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Complete List of Authors:	Birnie, Karen; King's College London School of Medical Education, Faculty of Life Sciences and Medicine Stewart, Robert; King's College London, Department of Psychological Medicine; South London and Maudsley NHS Foundation Trust kolliakou, Anna; King's College London, Department of Psychological Medicine
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Recorded atypical hallucinations in psychotic and affective disorders and associations with non-benzodiazepine hypnotic use: the South London and Maudsley Case Register

Running Title: Recorded atypical hallucinations

Karen I Birnie*[a], Robert Stewart[b,c] and Anna Kolliakou[b]

[a]Department of Health Psychology, King's College London, London, UK

[b]Department of Psychological Medicine, King's College London, London, UK

[c]South London and Maudsley NHS Foundation Trust, London, UK

Correspondence should be addressed to:

Karen I Birnie, King's College London, Guy's Campus, London, SE1 9RT

karen.birnie@kcl.ac.uk

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ABSTRACT

Objectives

Hallucinations are present in many conditions, notably psychosis. Although under-researched, atypical hallucinations, such as tactile, olfactory and gustatory (TOGHs), may arise secondary to hypnotic drug use, particularly non-benzodiazepine hypnotics ('Z drugs'). We investigated the frequency of TOGHs and their associations with prior Z drug use in a large mental healthcare database.

Methods

TOGHs were ascertained in 2014 using a bespoke natural language processing algorithm and were analysed against covariates (including use of Z drugs, demographic factors, diagnosis, disorder severity and other psychotropic medications) ascertained prior to 2014.

Results

In 43,339 patients with ICD-10 schizophreniform or affective disorder diagnoses, 324 (0.75%) had any TOGH recorded (0.54% tactile, 0.24% olfactory, 0.06% gustatory hallucinations). TOGHs were associated with male gender, Black ethnicity, schizophreniform diagnosis and higher disorder severity on Health of the National Outcome Scales. In fully adjusted models, tactile and olfactory hallucinations remained independently associated with prior mention of Z drugs (odds ratios 1.86 and 1.60 respectively).

Conclusions

We successfully developed a natural language processing algorithm to identify instances of TOGHs in the clinical record. TOGHs overall, tactile and olfactory hallucinations were shown to be associated with prior mention of Z drugs. This may have implications for the diagnosis and treatment of patients with comorbid sleep and psychiatric conditions.

Strengths and limitations of this study

* This was a large study involving 43 339 patients

* The prospective study design reduced recall bias.

* The NLP tool, developed to recognise references to TOGHs from a naturalistic data source, has great potential for applicability in other data sources.

* This study utilised routine healthcare records, thus requiring clinicians to recognise and record TOGHs accurately.

* We were not able to conclude that medication use always antedated TOGHs.

Keywords: psychosis, olfactory, tactile, gustatory, Z drugs, electronic health records

1

Introduction

Although hallucinations are not necessarily abnormal experiences, they are commonly associated with psychotic and organic disorders (1,2). They can occur in any sensory modality although the most commonly reported hallucinations in patients with schizophrenia are auditory and visual with estimated prevalences of around 70%, and ranging from 15-60% respectively (3,4). Similar prevalences have been described in bipolar disorder (approximately 70% and 25%, respectively) (5). Tactile, olfactory and gustatory hallucinations (TOGHs) are recognised to occur in psychotic disorders, but have received substantially less investigation. In samples with either schizophrenia or severe mental illness more generally, tactile hallucination prevalences have ranged from 15-27% (3,6-8), and are recognised to be associated with substance abuse and withdrawal regardless of diagnosis (9),. The prevalence of olfactory hallucinations has ranged from 15-27% (6,7), although this is likely to be an underestimate because of the tendency for traditional questionnaires to examine hallucinations generally rather than by modality (10). The prevalence of gustatory hallucinations has ranged from 4-14% (6,7). Hypnotic use in the general population has been found to be associated with higher reported tactile and gustatory hallucinations (11) and hallucinations in all/most modalities have been described as increased in people receiving non-benzodiazepine hypnotics, specifically 'Z drugs' (zolpidem, zopiclone or zaleplon) (12,13), possibly potentiated by other psychotropic agents (14). However, these observations have been largely been derived case studies and small samples.

The aim of this study was to ascertain the frequency of TOGHs in a large sample of people receiving mental health services with schizophreniform or affective disorder diagnoses, and to test a hypothesised association between TOGHs and Z drug use.

2

Methods

2.1

Setting

The South London and Maudsley NHS Foundation Trust (SLaM) is one of Europe's largest mental healthcare providers, serving a geographic catchment of four south London boroughs (Croydon, Lambeth, Lewisham, Southwark) with approximately 1.2 million residents. Since 2006, an electronic health records system has been used throughout SLaM, and the Clinical Record Interactive Search (CRIS) system, developed in 2008, allows researchers to retrieve de-identified information from these records for around 280,000 cases to date (15,16). CRIS has been approved as a database for secondary analysis by the Oxfordshire Research Ethics Committee C (Ethics ID: 08/H0606/71+5) and a service-user led committee provides oversight for projects using these data (17).

2.2

Study population

The baseline sample derived from CRIS comprised a cohort of all patients, aged 18-65 on 1st January 2014, who had received a diagnosis of a schizophrenia-related disorder (extracted using ICD-10 code:F2x) and/or a mood/affective disorder (ICD-10 code:F3x) prior to that date. Case records from the cohort were then searched for instances of TOGHs between 1st January 2014 and 31st December 2014.

2.3

Patient involvement

We did not directly incorporate PPI into this particular study but the SLAM BRC Case Register used in the analysis was developed with extensive PPI and is overseen by a committee that includes service-user representatives.

2.4

Outcome – tactile, olfactory and gustatory hallucinations

A pre-existing natural language processing algorithm designed to detect mentions of hallucinations in text fields (18) was further adapted to search and retrieve references to TOGHs. Three keywords were added to search for references to hallucinations mentioned in the free-text fields of CRIS (including written assessments, progress notes and correspondence). These were 'olfactory', 'tactile' or 'gustat*' (and 'hallucinations'). The application query retrieved 20,924 instances across CRIS; 1,000 randomly selected instances were annotated for reference to TOGHs, of which 300 instances were double-annotated resulting in a kappa statistic of 0.83 (95% CI 0.71-0.89). The information extraction algorithm was developed using 500 annotated records (training set), seeking to identify linguistic patterns indicating a true reference to any of the three hallucination types (i.e. rather than negation statements, irrelevant mentions, or mentions of the symptom occurring in someone other than the patient). Having developed the algorithm using General Architecture for Text Engineering (GATE) machine learning software (19), it was tested on another 500 annotated records (gold standard set), and achieved a precision score (positive predictive value) of 0.91 and a recall (sensitivity) score of 1.00. Deploying the algorithm over the complete dataset of 20,924 instances, 17,066 were identified as true positive references to TOGHs. Binary outcome variables were thereby created representing the occurrence of hallucinations in each or any modality (olfactory, tactile, gustatory, any of the three).

2.5

Covariates

Covariates were extracted to indicate status at the index date (1st January 2014). Demographic factors comprised age, gender, and recorded ethnicity – the latter categorised into three groups: black background (including Caribbean, African and any other black background), white background

(British, Irish, and any other white background), and other (including mixed or multiple ethnic backgrounds).

Regarding clinical factors, the sample was categorised into those who had previously received a diagnosis of schizophreniform disorder, a mood disorder diagnosis, or both. In addition, we made use of the Health of the Nations Outcome Scales (HoNOS) assessment, routinely administered in UK mental health services (20), including the total score (an indicator of overall functioning), and the score relating to alcohol and substance use problems (categorising the problem as present on the basis of a score of 2 or more on the 0-4 scale), extracting scores closest to the index date.

Hypnotic agent use before the index date was determined from structured medication fields in the record, supplemented by a natural language processing algorithm which ascertains recorded pharmacotherapy from open-text fields. Ascertained agents were classified into Z drugs (zopiclone, zaleplon and zolpidem) and all other hypnotics licensed for use in insomnia or where sedation is needed (diazepam, flurazepam, loprazolam, lorazepam, lormetazepam, nitrazepam, temazepam, trimipramine, doxepin, chloral hydrate, clomethiazole, melatonin, promethazine hydrochloride). Antidepressant use during the same period was identically extracted, and classified into two groups; those acting primarily through the serotonergic system (citalopram, escitalopram, paroxetine, fluoxetine, fluvoxamine, sertraline, duloxetine, venlafaxine, trazodone, amitriptyline, clomipramine, dosulepin, doxepin, imipramine, trimipramine, mianserin, mirtazapine, isocarboxazid, phenelzine, tranylcypromine, moclobemide, and agomelatin) and those with other primary targets (non-serotonergic - reboxetine, flupentixol and nortriptyline) (21).

2.6

Analyses

Percentages were used to describe all categorical variables. Mean and standard deviation (SD) were used to describe age and HoNOS total scores were described by median and interquartile range

(IQR). Chi-square (χ^2) test statistics were calculated to identify any differences in socio-demographic and clinical characteristics between patients with or without TOGHs overall and for each modality. Binomial logistic regression models were used to test the association between overall/individual TOGHs and mention of Z drugs. Socio-demographic and clinical characteristics associated with individual outcomes at $p<0.05$ were entered in the final regression model. Because of missing data pertaining to HoNOS scores, a post-hoc analysis was conducted, restricting the sample to those with scores present before investigating the impact of adjusting for HoNOS-derived covariates. All analyses were conducted using Stata, V.13 (22).

3

Results

The analysed sample consisted of 43,339 patients. The mean age was 41.4 years (SD 12.2) and 53.5% of the sample was female. One quarter of the sample was of a Black background and 57.9% were of a White background. Regarding previous diagnosis, over two thirds had received a mood disorder diagnosis only (67.0%) and 24.4% a schizophreniform diagnosis only; 22.6% of the total sample had mention of Z drugs in their record and 25.7% had mention of other hypnotic drugs. The median of the HoNOS total scores was 8 (IQR 0-40).

The natural language processing algorithm identified 324 patients in the sample with at least one modality of TOGH recorded in 2014 case notes: 0.75% of the sample. Within this group, tactile hallucinations were most common (71.6%), followed by olfactory (31.8%) and gustatory (7.4%) modalities. The proportion of patients who reported any TOGH did not differ significantly from the remainder of the sample by age ($\chi^2(3) = 5.22$, $p = .157$) or HoNOS problems with drugs and alcohol ($\chi^2(1) = 2.78$, $p = .095$) but did with respect to gender ($\chi^2(1) = 5.66$, $p = .017$) and ethnicity ($\chi^2(2) = 74.30$, $p < .001$), with over-representation of men and patients from black ethnic groups (Table 1). In regard to clinical features, significant differences were observed between patients with any TOGH and the rest of the sample with respect to diagnosis ($\chi^2(2) = 272.97$, $p < .001$), and were more likely to have recorded Z drug use ($\chi^2(1) = 118.78$, $p < .001$), other hypnotic use ($\chi^2(1) = 149.54$, $p < .001$) and non-serotonergic antidepressant use ($\chi^2(1) = 23.81$, $p < .001$). Prevalence of any TOGH by diagnostic group was 1.5% in F2, 0.24% in F3 and 1.7% in those with both diagnoses recorded.

In unadjusted regression analysis (Table 2), recorded Z-drug use was significantly associated with any TOGH (OR 3.17, 95% CI 2.54 – 3.95), tactile (3.22, 2.49 – 4.17), olfactory (2.77, 1.88 – 4.09) and gustatory hallucinations (3.43, 1.54 – 7.63) specifically. After adjusting for confounders all 4 models remained significant, albeit attenuated, with recorded Z drugs associated with any TOGH mention

(2.02, 1.57 – 2.77), tactile (2.09, 1.57 – 2.78), olfactory (1.69, 1.10 – 2.59) and gustatory hallucinations (2.58, 1.06 – 6.28).

Restricting the sub-sample to patients who had a HoNOS total score available in the clinical record (n=26,201), after adjusting for the confounders indicated in Table 2, associations with recorded Z-drug use remained significant for any TOGH (1.82, 1.41 – 2.34), tactile (1.81, 1.41 – 2.34) and olfactory hallucinations (1.60, 1.01 – 2.54) and but not for gustatory hallucinations (2.19, 0.87 – 5.55). Further adjustment for HoNOS total scores and HoNOS problems with drugs and alcohol in this regression model did not alter findings substantially for any TOGH (1.80, 1.40 – 2.32), tactile (1.86, 1.38 – 2.51), olfactory (1.60, 1.01 – 2.54), or gustatory hallucinations (2.19, 0.86 – 5.55) (Table 3).

4

Discussion

In a large database derived from mental healthcare electronic records we investigated the 1-year period frequency of recorded tactile, olfactory and gustatory hallucinations in patients with schizophreniform or affective disorders, having developed an algorithm to detect recorded mentions of these symptoms with a reasonable level of accuracy. Because of the relative rarity of these symptoms, large administrative databases present an opportunity for better definition and aetiological investigation. However, symptom profiles are not routinely recorded in structured fields within mental health records, so the development and application of natural language processing techniques are similarly essential for improving understanding – rendering information available at scale which would have previously been unrealised, and generating databases which are both large and detailed (18,23).

Frequencies within the sample were 0.54%, 0.24% and 0.06% for tactile, olfactory and gustatory hallucinations respectively. These are clearly substantially lower than prevalence reports in samples with severe mental illness of 15-27% for tactile hallucinations (3,6,7), 15-19% for olfactory hallucinations in schizophrenia (6,8), and 4-9% for gustatory hallucinations (6,8). However, research to date has ascertained these symptoms from lifetime recollections derived from fully-structured diagnostic questionnaires, utilising specific questions relating to these hallucinations (3,6,7), whereas our estimates were 1-year rates of reference to TOGHS, derived from information contained in routine healthcare records. It should be noted that clinical records likely underestimate the prevalence of TOGHs, given that they may not be recorded systematically in clinical practice. The relatively broadly defined sample should also be borne in mind, as the frequencies of TOGHs were substantially higher in patients who had received a schizophreniform diagnosis alone or in combination (1.5% and 1.7% prevalences respectively), compared to that in patients who had received an affective disorder diagnosis alone (0.24%), consistent with other reports (6).

We also specifically investigated associations with Z drug (zopiclone, zolpidem, zaleplon) hypnotic use, given previous cited associations with hallucinations. Neuropsychiatric adverse effects of Z drugs, including hallucinations and psychosis, have been described for over 15 years (24-27), including atypical and/or multimodal hallucinations (28). Most often this has been related to zolpidem, although this may reflect higher usage rates (29). While mechanisms underlying other adverse effects, such as parasomnias have been investigated (30), the explanation for associations with hallucinations remains unclear, although it does not appear to be related directly to dose or plasma concentrations, and at least some excess adverse event reporting has been suggested in association with media exposure (31). Interactions have also been reported with other psychotropic agents (32). In line with our hypothesis, patients with use of Z drugs mentioned in their previous clinical record were more likely to experience TOGHs overall and tactile and olfactory hallucinations specifically. Associations with gustatory hallucinations appeared similar in strength but were not statistically significant in all models because of the relative rarity of hallucinations in this modality being recorded. Unlike previous studies, which have tended to involve patient interviews subsequent to drug use, our analysis investigated associations between mentions of drug categories at any time preceding 2014 and recorded TOGHs during 2014. A large multi-national general population survey found that overall hypnotic use was associated with tactile and gustatory hallucinations; however, we only found independent evidence of other hypnotics (non-Z-drugs) being associated with tactile hallucinations (Table 2).

Secondary findings suggest that other factors, such as diagnosis and ethnicity, may play a role in susceptibility to TOGHs. These associations have not been identified in previous research, although this may reflect differences in sample size, since higher non-Caucasian ethnicity was found in one previous study (6), and lower levels of TOGHs were found in patients from India compared to the USA in another study (7), which may suggest some international/ethnic variation in prevalence. In final models (Table 3), higher HoNOS total score was associated with TOGHs generally, which has

some concordance with findings from other studies of associations with more severe psychotic syndromes (particularly in relation to delusional symptoms) (6), although this was only present for tactile hallucinations.

Strengths of the study include the large sample size, the prospective study design, the range of covariates assessed and the naturalistic source of data. The development of the natural language processing algorithm was successful, resulting in a tool that can be used to automatically extract data on TOGHs from the electronic health record, in addition to the growing number of other information extraction algorithms being developed (16,18). Given the relative simplicity of the underlying construct (TOGHs) being ascertained from text fields, we would anticipate good cross-applicability to other data sources. The sample itself ought also to be reasonably generalisable, coming from a mixed inner and outer urban catchment with high social diversity (16).

The nature of the source data needs to be borne in mind when drawing conclusions; in particular, the fact that hallucinations were ascertained from routine mental healthcare records rather than from a research instrument. Presence of TOGHs in the CRIS database therefore depends on a clinician asking about or noticing the symptom, on their recording it, and on their recording it in such a way that it was extracted by the natural language processing algorithm (i.e. recorded as a phenomenological term: e.g. 'tactile hallucination' rather than 'feels that insects are crawling over his skin'). As described, the algorithm itself was efficient at identifying these terms, with high precision and recall statistics; however, symptoms will have been missed if they went unnoticed or unrecorded in clinical care. The alternative approach in this field has been to evaluate them in a recruited sample with a formal questionnaire, and to our knowledge, this is how all previous prevalence estimates have been derived, most often using the Structured Clinical Interview for DSM (SCID) (3,6). However, this approach generally depends on responses to one or two questions in a long interview schedule administered for other purposes and deriving lifetime rather than current occurrences. There is therefore considerable potential for recall bias, as well as potential selection

bias arising from the sample recruited which are less likely to influence data from routine healthcare. Ultimately it has not yet been established whether data extracted from clinical records are an underestimate of true prevalence, or whether recalled self-report data elicited from diagnostic instruments are an overestimate, and this requires further evaluation.

Considering the hypothesis under investigation, while the prospective study design reduces effects of recall bias, whereby participants may have had difficulty remembering details about their hallucinations or medication use, establishing causality is difficult. Although mentions of medication were ascertained prior the observation period, we were not able to conclude that medication use always antedated hallucinations. In addition, medication, while mentioned, was not necessarily used, and dosage was not accounted for; neither were different Z drugs distinguished. In addition, patients prescribed certain drugs may have more clinical contact and care around prescribing, perhaps leading to decreased vulnerability.

This study could be improved in the future by fine-tuning of the application – for example, including other keywords that may indicate the presence of TOGHs – terms such as disturbance or unusual experience/sensation, may identify more instances of TOGHs. The development of an application that explored medication use, not just mentions, could be used to determine the nature of any relationship with hallucinations. This would be valuable information for patients who are known to be at risk of unusual sensory phenomena, where clinicians could make more informed decisions about prescribing. Our findings are preliminary but if replicated could have implications for patients with comorbid disordered sleep or mood symptoms.

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Contributorship

This research was completed as part of an intercalated BSc in Psychology. KB, AK and RS all contributed to the study design and manuscript preparation. KB took primary responsibility for data collection and analysis. All authors contributed to and have approved the final manuscript.

Competing interests

None.

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Data sharing

There are no additional data available.

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Table 1 Demographic and clinical characteristics of total and individual samples

	Total sample (n=43339)	Groups with tactile, olfactory or gustatory hallucinations (TOGH)			
		Any TOGH (n=324)	Tactile (n=232)	Olfactory (n=103)	Gustatory (n=24)
Age %					
18-31	24.8	29.0	28.4	35.9	20.8
32-41	25.4	27.2	29.7	19.4	29.2
42-50	24.7	22.5	21.1	26.2	16.7
51-65	25.1	21.3	20.7	18.4	33.3
Female gender %	53.5	46.9	41.8	54.4	62.5
Ethnicity %					
Black	25.0	45.1	46.1	46.6	37.5
White	57.9	38.6	37.1	37.9	41.7
Other	17.1	16.0	16.4	15.5	20.8
Diagnosis %					
F2	24.3	54.9	56.0	55.3	50.0
F3	67.0	24.1	26.3	17.5	20.8
Both	8.6	21.0	17.7	27.2	29.2
Medication use %					
Z-drugs	22.6	47.8	48.3	44.7	50.0
Other hypnotics	25.7	55.2	56.0	54.4	45.8
Serotonin-related antidepressants	54.6	54.3	55.2	50.5	54.2
Non-serotonin antidepressants	4.2	9.6	10.3	10.7	0
HoNOS					
Total (Median (IQR)	8.0 (0-40)[1]	10 (0-34)[2]	10 (0-34)[3]	9 (0-29)[4]	6 (0-24)[5]
Problem with alcohol and drug use %	15.2[6]	18.6[7]	20.6[8]	15.1[9]	13.6[10]

[1](n=26201) [2](n=284) [3](n=204) [4](n=86) [5](n=21) [6](n=27047) [7](n=295) [8](n=209) [9](n=93) [10](n=22)

Table 2 Adjusted logistic regression model assessing the association between Z-drug use and tactile, olfactory or gustatory hallucinations

	All modalities		Tactile		Olfactory		Gustatory	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Z drugs	2.02 (1.59 –2.57)	<.001	2.09 (1.57 – 2.77)	<.001	1.69 (1.10 – 2.59)	.016	2.58 (1.06 – 6.28)	.036
Gender	.90 (.71 – 1.12)	.347	1.12 (.86 – 1.47)	.402	-	-	-	-
Age								
32-41	-	-	-	-	Ref		-	-
18-31	-	-	-	-	2.11 (1.22 – 3.64)	.008	-	-
42-51	-	-	-	-	1.31 (.73 – 2.35)	.355	-	-
51-65	-	-	-	-	.99 (.52 – 1.85)	.963	-	-
Ethnicity								
White	Ref		Ref		Ref		-	-
Black	1.66 (1.30 – 2.13)	<.001	1.82 (1.36 – 2.45)	<.001	1.57 (1.02 – 2.43)	.042	-	-
Other	1.34 (.97 – 1.86)	.080	1.45 (.98 – 2.12)	.060	1.23 (.68 – 2.21)	.492	-	-
Diagnosis								
F3	Ref		Ref		Ref		Ref	
F2	4.82 (3.61 – 6.45)	<.001	4.04 (2.90 – 5.64)	<.001	6.63 (3.81-11.55)	<.001	6.30 (2.19-18.14)	.001
F2/F3	3.86 (2.73 – 5.47)	<.001	2.72 (1.79 – 4.16)	<.001	7.44 (3.97-13.95)	<.001	8.21 (2.47-27.28)	.001
Hypnotic use	1.76 (1.37 – 2.25)	<.001	1.86 (1.39 – 2.49)	<.001	1.54 (.99 – 2.37)	.053	1.02 (.42 – 2.51)	.958
Non-serotonin antidepressants	.99 (.68 – 1.45)	.970	1.09 (.70 – 1.68)	.704	1.21 (.63 – 2.31)	.565	-	-

- variable not entered in regression model

Table 3 Adjusted logistic regression model assessing the association between Z-drug use and tactile, olfactory, or gustatory hallucinations in the subsample of patients with Health of the National Outcome Scales (HoNOS) data present

	All modalities		Tactile		Olfactory		Gustatory	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Z drugs	1.80 (1.40 – 2.32)	<.001	1.86 (1.38 – 2.51)	<.001	1.60 (1.01 – 2.54)	.043	2.19 (.86 – 5.55)	.099
Gender	.90 (.70 – 1.14)	.382	1.16 (.86 – 1.55)	.324	-	-	-	-
Age								
32-41	-	-	-	-	Ref		-	-
18-31	-	-	-	-	1.52 (.84 – 2.73)	.163	-	-
42-51	-	-	-	-	1.07 (.58 – 1.96)	.835	-	-
51-65	-	-	-	-	.92 (.49 – 1.75)	.795	-	-
Ethnicity								
White	Ref		Ref		Ref		-	-
Black	1.66 (1.27 – 2.16)	<.001	1.86 (1.36 – 2.55)	<.001	1.54 (.95 – 2.50)	.078	-	-
Other	1.28 (.89 – 1.83)	.182	1.33 (.86 – 2.04)	.194	1.22 (.63 – 2.36)	.549	-	-
Diagnosis								
F3	Ref		Ref		Ref		Ref	
F2	4.67 (3.39 – 6.43)	<.001	3.84 (2.65 – 5.55)	<.001	8.19 (4.14-16.17)	<.001	4.39 (1.48-13.04)	.008
F2/F3	3.68 (2.55 – 5.31)	<.001	2.63 (1.70 – 4.10)	<.001	9.24 (4.45-19.01)	<.001	5.01 (1.46-17.21)	.010
Hypnotic use	1.59 (1.22 – 2.06)	.001	1.76 (1.29 – 2.40)	<.001	1.26 (.79 – 2.01)	.334	.97 (.38 – 2.49)	.954
Non-serotonin antidepressants	.86 (.57 – 1.05)	.455	.98 (.62 – 1.53)	.920	.97 (.48 – 1.98)	.940	-	-
HoNOS total	1.03 (1.01 – 1.04)	.005	1.03 (1.01 – 1.50)	.002	.99 (.96 – 1.03)	.972	.94 (.86 – 1.02)	.130
HoNOS problem with drug and alcohol	-	-	1.03 (.71 – 1.50)	.861	-	-	-	-

- variable not entered in regression model

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Recorded atypical hallucinations in psychotic and affective disorders and associations with non-benzodiazepine hypnotic use: the South London and Maudsley Case Register

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Recorded atypical hallucinations in psychotic and affective disorders and associations with non-benzodiazepine hypnotic use: the South London and Maudsley Case Register

Running Title: Recorded atypical hallucinations

Karen I Birnie*[a], Robert Stewart[b,c] and Anna Kolliakou[b]

[a]Department of Health Psychology, King's College London, London, UK

[b]Department of Psychological Medicine, King's College London, London, UK

[c]South London and Maudsley NHS Foundation Trust, London, UK

Correspondence should be addressed to:

Karen I Birnie, King's College London, Guy's Campus, London, SE1 9RT

karen.birnie@kcl.ac.uk

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ABSTRACT

Objectives

Hallucinations are present in many conditions, notably psychosis. Although under-researched, atypical hallucinations, such as tactile, olfactory and gustatory (TOGHs), may arise secondary to hypnotic drug use, particularly non-benzodiazepine hypnotics ('Z drugs'). This retrospective case-control study investigated the frequency of TOGHs and their associations with prior Z drug use in a large mental healthcare database.

Methods

TOGHs were ascertained in 2014 using a bespoke natural language processing algorithm and were analysed against covariates (including use of Z drugs, demographic factors, diagnosis, disorder severity and other psychotropic medications) ascertained prior to 2014.

Results

In 43,339 patients with ICD-10 schizophreniform or affective disorder diagnoses, 324 (0.75%) had any TOGH recorded (0.54% tactile, 0.24% olfactory, 0.06% gustatory hallucinations). TOGHs were associated with male gender, Black ethnicity, schizophreniform diagnosis and higher disorder severity on Health of the National Outcome Scales. In fully adjusted models, tactile and olfactory hallucinations remained independently associated with prior mention of Z drugs (odds ratios 1.86 and 1.60 respectively).

Conclusions

We successfully developed a natural language processing algorithm to identify instances of TOGHs in the clinical record. TOGHs overall, tactile and olfactory hallucinations were shown to be associated with prior mention of Z drugs. This may have implications for the diagnosis and treatment of patients with comorbid sleep and psychiatric conditions.

Strengths and limitations of this study

* This was a large study involving 43 339 patients

* The prospective study design reduced recall bias.

* The NLP tool, developed to recognise references to TOGHs from a naturalistic data source, has great potential for applicability in other data sources.

* This study utilised routine healthcare records, thus requiring clinicians to recognise and record TOGHs accurately.

* We were not able to conclude that medication use always antedated TOGHs.

Keywords: psychosis, olfactory, tactile, gustatory, Z drugs, electronic health records

1

Introduction

Although hallucinations are not necessarily abnormal experiences, they are commonly associated with psychotic and organic disorders (1,2). They can occur in any sensory modality although the most commonly reported hallucinations in patients with schizophrenia are auditory and visual with estimated prevalences of around 70%, and ranging from 15-60% respectively (3,4). Similar prevalences have been described in bipolar disorder (approximately 70% and 25%, respectively) (5). Tactile, olfactory and gustatory hallucinations (TOGHs) are recognised to occur in psychotic disorders, but have received substantially less investigation. In samples with either schizophrenia or severe mental illness more generally, tactile hallucination prevalences have ranged from 15-27% (3,6-8), and are recognised to be associated with substance abuse and withdrawal regardless of diagnosis (9). The prevalence of olfactory hallucinations has ranged from 15-27% (6,7), although this is likely to be an underestimate because of the tendency for traditional questionnaires to examine hallucinations generally rather than by modality (10). The prevalence of gustatory hallucinations has ranged from 4-14% (6,7). Hypnotic use in the general population has been found to be associated with higher reported tactile and gustatory hallucinations (11) and hallucinations in all/most modalities have been described as increased in people receiving non-benzodiazepine hypnotics, specifically 'Z drugs' (zolpidem, zopiclone or zaleplon) (12,13), possibly potentiated by other psychotropic agents (14). However, these observations have been largely been derived case studies and small samples.

The aim of this study was to ascertain the frequency of TOGHs in a large sample of people receiving mental health services with schizophreniform or affective disorder diagnoses, and to test a hypothesised association between TOGHs and Z drug use.

2

Methods

2.1

Setting

The South London and Maudsley NHS Foundation Trust (SLaM) is one of Europe's largest mental healthcare providers, serving a geographic catchment of four south London boroughs (Croydon, Lambeth, Lewisham, Southwark) with approximately 1.2 million residents. Since 2006, an electronic health records system has been used throughout SLaM, and the Clinical Record Interactive Search (CRIS) system, developed in 2008, allows researchers to retrieve de-identified information from these records for around 280,000 cases to date (15,16). CRIS has been approved as a database for secondary analysis by the Oxfordshire Research Ethics Committee C (Ethics ID: 08/H0606/71+5) and a service-user led committee provides oversight for projects using these data (17).

2.2

Study population

The baseline sample derived from CRIS comprised a cohort of all patients, aged 18-65 on 1st January 2014, who had received a diagnosis of a schizophrenia-related disorder (extracted using ICD-10 code:F2x) and/or a mood/affective disorder (ICD-10 code:F3x) prior to that date. Case records from the cohort were then searched for instances of TOGHs between 1st January 2014 and 31st December 2014.

2.3

Patient involvement

We did not directly incorporate PPI into this particular study but the SLAM BRC Case Register used in the analysis was developed with extensive PPI and is overseen by a committee that includes service-user representatives.

2.4

Outcome – tactile, olfactory and gustatory hallucinations

A pre-existing natural language processing algorithm designed to detect mentions of hallucinations in text fields (18) was further adapted to search and retrieve references to TOGHs. Three keywords were added to search for references to hallucinations mentioned in the free-text fields of CRIS (including written assessments, progress notes and correspondence). These were 'olfactory', 'tactile' or 'gustat*' (and 'hallucinations'). The application query retrieved 20,924 instances across CRIS; 1,000 randomly selected instances were annotated for reference to TOGHs, of which 300 instances were double-annotated resulting in a kappa statistic of 0.83 (95% CI 0.71-0.89). The information extraction algorithm was developed using 500 annotated records (training set), seeking to identify linguistic patterns indicating a true reference to any of the three hallucination types (i.e. rather than negation statements, irrelevant mentions, or mentions of the symptom occurring in someone other than the patient). Having developed the algorithm using General Architecture for Text Engineering (GATE) machine learning software (19), it was tested on another 500 annotated records (gold standard set), and achieved a precision score (positive predictive value) of 0.91 and a recall (sensitivity) score of 1.00. Deploying the algorithm over the complete dataset of 20,924 instances, 17,066 were identified as true positive references to TOGHs. Binary outcome variables were thereby created representing the occurrence of hallucinations in each or any modality (olfactory, tactile, gustatory, any of the three).

2.5

Covariates

Covariates were extracted to indicate status at the index date (1st January 2014). Demographic factors comprised age, gender, and recorded ethnicity – the latter categorised into three groups: black background (including Caribbean, African and any other black background), white background (British, Irish, and any other white background), and other (including mixed or multiple ethnic backgrounds).

Regarding clinical factors, the sample was categorised into those who had previously received a diagnosis of schizophreniform disorder, a mood disorder diagnosis, or both. In addition, we made use of the Health of the Nations Outcome Scales (HoNOS) assessment, routinely administered in UK mental health services (20), including the total score (an indicator of overall functioning), and the score relating to alcohol and substance use problems (categorising the problem as present on the basis of a score of 2 or more on the 0-4 scale), extracting scores closest to the index date.

Hypnotic agent use before the index date was determined from structured medication fields in the record, supplemented by a natural language processing algorithm which ascertains recorded pharmacotherapy from open-text fields. Ascertained agents were classified into Z drugs (zopiclone, zaleplon and zolpidem) and all other hypnotics licensed for use in insomnia or where sedation is needed (diazepam, flurazepam, loprazolam, lorazepam, lormetazepam, nitrazepam, temazepam, trimipramine, doxepin, chloral hydrate, clomethiazole, melatonin, promethazine hydrochloride). Antidepressant use during the same period was identically extracted, and classified into two groups; those acting primarily through the serotonergic system (citalopram, escitalopram, paroxetine, fluoxetine, fluvoxamine, sertraline, duloxetine, venlafaxine, trazodone, amitriptyline, clomipramine, dosulepin, doxepin, imipramine, trimipramine, mianserin, mirtazapine, isocarboxazid, phenelzine, tranylcypromine, moclobemide, and agomelatin) and those with other primary targets (non-serotonergic - reboxetine, flupentixol and nortriptyline) (21).

2.6

Analyses

Percentages were used to describe all categorical variables. Mean and standard deviation (SD) were used to describe age and HoNOS total scores were described by median and interquartile range (IQR). Chi-square (χ^2) test statistics were calculated to identify any differences in socio-demographic and clinical characteristics between patients with or without TOGHs overall and for each modality.

Binomial logistic regression models were used to test the association between overall/individual TOGHs and mention of Z drugs. Socio-demographic and clinical characteristics associated with individual outcomes at $p<0.05$ were entered in the final regression model. Because of missing data pertaining to HoNOS scores, a post-hoc analysis was conducted, restricting the sample to those with scores present before investigating the impact of adjusting for HoNOS-derived covariates. All analyses were conducted using Stata, V.13 (22).

3

Results

The analysed sample consisted of 43,339 patients. The mean age was 41.4 years (SD 12.2) and 53.5% of the sample was female. One quarter of the sample was of a Black background and 57.9% were of a White background. Regarding previous diagnosis, over two thirds had received a mood disorder diagnosis only (67.0%) and 24.4% a schizophreniform diagnosis only; 22.6% of the total sample had mention of Z drugs in their record and 25.7% had mention of other hypnotic drugs. The median of the HoNOS total scores was 8 (IQR 0-40).

The natural language processing algorithm identified 324 patients in the sample with at least one modality of TOGH recorded in 2014 case notes: 0.75% of the sample. Within this group, tactile hallucinations were most common (71.6%), followed by olfactory (31.8%) and gustatory (7.4%) modalities. The proportion of patients who reported any TOGH did not differ significantly from the remainder of the sample by age ($\chi^2(3) = 5.22$, $p = .157$) or HoNOS problems with drugs and alcohol ($\chi^2(1) = 2.78$, $p = .095$) but did with respect to gender ($\chi^2(1) = 5.66$, $p = .017$) and ethnicity ($\chi^2(2) = 74.30$, $p < .001$), with over-representation of men and patients from black ethnic groups (Table 1). In regard to clinical features, significant differences were observed between patients with any TOGH and the rest of the sample with respect to diagnosis ($\chi^2(2) = 272.97$, $p < .001$), and were more likely to have recorded Z drug use ($\chi^2(1) = 118.78$, $p < .001$), other hypnotic use ($\chi^2(1) = 149.54$, $p < .001$) and non-serotonergic antidepressant use ($\chi^2(1) = 23.81$, $p < .001$). Prevalence of any TOGH by diagnostic group was 1.5% in F2, 0.24% in F3 and 1.7% in those with both diagnoses recorded.

In unadjusted regression analysis (Table 2), recorded Z-drug use was significantly associated with any TOGH (OR 3.17, 95% CI 2.54 – 3.95), tactile (3.22, 2.49 – 4.17), olfactory (2.77, 1.88 – 4.09) and gustatory hallucinations (3.43, 1.54 – 7.63) specifically. After adjusting for confounders all 4 models remained significant, albeit attenuated, with recorded Z drugs associated with any TOGH mention

(2.02, 1.57 – 2.77), tactile (2.09, 1.57 – 2.78), olfactory (1.69, 1.10 – 2.59) and gustatory hallucinations (2.58, 1.06 – 6.28).

Restricting the sub-sample to patients who had a HoNOS total score available in the clinical record (n=26,201), after adjusting for the confounders indicated in Table 2, associations with recorded Z-drug use remained significant for any TOGH (1.82, 1.41 – 2.34), tactile (1.81, 1.41 – 2.34) and olfactory hallucinations (1.60, 1.01 – 2.54) and but not for gustatory hallucinations (2.19, 0.87 – 5.55). Further adjustment for HoNOS total scores and HoNOS problems with drugs and alcohol in this regression model did not alter findings substantially for any TOGH (1.80, 1.40 – 2.32), tactile (1.86, 1.38 – 2.51), olfactory (1.60, 1.01 – 2.54), or gustatory hallucinations (2.19, 0.86 – 5.55) (Table 3).

4

Discussion

In a large database derived from mental healthcare electronic records we investigated the 1-year period frequency of recorded tactile, olfactory and gustatory hallucinations in patients with schizophreniform or affective disorders, having developed an algorithm to detect recorded mentions of these symptoms with a reasonable level of accuracy. Because of the relative rarity of these symptoms, large administrative databases present an opportunity for better definition and aetiological investigation. However, symptom profiles are not routinely recorded in structured fields within mental health records, so the development and application of natural language processing techniques are similarly essential for improving understanding – rendering information available at scale which would have previously been unrealised, and generating databases which are both large and detailed (18,23).

Frequencies within the sample were 0.54%, 0.24% and 0.06% for tactile, olfactory and gustatory hallucinations respectively. These are clearly substantially lower than prevalence reports in samples with severe mental illness of 15-27% for tactile hallucinations (3,6,7), 15-19% for olfactory hallucinations in schizophrenia (6,8), and 4-9% for gustatory hallucinations (6,8). However, research to date has ascertained these symptoms from lifetime recollections derived from fully-structured diagnostic questionnaires, utilising specific questions relating to these hallucinations (3,6,7), whereas our estimates were 1-year rates of reference to TOGHS, derived from information contained in routine healthcare records. It should be noted that clinical records likely underestimate the prevalence of TOGHs, given that they may not be recorded systematically in clinical practice. The relatively broadly defined sample should also be borne in mind, as the frequencies of TOGHs were substantially higher in patients who had received a schizophreniform diagnosis alone or in combination (1.5% and 1.7% prevalences respectively), compared to that in patients who had received an affective disorder diagnosis alone (0.24%), consistent with other reports (6).

We also specifically investigated associations with Z drug (zopiclone, zolpidem, zaleplon) hypnotic use, given previous cited associations with hallucinations. Neuropsychiatric adverse effects of Z drugs, including hallucinations and psychosis, have been described for over 15 years (24-27), including atypical and/or multimodal hallucinations (28). Most often this has been related to zolpidem, although this may reflect higher usage rates (29). While mechanisms underlying other adverse effects, such as parasomnias have been investigated (30), the explanation for associations with hallucinations remains unclear, although it does not appear to be related directly to dose or plasma concentrations, and at least some excess adverse event reporting has been suggested in association with media exposure (31). Interactions have also been reported with other psychotropic agents (32). In line with our hypothesis, patients with use of Z drugs mentioned in their previous clinical record were more likely to experience TOGHs overall and tactile and olfactory hallucinations specifically. Associations with gustatory hallucinations appeared similar in strength but were not statistically significant in all models because of the relative rarity of hallucinations in this modality being recorded. Unlike previous studies, which have tended to involve patient interviews subsequent to drug use, our analysis investigated associations between mentions of drug categories at any time preceding 2014 and recorded TOGHs during 2014. A large multi-national general population survey found that overall hypnotic use was associated with tactile and gustatory hallucinations; however, we only found independent evidence of other hypnotics (non-Z-drugs) being associated with tactile hallucinations (Table 2).

Secondary findings suggest that other factors, such as diagnosis and ethnicity, may play a role in susceptibility to TOGHs. These associations have not been identified in previous research, although this may reflect differences in sample size, since higher non-Caucasian ethnicity was found in one previous study (6), and lower levels of TOGHs were found in patients from India compared to the USA in another study (7), which may suggest some international/ethnic variation in prevalence. In final models (Table 3), higher HoNOS total score was associated with TOGHs generally, which has

some concordance with findings from other studies of associations with more severe psychotic syndromes (particularly in relation to delusional symptoms) (6), although this was only present for tactile hallucinations.

Strengths of the study include the large sample size, the prospective study design, the range of covariates assessed and the naturalistic source of data. The development of the natural language processing algorithm was successful, resulting in a tool that can be used to automatically extract data on TOGHs from the electronic health record, in addition to the growing number of other information extraction algorithms being developed (16,18). Given the relative simplicity of the underlying construct (TOGHs) being ascertained from text fields, we would anticipate good cross-applicability to other data sources. The sample itself ought also to be reasonably generalisable, coming from a mixed inner and outer urban catchment with high social diversity (16).

The nature of the source data needs to be borne in mind when drawing conclusions; in particular, the fact that hallucinations were ascertained from routine mental healthcare records rather than from a research instrument. Presence of TOGHs in the CRIS database therefore depends on a clinician asking about or noticing the symptom, on their recording it, and on their recording it in such a way that it was extracted by the natural language processing algorithm (i.e. recorded as a phenomenological term: e.g. 'tactile hallucination' rather than 'feels that insects are crawling over his skin'). As described, the algorithm itself was efficient at identifying these terms, with high precision and recall statistics; however, symptoms will have been missed if they went unnoticed or unrecorded in clinical care. The alternative approach in this field has been to evaluate them in a recruited sample with a formal questionnaire, and to our knowledge, this is how all previous prevalence estimates have been derived, most often using the Structured Clinical Interview for DSM (SCID) (3,6). However, this approach generally depends on responses to one or two questions in a long interview schedule administered for other purposes and deriving lifetime rather than current occurrences. There is therefore considerable potential for recall bias, as well as potential selection

bias arising from the sample recruited which are less likely to influence data from routine healthcare. Ultimately it has not yet been established whether data extracted from clinical records are an underestimate of true prevalence, or whether recalled self-report data elicited from diagnostic instruments are an overestimate, and this requires further evaluation.

Considering the hypothesis under investigation, while the prospective study design reduces effects of recall bias, whereby participants may have had difficulty remembering details about their hallucinations or medication use, establishing causality is difficult. Although mentions of medication were ascertained prior the observation period, we were not able to conclude that medication use always antedated hallucinations. In addition, medication, while mentioned, was not necessarily used, and dosage was not accounted for; neither were different Z drugs distinguished. In addition, patients prescribed certain drugs may have more clinical contact and care around prescribing, perhaps leading to decreased vulnerability.

This study could be improved in the future by fine-tuning of the application – for example, including other keywords that may indicate the presence of TOGHs – terms such as disturbance or unusual experience/sensation, may identify more instances of TOGHs. The development of an application that explored medication use, not just mentions, could be used to determine the nature of any relationship with hallucinations. Further research could also explore differences between genders, given the sex-related pharmacokinetics of zolpidem (33). This would be valuable information for patients who are known to be at risk of unusual sensory phenomena, where clinicians could make more informed decisions about prescribing. Our findings are preliminary but if replicated could have implications for patients with comorbid disordered sleep or mood symptoms.

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Contributorship

This research was completed as part of an intercalated BSc in Psychology. KB, AK and RS all contributed to the study design and manuscript preparation. KB took primary responsibility for data collection and analysis. All authors contributed to and have approved the final manuscript.

Competing interests

None.

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Data sharing

There are no additional data available.

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Table 1 Demographic and clinical characteristics of total and individual samples

	Total sample (n=43339)	Groups with tactile, olfactory or gustatory hallucinations (TOGH)			
		Any TOGH (n=324)	Tactile (n=232)	Olfactory (n=103)	Gustatory (n=24)
Age %					
18-31	24.8	29.0	28.4	35.9	20.8
32-41	25.4	27.2	29.7	19.4	29.2
42-50	24.7	22.5	21.1	26.2	16.7
51-65	25.1	21.3	20.7	18.4	33.3
Female gender %	53.5	46.9	41.8	54.4	62.5
Ethnicity %					
Black	25.0	45.1	46.1	46.6	37.5
White	57.9	38.6	37.1	37.9	41.7
Other	17.1	16.0	16.4	15.5	20.8
Diagnosis %					
F2	24.3	54.9	56.0	55.3	50.0
F3	67.0	24.1	26.3	17.5	20.8
Both	8.6	21.0	17.7	27.2	29.2
Medication use %					
Z-drugs	22.6	47.8	48.3	44.7	50.0
Other hypnotics	25.7	55.2	56.0	54.4	45.8
Serotonin-related antidepressants	54.6	54.3	55.2	50.5	54.2
Non-serotonin antidepressants	4.2	9.6	10.3	10.7	0
HoNOS					
Total (Median (IQR)	8.0 (0-40)[1]	10 (0-34)[2]	10 (0-34)[3]	9 (0-29)[4]	6 (0-24)[5]
Problem with alcohol and drug use %	15.2[6]	18.6[7]	20.6[8]	15.1[9]	13.6[10]

[1](n=26201) [2](n=284) [3](n=204) [4](n=86) [5] (n=21) [6] (n=27047) [7] (n=295) [8](n=209) [9] (n=93) [10](n=22)

Table 2 Adjusted logistic regression model assessing the association between Z-drug use and tactile, olfactory or gustatory hallucinations

	All modalities		Tactile		Olfactory		Gustatory	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Z drugs	2.02 (1.59 –2.57)	<.001	2.09 (1.57 – 2.77)	<.001	1.69 (1.10 – 2.59)	.016	2.58 (1.06 – 6.28)	.036
Gender	.90 (.71 – 1.12)	.347	1.12 (.86 – 1.47)	.402	-	-	-	-
Age								
32-41	-	-	-	-	Ref		-	-
18-31	-	-	-	-	2.11 (1.22 – 3.64)	.008	-	-
42-51	-	-	-	-	1.31 (.73 – 2.35)	.355	-	-
51-65	-	-	-	-	.99 (.52 – 1.85)	.963	-	-
Ethnicity								
White	Ref		Ref		Ref		-	-
Black	1.66 (1.30 – 2.13)	<.001	1.82 (1.36 – 2.45)	<.001	1.57 (1.02 – 2.43)	.042	-	-
Other	1.34 (.97 – 1.86)	.080	1.45 (.98 – 2.12)	.060	1.23 (.68 – 2.21)	.492	-	-
Diagnosis								
F3	Ref		Ref		Ref		Ref	
F2	4.82 (3.61 – 6.45)	<.001	4.04 (2.90 – 5.64)	<.001	6.63 (3.81-11.55)	<.001	6.30 (2.19-18.14)	.001
F2/F3	3.86 (2.73 – 5.47)	<.001	2.72 (1.79 – 4.16)	<.001	7.44 (3.97-13.95)	<.001	8.21 (2.47-27.28)	.001
Hypnotic use	1.76 (1.37 – 2.25)	<.001	1.86 (1.39 – 2.49)	<.001	1.54 (.99 – 2.37)	.053	1.02 (.42 – 2.51)	.958
Non-serotonin antidepressants	.99 (.68 – 1.45)	.970	1.09 (.70 – 1.68)	.704	1.21 (.63 – 2.31)	.565	-	-

- variable not entered in regression model

Table 3 Adjusted logistic regression model assessing the association between Z-drug use and tactile, olfactory, or gustatory hallucinations in the subsample of patients with Health of the National Outcome Scales (HoNOS) data present

	All modalities		Tactile		Olfactory		Gustatory	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Z drugs	1.80 (1.40 – 2.32)	<.001	1.86 (1.38 – 2.51)	<.001	1.60 (1.01 – 2.54)	.043	2.19 (.86 – 5.55)	.099
Gender	.90 (.70 – 1.14)	.382	1.16 (.86 – 1.55)	.324	-	-	-	-
Age								
32-41	-	-	-	-	Ref		-	-
18-31	-	-	-	-	1.52 (.84 – 2.73)	.163	-	-
42-51	-	-	-	-	1.07 (.58 – 1.96)	.835	-	-
51-65	-	-	-	-	.92 (.49 – 1.75)	.795	-	-
Ethnicity								
White	Ref		Ref		Ref		-	-
Black	1.66 (1.27 – 2.16)	<.001	1.86 (1.36 – 2.55)	<.001	1.54 (.95 – 2.50)	.078	-	-
Other	1.28 (.89 – 1.83)	.182	1.33 (.86 – 2.04)	.194	1.22 (.63 – 2.36)	.549	-	-
Diagnosis								
F3	Ref		Ref		Ref		Ref	
F2	4.67 (3.39 – 6.43)	<.001	3.84 (2.65 – 5.55)	<.001	8.19 (4.14-16.17)	<.001	4.39 (1.48-13.04)	.008
F2/F3	3.68 (2.55 – 5.31)	<.001	2.63 (1.70 – 4.10)	<.001	9.24 (4.45-19.01)	<.001	5.01 (1.46-17.21)	.010
Hypnotic use	1.59 (1.22 – 2.06)	.001	1.76 (1.29 – 2.40)	<.001	1.26 (.79 – 2.01)	.334	.97 (.38 – 2.49)	.954
Non-serotonin antidepressants	.86 (.57 – 1.05)	.455	.98 (.62 – 1.53)	.920	.97 (.48 – 1.98)	.940	-	-
HoNOS total	1.03 (1.01 – 1.04)	.005	1.03 (1.01 – 1.50)	.002	.99 (.96 – 1.03)	.972	.94 (.86 – 1.02)	.130
HoNOS problem with drug and alcohol	-	-	1.03 (.71 – 1.50)	.861	-	-	-	-

- variable not entered in regression model

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5, 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	5
		(*b*) For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6, 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6, 7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how matching of cases and controls was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,10
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers in each exposure category, or summary measures of	9

		exposure	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11, 13, 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11 - 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.