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Catatonia is associated with higher rates of negative affect amongst patients with schizophrenia and schizoaffective disorder

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ABSTRACT

Catatonia is a complex syndrome encompassing motor, behavioral, and affective symptoms seen in a significant proportion of patients with schizophrenia. There is growing evidence to suggest affective dysregulation is a salient feature of both catatonia and schizophrenia. To test the hypothesis of a linkage between affective dysregulation and catatonia in schizophrenia, we searched electronic medical records from 36,839 patients with schizophrenia, using anxiety and depression diagnoses as proxies for affective dysregulation. Catatonia was found in 4.7 % of the cohort. Analyses indicated that catatonia was significantly associated with both anxiety and depression co-morbidities: schizophrenia patients with catatonia were 1.71 times more likely to have anxiety and 1.80 times more likely to have depression than those without catatonia. Benzodiazepine usage was also 7.73 times more common in schizophrenia patients with a catatonia diagnosis than without that diagnosis. Taken together, the findings could be related to GABAergic dysfunction underlying schizophrenia, catatonia, and affective dysregulation.

1. Introduction

Catatonia is a syndrome of motor, affective, and behavioral symptoms that can be seen as a complication of numerous psychiatric and medical conditions. While in the DSM-IV catatonia was listed as a subtype of schizophrenia, the DSM-5 categorizes catatonia as a syndrome which can occur in other psychopathological conditions. Although definitive studies are lacking, it is frequently reported that the majority of psychiatric inpatients presenting with catatonia have a primary affective disorder, not schizophrenia (Taylor and Fink, 2003; Walther et al., 2019). Nevertheless, catatonia is relatively common in schizophrenia, with a recent meta-analysis of studies across multiple continents and clinical settings suggesting a prevalence of nearly 10 % (Solmi et al., 2018). This is clinically significant, as catatonia is associated with worse social and functional outcomes, including the Global Assessment of Functioning Scale (Nadesalingam et al., 2022). The occurrence of catatonia in patients with affective disorders such as bipolar disorder and major depressive disorder raises the question as to whether the syndrome represents a transdiagnostic affective diathesis.

If catatonia reflects an affective diathesis, then one would expect to see evidence of affective dysregulation in schizophrenia patients who also exhibit catatonia in the course of their illness. Although schizophrenia has traditionally been considered a "non-affective psychosis," psychosis rating scales consistently show evidence of an anxious/depressed dimension (Sawamura et al., 2010). Persons with a diagnosis of schizophrenia exhibit high rates of anxiety and depression co-morbidities (Myin-Germeys and van Os, 2007) and theoretical formulations have identified core pathophysiology with affective dysregulation, in the form of stress sensitivity (Howes et al., 2017; Taylor et al., 2019).

A link between catatonia and affective dysregulation might reflect an underlying mechanism, such as the gamma-amino-butyric-acid (GABA) system. Patients with catatonia frequently exhibit a dramatic and rapid response to first line therapies potentiating GABA function, such as benzodiazepines and barbiturates (Rosebush and Mazurek, 2010). Similarly, modulation of GABAergic function with benzodiazepines is one of the most common, if controversial, pharmacotherapies to manage affective dysregulation, particularly anxiety (Cloos and Ferreira, 2009). Electroconvulsive therapy, also linked with GABA potentiation, often reverses symptoms of catatonia after 1 or 2 treatments (Lloyd et al., 2020). The pathophysiology of catatonia has been linked to dysfunction of GABA neural circuitry, as demonstrated by reduced GABAergic binding within the right orbitofrontal cortex (OFC) in catatonic patients (Northoff et al., 1999b). A systematic review of neuroimaging studies

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using catatonia scales with affective subscales have found $GABA_A$ receptor abnormalities in the medial and lateral OFC, prefrontal, and posterior parietal cortices (Hirjak et al., 2020). Benzodiazepines have been shown to regulate activity in the OFC during emotional processing in catatonia (Richter et al., 2010). While older work focused primarily on the motor and behavioral symptoms of catatonia, there has been a more recent focus on the accompanying affective symptoms of the syndrome (Northoff et al., 1999a). Patients who have recovered from catatonia describe intense feelings of anxiety and being overwhelmed by their environment while they were in the catatonic state (Northoff et al., 1998). Such information also has implications for treatment and prognosis, as catatonic patients who responded immediately to lorazepam reported more anxiety and emotional dysregulation with their catatonia compared with those who did not have an immediate response to a benzodiazepine (Northoff et al., 1998).

In this study, we sought to test the hypothesis that, amongst patients with schizophrenia, those who present with diagnoses of catatonia would be more likely to exhibit signs of affective dysregulation than those patients who never presented with catatonia. We utilized an electronic medical record search tool to identify an association between affective dysregulation, for which we identified proxies in the form of comorbid anxiety and depression diagnoses, and catatonia in a cohort of patients with schizophrenia and schizoaffective disorder. The tool used in this study, EMERSE (Electronic Medical Record Search Engine), specifically searches clinical documentation within the electronic medical records at a large midwestern academic medical center, searching through >2 million unique patients (Hanauer et al., 2015). By utilizing the rich and complex data contained in the clinicians' visit notes, the tool avoids the pitfalls of diagnostic inaccuracy seen with tools querying on ICD and billing codes, which are particularly limited in the case of catatonia. Further analyses evaluated benzodiazepine use rates per group as a means of providing secondary confirmation regarding the accuracy of our approach. Additional exploratory analyses were performed to investigate associations with illness severity per the Global Assessment of Functioning (GAF) Scale.

2. Methods

2.1. Patient identification

We conducted a retrospective review of patients diagnosed with schizophrenia or schizoaffective disorder at the University of Michigan from 1995 to 2022. Patients aged 14 years and older were identified through the EPIC-linked search tool EMERSE (Electronic Medical Record Search Engine) by search keywords including "schizophrenia," "schizoaffective disorder," "schizoaffective," and "schizophreniform disorder." The most common misspellings of these respective terms were also included. Additional exclusion phrases were utilized to reduce risk of false positives (i.e. "family history of schizophrenia," "no signs of schizophrenia," etc.). A second filter was applied to the resulting schizophrenia/schizoaffective cohort to separate those with catatonia from those without using inclusion phrases "catatonia," "catatonic," and common misspellings. Exclusion phrases were utilized as above to reduce risk of false positives (i.e. "no catatonia"). No individual symptoms of catatonia were included in the search terms (i.e., waxy flexibility), primarily because many symptoms are nonspecific and no set number of symptoms qualify a catatonia diagnosis. Therefore, catatonia was defined by primarily by the clinicians in their final patient formulation/diagnosis. We additionally did not search for the ICD-10 codes for these diagnoses, as the code itself is rarely included in clinician notes and the search terms included ICD-10 diagnosis terminology.

The resulting cohorts were then filtered for diagnosis of anxiety disorders, including "generalized anxiety disorder," "social anxiety," "social phobia," "panic disorder," "obsessive-compulsive disorder," and "anxiety NOS." For unipolar depression diagnoses, terms including "major depression," "major depressive disorder," "depression NOS," "unspecified depression," "depressive disorder," and "schizoaffective depressive type" were used. A review of 100 randomly selected charts of each resulting cohort was completed to ensure adequate diagnostic accuracy.

Searches for benzodiazepines within each cohort were conducted using a filter including lorazepam, alprazolam, clonazepam, and diazepam, with respective brand names and common misspellings. To determine the global impact of catatonia on functioning, we identified the lowest Global Assessment of Functioning (GAF) Scale decile within each cohort, determined using separate filters for each 10-point score range with an individual inclusion term for each point (i.e. "GAF 7" term within "GAF 1–10" filter). Details regarding demographics were extracted from clinical records. All study procedures were approved by the University of Michigan Institutional Review Board.

2.2. Statistical analysis

To investigate the relations between catatonia and negative affect (anxiety and depression), chi-square analyses were conducted and corresponding odds ratio (OR) were calculated. The same analyses were conducted to investigate the relations between benzodiazepine and catatonia/negative affect. All chi-square tests had a degrees of freedom of 1. Finally, to investigate the unique associations of catatonia and benzodiazepine (predictors) to GAF (outcome), a hierarchical multiple regression analysis was conducted. Sex, race, and Sex × Race interaction were included as covariates and used in the baseline model. All analyses were conducted in R using psych (version 2.1.3) for descriptive and correlational analyses and stats (version 4.1.0) for chi-square and multiple regression analyses (Revelle, 2020).

3. Results

3.1. Demographics

A total of 36,839 patients with schizophrenia or schizoaffective disorder presenting to the University of Michigan between 1995 and 2022 were identified. The sample was 52.3 % female; 71.7 % White or Caucasian, 17.5 % Black or African American, 1.9 % Asian, 0.5 % American Indian and Alaska Native, 0.1 % Native Hawaiian and Other Pacific Islander, and 2.1 % Other (6.2 % Not available, Unknown, or Patient Refused). Proportion of patients with the variables in their record are presented in Table 1. A total of 1749 patients (4.7 %) of the schizophrenia/schizoaffective disorder cohort were identified as having catatonia.

3.2. Catatonia and its association with anxiety and depression

Chi-square tests indicated that catatonia was associated with both

Table 1
Descriptive statistics.

Variables (N = 36,839)	Proportion
Anxiety	43.6 %
Depression	40.6 %
Catatonia	4.7 %
Benzodiazepine	61.4 %

Variables (N = 9209)	Mean (SD)
GAF (deciles)	5.49 (1.84)

Notes. GAF = Global Assessment of Functioning, SD = standard deviation.

anxiety and depression (Table 2; $p < 0.001$), such that having catatonia increased the likelihood of having anxiety and depression. Of patients with catatonia, 56.3 % had anxiety disorder (whereas only 43 % had anxiety if they did not have catatonia), and 54.5 % had depression (whereas only 39.9 % had depression if they did not have catatonia). ORs indicated those with catatonia were 1.71 times more likely to have anxiety and 1.80 times more likely to have depression than those without catatonia.

3.3. Benzodiazepine prescription and its association with catatonia, anxiety, and depression

Chi-square tests indicated that benzodiazepine prescription was associated with catatonia, anxiety, and depression (Table 3; $p < 0.001$). ORs indicated that those with benzodiazepine prescriptions were 7.76 times more likely to have catatonia, 2.73 times more likely to have anxiety, and 3.01 times more likely to have depression than those without benzodiazepines in their charts.

3.4. Relations between GAF with catatonia and benzodiazepine prescription

GAF score was available for 9209 participants (25 % of total data). A summary of the hierarchical multiple regression with lowest GAF as outcome variable is presented in Table 4. Both benzodiazepine and catatonia were uniquely associated with GAF score and the final model included the main effects of both predictor variables. There were no interaction effects. Regression coefficient estimates are presented in Table 5. Catatonia was associated with a 7.43-point decrease in GAF and benzodiazepine prescription was associated with 11.37-point decrease. Main effects of demographic variables indicated male patients had 1.72-point lower GAF thane female patients and Black or African American patients had 2.57-point lower GAF score than White or Caucasian patients (reference group). No other demographic groups were statistically significantly different from the reference group.

4. Discussion

This study examined the relationship between catatonia and affective dysregulation in patients with schizophrenia spectrum disorders. The overall rate of anxiety disorders in the cohort was 43 %, which was comparable to previous literature on rates of anxiety comorbidity in schizophrenia, including a review conducted in 2013 which found 38.3 % of subjects had a comorbid anxiety disorder (Braga et al., 2013). Patients with catatonia were 1.71 times more likely to have an anxiety disorder compared to those without catatonia. The overall rate of depression diagnoses in our cohort was 40 %. Previous studies have suggested varying rates of comorbid depression diagnoses, with one systematic review citing a wide range of 7–83 % (Buckley et al., 2009) and another review citing a modal frequency of 25 % (Siris, 2001). Those with catatonia were also 1.8 times more likely to have a unipolar depressive disorder compared to those without catatonia.

Consistent with past work, the present study found affective symptoms were significantly higher in patients with catatonia from underlying schizophrenia or affective psychosis compared to psychiatric controls (Northoff et al., 1998). Affective symptoms have been associated with general catatonic symptoms using scales such as the Northoff Catatonia Rating Scale (NCRS), which also accounts for the affective component of catatonia (Northoff et al., 1999a). The inability to control emotions and affect has also been noted in patients with catatonia, and impacts patients' motor and behavioral symptoms (Northoff et al., 1998). Catatonia has also been associated with lesions in the limbic system (Ahuja, 2000), as well as functional abnormalities in brain regions responsible for processing negative stimuli (Hirjak et al., 2020). Perhaps as a downstream complication of this propensity towards negative affect, two population-based studies in catatonic schizophrenia suggest that catatonic patients were significantly more likely to attempt suicide compared with the rest of the schizophrenia group (Kleinhaus et al., 2012; Mimica et al., 2001). Several studies have found catatonic symptoms are indicators of poor prognosis in schizophrenia, including an association with early age of onset, negative symptoms, and longer and more frequent hospitalizations (Ungvari et al., 2018).

Mechanistically, we suggest that these findings could be explained by a link between GABAergic pathology in schizophrenia and affective dysregulation. Several lines of evidence support the involvement of GABA systems in schizophrenia, including post-mortem studies finding decreased GABA transporter-1 density (Nakazawa et al., 2012), decreased in GAD67 gene expression in GABAergic parvalbumin positive interneurons (PVI) (Lewis et al., 2005), and alterations in post-synaptic GABA receptor binding (Schmidt and Mirnics, 2015). Additionally, electroconvulsive therapy increases GABA concentrations in the medial prefrontal cortex in patients with schizophrenia (Xia et al., 2018). The dysfunction of GABAergic PVI is hypothesized to lead to downstream impacts on neural circuitry implicated in increased sensitivity to stress and affective dysregulation (Taylor et al., 2019). Studies in persons with schizophrenia have found reduced connectivity between the amygdala and dorsomedial prefrontal cortex while processing emotional stimuli (Bjorkquist et al., 2016; Das et al., 2007). Negative affective states have been correlated with an abnormal response to a lorazepam challenge in the dorsal medial prefrontal cortex of patients with schizophrenia (Taylor et al., 2014). In line with the notion that catatonia is a transdiagnostic syndrome, post-mortem findings of GABAergic PVI interneurons have been reported for bipolar patients (Guidotti et al., 2000; Woo et al., 2008) and GABA dysregulation has also been identified in major depressive disorder (Duman et al., 2019; Torrey et al., 2005). In this interpretation of our results, GABAergic dysfunction could manifest both as affective dysregulation, leading to more frequent diagnoses of anxiety and depressive disorders, as well as catatonic states in some patients. Other explanations are possible, and we do not mean to suggest that all anxiety and depression in schizophrenia suggests a liability to catatonia. There may additionally be separate pathophysiological underpinnings within the persistent catatonic states seen in a subset of schizophrenia patients, which shows generally limited response to benzodiazepines (Ungvari et al., 1999). Nevertheless, taken together, the results suggest the need for future

Table 2
Crosstabs of relations of catatonia with anxiety and depression.

Variables		Catatonia		χ^2	OR
		Absent	Present		
Anxiety	Absent	54.3 %	2.1 %	118.9	1.71
	Present	40.9 %	2.7 %		
Anxiety given catatonia		43.0 %	56.3 %		
Depression	Absent	57.2 %	2.2 %	145.4	1.80
	Present	38.1 %	2.6 %		
Depression given catatonia		39.9 %	54.5 %		

Note. χ^2 = chi-square statistic, OR = odds ratio.

Table 3
Crosstabs of relations of benzodiazepine prescription with catatonia, anxiety, and depression.

Variables		Benzodiazepine		χ^2	OR
		Absent	Present		
Catatonia	Absent	38.2 %	57.0 %		
	Present	0.4 %	4.4 %	726.1	7.76
Anxiety	Absent	27.4 %	29.0 %		
	Present	11.2 %	32.4 %	1991.8	2.73
Depression	Absent	28.9 %	30.5 %		
	Present	9.7 %	30.9 %	2290.6	3.01

Note. χ^2 = chi-square statistic, OR = odds ratio.

Table 4
Hierarchical multiple regression predicting GAF.

Variables	R^2	Comparison model	R^2 change	*df*	SS	*F*	*p*
Dem only	0.007						
Dem, Cat (main only)	0.056	Dem only	0.049	1	1462.70	456.63	<0.0001
Dem, Cat, and Dem × Cat	0.056	Dem, Cat (main only)	0.000	9	13.23	0.46	0.9028
Dem, Ben (main only)	0.085	Dem only	0.078	1	2335.70	752.25	<0.0001
Dem, Ben and Dem × Ben	0.085	Dem, Ben (main only)	0.000	10	12.91	0.42	0.9401
Dem, Cat, and Ben (main only)	0.119	Dem, Cat (main only)	0.063	1	1892.90	633.01	<0.0001
		Dem, Ben (main only)	0.034	1	1020.00	341.08	<0.0001
Dem, Cat, Ben, and Cat × Ben	0.119	Dem, Cat, and Ben (main only)	0.000	1	6.1713	2.06	0.1508

Note. Cat = catatonia; Ben = benzodiazepine prescription; df = degrees of freedom; SS = sums of squares; *F* = *F*-statistic, Dem = sex, race, and sex × race interaction terms.

Table 5
Demographic, catatonia, and benzodiazepine (main only) model coefficients.

Variables	Estimate	SE	*t*	*p*
Male	−0.172	0.042	−4.107	<0.0001
American Indian and Alaska Native	−0.331	0.328	−1.008	0.3136
Asian	−0.112	0.151	−0.744	0.4570
Black or African American	−0.257	0.066	−3.880	0.0001
Native Hawaiian and Other Pacific Islander	0.222	0.865	0.257	0.7974
Other	0.029	0.170	0.166	0.8683
Benzo	−1.137	0.046	−25.160	<0.0001
Cat	−0.743	0.295	−18.468	<0.0001

Note. SE = standard error; *t* = *t*-statistics. Sex × race interaction terms excluded.

research which would have implications for treatment and targeted pharmacotherapy.

Overall, our findings around catatonia frequency and treatment are consistent with the literature. A 2017 study suggested prevalence of 9.8 % (8–12 % CI) nearly double the rate of 4.7 % that we found, but the same study also noted lower rates of catatonia in outpatient services (Solmi et al., 2018). The present study includes both inpatient and outpatient encounters, which may explain the lower observed rates of catatonia. Although our data extraction method did not allow a direct association between treatment and catatonic symptoms, patients with catatonia were 7.76 times more likely to have been prescribed a benzodiazepine than those without, providing a secondary confirmation that our method extracted true diagnoses, as the use of benzodiazepines to treat catatonia has become a standard of practice (Pelzer et al., 2018).

Catatonia was associated with lower GAF scores, which is expected given catatonia is typically associated with more severe symptom burden. A recent study of patients with schizophrenia and motor abnormalities found that the presence of catatonia was associated with lower GAF and Social and Occupational Functioning Assessment Scale scores (Nadesalingam et al., 2022). Catatonia symptoms in patients with first episode psychosis have been associated with poor psychosocial functioning as well (Cuesta et al., 2018). Patients with a benzodiazepine in their chart also had lower GAF scores. A 2021 study of patients with psychosis spectrum disorders found that long term benzodiazepine prescription was associated with lower global and cognitive functioning (Savić et al., 2021). Tapering of long-term benzodiazepines in schizophrenia has also been associated with improvements to quality-of-life measures, negative symptoms, and cognitive testing (Kitajima et al., 2012). Importantly, benzodiazepine prescription and catatonia had unique contributions to lower GAF scores, suggesting that situations that prompt clinicians to prescribe benzodiazepine provides incremental information about overall functioning beyond catatonia itself.

In contrast to prior epidemiologic studies suggesting a male to female incidence closer to 1.4:1 (Abel et al., 2010), the ratio of males to females within our cohort of schizophrenia/schizoaffective patients was close to 1:1. However, previous research on catatonic schizophrenia suggests that both sexes at equal risk (Ungvari et al., 2018), which our data supports.

Our study has several limitations, principally due to the method of data gathering. This study utilized an electronic medical record search engine that specifically queried unstructured clinical documentation across encounters (Hanauer et al., 2015). Previous studies have found support for the use of free text data in research, as potential cases can be missed or wrongly coded, and diagnostic suspicions are frequently found in clinical documentation (Ford et al., 2013). Unstructured clinical data has been used to recruit patients for clinical trials (Raghavan et al., 2014) and to determine prevalence rates of conditions not readily associated with billing codes (Kharrazi et al., 2018). The latter is particularly salient in this study, given catatonia is a heterogenous condition with limited ICD code representation. This methodology permitted the analysis of a large volume of medication records, but the data set has several limitations. As it only represents a single medical system in the upper Midwest of the USA, results might not be generalized to other parts of the world. We were unable to obtain age at time of diagnosis due to the nature of the search system looking across all encounters over three decades, thus an effect of age could not be established. Significant chart review was conducted to reduce risk of false positives and accuracy was >90 %; however, the risk of false positives (i.e., meeting criteria due to chart stating family history of catatonia) could not be completely mitigated. The actual use or administration of a benzodiazepine could not be correlated with the presence of a benzodiazepine term in a given chart, and our GAF analysis was limited by inability to calculate average GAF scores for a given patient, as well as the majority of patients not having a GAF documented. Finally, only search results of all notes within a patient's chart could be extracted, thus the temporal relations and co-occurrence cannot be inferred. As such, we are unable to infer whether the identified catatonia cohort were experiencing antipsychotic-induced catatonia. The results are conceptually similar to lifetime co-occurrence, but with varying degrees of coverage of time (some patients could be seen for a few months and some could be seen for decades). Nevertheless, in spite of these limitations, the robust statistical findings support the validity of our results.

Future work could identify potential phenomenological differences in anxiety and depressive disorders in patients with comorbid schizophrenia and catatonia compared to the affective and anxious symptoms seen in catatonic patients. Given the potential overlap in psychomotor symptoms seen in schizophrenia with those secondary to depression, anxiety, or catatonia, we focused our search on disorders diagnoses rather than the specific symptoms themselves. Our inability to determine temporal relations between symptoms and diagnoses preclude this analysis as part of the present study, but in theory, a more powerful search tool may be able to separate catatonic episodes from periods without catatonia. In addition, a more granular search with natural language processing might be able to isolate specific catatonic symptoms contributing to the diagnosis. Further research should also explore the pathophysiology underlying chronic catatonic symptoms seen in some patients with schizophrenia, as these potentially have other neurotransmitter involvement (Ungvari et al., 1999). Again, we were unable to discern whether patients were experiencing acute or chronic catatonia at time of presentation and subsequent inclusion in the study.

In this study, it was demonstrated that catatonia was meaningfully associated with negative affect, as inferred by presence of anxiety and depressive disorders, in patients with schizophrenia and schizoaffective disorder. We hypothesize that this relationship is at least in part related to GABAergic dysfunction underlying schizophrenia, catatonia, and affective dysregulation. Additional research is needed to further characterize the relationship between negative affect and catatonia in order to deepen our understanding of these complex pathologies.

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CRediT authorship contribution statement

CLK conducted cohort identification, chart review, and drafted the initial manuscript. TS contributed results and conducted statistical analyses. MS conducted statistical analyses. SFT contributed to conception and design of study, analysis and interpretation of results, and manuscript drafting. All authors reviewed the final manuscript.

Declaration of competing interest

None.

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The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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