott Katherine, and Frank Janis. 2000 “Trail Making Test, Part B as a measure of executive control: Validation using a set-switching paradigm.” Journal of Clinical and Experimental Neuropsychology 22 (4):518–528. doi: 10.1076/1380-3395(200008)22:4;1-0;FT518. [PubMed: 10923061]

Bowie Christopher R, and Harvey Philip D 2006 “Administration and interpretation of the Trail Making Test.” Nature Protocols 1 (5):2277–2281. doi: 10.1038/nprot.2006.390. [PubMed: 17406468]

Capella, del Mar Maria, Benaiges Irina, and Adan Ana 2015 “Neuropsychological performance in polyconsumer men under treatment: Influence of age of onset of substance use.” Scientific Reports 5:12038. doi: 10.1038/srep12038. [PubMed: 26155725]

Chawarski MC, Vicknasingam B, Mazlan M, & Schottenfeld RS 2012 “ATS abuse and increased HIV risk among not-in-treatment opiate injectors in Malaysia.” Drug and Alcohol Dependence 124:177–180. doi: 10.1016/j.drugalcdep.2011.12.024. [PubMed: 22266088]

Clark Luke, Robbins Trevor W., Ersche Karen D., and Sahakian Barbara J.. 2006 “Reflection impulsivity in current and former substance users.” Biological Psychiatry 60 (5):515–522. doi: 10.1016/j.biopsych.2005.11.007. [PubMed: 16448627]

Desrosiers A, Chooi WT, Zaharim NM, Ahmad I, Mohd Yasin MA, Syed Jaapar SZ, Schottenfeld RS, Vicknasingam B, Chawarski MC 2016 “Emerging drug use trends in Kelantan, Malaysia.” Journal of Psychoactive Drugs, 48(3):218–26. doi: 10.1080/02791072.2016.1185553.. [PubMed: 27224011]

Ersche K, and Sahakian BJ. 2007 “The neuropsychology of amphetamine and opiate dependence: Implications for Treatment.” Neuropsychology Review 17:317–336. doi: 10.1007/s11065-007-9033-y. [PubMed: 17690986]

Ersche, Karen D, Clark Luke, London Mervyn, Robbins Trevor W, and Sahakian Barbara J 2006 “Profile of executive and memory function associated with amphetamine and opiate dependence.” Neuropsychopharmacology 31:1036–1047. doi: 10.1038/sj.npp.1300889. [PubMed: 16160707]

Fontes, Alice Maria, Bolla Karen I., Cunha Paulo Jannuzzi, Almeida Priscila Previato, Jungerman Flávia, Laranjeira Ronaldo Ramos, Bressan Rodrigo A., and Lacerda Acioly L. T. 2011 “Cannabis use before age 15 and subsequent executive functioning.” The British Journal of Psychiatry 198 (6): 442–447. doi: 10.1192/bjp.bp.110.077479. [PubMed: 21628706]

Hanson Karen L., Medina Krista Lisdahl, Padula Claudia B., Tapert Susan F., and Brown Sandra A.. 2011 “Impact of Adolescent Alcohol and Drug Use on Neuropsychological Functioning in Young Adulthood: 10-Year Outcomes.” Journal of Child & Adolescent Substance Abuse 20 (2):135–154. doi: 10.1080/1067828X.2011.555272. [PubMed: 21532924]

Hartigan JA, and Wong MA. 1979 “Algorithm AS 136: a K-means clustering algorithm.” Journal of the Royal Statistical Society. Series C (Applied Statistics) 28 (1):100–108.

Hoffman William F., Moore Meredith, Templin Raymond, McFarland Bentson, Hitzemann Robert J., and Mitchell Suzanne H.. 2006 “Neuropsychological function and delay discounting in

methamphetamine-dependent individuals." Psychopharmacology 188 (2):162–170. doi: 10.1007/s00213-006-0494-0. [PubMed: 16915378]

Killikelly Clare, and Szücs. Dénes 2010 "The development of interference control: A pilot study using the manual colour word Stroop paradigm." Procedia - Social and Behavioral Sciences 2 (2):4842–4847. doi: 10.1016/j.sbspro.2010.03.781.

Lauriola Marco, Panno Angelo, Lewin Irwin P., and Lejuez Carl W.. 2014 "Individual differences in risky decision making: A meta-analysis of sensation seeking and impulsivitiy with the Balloon Analogue Risk Task." Journal of Behavioral Decision Making 27:20–36. doi: 10.1002/bdm.1784.

Leark Robert A., Greenberg Lawrence M., Kindschi Carol L., Dupuy Tammy R., and Hughes Steven J.. 2007 T.O.V.A. Professional Manual: Test of Variables of Attention Continuous Performance Test. California, USA: The TOVA Company.

Lejuez Carl W., Read Jennifer P., Kahler Christopher W., Richards Jerry B., Ramsey Susan E., Stuart Gregory L., Strong David R., and Brown Richard A.. 2002 "Evaluation of a Behavioral Measure of Risk Taking: The Balloon Analogue Risk Task (BART)." Journal of Experimental Psychology: Applied 8 (2):75–84. [PubMed: 12075692]

Lubman Dan I., Cheetham Ali, and Yucel Murat. 2015 "Cannabis and adolescent brain development." Pharmacology & Therapeutics 148:1–6. doi: 10.1016/j.pharmthera2014.11.009. [PubMed: 25460036]

Mattila MJ, Aranko K, Mattila ME, and Paakkari I. 1994 "Effects of psychotropic drugs on digit substition: comparison of the computerized symbol-digit substitution and traditional digit-symbol substitution tests." Journal of Psychopharmacology 8 (2):81–87. doi: 10.1177/026988119400800202. [PubMed: 22298533]

McCabe SE, Veliz P, and Boyd CJ. 2016 "Early exposure to stimulant medications and substance-related problems: The role of medical and nonmedical contexts." Drug and Alcohol Dependence 163:55–63. [PubMed: 27129621]

Meier Madeline H., Caspi Avshalom, Ambler Antony, Harrington HonaLee, Houts Renate, Keefe Richard S. E., Kay McDonald Aimee Ward, Poulton Richie, and Moffitt Terrie E.. 2012 "Persistent cannabis users show neuropsychological decline from childhood to midlife." Proceedings of the National Academy of Sciences 109 (40):E2657–E2664. doi: 10.1073/pnas.1206820109.

Moon Mijung, Kyung Soo Do Jaewoo Park, and Kim Daijin. 2007 "MEMORY IMPAIRMENT IN METHAMPHETAMINE DEPENDENT PATIENTS." International Journal of Neuroscience 117 (1):1–9. doi: 10.1080/00207450500535503. [PubMed: 17365096]

Moore Rod. 1990 " Ethnographic assessment of pain coping perceptions." Psychosomatic Medicine 52 (2):171–181. [PubMed: 2330390]

NADA, Malaysia National Anti-Drug Agency. 2015 "Drug Information 2014." Accessed 3 March 2016. http://www.adk.gov.my/html/laporandadah/2014/FINAL%20BUKU%20MAKLUMAT%20DADAH%202014.pdf.

Ornstein TJ, Iddon JL, Baldacchino AM, Sahakian BJ, London M, Everitt BJ, and Robbins TW 2000 "Profiles of cognitive dysfunction in chronic amphetamine and heroin abusers." Neuropsychopharmacology 23:113–126. doi: 10.1016/S0893-133X(00)00097-X. [PubMed: 10882838]

Pope, Jr, Harrison G, Gruber Amanda J., Hudson James I., Cohane Geoffrey, Huestis Marilyn A., and Yurgelun-Todd. Deborah 2003 "Early-onset cannabis use and cognitive deficits: What is the nature of the association?" Drug and Alcohol Dependence 69 (3):303–310. doi: 10.1016/S0376-8716(02)00334-4. [PubMed: 12633916]

Raven J 1981 Manual for Raven's Progressive Matrices and Vocabulary Scales. Research Supplement No. 1: The 1979 British Standardisation of the Standard Progressive Matrices and Mill Hill Vocabulary Series, Together With Comparative Data from Earlier Studies in the UK, US, Canada, Germany and Ireland. San Antonio, TX: Harcourt Assessment.

Raven J, and Raven J 2003 "Raven Progressive Matrices" In Handbook of Nonverbal Assessment, edited by Steve McCallum R, 223–237. New York: Springer US.

Riccio, Cynthia A, Reynolds Cecil R, Lowe Patricia, and Moore Jennifer J. 2002 "The continuous performance test: A window on the neural substrates for attention?" Archives of Clinical Neuropsychology 17 (3):235–272. doi: 10.1016/S0887-6177(01)00111-1. [PubMed: 14589726]

Salo, Ruth, Nordahl Thomas E, Galloway Gantt P., Moore Charles D., Waters Christy, and Leamon Martin H.. 2009 “Drug abstinence and cognitive control in methamphetamine-dependent individuals.” Journal of Substance Abuse Treatment 37 (3):292–297. doi: 10.1016/j.jsat.2009.03.004. [PubMed: 19339145]

Salthouse, Timothy A 2011 “What cognitive abilities are involved in trail-making performance?” Intelligence 39 (4):222–232. doi: 10.1016/j.intell.2011.03.001. [PubMed: 21789028]

Schroeder, David H, and Salthouse Timothy A.. 2004 “Age-related effects on cognition between 20 and 50 years of age.” Personality and Individual Differences 36:393–404. doi: 10.1016/S0191-8869(03)00104-1.

Schulte, Mieke HJ, Cousijn Janna, den Uyl Tess E., Goudriaan Anna E., van den Brink Wim, Veltman Dick J., Schilt Thelma, and Wiers. Reinout W. 2014 “Recovery of neurocognitive functions following sustained abstinence after substance dependence and implications for treatment.” Clinical Psychology Review 34:531–550. [PubMed: 25240109]

Shin Min-Sup, Park Sun-Young, Park Se-Ran, Seol Soon-Ho, and Soo Kwon Jun. 2006 “Clinical and empirical applications of the Rey-Osterrieth Complex Figure Test.” Nature Protocols 1 (2):892–899. doi: 10.1038/nprot.2006.115. [PubMed: 17406322]

Singh Darshan, Charwarski Marek C., Schottenfeld Richard S., and Vicknasingam Balasingam. 2013 “Substance Abuse and HIV Situation in Malaysia.” Journal of Drug and Food Analysis. Special Issue on Promoting Global Health—Treatment and Prevention of Substance Abuse and HIV in Asia 21 (4):S46–S51. doi: 10.1016/j.jfda.2013.09.033.

Smith A 1968 “The symbol-digit modalities test: A neuropsychologic test of learning and other cerebral disorders” In Learning disorders, Special Child Publications, edited by Helmuth J, 83–91. Seattle.

Stern RA, Singer EA, Duke LM, Singer NG, Morey CE, Daughtrey EW, and Kaplan E. 1994 “The Boston qualitative scoring system for the Rey-Osterrieth Complex Figure: Description and interrater reliability.” The Clinical Neuropsychologist 8:309–322.

Thoma Robert J., Monnig Mollie A., Lysne Per A., Ruhl David A., Pommy Jessica A., Bogenschutz Michael, Tonigan J. Scott, and Yeo Ronald A.. 2011 “Adolescent Substance Abuse: The Effects of Alcohol and Marijuana on Neuropsychological Performance.” Alcoholism: Clinical and Experimental Research 35 (1):39–46. doi: 10.1111/j.1530-0277.2010.01320.x.

UNODC. 2014 2014 Global Synthetic Drug Assessment - Amphetamine-type stimulants and new psychoactive substances. New York: United Nations.

UNODC. 2015 World drug report 2015. Vienna, Austria.

Volkow Nora D., Swanson James M., Evins A. Eden, DeLisi Lynn E., Meier Madeline H., Gonzalez Raul, Bloomfield Michael A. P., Curran H. Valerie, and Baler Ruben. 2016 “Effects of cannabis use on human behavior including cognition, motivation and psychosis: A review.” JAMA Psychiatry 73 (3):292–297. doi: 10.1001/jamapsychiatry.2015.3278. [PubMed: 26842658]

Wechsler D 1997 Wechsler Adult Intelligence Scale 3ed. San Antonio, TX: Psychological Corporation.

Woods David L., Kishiyama Mark M., Yund E. William, Herron Timothy J., Edwards Ben, Poliva Oren, Hink Robert F., and Reed Bruce. 2011 “Improving digit span assessment of short-term verbal memory.” Journal of Clinical and Experimental Neuropsychology 33 (1):101–111. doi: 10.1080/13803395.2010.493149. [PubMed: 20680884]

Table 1:

Demographic characteristics of study participants (N = 50).

Sample characteristics	%
Education level (years of schooling)	
Completed high school (11)	48
Completed junior high (9)	44
Completed primary school (6)	8
Marital status	
Never married	58
Married	26
Divorced	10
Widowed	6
Employment status	
Full-time	36
Part-time	44
Unemployed	20
Duration of alcohol use	
0 – 5 years	26
6 – 25 years	18
No reported history of alcohol use	56

Table 2:

Drug use pattern among study participants (N = 50).

Drug Use Patterns	Mean [95% CI]
Duration of heroin use	14.0[12.0, 16.0] years
Days of heroin use in the month prior to study admission	29.9 [29.7, 30.0] days
Daily frequency of heroin use	4.8 [4.2, 5.4] times/day
Method of heroin use:	%
Chasing (inhalation of drug smoke or vapor)	22
Injecting	78)
Duration of ATS use	11.0 [9.6, 12.2] years
Days of ATS use in the month prior to study admission	17.5 [14.6, 20.4] days
Weekly frequency of ATS use	6.1 [4.3, 8.0] times/week
Method of ATS use:	%
Chasing	60
Injecting	32
Combined chasing and injecting	8

Table 3:

Comparisons of baseline cognitive performance for each cluster by independent t-tests.

Cognitive measures	Cluster 1 Lower CP (n=21)	Cluster 2 Higher CP (n=29)	
	Mean [95% CI]	Mean [95% CI]	*p*-value
Raven's SPM total score	25.8 [22.2, 29.4]	38.8 [36.2, 41.4]	$p < 0.001$
ROCF total recall score	16.5 [13.4, 19.6]	32.7 [29.6, 35.7]	$p < 0.001$
Digit Span Forward	5.1 [4.4, 5.9]	6.0 [5.6, 6.6]	$p = 0.036$
Digit Span Backward	3.7 [3.2, 4.2]	4.4 [3.9, 4.9]	$p = 0.059$
Total DST (F+B)	8.9 [8.0, 9.7]	10.5 [9.6, 11.3]	$p = 0.011$
TMT ratio (B/A)	2.2 [1.9, 2.6]	1.7 [1.5, 1.9]	$p = 0.008$
SDST total errors	2.1 [1.2, 3.0]	2.0 [1.2, 2.7]	$p = 0.808$

Table 4:

Comparisons of demographic and drug use characteristics for each cluster (N = 50).

	Lower CP cluster (n=21) Mean [Range]	Higher CP cluster (n=29) Mean [Range]
Age	**32.0 [22, 43]**	**36.0 [24, 48]**
Age of ATS use initiation	**20.9 [13, 36]**	**25.2 [13, 42]**
Total years of ATS use	11.2 [6, 18]	10.9 [3, 19]
Number of days ATS use in the month prior to study	15.6 [1, 30]	18.9 [2, 30]
ATS weekly frequency of use (times/week)	7.1 [2, 28]	5.4 [2, 21]
Age of first heroin use	19.4 [13, 26]	20.6 [12, 28]
Total years of heroin use	12.6 [3, 25]	15.0 [2, 26]
Number of days heroin use in the month prior to study	29.8 [25, 30]	30 [30, 30]
Heroin daily frequency of use (times/day)	5.2 [1, 30]	4.6 [2, 10]
Education (years of schooling)		
Completed high school (11)	57.1%	44.8%
Completed junior high (9)	23.8%	51.7%
Completed primary school (6)	19.0%	3.4%
Marital status		
Never married	52.4%	62.1%
Married	28.6%	24.1%
Divorced	19.0%	3.4%
Widowed	0%	10.3%
Employment status		
Full-time	38.1%	34.5%
Part-time	38.1%	48.3%
Unemployed	23.8%	17.2%
Duration of alcohol use		
0 – 5 years	14.3%	34.5%
6 – 25 years	23.8%	13.8%
No reported history of alcohol use	61.9%	51.7%

Note: The between cluster differences on current age and the age of ATS use initiation are statistically different (boldface). All other comparisons in Table 4 are not statistically different.