Cognitive Impairment in Patients Clinically Recovered from Central Nervous System Depressant Drug Overdose

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ABSTRACT

CNS-depressant drugs (CNS-Ds) are known to impair cognitive functions. Overdose of these drugs is common and the majority of the hospital-treated patients are discharged within 24–48 hours. No previous studies have examined whether they have residual impairment at the time of discharge. Our aim was to evaluate whether patients with CNS-D overdose are impaired in cognitive domains important in daily activities at that time. We compared visuomotor skills (Trail-Making A and choice reaction time), executive functions (viz. attentional set-shifting: Trail-Making B, and planning: Stockings of Cambridge task [SOC] from the Cambridge Neuropsychological Test Automated Battery [CANTAB]), working memory (Letter-Number Sequencing) and impulsivity and decision-making (CANTAB Information Sampling) in 107 patients with CNS-D overdose (benzodiazepines, opioids or antipsychotics) with a Control Group of 68 with non-CNS-D overdose (acetaminophen, SSRI and SNRIs) on discharge from hospital. Outcome measures were adjusted for demographic and clinical covariates in multivariate regression models. Compared to the Controls, the CNS-D Group was significantly impaired in all domains: they had prolonged Trail-Making completion times and reaction times, poorer working memory and planning and were more impulsive in decision-making. Their SOC performance was comparable to the Control Group for simple problems but worsened with increasing task complexity. The results show that patients with CNS-D overdose could be impaired in multiple cognitive domains underlying everyday functioning even at the time they are deemed medically fit to be discharged. Such impairments could adversely affect social and professional lives of this relatively young population during the immediate post-discharge period.

INTRODUCTION

Many individuals in the community are prescribed drugs with central nervous system (CNS) depressant effects. A single dose of central nervous system depressant drugs (CNS-Ds) including benzodiazepines, opioids and tricyclic antidepressants can cause acute impairment in activities such as driving,[1, 2] and an array of cognitive and psychomotor functions underlying everyday activities.[3-6] These cognitive and psychomotor effects include impaired visual attention and reaction time,[3, 7-10] attentional set-shifting,[11] planning,[12] and working memory,[13] and increased impulsivity.[14] Similarly, acute cognitive effects have also been reported with atypical antipsychotics.[10, 15-17] These acute effects have been demonstrated in experimental studies conducted mostly on healthy volunteers and to a lesser extent, on patient groups.

In contrast, research is lacking on the extent of impairment in patients who take CNS-Ds in overdose even though CNS-D overdose is one of the most common modes of poisoning in developed countries, accounting for around 71,000 hospital-treated drug overdoses in the US (2006),[18] 39,000 in the UK (mid 2009 – mid 2010)[19] and 12,000 in Australia (mid 2007 – mid 2008).[20] An extensive literature search retrieved only two studies that examined cognitive functioning following CNS-D overdose. Both reported anterograde amnesia following benzodiazepine overdose in ward patients, which improved from day 1 to day 2 after overdose.[21, 22] Given the evidence of acute effects of single doses of a variety of CNS-Ds, the sedative effects of overdose would obviously lead to profound impairments in number of cognitive and psychomotor domains in the acute stage. While such deficits are unlikely to be pertinent to the functionality of an inpatient who is under scrutiny of medical staff, in

contrast, even a subclinical cognitive impairment could be consequential if the effects persist at the time of discharge, when the individual is otherwise deemed fit enough to return to the community. Length-of-hospital-stay statistics, particularly those in the UK[19] and Australia[20] indicate that majority of these patients are discharged from hospitals within 24–48 hours of admission. Given that acute effects of even therapeutic doses can last overnight,[1] the length of hospital stay following overdose could be too short for the adverse cognitive effects of the drugs to wear off – yet these effects may not be detected on the basis of routine history and clinical examination by staff making the decision to discharge the patient.

The aim of the present study was to determine whether patients with CNS-D overdose are cognitively impaired at the time they are clinically deemed fit to be discharged from hospital. We focused our assessment on three neurocognitive domains underpinning daily activities of social and professional life:

a) visual attention and visuomotor skills,

b) executive functions and working memory and

c) impulsivity and decision-making.

Using a battery of neuropsychological tests tapping into the above domains, we compared the performance of a group of patients following CNS-D overdose with that of a Control Group with non-CNS-depressant drug (CNS-ND) overdose at the point of discharge from the hospital-treated overdose episode. Given the broad range of acute cognitive deficits caused by therapeutic doses of CNS-D, we hypothesized the CNS-D Group would be impaired in all domains when compared to the Control Group.

METHOD

Recruitment of participants

The study was carried out in the Department of Clinical Toxicology and Pharmacology of the Calvary Mater Newcastle (CMN) Hospital, which is the tertiary referral centre for poisonings in the Hunter and New England Region of New South Wales, Australia. All deliberate self-poisoning patients at CMN are admitted by the Department of Clinical Toxicology and Pharmacology. These patients are also seen by the Consultation-Liaison Psychiatry Team who determines the psychiatric diagnosis according to DSM-IV criteria. This model of management has been previously described.[23] All admissions to the Department of Clinical Toxicology and Pharmacology are recorded in the Hunter Area Toxicology Services (HATS) Database, which is used as a digital repository for clinical and research purposes. The structure of this database has been described elsewhere.[24] Ethics approval for the study was granted by the Hunter New England Human Research Ethics Committee.

Patients aged between 18 and 70 years admitted to the hospital following deliberate self-poisoning were prospectively screened for eligibility during daily ward-rounds. Those who overdosed with benzodiazepines, atypical antipsychotics or opioids were considered for inclusion into the CNS-D Group, whereas those who overdosed with acetaminophen, selective serotonin-reuptake inhibitors (SSRIs) or serotonin-noradrenaline-reuptake inhibitors (SNRIs) were considered for inclusion into the Control Group. Drug overdose was ascertained based on history, clinical picture and circumstantial evidence (e.g. availability of empty blister packs). A drug overdose was defined as acute administration of 2 or more times the defined daily dose (DDD: the assumed average maintenance dose per day for a drug used for its

main indication in adults) as specified by WHO Collaborating Centre for Drug Statistics Methodology.[25] Overdoses with multiple drugs, or subsequent admissions of already tested participants were not considered for inclusion in the study. Patients were excluded if they had any neurological illness that may affect cognitive functions, a history of head injury causing neurological damage, vision or hearing impairment, or acute psychosis or aggression at the time of clinical encounter, or if their first language was not English. Eligible participants were introduced to the study once they were deemed medically fit to be discharged from the Toxicology Service. Informed written consent was obtained from those who were willing to participate. Neuropsychological assessment was carried out just before they were due to leave the hospital.

Neuropsychological assessment

Three neurocognitive domains and general intelligence were assessed using a battery of validated neuropsychological tests.

a) *Visual attention and visuomotor skills:* Trail-Making Test A (TMT-A)[26] and Cambridge Neuropsychological Test Automated Battery (CANTAB) choice reaction time (CRT)[27]

b) *Executive functions and working memory:* Trail-Making Test B (TMT-B),[26] CANTAB Stocking of Cambridge (SOC)[27] and Letter-Number Sequencing Test (LNS)[28]

c) *Impulsivity and decision-making:* CANTAB information sampling task (IST)[27]

d) *Premorbid intelligence* (IQ): National Adult Reading Test (NART).[29]

A medically qualified graduate trained to perform individual tests (author TLD) administered all tests for each study participant. Test instructions were followed verbatim based on the detailed criteria provided with each component test administration guide, in order to maintain uniformity of administration. Those patients who had their own room in the ward were tested there, whereas those who did not were tested in a separate interview room. The tests were administered in the order TMT-A, TMT-B, LNS, NART, CRT, IST and SOC.

1. Trail-Making Test (TMT)[26] (duration: 5 – 10 minutes).

TMT-A consists of encircled numbers from 1 to 25 positioned irregularly on a sheet of paper. Subjects must connect these numbers in ascending order using a pencil as quickly as possible. TMT-B has numbers 1–13 and letters A–L. Subjects have to connect the numbers in ascending order and letters in alphabetical order, alternating between the two. Any errors are pointed out by the examiner as soon as they are made and thus errors are taxed with an increase in the test completion time, which is the main outcome measure in each part. TMT-A measures attention and visual scanning. TMT-B in addition taps into cognitive flexibility or the ability to switch attention between two conceptual sets.[30-32] The difference between the completion times of TMT-B and TMT-A (TMT B-A) reflects the executive component of the task as it is generally agreed that subtraction controls for visual scanning and movement time.

2. Letter-Number Sequencing (LNS)[28] (duration: ~ 5 minutes).

This is a test of working memory capacity. The examiner reads aloud a group of numbers and letters (e.g. V–1– J–5) and the subjects have to answer by recalling the numbers first in ascending order and then the letters in alphabetical order (1–5–J–V).

The test starts with a sequence of two items (one number and one letter), and the span is increased until the subject fails all three sequences at a given length. The number of correct sequences is the test score.

3. National Adult Reading Test (NART)[29] (duration: ~ 5 minutes).

The NART was administered to estimate pre-overdose IQ, as a potential covariate of the neuropsychological measures of the present study. Verbal responses were recorded, and scored by one of the authors (PTM) who was blind to the type of overdose of participants. Wechsler Adult Intelligence Scale (WAIS) full scale IQ was estimated using the regression equation derived by Crawford et al., 1989: IQ=128.50-0.84 (NART errors).[33]

4. Cambridge Neuropsychological Test Automated Battery (CANTAB)[27] (duration: 35 – 40 minutes).

The component tests of CANTAB have been modified from well documented animal testing paradigms, so that behavioral data can be also related to neural systems underlying distinct cognitive domains analyzed by component tests.[31] Test administration and scoring is computerized so that minimizing any biases that can be introduced during test administration. A selected set of CANTAB tests were administered on a Paceblade Slimbook™ 110 Series 12.1" tablet PC. Two obligatory training tests, viz. Motor-Screening (MOT, duration 3 minutes) and Big/Little Circles (BLC, duration 3 minutes) were administered initially to introduce the subjects to the test system. Upon completion of the two screening tests, 3 further tests were administered:

Choice Reaction Time (CRT, duration ~ 7 minutes). This is a test of attention and psychomotor speed. An arrow-shape stimulus is displayed on either the right or the left hand side of the screen and the subject presses the right or left hand button of a press-pad depending on the side of the screen where the stimulus appears. The subject has to respond as quickly as possible without making mistakes. Average CRT calculation was based on 100 trials. Also calculated were the number of correct trials, incorrect trials (where the wrong button was pressed) and omissions.

Information Sampling Task (IST, duration 10 – 15 minutes). IST tests the rationality and impulsivity in decision-making. Twenty-five gray boxes and two colored panels are presented on the screen. Boxes open when touched to assume one of the two colors from the panels, and remain open. The subjects are instructed that they are playing a game for points. They have to open one box at a time, and decide which color is inside the majority of the 25 boxes based on the sample of boxes opened. Once their decision is made, the subject registers their choice by touching the correspondingly colored panel. The test has two conditions. In the Fixed-Win Condition, correct decisions are rewarded with 100 points regardless of the number of boxes opened at the time of decision-making. In the Decreasing-Win Condition, the maximum points that could be won starts with 250 and drops by 10 with each box opened. In both conditions, incorrect decisions cost 100 points. The test has 10 assessed trials each in the Fixed-Win Condition and the Decreasing-Win Condition. The order of the two conditions was counterbalanced among subjects in each group. The main outcome measure of interest is designated P, which is the probability that the color chosen by the subject at the point of decision is correct (with a maximum possible value of 1), based on the evidence available at that time, and assuming each

box has a 0.5 probability of assuming one of the two colors. Thus, P is an index of the rationality of the decision made by the subject: lower the P value, the more impulsive the decision is. P was calculated separately for the Fixed-Win (IST-FWP) and Decreasing-Win Conditions (IST-DWP).

Stockings of Cambridge (SOC, duration ~ 10 minutes). SOC is a computerized version of the Tower of London task and tests planning and spatial working memory.[34] The goal of the task is to rearrange a set of three balls in a minimum number of moves to match a sample pattern. Therefore, subjects have to plan their moves before starting to move the balls. The assessed task has 12 trials (2 x 2-move, 2 x 3-move, 4 x 4-move and 4 x 5 move problems). The outcome measures that we focused on were the number of problems solved in minimum moves and the mean number of the moves spent in solving an n-move problem (Mean-n-Moves), n being 2, 3, 4 or 5.

Demographic and clinical data

Demographic information (gender, age, and years of education) was collected at the time of testing. The following clinical data related to the present study were extracted from the Hunter Area Toxicology Services (HATS) database:

The data fields retrieved from the HATS database include those related to long-term clinical conditions (viz. major psychiatric illnesses, regular medication) and the episode of drug-overdose (viz. type and dose of drug taken in overdose, time of overdose, length of hospital stay, co-ingestion of alcohol, lowest GCS score recorded, any mechanical ventilation and in-ward treatment with potentially sedative drugs).

Data analysis

Sample characteristics were compared between the two groups with independent sample t-tests (for continuous variables) and Chi-squared tests (for categorical variables) (Table 1).

The main outcome measures analyzed in the present study were: TMT-A completion time, TMT-B completion time, TMT B-A, LNS number of correctly recalled sequences, CRT latency, IST-FWP, IST-DWP and SOC problems solved in minimum moves and SOC Mean-n-Moves. Because all outcome measures were continuous variables, the values beyond four standard deviations away from the mean were considered extreme outliers and were removed before analysis.

Planned intergroup comparisons

Each outcome measure except SOC Mean-n-Moves was modeled in multiple linear regression (MLR) models entering Group, gender, age, number of years of education, IQ, presence of a potentially cognitively impairing psychiatric illness, co-ingestion of alcohol, and in-ward treatment with potentially sedative drugs as explanatory variables. Stepwise MLR models were used so that only the statistically significant variables were retained in the final MLR model. Since NART testing to estimate premorbid IQ could be conducted only in 133 participants, MLR models were created in two steps for each main outcome measure. The first model was created for the subsample with IQ scores, entering IQ and the other independent variables. If IQ remained as a significant predictor, that model was retained as the appropriate. If IQ was dropped in the process of this first stepwise regression, another stepwise regression model was fitted to the full sample entering only the other

independent variables. MLR assumptions were checked for each model by creating histograms for regression standardized residuals and scatter plots for standardized residuals vs. standardized predicted values.

SOC Mean-n-Moves was analyzed in a mixed analysis-of-variance (ANOVA) model with Group as a between-subject factor, Task difficulty (i.e. minimum possible moves for a problem: 2, 3, 4 or 5) as the within-subject factor and other independent variables as covariates. Greenhouse-Geisser epsilon was used to correct for violations of sphericity.

The level of significance for the planned comparisons was set at a cut-off p value of 0.05.

Unplanned within-Group comparisons

After observing of the results of intergroup comparisons, we conducted two types of analyses within Groups: 1) *Subgroup comparisons* based on the drug class and half-life, 2) *Intra-Group MLR analysis for CNS-D overdose* to explore the factors associated with cognitive impairment in the CNS-D Group. Since these unplanned comparisons were made for nine outcome measures, the cut-off level of significance for subgroup comparisons and MLR models was set at a p value of 0.005.

All statistical analyses were conducted using SPSS Statistics™ version 17 for Windows™.

RESULTS

Sample characteristics

We considered 236 patients for eligibility, excluded 27 and approached 209 (128 CNS-D and 81 CNS-ND) to participate in the study (Figure 1). One-hundred and seventy five patients completed the TMT: 107 with CNS-D overdose (response rate: 83.6%) and 68 with CNS-ND overdose (response rate: 84.0%) (Figure 1). The CNS-D Group comprised 57 patients who overdosed with benzodiazepines (25 diazepam, 18 temazepam, 10 alprazolam, 3 clonazepam, and 1 lorazepam), 25 with atypical antipsychotics (20 quetiapine, 4 olanzapine and 1 risperidone), and 25 with opioids (11 codeine, 7 oxycodone, 3 morphine, 2 methadone, 1 dextropropoxyphene and 1 tramadol). The control group consisted of 34 patients who overdosed with SSRIs or SNRIs (11 desvenlafaxine, 5 escitalopram, 5 sertraline, 4 citalopram, 2 paroxetine, 1 duloxetine and 1 fluoxetine) and 34 with acetaminophen.

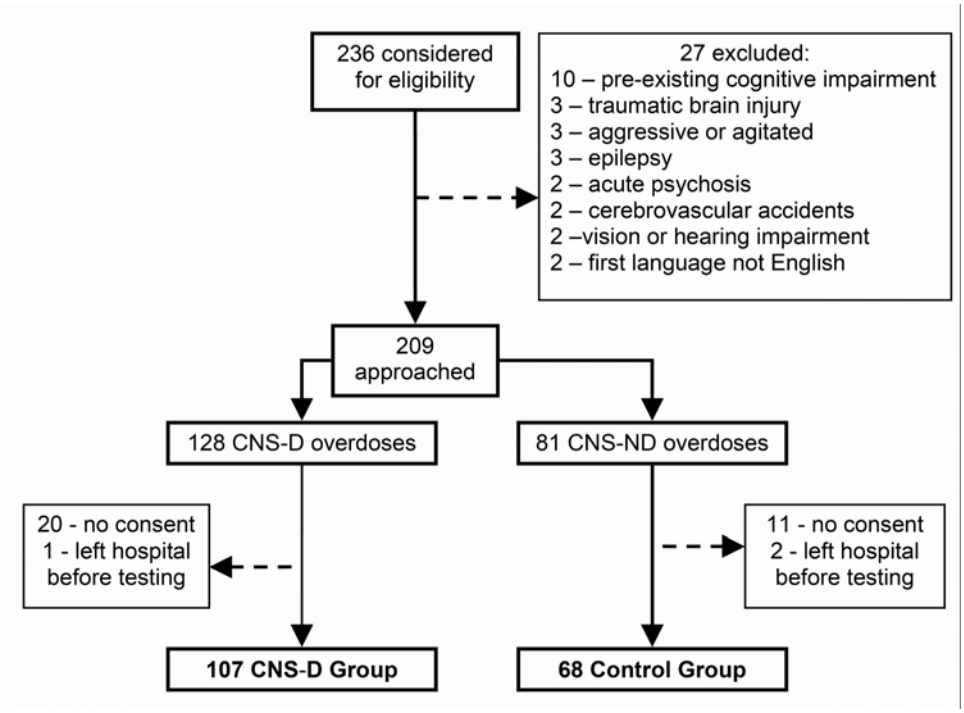

Figure 1: Participant recruitment

The sample characteristics are displayed in Table 1. The CNS-D Group was significantly older than the Control Group. Gender distribution, level of education, IQ, time from overdose to testing and the magnitude of overdose were similar between the two groups. Nearly half of the participants in each group had a major psychiatric illness (those diagnosed in the present sample were major depression, bipolar disorder and schizoaffective disorder). Around one third of each group had co-ingested alcohol. Nine patients in the CNS-D group had a lowest recorded GCS score less than nine after overdose. Of these, eight received mechanical ventilation. The mean time from exposure to testing in the CNS-D Group was 32 hours, and 85% of this group were tested within 48 hours after exposure.

Table 1: Demographic and clinical characteristics of the study groups.

	CNS-D Group (n = 107)	**Control Group (n = 68)**	**Significance (p)**
Number (%) of females	74 (69.2)	51 (75.0)	NS
Mean (SD) age (years)	37.5 (12.5)	30.1 (12.9)	0.0002
Mean (SD) years of education	11.4 (1.9)	11.8 (2.3)	NS
Mean IQ (SD)	106.4 (6.2)	107.4 (6.8)	NS
Number (%) with major psychiatric illness	53 (49.5)	33 (48.5)	NS
Mean (SD) time from exposure to testing (hours)	31.9 (21.8)	26.4 (18.2)	NS
Mean (SD) length of hospital stay (hours)	29.2 (20.3)	25.5 (16.6)	NS
Mean (SD) amount taken (x DDD)	14.4 (22.6)	16.5 (16.0)	NS
Number (%) co-ingested alcohol	39 (36.4)	22 (32.4)	NS

CNS-D = central nervous system depressant, **DDD =** defined daily dose

Group comparisons of neurocognitive measures

One extreme outlier for TMT-A and one for CRT latency were removed from the dataset prior to analysis. Summary measures based on the rest of the data are displayed in Table 2. All outcome measures were significantly impaired in the CNS-D Group compared with the Control Group. Other significant determinants of performance were age and IQ. Education, gender, psychiatric illnesses, co-ingestion of alcohol, in-ward sedative treatment and time from exposure to testing were not significantly associated with any of the outcome measures in the MLR analysis. Having observed a significant Group and Age effect on many outcome measures, a new variable Group x age interaction was entered into the MLR models to explore any difference in the effect of age on outcome measures in two Groups. However, that did not significantly improve any of the models, so the final MLR models contained only the main effects (Table 2).

Visual attention and visuomotor skills

Both TMT-A and CRT were significantly prolonged in the CNS-D Group. Test performance was also impaired with increasing age but was not influenced by IQ. The regression models with Group and age explained 20.8% of the variation in TMT-A [adjusted R^2 =0.208, $F(2,171)=23.75$, $p<0.0001$] and 20.7% of the variation in CRT [adjusted R^2=0.207, $F(2,139)=19.37$, $p<0.0001$]. TMT-A completion time and CRT were moderately correlated ($r=0.393$, $p<0.0001$). Based on the fitted regression equation, a participant in the CNS-D group had a predicted TMT-A completion time equal to that of Control Group participant 22 years older, and a predicted CRT latency equal to that of a Control participant 15 years older.

Table 2: Summary results of neuropsychological measures

Outcome measure	CNS-D Group		Control Group		Multiple linear regression modelling							
					Significance of regression coefficients (p)			Adjusted R^2	F	Significance of overall model (p)	Being in the CNS-D Group is equivalent to,	
	n	Mean (SD)	n	Mean (SD)	CNS-D vs. Control	Age	IQ				increase in age by (years),	Reduction in IQ by (units),
Visual attention and visuomotor skills												
TMT-A (s)	107	36.2 (13.6)	68	27.4 (7.7)	0.0001	<0.0001	NS	0.208	23.75	<0.0001	21.9	_
CRT latency (ms)	85	390.3 (110.9)	57	329.4 (56.5)	0.01	<0.0001	NS	0.207	19.37	<0.0001	15.3	_
Executive functions and working memory												
TMT-B (s)	107	103.9 (62.9)	67	68.5 (39.5)	0.005	<0.0001	0.004	0.342	23.88	<0.0001	12.6	13.5
TMT B-A (s)	107	66.8(55.1)	67	41.3 (37.9)	0.03	<0.0001	0.005	0.287	18.74	<0.0001	10.7	10.4
LNS[a]	86	8.80 (2.19)	58	10.02 (2.15)	0.0003	NS	0.003	0.152	12.69	<0.0001	_	16.3
SOC-Correct[b]	79	7.72 (1.87)	54	9.07 (1.75)	0.001	<0.0001	NS	0.212	18.72	<0.0001	20.9	_
SOC Slope	79	1.822 (0.518)	54	1.514 (0.391)	0.0003	NS	NS	0.088	13.58	0.0003	_	_
Impulsivity and decision-making												
ISTFWP	84	0.780 (0.096)	57	0.837 (0.109)	0.003	0.034	0.028	0.1	5.634	0.001	-38.2[c]	18.6
ISTDWP	84	0.721 (0.075)	56	0.755 (0.089)	0.002	0.002	NS	0.092	8.304	0.001	-26.5[c]	_

[a]LNS: Number of sequences recalled correctly, [b]SOC Correct: SOC problems solved in minimum moves.

[c]IST-FWP and IST-DWP increased (i.e. impulsivity decreased) with age and thus negative values signify greater impulsivity in CNS-D Group

CNS-D = central nervous system-depressant, **TMT =** Trail Making Test, **CRT** = Choice Reaction Time, **LNS** = Letter Number Sequencing, **SOC =** Stockings of Cambridge, **ISTFWP =** rationality in the fixed-win condition of Information Sample Task, **ISTDWP =** rationality in the decreasing-win condition of Information Sample Task

Executive functions and working memory

TMT-B. TMT-B completion time was significantly delayed in CNS-D overdose (p=0.005), with increasing age (p<0.0001) and lower IQ (p=0.004). In combination, these factors accounted for 34% of the variation of TMT-B [R^2=0.342, F(1,129)=23.88, p<0.0001]. The results of regression analysis of TMT B-A were very similar (Table 2).

LNS. CNS-D Group performed worse than the Control Group in the LNS task (p=0.0003). The test performance also correlated positively with IQ (p=0.003), but there was no significant association with age. Based on the regression equation, the predicted performance of a CNS-D participant was equal to that of a Control participant with an IQ of 16 points less.

SOC. On average, the CNS-D Group solved less SOC problems in minimum moves than the Control group (p=0.001). The number solved in minimum moves also declined with increasing age (p<0.0001). The predicted number of problems solved by a CNS-D Group participant was equal to the number solved by a Control participant 20 years older.

In the mixed ANOVA models for the SOC Mean-n-Moves based on Group (between-subject factor), task difficulty (i.e. minimum possible moves for a problem: 2, 3, 4 or 5: within-subject factor) and other covariates, only age turned out to be a significant covariate so that the final analysis for Group x Task Difficulty model was adjusted only for age (Figure 2). Both Group [F(1,129)=10.39, p=0.002] and age [F(1,129)=7.466, p=0.007] were significant predictors of Mean-n-Moves signifying that the Mean-n-Moves was greater in the CNS-D Group and increased with age. Group x Task difficulty interaction was significant [F(1.78, 229.61)=4.78, p=0.012],

indicating the CNS-D Group took more moves to solve the problems than Control Group as task difficulty increased. The interaction exhibited a significant linear contrast [F(1,129)=9.901, p=0.002], indicating that the Group performance diverged linearly with increasing task difficulty. Consequently, we modeled the increase in Mean-n-Moves against task difficulty as a linear function, (viz. SOC slope) such that if one completes all problems in minimum moves (i.e. if Mean-n-moves=minimum moves) the slope would be 1. Similar to other outcome measures, SOC Slope was fitted in a MLR model (Table 2). The SOC Slope of the CNS-D Group (Mean=1.822, SD=0.518) was significantly steeper than that of the Control Group (Mean=1.514, SD=0.391), indicating that the performance of the CNS-D Group deteriorates linearly with increasing number of moves in SOC task [F(1,130)=13.58, p=0.0003]. However, Group identity accounted for only 8.8% of the variation in SOC Slope (R^2=0.088, F(1,130)=13.58, p=0.0003). None of the other independent variables had a significant association with SOC Slope.

Impulsivity and decision-making (IST)

Both IST-FWP (p=0.003) and IST-DWP (p=0.002) were significantly lower in CNS-D Group than those of the Control Group. In contrast to results on other domains of cognition, older persons performed better on the IST with increasing age correlating with better IST-FWP (p=0.034) and IST-DWP (p=0.002). Higher IQ was associated with higher IST-FWP (p=0.028) but not IST-DWP.

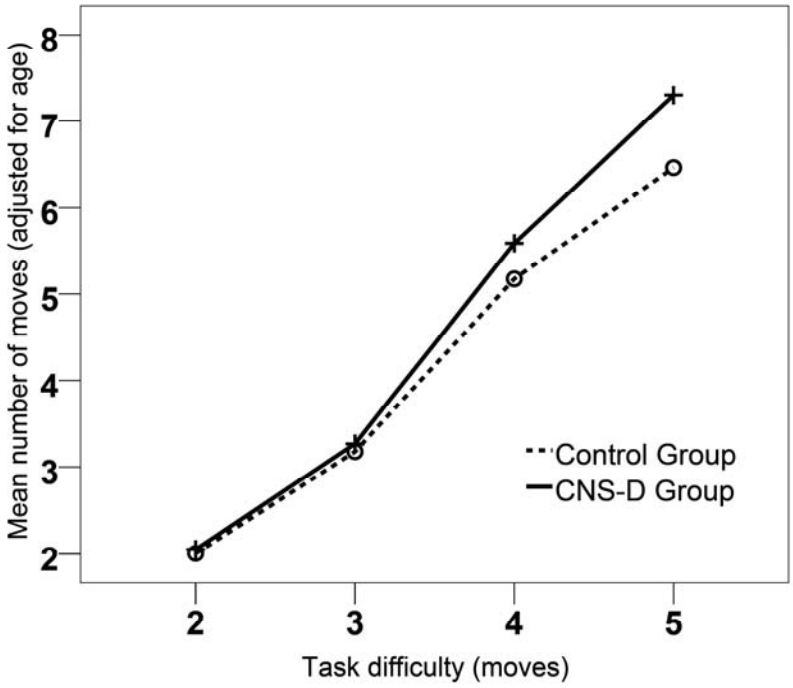

Figure 2: Group x Task Difficulty interaction in the Stockings of Cambridge Task: Mean number of moves taken to solve 2, 3, 4 and 5-move problems by the CNS-D and the Control Groups, adjusted for age (covariates appearing in the model are evaluated at age = 34.1 years).

Unplanned comparisons

Subgroup comparisons

Three subgroup analyses were conducted on each main outcome measure with series of one-way ANOVA tests and subsequent pairwise comparisons. These subgroup analyses were:

a) CNS-D subgroup analysis based on drug class- Benzodiazepines (n=57) vs. Atypical Antipsychotics (n=25) vs. Opioids (n=25),

b) CNS-D subgroup analysis based on half life - Short (<6h, n=49) vs. Medium (6-24h, n=29) vs. Long (>24h, n=34), and

c) non-CNS-D subgroup analysis based on drug class - Acetaminophen (n=34) vs. SSRIs/SNRIs (n=34).

One-way ANOVA tests and subsequent Bonferroni-corrected pairwise comparisons did not show any significant differences. No multivariate analyses were performed for these subgroups.

Intra-Group analysis for CNS-D overdose

Stepwise MLR models were fitted including the variables used in the main analysis and a new variable, lowest recorded GCS score following overdose (as a measure of degree of maximum CNS-depression caused by overdose) which was modelled as a dichotomous variable (<9 vs. ≥9). Increasing age was associated with impaired TMT-A, TMT-B, TMT B-A, CRT, LNS and SOC number of problems solved in minimum moves, lower IQ with impaired TMT-B, TMT B-A and LNS, and low GCS with impaired LNS. Older age was associated with higher IST-DWP.

DISCUSSION

To our knowledge, this is the first study that has examined subclinical impairment in a range of cognitive domains following clinical 'recovery' from CNS-D overdose. We focused on three domains of cognitive functions viz. visual attention and visuomotor skills, executive functions and working memory, and decision-making. The CNS-D Group was impaired in all test outcome measures in all three domains. In addition to the main effects, a Group x task difficulty interaction was observed in SOC task indicating that the patients may perform normally in simple

tasks but performance could fall behind as the executive demands become more complex.

Other factors associated with test performance were age and IQ. In line with previous findings in healthy populations, visuomotor skills viz. TMT-A[35] and CRT[36] were increasingly impaired with increasing age whereas these relatively low-level tasks were not dependent on IQ. As has been observed in healthy populations[35, 37] measures of executive functions and working memory were generally dependent on both age and IQ, except SOC which did not significantly correlate with IQ and LNS which did not correlate with age. In contrast to the other two domains, older age was associated with lower impulsivity and more rational decision-making.

Although we could not find comparable previous studies on cognitive effects of drug overdose, and the present CNS-D Group is too heterogeneous to compare with well-controlled samples in experimental studies on specific drugs, the cognitive deficits in the CNS-D Group are generally similar to the acute effects reported in previous experimental studies. Such adverse effects of benzodiazepines and opioids include impaired visual attention and psychomotor skills,[3, 7-10] attentional set-shifting,[11] planning[12] and working memory,[13] and increased impulsivity.[14]

Being a cross-sectional study, this study falls short of proving such causative association despite the biological plausibility of a causal relationship. However, we do not have any reason to believe that the results reflect a pre-overdose difference in intellectual functioning between CNS-D group and the Control Group because the estimated pre-morbid IQ in the CNS-D Group was normal and comparable with that of the Control Group. The only systematic intergroup difference was the higher age of

the CNS-D group, but cognitive impairment remained significant after adjusting for the effect of age and other confounding factors.

Residual cognitive impairments in patients discharged following CNS-D overdose could affect their daily activities during the immediate post discharge period. They represent a relatively young cross-section of the population and, unlike the elderly, they tend to return to social and working environments with high cognitive demands. In this respect, driving is one activity of concern in modern society. According to cognitive models of driving,[38, 39] visual attention, visuomotor skills, and ability to switch attentional-set are among major determinants of driving behavior. The regression models for tests that tap into these domains (CRT, TMT-A and TMT-B) suggest that drug effects could be equivalent to a cognitive aging by 10–20 years. This could be detrimental particularly because the impairment is acute and the patients do not have time to develop coping mechanisms as they do with normal ageing. The impairment associated with CNS-D overdose cannot be solely attributed to impaired processing speed however. Time-independent tasks (SOC, LNS and IST) show that CNS-D overdose is associated with impaired planning and working memory and higher impulsivity in decision making. Worsening SOC task performance observed with increasing executive demands is similar to the pattern that has been reported in patients with frontal lobe lesions.[34]

The findings of the present study have research and clinical implications. Follow up studies are required to delineate the time course of cognitive recovery in CNSD overdose. Epidemiological studies on real-life outcomes in the future should investigate how such impairment could affect someone who takes up driving or operating machinery in the immediate post-discharge period. However, findings of

the present study should make clinicians more aware of the possible subclinical effects of CNS-D overdose. While reassuring the discharged patients that they are not likely to experience long term complications of drug toxicity, clinicians should also warn them that their cognitive functions may not have fully recovered and they may not be fit enough to carry out certain daily activities immediately after discharge. Which activities a patient should refrain from depends on a patient's regular social and professional commitments. Driving would be one of these, owing to its complex and time-constrained cognitive and psychomotor demands and safety implications of errors. In the light of the observation that they tend to make more errors in executive tasks and more impulsive in decision-making, these patients should also be advised to be more cautious in making major decisions in their social and professional life on their own. For how long a patient should refrain from such activities is open to clinical judgment until evidence from follow up studies and real-life outcome studies is available.

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