Schizophrenia in High Risk Opioid Users: A Short Communication on an Autopsy Study

Keywords
Schizophrenia; opioid; overdose

1. Introduction

The relationship between schizophrenia and the problematic use of psychotropic substances, including opioid addiction and dependence has been well documented (Batel, 2000). To investigate the period prevalence of schizophrenia amongst opioid users at high risk of overdose, we conducted an autopsy study using linked and anonymised routine data.

2. Methods

We identified decedents of opioid overdose who died in Wales, a country in the UK with a population of approximately 3 million, between 1/1/2012 and 31/12/2015 by searching Office for National Statistics (ONS) mortality records. ONS mortality data is coded using the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) medical coding system (World Health Organisation, 2018). We used codes diagnostic codes F11 – F19 (mental and behavioural disorders due to psychoactive substance use), X40-69 (unintentional and intentional poisoning by and exposure to narcotics and psychodysleptics, X85 (assault by drugs, medicaments and biological substances) and Y10-19 (poisoning by and exposure to narcotics and psychodysleptics) and object codes T40.0-T40.4 to identify opioid overdose deaths.

ONS mortality records were linked with NHS Wales Informatics Service (NWIS) hospital and General Practice (GP) datasets. The matching algorithm used to link data brought in to the databank was devised at NWIS, and applies deterministic and probabilistic routines in a logical sequence. This approach to linkage of routine NWIS data in the Secure Anonymised Information Linkage (SAIL) databank allows for consistently accurate matching, demonstrating high specificity (>99%) and sensitivity (>95%) (Lyons et al., 2009).

Demographic, identifiable data were then separated from clinical data and records were each assigned a unique and encrypted Anonymised Linkage Field (ALF) number. Non-identifiable demographic data were then recombined with clinical data by ALF number; meaningless outside of the gateway allowing for privacy protection. Once the linked data were anonymised, they were analysed in the SAIL gateway (Jones et al., 2014; Lyons et al., 2009).

We searched for schizophrenia related codes in GP and hospital records of decedents of opioid overdose within our sample dataset. We used a coding framework previously applied by John and colleagues (John et al., 2018). Hospital data were coded using the ICD-10 system (diagnostic codes F20-F29), whilst the Read Clinical Terms Version 2 (CTV2) coding framework (NHS Digital, 2018.) is

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used to record GP episodes including events related to patient care, as well as administrative tasks, in Welsh NHS primary care services. We limited our search to capture data related to diagnostic codes which were attached to decedent's hospital and GP records during a period of 36 months prior to death. To help contextualise our findings, we also searched for diagnoses of depressive disorders using a coding framework devised by John and colleagues (John et al., 2016). We chose a 36 month observation period prior to overdose death as during this time decedents could be considered as being at high risk of opioid overdose.

3. Results

We found that a limited library of diagnostic codes related to schizophrenia had been attached to decedent's hospital and GP records in the 3 years prior to death. A total of seven ICD-10 'F' codes describing schizophrenia, schizotypal and delusional disorders were found, and six Read CTV2 codes describing schizophrenia and schizophrenia spectrum disorder related diagnoses, including schizoaffective disorder; paranoid psychosis; and delusional disorder.

We found that one or more of the schizophrenia related ICD-10 and/or Read CTV2 diagnostic codes had been attached to the hospital and/or GP records of 19 distinct decedents representing over 6% of our sample of decedents (n=312) in the 36 months prior to death. Stratified by year, we found that deaths increased over the course of the observation period. In 2012 there were 2 deaths, 5 in 2013 and 2014 respectively, and 7 in 2015. The decedents did not differ significantly from the wider sample in terms of gender ratio (73.68% male vs. 73.08% in the wider sample) and mean age at death (39.94 [13.59] vs. 40.72 [11.92]).

Most decedents had received a primary diagnosis at hospital admission or had both GP and hospital contact (n=8, 5.12%), whilst a minority were recorded as having GP contact only (n=3, 0.96%). These results are summarised in Table 1.

Table 1- GP and Hospital data goes here

Over the 36 months, 73.68% of the decedents who received a schizophrenia related diagnosis were diagnosed as having schizophrenia, paranoid or unspecified (n=14,). Half (n=7) of these overlapped with the next largest group, those who received a diagnosis of schizotypal disorder 57.89% (n=11). The remaining diagnosis received were 15.79% (n=3) schizoaffective disorder; 15.79% (n=3) unspecified paranoid state; 10.53% (n=2) unspecified psychotic disorder; and 5.26% (n=1) folie à deux.

In terms of intent, we found that 89.47% (n=17) of decedents were found to have died of accidental overdose, whilst the remaining deaths (n=2, 10.53%) were of undetermined intent.

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To help contextualise our findings, we searched for diagnoses of depressive disorder attached to GP and hospital records amongst our sample. We found that 8.97% (n=28) of our sample received a diagnosis of depressive disorder in the 3 years prior to their death.

4. Discussion

In 2008 McGrath and colleagues (McGrath et al., 2008) carried out a comprehensive systematic review of observational studies of the epidemiology of schizophrenia. They identified 34 studies concerned with the period prevalence of schizophrenia in the general population. By abstracting data from these studies, the authors found an estimated mean annual period prevalence of schizophrenia in the general population of 5.7 per 1000 people. Compared to McGrath et al's findings, our data suggests that the prevalence of schizophrenia spectrum disorder in high risk opioid users might be over 8 times the prevalence in the general population. However, in utilising John et al's coding framework, we included cases of schizotypal disorder, schizoaffective disorder and unspecified paranoid and psychotic states. As such it could be argued that we are not making a direct comparison with schizophrenia as defined in McGrath et al's study.

We found significant overlap between those who received a diagnosis of schizophrenia and those who received a diagnosis of schizotypal disorder. These data support the findings of Hjorthøj and colleagues (Hjorthøj et al., 2018), who found evidence for an association with opioid drug use and conversion of schizotypal disorder to schizophrenia.

The prevalence of depression amongst the total sample did not differ significantly from the European average prevalence of depressive disorder as estimated by the authors of the ODIN study who found an average overall prevalence of 8.56% (Ayuso-Mateos et al., 2001).

Although these data are inconclusive, they do raise questions related to high risk opioid use and schizophrenia. As most deaths were found to be accidental, the first is to what extent do people with schizophrenia spectrum disorders self-medicate with opioid drugs and place themselves at risk of overdose. There are certainly qualitative data to support the notion that illicit drugs including heroin are used by people with schizophrenia to self-medicate (Asher and Gask, 2010). Our data contradicts some (of the relatively scarce) quantitative data in this area suggesting that high-risk opioid use is either not associated, or is negatively associated with psychotic illness (Farrell et al., 2002; Sørensen et al., 2005). Another is whether enough being done to address high risk opioid use in patients with schizophrenia. Certainly, the deleterious effect of comorbid substance misuse disorder on health outcomes related to schizophrenia have been recognised for some time (Winklbaur et al., 2006), and yet specialist treatment pathways for opioid misuse in schizophrenic patients appear to have received little research attention or investment. Our sample included only high-risk opioid users who unfortunately died due to overdose, and so it is likely that high risk opioid use in this group, who are already known to suffer high levels of premature death, is more common than our sample suggests.

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The authors welcome further research to address these questions and further investigate the relationship between schizophrenia and high-risk opioid use.

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Table 1- GP and Hospital data

GP and hospital record codes	n=312	
	n	**%**
GP Episode only	3	0.96
Hospital Admission only	8	2.56
Both GP and Hospital	8	2.56
Total	19	6.09

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Table 1: Descriptive data and between group differences

Variable		Participant group			
		Controls *n* = 65	SAD *n* = 18	*t*	*d*
Gender (% female)		84.62%	67.86%	-	-
Age Mean (SD)		32.74 (11.32)	30.07 (10.47)	-1.07 *p* = 0.29	*d* = 0.24
SRAS Median (SD)		91 (32.96)	124 (23.26)	4.71 *p* = 0.001	*d = 1.13*
CDS- II Median (SD)		46 (11.57)	54.5 (9.54)	2.78 *p* = 0.007	*d = 0.63*
CDS-II Sub-scales	LOC Median (SD)	18 (5.46)	22 (5.23)	2.75 *p* = 0.007	*d = 0.62*
	Personal Control Median (SD)	16 (5.72)	18 (6.86)	0.34 *p* = 0.73	*d = 0.07*
	Stability Median (SD)	11 (5.4)	16 (3.7)	2.9 *p* = 0.005	*d = 0.68*

(SD)=Standard Deviation; SPIN=Social Phobia Inventory; SRAS=Social Responsibility Attitudes Scale; CDS-II=Causal Dimension Scale; LOC=Locus of Control

Table 2: Regression coefficients for demographic and psychometric variables

Predictor Variables	All Participants *n* = 83			
	β	*SE*	*t*	*p*
Group*	1.45	0.46	3.14	0.002
CDS-II LOC	0.03	0.05	0.62	0.54
CDS-II Stability	0.25	0.05	4.55	0.001
CDS-II Total	-0.006	0.03	-0.21	0.84

*Control group used as reference category. CDS-II = Causal Dimension Scale 2nd Revision; LOC = Locus of Control; PC = Personal Control.

Table 3: Descriptive statistics for cases (*n* = 18)

	Age*	SPIN	SRAS	APQ	SFA	SAFE	PEPQ-R
M	30.07	52	136.5	121.5	35	104.5	75.5
SD	10.47	10.29	16.3	15.98	6.72	17.44	23.22
Range	17-53	35-67	110-166	82-140	23-44	66-131	9-131

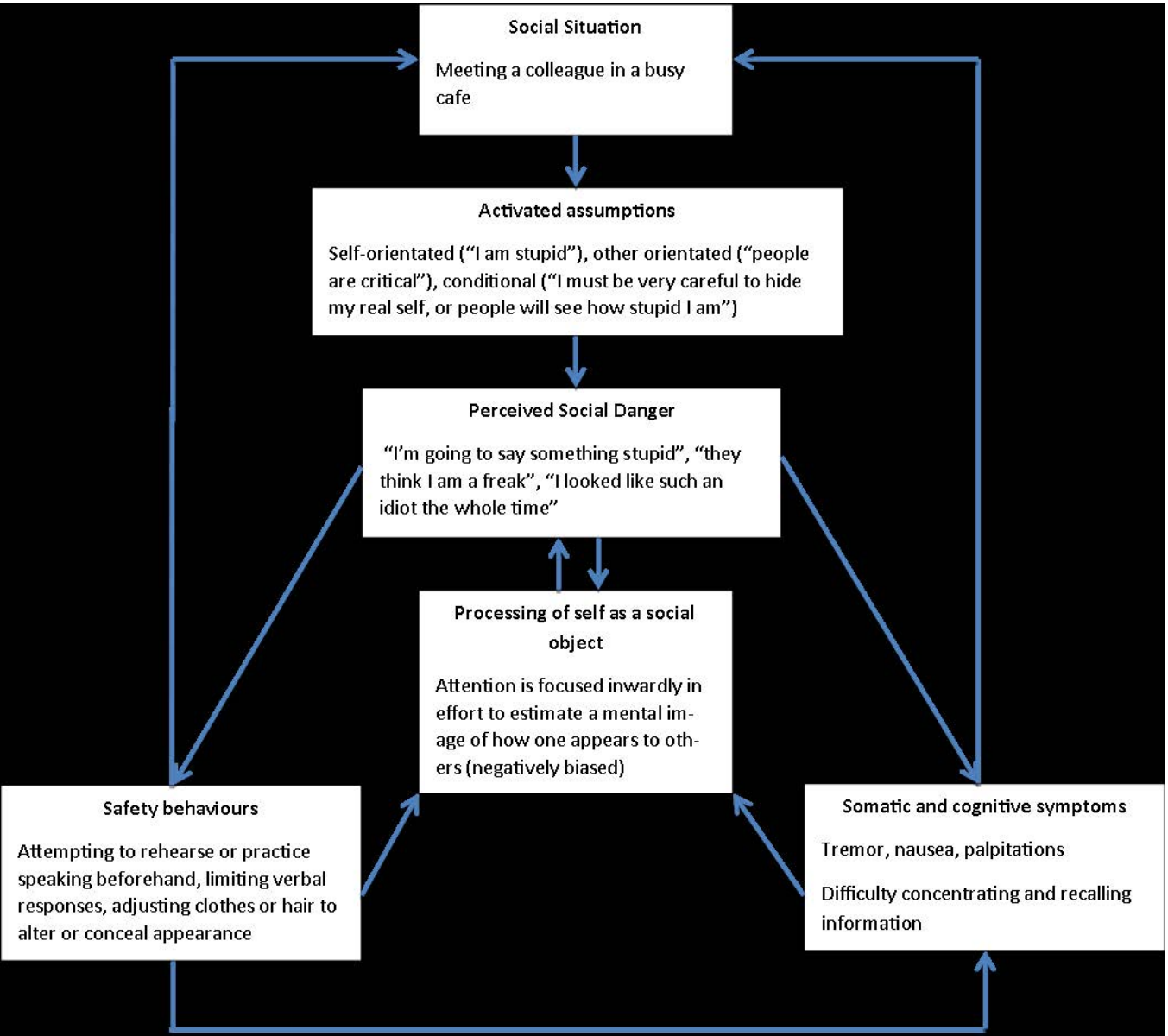
M=Median Average (Mean Average for Age*); SD=Standard Deviation. SPIN = Social Phobia Inventory; SRAS = Social Responsibility Attitudes Scale, APQ = Anticipatory Processing Questionnaire; SFA = Self-Focussed Attention scale; SAFE = Subtle Avoidance Frequency Examination; PEPQ-R = Post-Event Processing Questionnaire-Revised.

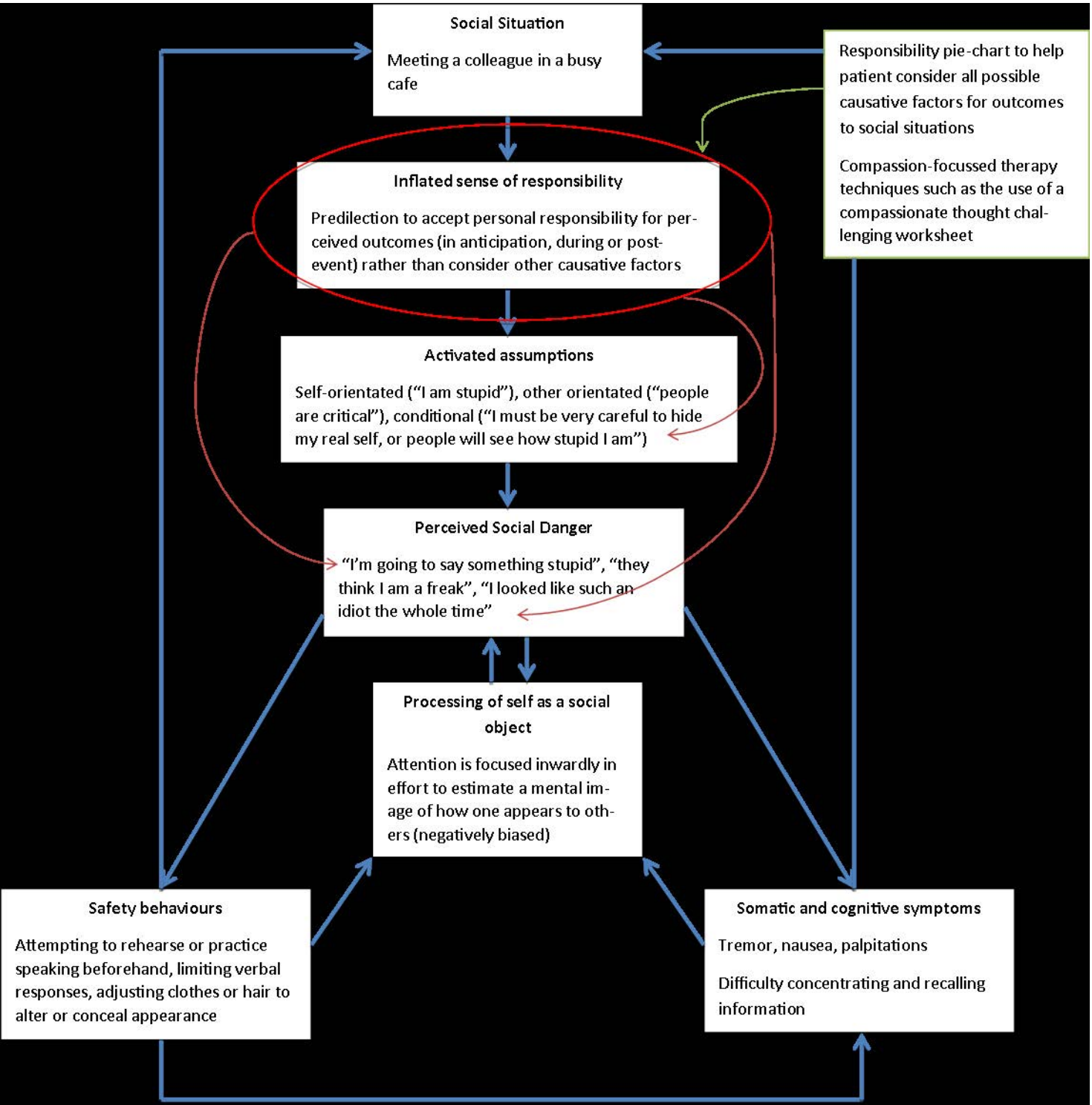
Table 4: Pearsons's product moment correlation

	Age	Gender	Meds	SPIN	SRAS	APQ	SFA	SAFE	PEPQ-R
Age		-0.09	0.10	0.41	0.13	0.21	-0.02	0.09	-0.39
Gender*	-0.09		-0.08	0.25	0.60**	0.18	0.48*	0.24	0.15
Meds**	0.10	-0.08		-0.22	0.34	0.17	-0.06	0.25	0.34
SPIN	0.41	0.25	-0.22		0.47*	0.14	0.14	0.20	-0.23
SRAS	0.13	0.60**	0.34	0.47*		0.32	0.19	0.47*	0.09
APQ	0.21	0.18	0.17	0.14	0.32		0.08	0.24	0.41
SFA	-0.02	0.48*	-0.06	0.14	0.19	0.08		0.29	-0.07
SAFE	0.09	0.24	0.25	0.20	0.47*	0.24	0.29		-0.11
PEPQ-R	-0.39	0.15	0.34	-0.23	0.09	0.41	-0.07	0.11	

*Gender 1= Female;** Meds 1 = currently using prescribed anti-anxiety medication. SPIN = Social Phobia Inventory; SRAS = Social Responsibility Attitudes Scale, APQ = Anticipatory Processing Questionnaire; SFA = Self-Focussed Attention scale; SAFE = Subtle Avoidance Frequency Examination; PEPQ-R = Post-Event Processing Questionnaire-Revised.

*p < .05, **p < .01, ***p < .001


Social Situation
Meeting a colleague in a busy cafe
Activated assumptions
Self-orientated ("I am stupid"), other orientated ("people are critical"), conditional ("I must be very careful to hide my real self, or people will see how stupid I am")
Perceived Social Danger
"I'm going to say something stupid", "they think I am a freak", "I looked like such an idiot the whole time"
Processing of self as a social object
Attention is focused inwardly in effort to estimate a mental image of how one appears to others (negatively biased)
Safety behaviours
Attempting to rehearse or practice speaking beforehand, limiting verbal responses, adjusting clothes or hair to alter or conceal appearance
Somatic and cognitive symptoms
Tremor, nausea, palpitations
Difficulty concentrating and recalling information


Social Situation
Meeting a colleague in a busy cafe
Responsibility pie-chart to help patient consider all possible causative factors for outcomes to social situations
Compassion-focussed therapy techniques such as the use of a compassionate thought challenging worksheet
Inflated sense of responsibility
Predilection to accept personal responsibility for perceived outcomes (in anticipation, during or post-event) rather than consider other causative factors
Activated assumptions
Self-orientated ("I am stupid"), other orientated ("people are critical"), conditional ("I must be very careful to hide my real self, or people will see how stupid I am")
Perceived Social Danger
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