Illness severity associated with comorbid substance use disorders in schizophrenia: an electronic health record study

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BACKGROUND

Approximately 50% of schizophrenia patients have comorbid substance use disorder (SUD).[1] Patients with dual diagnoses of schizophrenia and SUDs have poorer outcomes, such as higher rates of relapse and rehospitalizations.[2]

OBJECTIVE

To investigate the association between illness severity in schizophrenia patients and the prevalence of comorbid SUD using a largescale electronic health record (EHR) dataset.

METHOD

Cohort	Adults with a diagnosis of schizophrenia (ICD-10 F20*).
Index	Date of Schizophrenia diagnosis
Exposure	The presence of a comorbid SUD (F10* alcohol, F11* opioid, F12* cannabis, F14* cocaine, F15* stimulant, F17* nicotine.)
Outcome	Clinical Global Impression - Severity (CGI-S) score (2 categories – 1-4 and 5-7) documented within 30 days of index date.
Covariate	Age, gender, race, marital status, employment status and year of schizophrenia diagnosis - multivariable logistic regression analysis.

NeuroBlu™ database

50+ million rows of patient data | **560K+** Patients | **20+ years** Longitudinal Data

Patient volume by disease

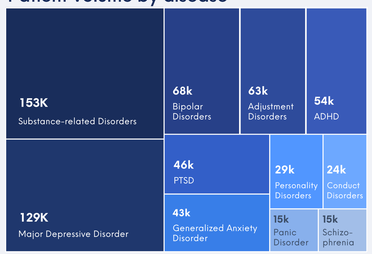

Figure 1. NeuroBlu Database overview

Structured Data

- **Outcome Measures (e.g., CGI-S, GAF)**
- Diagnosis Codes (ICD-9, ICD-10)
- Prescription Data
- Patient Demographics
- **Emergency Department, inpatient and outpatient** data across the same patients in 20 of 25 clinics

Unstructured Data

Mental Status Examination (MSE)
- Categorized notes on patient's function, appearance and mood at a visit
- Holmusk developed >30 advanced Neural Network models to predict structured labels from MSE
- Created >300 psychiatry specific labels in collaboration with clinicians to track disease progression over time

External Stressors
Social, relational and occupational events that may affect the patient's mental health

Data Source of US Health Facilities

De-identified EHR data were obtained from U.S. mental health services that use the MindLinc EHR system. The data were analysed in NeuroBlu, a secure Trusted Research Environment (TRE) that enables data assembly and analysis using an R/Python code engine.

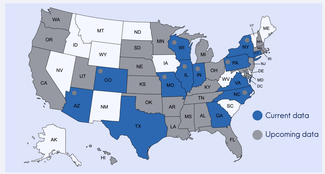

Figure 2. State specific data source for NeuroBlu

RESULTS

- A total of 13,634 adults with schizophrenia were included of which 12,676 (93.0%) had a documented CGI-S score.
- Comorbid cannabis use disorder (F12*) was associated with greater illness severity (mean CGI-S (SD): 4.89(1.14); OR: 1.68, 95% CI 1.32 to 2.14, p<0.001)
- Comorbid opioid use disorder (F11*) was associated with lower illness severity (mean CGI-S (SD): 4.23(1.23); OR: 0.56, 95% CI 0.37 to 0.83, p=0.004) compared to patients without comorbid SUD (mean CGI-S (SD): 4.57(1.23)).
- The associations between demographic and diagnostic factors and CGI-S scores are illustrated in Table 1.

Table 1. Logistic Regression for Baseline CGI-S scores Comparing Patients With and Without Comorbid Substance Use Disorders (SUD; n=12,676). Outcome variable: CGI-S score grouped into 2 categories – "mild/moderate: 1-4" and "moderate/severe: 5-7".

Variables	N (%)	Mean (SD)	Odds Ratio	Confidence Interval	p
SUD category					
Reference: No SUD	9,883 (78.0)	4.57 (1.23)			
Alcohol only	492 (3.9)	4.42 (1.45)	0.93	0.77 to 1.12	0.44
Cannabis only	336 (2.7)	4.89 (1.14)	1.68	1.32 to 2.14	< 0.001
Opioid only	111(0.9)	4.23 (1.23)	0.56	0.37 to 0.83	0.004
Cocaine only	104 (0.8)	4.63 (1.17)	1.15	0.77 to 1.71	0.50
Nicotine only	55 (0.4)	4.64 (1.39)	1.32	0.76 to 2.30	0.32
Stimulant only	42 (0.3)	4.98 (0.91)	2.05	1.03 to 4.07	0.04
Others only	642 (5.1)	4.95 (1.10)	1.67	1.40 to 1.99	< 0.001
Polysubstance	1,011(8.0)	4.69 (1.20)	1.22	1.06 to 1.40	0.005
Gender					
Reference: Female	4,737(37.4)	4.58 (1.22)			
Male	7,939 (62.6)	4.62 (1.24)	0.97	0.90 to 1.05	0.45
Age					
Reference: Age < 40	5,951 (46.9)	4.72 (1.20)			
Age 40 and above	6,725 (53.1)	4.50 (1.25)	0.83	0.77 to 0.90	< 0.001
Race					
Reference: Black	3,848 (30.4)	4.60 (1.20)			
White	4,890 (38.6)	4.61 (1.24)	1.10	1.01 to 1.20	0.038
Others	988 (7.8)	5.06 (1.10)	1.91	1.63 to 2.23	< 0.001
Unknown	2,950 (23.3)	4.39 (1.26)	0.92	0.83 to 1.02	0.12
Marital status					
Reference: Divorced/Separated	1,068 (5.5)	4.40 (1.33)			
Single	8,123 (42.1)	4.73 (1.17)	1.42	1.24 to 1.62	< 0.001
Married/Engaged/In a relationship	981 (4.4)	4.36 (1.22)	0.93	0.78 to 1.11	0.44
Widowed	208 (0.9)	4.42 (1.17)	1.32	0.97 to 1.78	0.075
Unknown	8,935 (40.4)	4.39 (1.33)	0.67	0.59 to 0.77	< 0.001
Employment status					
Reference: Disabled	1,000 (7.9)	4.80 (1.08)			
Employed	534 (4.2)	4.78 (1.17)	0.91	0.73 to 1.14	0.41
Unemployed/ Student/Retired	2,207 (17.4)	4.94 (1.09)	1.27	1.08 to 1.49	0.004
Unknown	8,935 (70.5)	4.49 (1.26)	0.67	0.59 to 0.77	< 0.001
Year of Schizophrenia diagnosis					
Reference: 2004 and before	216 (1.7)	4.77 (0.92)			
2005 - 2009	3,290 (26.0)	4.83 (1.16)	1.00	0.75 to 1.34	0.99
2010 – 2014	6,560 (51.8)	4.53 (1.27)	0.66	0.49 to 0.87	0.004
2015 - 2020	2,610 (20.6)	4.49 (1.19)	0.57	0.43 to 0.77	< 0.001

Comorbidity of SUD and CGI-S Score

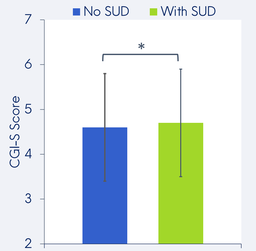

Figure 3. CGI-S score within 30 days of schizophrenia diagnosis of patients with (n = 2,793) and without (n = 9,883) comorbid SUDs. Data presented as Mean and Standard deviation. Analyzed with Mann-Whitney U tests with a significance threshold of < 0.05 (U = $1.48e^7$, p < 0.001).

CGI-S Score of schizophrenia patients with specific SUDs

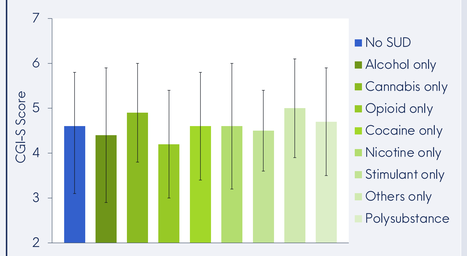

Figure 4. CGI-S score within 30 days of schizophrenia diagnosis of patients with specific SUDs (Alcohol, Cannabis, Opioid, Cocaine, Nicotine, Stimulant, Others and Polysubstance) and without comorbid SUDs. Data presented as Mean and Standard deviation.

CONCLUSION

- Amongst patients with comorbid SUDs, Polysubstance use disorder was the most prevalent.
- Comorbid SUDs are associated with increased illness severity in patients with schizophrenia.
- Comorbid SUDs vary in their associations with illness severity.
- Comorbid cannabis use disorder is associated with greatest illness severity consistent with its potential etiological role in schizophrenia.
- Conversely, opioid use disorder is associated with least illness severity.
- This could reflect differences in the clinical characteristics and functioning of individuals who use opioids compared to those who use other substances.
- Further analyses of healthcare service utilization could address the degree to which different comorbid SUDs are associated with worse clinical outcomes.

Conflicts of Interest: All authors report current employment with Holmusk Technologies, Inc. RP, MV, and SK report equity ownership in Holmusk Technologies, Inc

References:
1. Hunt GE, Large MM, Cleary M, Lai HMX, Saunders JB. Prevalence of comorbid substance use in schizophrenia spectrum disorders in community and clinical settings, 1990–2017: Systematic review and meta-analysis. *Drug Alcohol Depend.* 2018;191:234-258. doi: 10.1016/j.drugalcdep.2018.07.011
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