Cognitive skills underlying driving in patients discharged following self-poisoning with central nervous system depressant drugs

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ABSTRACT:

Background: Central nervous system depressant drugs (CNS-Ds) can impair cognitive functions and driving. They are also the most common drugs taken in overdose in hospital-treated episodes of self-poisoning. In Australia most of these patients are discharged within 48 hours, while they still have possible subclinical drug-effects. We aimed to determine whether patients treated for self-poisoning with CNS-Ds are impaired in the Trail-Making Test (TMT, part A and B), a neuropsychological test that is known to correlate with driving performance.

Methods: This study was a conducted from November 2008 to April 2011 in a referral center for poisonings in New South Wales, Australia. 107 patients discharged from the clinical toxicology unit following treatment for self-poisoning of CNS-Ds (benzodiazepines, atypical antipsychotics or opioids) and a Control Group of 68 discharged following self-poisoning of non-CNS-depressant drugs (acetaminophen or non-sedating antidepressants) were tested with the Trail-Making Test (TMT, part A and B). Owing to the known association of impaired TMT with driving impairment and increased risk of traffic accidents, performance $\leq$ the 10th percentile for age was defined as significant impairment in each part of the TMT. The odds ratio (OR) for impairment in each part was calculated in multivariate logistic regression (MLR) models adjusted for gender, education, IQ and presence of a major psychiatric illness. A secondary MLR analysis was conducted only for those patients (78 CNS-D and 54 Control Group participants) who were directly discharged home, after excluding those who were transferred for further psychiatric care.

Results: The odds of impairment in the CNS-D Group was 2.8 times that of the Control Group on TMT-A [38(35.5%) vs. 11(16.2%): adjusted OR=2.76, 95%CI:1.28–5.97], and 4.6 times on TMT-B [67(62.6%) vs. 22(32.4%): adjusted OR=4.63, 95%CI:2.06–10.42]. The results were similar in the subgroup of patients discharged home, with the odds of impairment in the CNS-D Group was 3.3 times that of the Control Group on TMT-A [25(32.1%) vs. 7(13.0%): adjusted OR=3.30, 95%CI:1.28–8.52], and 3.6 times on TMT-B [46(59.0%) vs. 17(31.5%): adjusted OR=3.64, 95%CI:1.44–9.20]. TMT-B impairment in the CNS-D Group remained significant even after adjusting for TMT-A performance.

Conclusions: Patients with CNS-D overdose may have significant impairment in cognitive skills underlying driving at the time of discharge from hospitals. Clinicians should warn these patients that

their driving skills might still be impaired, even if they are considered 'clinically' recovered, and advise them not to drive during the first 1-2 days following discharge.

KEYWORDS

central nervous system depressants, benzodiazepines, opioids, Trail-Making Test, cognitive impairment, driving

INTRODUCTION

A large body of literature shows that CNS-depressant drugs (CNS-Ds), even in therapeutic doses, are associated with increased risk of traffic accidents (Dassanayake et al. 2011, Rapoport et al. 2009, Vermeeren 2004) and can cause acute impairment in driving (Dassanayake et al. 2011, Vermeeren 2004) and cognitive skills underlying driving (Stewart 2005, Zacny 1995). In contrast, research is lacking on the extent of impairment in patients who take CNS-Ds in overdose even though it is the most common mode self-poisoning among adults in developed countries, accounting for around 71,000 hospital-treated drug overdoses in the US (Coben et al. 2010), 39,000 in the UK (National Institute of Health 2011) and 12,000 in Australia (Australian Institute of Health and Welfare 2011). Drug effects tend to last longer in overdose and thus it is possible that many patients with CNS-D overdose could have significant impairment in driving skills at the time of discharge from hospitals, which is less than 48 hours from the time of admission for the majority of these patients in the UK (National Institute of Health 2011) and Australia (Australian Institute of Health and Welfare 2011). In Australia the discharge decision is based on clinical examination, and no specific psychometric tests are administered to evaluate recovery of cognitive skills.

The primary aim of the present study was to examine whether patients treated for self-poisoning of CNS-Ds are impaired in cognitive skills underlying driving at the time of discharge, when they are deemed clinically fit-enough to return to the community. In the absence of pre-overdose baseline measurements, we compared their performance with that of a Control Group of patients discharged after self-poisoning of a non-CNS-depressant (CNS-ND).

We tested driving-related cognitive skills in our participants using the Trail-Making Test (TMT, part A and B) (Bowie and Harvey 2006, Reitan 1986) a neuropsychological test that has been widely applied in off-road evaluation of fitness-to-drive (Korner-Bitensky et al. 2006). Previous research,

albeit based on elderly participants, shows that individuals with TMT-B completion time ≤ the 10th percentile for age have 2.5-fold increase in risk of failing a standardized driving test (Classen et al. 2008) and 1.5-fold increase in risk of a traffic accident (Stutts et al. 1998). The TMT-B was found to be a feasible bedside test that can be administered in a busy emergency department setting (Betz and Fisher 2009).

METHODS

Setting and Study Design

This was a cross-sectional study carried out in the Department of Clinical Toxicology and Pharmacology of the Calvary Mater Newcastle (CMN) hospital from November 2008 to April 2011. CMN is the tertiary referral centre for poisonings in the Hunter New England Region of New South Wales, Australia. All patients with self-poisoning at CMN are admitted by the Department of Clinical Toxicology and Pharmacology and 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 (Whyte et al. 1997). Once cleared by the Clinical Toxicology Team and seen by the Consultation-Liaison Psychiatry Team, patients are either discharged home or – in case of high-suicidal-risk patients – transferred to the Psychiatric Emergency Care Centre (PECC). Some patients assessed at PECC are discharged home on the same day while others are kept longer as inpatients. 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 (Whyte et al. 2002). Ethics approval for this study was granted by the Hunter New England Human Research Ethics Committee.

Participants

The study sample was prospectively recruited from the patients admitted under the care of the Department of Clinical Toxicology and Pharmacology at the CMN. We considered patients aged 18–70 years admitted following self-poisoning with any drug belonging to one of 3 classes of CNS-D

drugs (viz. benzodiazepines, atypical antipsychotics, opioids) or 2 classes of CNS-ND drugs (viz. non-sedating antidepressants consisting of selective serotonin reuptake inhibitors and serotonin noradrenalin reuptake inhibitors, and acetaminophen), for eligibility for the CNS-D Group or the Control Group, respectively.

We ascertained self-poisoning based on history, clinical picture and circumstantial evidence, and only included those who took two 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 (Centre for Drug Statistics Methodology 2010)] of a drug of interest. Patients with multiple drug ingestions were not eligible.

Patients were excluded if they had any cognitively-impairing neurological illness, a history of head injury causing neurological damage, uncorrected vision or hearing impairment, or acute psychosis or aggression, or if their first language was not English.

The patients who fulfilled the eligibility criteria were identified during daily clinical toxicology ward rounds. We introduced the study to eligible patients after they were deemed medically fit to be discharged from the unit by the clinical toxicologist and obtained informed written consent from those who were willing to participate. Irrespective of the intended destination of discharge (i.e. home or PECC), all consented patients were tested just before they were due to leave the Department of Clinical Toxicology (i.e. once they were cleared by the Clinical Toxicology Team and seen by the Consultation-Liaison Psychiatry Team).

Test Instruments

Trail-Making Test (TMT): The TMT(Reitan 1986) is a timed paper and pencil test consisting of two parts: A and B. TMT-A has circled numbers from 1 to 25 positioned irregularly on a sheet of paper, and the participant is instructed to connect the numbers in ascending order as quickly as possible. TMT-B has numbers 1-13 and letters A-L, and the numbers must be connected in ascending order and the letters in alphabetical order, alternating between the two sets (1–A–2–B.. etc). In each part, if the subject makes an error the examiner points that out promptly and the subject has to go back to the last correctly linked circle and resume the task. Time to complete each part – which depends on both speed and accuracy – is measured in seconds. The test administration takes only 5-10 minutes. Performance in both parts depends on visuomotor skills and processing speed, however part B in

addition demands the ability to switch attention between two conceptual sets (Bowie and Harvey 2006, Strauss et al. 2006).

We dichotomized TMT results, so that performance $\leq$ the 10^{th} percentile for their age was defined as impaired in the respective part of the test (i.e. in part A and part B). Test instructions, administration criteria and the age-stratified percentiles were adopted from Strauss et al. (2006).

National Adult Reading Test (NART): NART (Nelson and Willison 1991), a validated premorbid estimate of intelligence quotient (IQ) was administered to assess general intelligence which is a potential covariate affecting TMT performance. The test-sheet comprises 50 phonetically irregular words that the participants read aloud at their own pace. Verbal responses were recorded, and scored by a different researcher blind to the type of overdose of participants. Wechsler Adult Intelligence Scale (WAIS) full scale IQ was estimated from the number of errors, using the regression equation derived by Crawford et al. (1989): IQ = 128.50 – 0.84 (NART errors).

Testing for driving-fitness was conducted as part of a more extensive study that was aimed at determining the spectrum of neurocognitive impairment in CNS-D overdose. The participants subsequently took part in several other neuropsychological tests that are not reported in this paper.

Clinical Data

The clinical data on long-term clinical conditions (e.g. 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 intensive care and mechanical ventilation) were extracted from the HATS database. It was not feasible to obtain data on time of discharge from PECC, in those who were transferred to that unit.

Data Analysis

The initial data analysis included all patients recruited irrespective of the destination of discharge or transfer. As the patients transferred to the PECC may have been kept longer, they were excluded and a secondary analysis was conducted only on those who were discharged home directly after the testing session.

Sample characteristics were compared between the CNS-D and Control Groups with independent sample t-tests (for continuous variables) and Chi-squared tests (for categorical variables) (Table 1). A series of preliminary univariate logistic regressions were also carried out to explore associations between each demographic / clinical variable (except age for which TMT results were already stratified) and TMT outcome.

The association of the type of overdose (CNS-D vs. Control Group) with impairment in each part of the TMT was examined initially with univariate logistic regression and then in multivariate logistic regression (MLR) models. MLR models were adjusted for demographic (viz. gender, IQ and years of education) covariates. Presence of a major psychiatric illness was also incorporated into the MLR model as a covariate since those illnesses are known to impair TMT performance (Bora et al. 2009, Bowie and Harvey 2006). We did not include co-ingestion of alcohol as a covariate in the MLR model because we expected any effects of alcohol (if co-ingested with drugs) to have worn-off at the time of testing, and co-ingestion of alcohol was not a significant predictor of test impairment in univariate analysis.

Since NART testing to estimate premorbid IQ could not be conducted in all participants, two MLR models were created for each part of the TMT: the first, for the full sample entering Group, gender, years of education, major psychiatric illness as independent variables, and the second, for the subsample with IQ estimates entering IQ and the other independent variables (Table 4).

Sedation associated with drug overdose can impair psychomotor speed and coordination thus increasing both TMT-A and TMT-B completion times. We aimed to eliminate the influence of psychomotor slowing by fitting another MLR model comparing TMT-B performance in two Groups adjusting for TMT-A performance and other covariates (Table 5). This analysis was also conducted for the full sample and the subsample with IQ estimates.

Level of significance was set at a p value of 0.05 for all analyses. Statistical analysis was conducted using STATA® version 11.1 (Statacorp, College Station, Texas).

RESULTS

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%). Of these, 78 (72.9%) patients with CNS-D overdose and 54 (79.45%) with CNS-ND overdose were directly discharged home from the Department of Clinical Toxicology.

Sample Characteristics

The gender distribution, education, co-ingestion of alcohol with overdose, prevalence of major psychiatric illnesses, and the time from exposure to testing were similar between the CNS-D and Control Groups (Table 1). The CNS-D Group was on average 7 years older than the Control Group. The NART was administered to 97 participants (57 CNS-D and 40 Control Group), so only their IQs could be estimated. The characteristics of this subsample with IQ scores were very similar to that of the full sample (Table 1). The mean IQs of both groups were similar and were slightly above the mean expected in the general population.

The numbers of patients who took different drugs are shown in Table 2. Forty two (73.7%) out of 57 patients overdosed with benzodiazepines, 19 (76.0%) out of 25 overdosed with atypical antipsychotics, 10 (40.0%) out of 25 overdosed with opioids, 32 (94.1%) out of 34 overdosed with non-sedating antidepressants and 2 (5.9%) out of 34 with acetaminophen overdose had been taking the same drug in therapeutic doses before the episode of overdose. In the subsample of patients who were directly discharged home, 31 patients overdosed with benzodiazepines, 14 overdosed with antipsychotics, 9 overdosed with opioids, 25 overdosed with non-sedating antidepressants and one patient overdosed with acetaminophen had been taking the same drug in therapeutic doses.

Among all patients tested, around half of the patients in each group had an underlying major psychiatric illness (Table 1). This was around 40% among patients who were discharged home. By far the most prevalent psychiatric illness was depressive disorder (Table 3). In addition, 4 patients in the CNS-D Group had bipolar disorder and 2 had schizoaffective disorder. Nine patients in the CNS-D Group had a lowest GCS score of less than nine after the overdose. Of these, eight received mechanical ventilation. The lowest recorded GCS score in the Control Group participant was 13.

Of the patients discharged home, 70 (89.7%) in the CNS-D Group and 46 (85.1%) in the Control Group reported that they regularly drive a motor vehicle. In this sample of patients, 69 (88.4%) participants of the CNS-D Group and 49 (90.7%) of the Control Group were discharged within 48 hours after admission.

Trail-Making Test

All tested patients:

Based on the age-stratified 10th percentile cut-off, 38 (35.5%) of the CNS-D Group and 11 (16.2%) of the Control Group had impaired TMT-A performance (unadjusted OR=2.85, 95%CI: 1.34–6.09), whereas 67 (62.6%) of the CNS-D Group and 22 (32.4%) of Control Group were impaired in TMT-B (unadjusted OR=3.5, 95%CI: 1.84–6.65).

The MLR models created for TMT-A and TMT-B, in the full sample and the subsample with IQ scores (Table 4). For TMT-A, only the MLR model that used the full dataset was significant. In this model the odds of impairment in TMT-A in the CNS-D Group was 2.8 times that of the Control Group (adjusted OR=2.76, 95%CI: 1.28–5.97). In addition, psychiatric illness was a significant predictor of TMT-A impairment, with the odds of impairment in those who had a pre-existing major psychiatric illness was twice that of those who did not (adjusted OR=2.13, 95%CI: 1.06–4.30).

Both MLR models for TMT-B were statistically significant. The model without IQ explained only 9.5% of the variation in the outcome, whereas that with IQ scores explained 17.5% of the variation in the impairment in TMT-B. In the second model (that adjusted for gender, years of education, IQ and psychiatric illness) the odds of TMT-B impairment in the CNSD Group was 4.6 times the odds of impairment in the Control Group (adjusted OR=4.63, 95%CI: 2.06–10.42). TMT-B performance also improved with better education: each additional year of education was associated with 25% reduction in the odds of impairment (adjusted OR=0.75, 95%CI: 0.60–0.93).

Impairment of TMT-B in the CNS-D Group remained significant even after making additional adjustments for TMT-A performance (adjusted OR = 4.37, 95%CI: 1.92–9.97, Table 5).

Patients discharged home:

The results were similar in the analysis that was restricted to the patients who were discharged home after testing: 25 (32.1%) of the CNS-D Group and 7 (13.0%) of the Control Group had impaired TMT-A performance (unadjusted OR=3.17, 95%CI: 1.26–7.99), whereas 46 (59.0%) of the CNS-D Group and 17 (31.5%) of Control Group were impaired in TMT-B (unadjusted OR=3.13, 95%CI: 1.51–6.49).

On MLR analysis (Table 4), odds of impairment in the CNS-D Group was 3.3 times that of the Control Group on TMT-A (adjusted OR=3.30, 95%CI: 1.28–8.52), and 3.6 times on TMT-B (adjusted

OR=3.64, 95%CI: 1.44–9.20). Impairment of TMT-B in the CNS-D Group remained significant even after adjusting for TMT-A performance (adjusted OR=3.59, 95%CI: 1.40–9.20, Table 5).

DISCUSSION

Our findings show that patients deemed clinically recovered from CNS-D overdose tend to show subclinical deficits when challenged with a task that taps into the cognitive skills underlying driving. The patients with CNS-D overdose who were discharged home were 3.3 times more likely to be impaired in TMT-A and 3.6 times in TMT-B compared with a comparable Control Group of patients discharged following overdose of CNS-NDs. The impairment was more evident in TMT-B with around 60% of the patients with CNS-D overdose performing $\leq$ the 10th percentile for their age. Impaired TMT-B performance in the CNS-D Group was evident even after adjusting for TMT-A impairment, indicating that the observed cognitive impairment was not simply a reflection of psychomotor impairment.

Strengths and Limitations

To our knowledge, this is the first study demonstrating subclinical cognitive impairment following CNS-D overdose. Given this study involved prospective recruitment of patients with self-poisoning, with both groups having high and similar response rates, we believe the chances of any systematic bias in consenting to participate was low. The research question and the target clinical population led us to select an observational cross-sectional design and hence the study falls short of proving that CNS-depressant overdose caused the cognitive impairment. However, we attempted to minimize the influence of confounding factors by selecting an appropriate control group and by adjusting the outcome-measure estimates for potential demographic and clinical covariates. Apart from these, other non-specific factors such as psychological disturbances and lower motivation that could follow the attempt of self-harm may have reduced the test performance. However, there is no reason to believe that these factors are systematically different between the CNS-D and the Control Groups of participants. It is also unlikely that the CNS-D sample represent a group of individuals with low overall cognitive capabilities, because we excluded those who had pre-existing cognitive impairment and the recruited CNS-D group had an average IQ estimate that is similar to that of the Control Group. Around 75% of the patients with CNS-D overdose were discharged home directly

following clinical recovery from the overdose. Of those nearly 90% were discharged within 48 hours after admission. This is similar to the length-of-hospital stay data for CNS-depressant overdoses across Australia (Australian Institute of Health and Welfare 2011) and the UK (National Institute of Health 2011).

A limitation of this study is that patients were not asked to make a subjective assessment of their ability to drive during the immediate post-discharge period. Correlating the findings of such assessment with TMT results would have helped to elucidate whether patients can make an accurate assessment of their impairment and thus capable of self limiting their driving during the post-discharge period. Another possible limitation is that the drug taken in overdose is based on self-report and circumstantial evidence, not on comprehensive laboratory analysis for a variety of possible drugs. It is possible that other drugs were taken in addition to the ones named by the patients. However, we do not expect such episodes to be systematically different between the two Groups.

Implications for Fitness to Drive

Both TMT-A and TMT-B require the individual to scan the visual environment and make appropriate moves (albeit with a pencil) as quickly as possible. Cognitive models of driving signify these visuomotor skills as a basic component in driving behavior (Michon 1985, Ranney 1994). In addition to visuomotor skills, TMT-B requires switching attention between the numbers and letters while keeping the relevant numerical and alphabetical order rules in working memory. This taps into more demanding cognitive skills where one has to switch attention voluntarily between two sets of information (Bowie and Harvey 2006, Strauss et al. 2006), such as in more complex traffic situations where a driver needs to switch attention between the vehicle in front and the oncoming traffic while keeping relevant road rules in mind. In line with this, Richardson and Marottoli (2003) found TMT-B performance to have a moderate correlation with simple driving maneuvers (e.g. turning the vehicle: r =0.38) and a strong correlation with more complex maneuvers (e.g. lane change: r=0.73). We chose the 10^{th} percentile cut-off limit based on studies in healthy older drivers that showed that a TMT-B performance within 10^{th} percentile limit for age is associated with 2.5-fold increased risk of failing a standardized driving test (Classen et al. 2008) and a 1.5-fold increase in the risk of a traffic accident (Stutts et al. 1998). According to pioneering studies on alcohol and traffic accidents (Allsop 1966), such increase in accident risk in turn is equivalent to that associated with a blood alcohol level of

0.07% which is above the legal limit for driving in most countries. Same risk-estimates may not be valid for a younger population discharged from hospitals after self-poisoning with CNS-Ds, our finding that nearly 60% of the patients return to the community with a cognitive impairment of a similar extent warrants clinical attention and further research.

Research and Clinical Implications

Future research should aim to estimate the impact of CNS-D overdose on the risk of major driving-related adverse outcomes such as traffic accidents and infringements during the post-discharge period. Such adverse events are rare so that the most feasible and statistically powerful design would be large-scale epidemiological studies that link hospital admission databases with traffic event databases so that the researchers can create retrospective cohorts and investigate whether the patients are more prone to traffic accidents or infringements during the period following discharge. We could not perform follow up cognitive assessments in the patients with CNS-D overdose. Such serial assessments in the post-discharge period would help to delineate the temporal nature of cognitive recovery in CNS-D overdose.

Until such evidence is available, we believe that the association between CNS-D overdose and impairment in cognitive skills underlying driving on discharge is compelling enough to influence clinical care of these patients. With increasing demand on hospital beds, it may be impossible to keep these patients longer in hospital wards, however, clinicians should explain to patients who are 'clinically' cleared and are considered fit enough to go home, that their driving skills might still be impaired after a CNS-D overdose, and advise them not to drive during the first day or two following discharge. As our results also indicate that this impairment becomes more evident in situations that require higher levels of cognitive skills, the patients themselves may not realize that they cannot cope, until they are actually in a complex driving situation.

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Figure Captions:

Figure 1: Participant recruitment

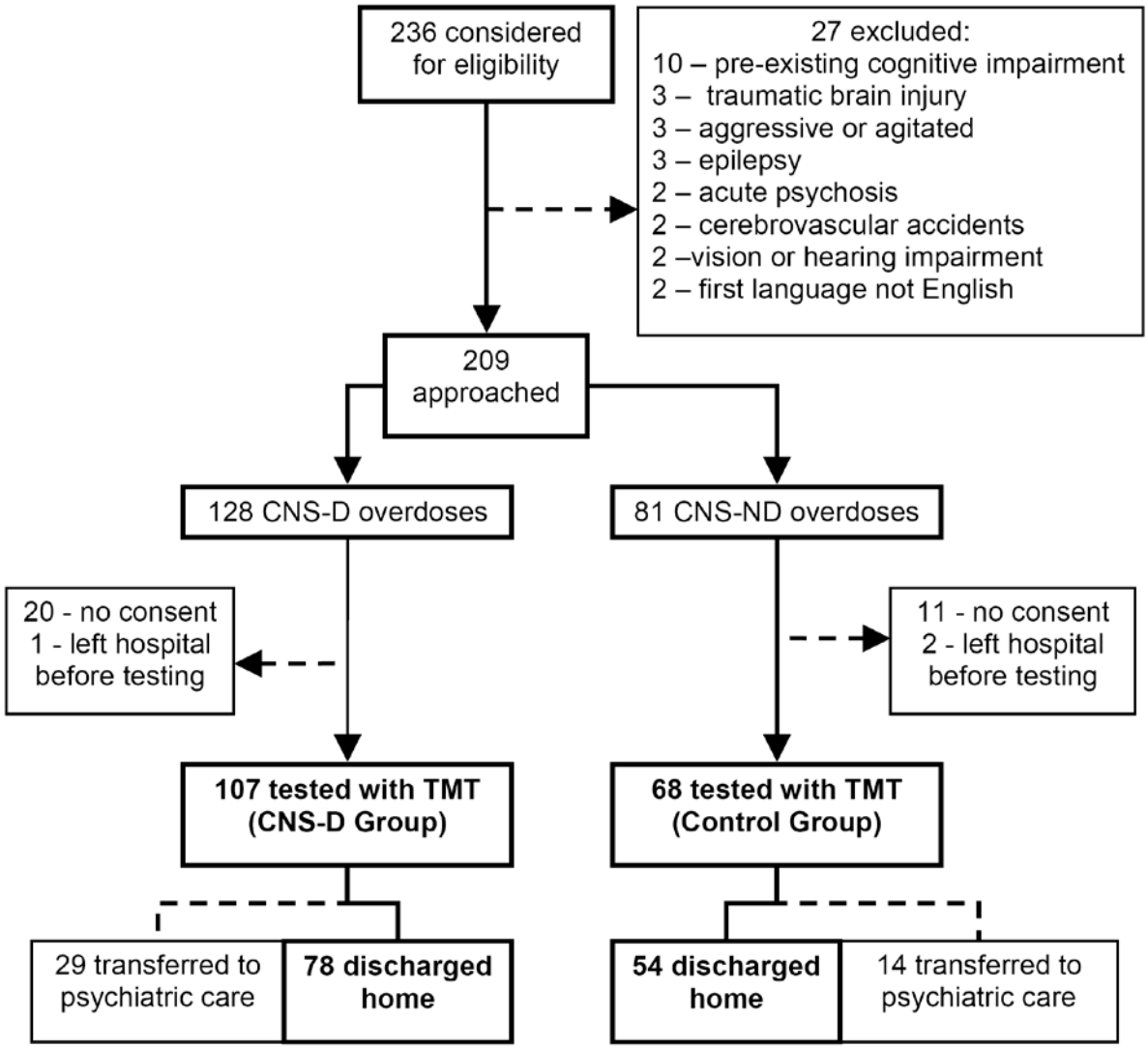
236 considered for eligibility
27 excluded:
10 – pre-existing cognitive impairment
3 – traumatic brain injury
3 – aggressive or agitated
3 – epilepsy
2 – acute psychosis
2 – cerebrovascular accidents
2 –vision or hearing impairment
2 – first language not English
209 approached
128 CNS-D overdoses
81 CNS-ND overdoses
20 - no consent
1 - left hospital before testing
11 - no consent
2 - left hospital before testing
107 tested with TMT (CNS-D Group)
68 tested with TMT (Control Group)
29 transferred to psychiatric care
78 discharged home
54 discharged home
14 transferred to psychiatric care

Table 1: Sample characteristics

	All tested patients						Patients discharged home					
	Total sample (n = 175)			Subsample with IQ scores (n = 133)			Total sample (n = 132)			Subsample with IQ scores (n = 97)		
	CNS-D (n = 107)	Control (n = 68)	p value	CNS-D (n = 81)	Control (n = 52)	p value	CNS-D (n = 78)	Control (n = 54)	p value	CNS-D (n = 57)	Control (n = 40)	p value
Continuous variables: Mean (SD)												
Age (years)	37.5 (12.5)	30.1 (12.9)	0.0002	37.2 (12.4)	30.2 (13.5)	0.002	35.9 (11.7)	30.1 (127)	0.009	35.1 (11.2)	29.9 (13.3)	0.04
Education (years)	11.4 (1.9)	11.8 (2.3)	NS	11.3 (1.9)	12.0 (2.4)	NS	11.4 (1.6)	11.6 (2.4)	NS	11.3 (1.7)	11.8 (2.7)	NS
IQ score	-	-		106.4 (6.2)	107.4 (6.8)	NS	-	-		105.7 (6.5)	106.8 (6.9)	NS
Time from exposure to testing (hours)	31.9 (21.8)	26.4 (18.2)	NS	31.3 (20.1)	26.7 (19.4)	NS	31.2 (20.8)	26.7 (19.4)	NS	33.1 (21.4)	27.3 (21.0)	NS
Length of hospital stay (hours)	29.2 (20.3)	25.5 (16.6)	NS	29.7 (19.4)	25.4 (17.0)	NS	27.4 (18.3)	25.3 (16.0)	NS	29.6 (19.8)	25.1 (15.9)	NS
Number of defined daily doses taken	14.4 (22.6)	16.5 (16.0)	NS	15.5 (25.9)	16.0 (17.1)	NS	15.1 (25.5)	14.1 (13.3)	NS	16.4 (29.5)	13.5 (15.0)	NS
Categorical variables: number (%)												
Females	74 (69.2)	51 (75.0)	NS	54 (65.9)	39 (75.0)	NS	58 (74.4)	38 (70.4)	NS	40 (70.2)	28 (70.0)	NS
Psychiatric Illness	53 (49.5)	33 (48.5)	NS	25 (48.1)	40 (49.4)	NS	32 (41.0)	22 (40.7)	NS	22 (38.6)	16 (40.0)	NS
Co-ingestion of alcohol	39 (36.4)	22 (32.4)	NS	33 (40.7)	17 (32.7)	NS	28 (35.9)	20 (37.0)	NS	23 (40.4)	15 (37.5)	NS

Table 2: Numbers of patients overdoses with different drugs

Drug	Among all tested patients	Among patients discharged home
Benzodiazepines	**57**	**40**
Diazepam	25	19
Temazepam	18	12
Alprazolam	10	7
Clonazepam	3	1
Lorazepam	1	1
Atypical antipsychotics	**25**	**19**
Quetiapine	20	17
Olanzapine	4	2
Risperidone	1	-
Opioids	**25**	**19**
Codeine	11	7
Oxycodone	7	6
Morphine	3	2
Methadone	2	2
Dextropropoxyphene	1	1
Tramadol	1	1
Non-sedating antidepressants	**34**	**26**
Desvenlafaxine	11	8
Escitalopram	5	4
Sertraline	5	2
Venlafaxine	5	4
Citalopram	4	4
Paroxetine	2	2
Duloxetine	1	1
Fluoxetine	1	1
Acetaminophen	**34**	**28**

Table 3: Numbers of patients with major psychiatric illnesses

Psychiatric illness	Among all tested patients		Among patients discharged home	
	CNS-D Group	Control Group	CNS-D Group	Control Group
	(n = 107)	(n = 68)	(n = 78)	(n = 54)
Depressive disorder	46	33	27	22
Bipolar disorder	5	-	4	-
Schizoaffective disorder	2	-	1	-

Table 4: Multiple logistic regression models for TMT-A and TMT-B in the CNS-D vs. Control Groups adjusted for demographic and clinical covariates.

	All tested patients				Patients discharged home			
	TMT-A		TMT-B		TMT-A		TMT-B	
	Total sample (n = 175)				Total sample (n = 132)			
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
CNS-D vs. Control	2.76 (1.28 – 5.97)	0.01	3.40 (1.76 – 6.57)	<0.001	3.30 (1.28 – 8.52)	0.013	3.20 (1.51 – 6.75)	0.002
Females vs. Males	0.88 (0.41 – 1.88)	0.740	1.16 (0.57 – 2.35)	0.685	0.76 (0.29 – 1.94)	0.561	0.75 (0.33 – 1.72)	0.507
Education (per additional year)	0.91 (0.76 – 1.08)	0.284	0.80 (0.67 – 0.95)	0.012	0.85 (0.67 – 1.07)	0.234	0.82 (0.68 – 1.01)	0.057
Psychiatric Illness	2.13 (1.06 – 4.30)	0.034	1.38 (0.72 – 2.63)	0.323	2.35 (0.98 – 5.61)	0.055	1.38 (0.65 – 2.93)	0.398
Overall model	χ^2 = 13.51, df = 4, p = 0.009 R^2 = 0.0651		χ^2 = 23.10, df = 4, p = 0.0001 R^2 = 0.0952		χ^2 = 11.60, df = 4, p = 0.02 R^2 = 0.0793		χ^2 = 14.23, df = 4, p = 0.007 R^2 = 0.0779	
	Subsample with IQ scores (n = 133)				Subsample with IQ scores (n = 133)			
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
CNS-D vs. Control	2.09 (0.87 - 5.02)	0.098	4.63 (2.06 – 10.42)	<0.001	1.57 (0.56 – 4.45)	0.388	3.64 (1.44 – 9.20)	0.006
Females vs. Males	0.75 (0.32 – 1.75)	0.502	1.59 (0.68 – 3.75)	0.284	0.77 (0.31 – 1.71)	0.640	1.13 (0.43 – 3.02)	0.795
Education (per additional year)	0.83 (0.68 – 1.03)	0.085	0.75 (0.60 – 0.93)	0.01	0.83 (0.27 – 2.26)	0.081	0.78 (0.62 – 1.00)	0.05
IQ (per additional 1 point)	0.99 (0.93 – 1.06)	0.774	0.95 (0.89 – 1.02)	0.14	0.96 (0.88 – 1.04)	0.294	0.94 (0.87 – 1.01)	0.09
Psychiatric Illness	1.67 (0.74 – 3.78)	0.221	1.70 (0.76 – 3.78)	0.194	2.01 (0.70 – 5.80)	0.194	1.794 (0.69 – 4.70)	0.232
Overall model	χ^2 = 9.66, df = 5, p = 0.085 R^2 = 0.0622		χ^2 = 32.28, df = 5, p < 0.0001 R^2 = 0.1751		χ^2 = 6.134, df = 5, p = 0.29 R^2 = 0.0591		χ^2 = 19.32, df = 5, p = 0.002 R^2 = 0.1445	

Table 5: Multiple logistic regression models for TMT-B in CNS-D vs. Control Groups adjusted for TMT-A, demographic and clinical covariates.

	All tested patients				**Patients discharged home**			
	Total sample (n = 175)		**Subsample with IQ (n = 133)**		**Total sample (n = 132)**		**Subsample with IQ (n = 97)**	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
CNS-D vs. Control	2.90 (1.46 – 5.74)	0.002	4.37 (1.92 – 9.97)	<0.001	2.62 (1.20 – 5.69)	0.02	3.59 (1.40 – 9.20)	0.008
TMT-A	4.29 (1.91 – 9.62)	<0.001	2.65 (1.05 – 6.71)	0.04	4.70 (1.77 – 12.50)	0.002	2.62 (0.87 – 7.93)	0.09
Females vs. Males	1.21 (0.57 – 2.53)	0.619	1.73 (0.72 – 4.15)	0.222	0.80 (0.34 – 1.88)	0.609	1.22 (0.45 – 3.32)	0.697
Education (per additional year)	0.80 (0.67 – 0.96)	0.018	0.76 (0.61 – 0.95)	0.016	0.84 (0.69 – 1.03)	0.105	0.80 (0.63 – 1.02)	0.07
IQ (per additional 1 point)	-	-	0.95 (0.89 – 1.02)	0.139	-		0.94 (0.87 – 1.02)	0.164
Psychiatric Illness	1.14 (0.58 – 2.24)	0.704	1.58 (0.70 – 3.56)	0.274	1.11 (0.50 – 2.46)	0.793	1.62 (0.61 – 4.31)	0.311
Overall model	$\chi^2 = 36.99$, df = 5, $p < 0.0001$, $R^2 = 0.1525$		$\chi^2 = 36.70$, df = 5, $p < 0.0001$, $R^2 = 0.1991$		$\chi^2 = 25.12$, df = 5, $p = 0.0001$, $R^2 = 0.1375$		$\chi^2 = 22.34$, df = 6, $p < 0.001$, $R^2 = 0.1672$	