



The role of substance use and adult sexual assault severity in the course of schizophrenia: An epidemiological catchment study of sexual assault victims

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ARTICLE INFO

Article history:

Received 12 April 2018

Received in revised form 5 January 2019

Accepted 5 January 2019

Available online 15 January 2019

Keywords:

Schizophrenia

Sexual assault

Sexual victimization

Substance use

Longitudinal

Epidemiology

ABSTRACT

Background: Childhood trauma increases the risk of schizophrenia, yet the role of adult sexual assault in the course of schizophrenia is unknown. This study aims to examine the associations between substance use and sexual assault severity characteristics with the course of schizophrenia among adult sexual assault victims using an epidemiologic study design.

Methods: Sexual assault data on all individuals received from 2000 to 2010 ($N = 2147$) at the Center for Care of Sexual Assault Victims at Wolfson Medical Center, the largest medical center for sexual assault victims in the country, were merged with the Israel National Psychiatric Case Registry, that consisted of lifetime psychiatric hospitalizations of schizophrenia (birth to 6 years post-assault). The associations between substance use and adult sexual assault severity characteristics with hospitalizations were quantified using recurrent events Cox modeling.

Results: Schizophrenia with sexual assault survivors occurred in 117 persons. Cox modeling showed that recurrent psychiatric hospitalizations were associated with younger age, sexual assault at older age, previous diagnosis of psychosis, and drug use shortly before or during the assault. Other assault characteristics (number of assailants, means of subdual, penetration type, perpetrator violence, physical injury of the victim) and immediacy of seeking help had a null association with the course of psychiatric hospitalization. These results replicated in two sensitivity analyses.

Conclusions: Substance use among victims of sexual assault was associated with an exacerbated course of schizophrenia, pointing to a possibly modifiable risk factor that should be targeted in prevention, assessment, treatment formulation and implementation.

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1. Introduction

Many studies have demonstrated that various childhood adversities substantially increase the risk of schizophrenia (Bailey et al., 2018; Bendall et al., 2007; Van Dam et al., 2015; Varese et al., 2012). Specifically, childhood sexual abuse exposure is linked with the risk of psychosis, higher rates of psychotic symptoms, comorbid disorders, cognitive deficits, treatment resistance, earlier and more frequent hospitalizations compared to those with no trauma exposure (Hassan and De Luca, 2015; Longden et al., 2016; Schenkel et al., 2005). Despite a large literature on childhood sexual assault, few studies examine adult sexual

assault, and the extent to which it is possible to extrapolate from child to adult sexual assault risk factors is unknown. However, child sexual abuse and adult sexual assault have some common factors (Barnett et al., 2005). Adult sexual assault is associated with adverse psychiatric outcomes, including severe mental health disorders, such as posttraumatic stress disorder (PTSD), major depressive episodes, and substance use disorders (SUD) (Kilpatrick et al., 2007; Zinzow et al., 2012a; Zinzow et al., 2010), that are highly comorbid with psychotic disorders (Buckley et al., 2008). However, the association between adult sexual assault and the course of schizophrenia is yet to be examined using an epidemiological study design.

Sexual assault is a physical assault of a sexual nature directed toward another individual without his or her consent. The assault may range from unwanted touching to sexual penetration, including rape, attempted rape, aggravated sexual assault or penetration by objects or

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forced sexual activity that did not result in penetration. Sexual assault is a crime, with a legal definition that may vary between states (Cameron et al., 2014).

To date, only a few small-scale clinical studies have examined the association between adult sexual assault and symptoms of schizophrenia. One explored retrospective self-reported traumatic life events timing and severity 1–40 years after the assault (Kilcommons et al., 2008) and found that of the 26 victims, 46% experienced hallucinations at some point in their lives. Severity of sexual assault, as defined by the number of unwanted sexual events, was associated with severity of hallucinations reported. Another study of psychiatric records before and after attending a center for rape victims showed that sexual assault increased the likelihood of a diagnosis of psychosis among 103 victims (Elklit and Shevlin, 2010). However, post-assault psychosis was most strongly associated with a prior diagnosis of psychosis. This indicates that temporal precedence of psychosis prior to assault may influence the course of the disorder. Assault severity characteristics were not considered for the whole sample or for the 13 victims diagnosed with schizophrenia. To our knowledge, no study has examined the lifetime course of the disorder in adult sexual assault victims.

Among persons with psychosis who were sexually assaulted during childhood, research shows that the severity of trauma was associated with psychosis symptom severity (Schalinski et al., 2015). Although research suggested that persons with schizophrenia are particularly at risk for sexual victimization (Darves-Bornoz et al., 1995), to date, no study has examined this association among victims of adult sexual assault with schizophrenia. Adult sexual assault characteristics that correlate with severity of various mental illnesses other than schizophrenia include penetration type (Pinsky et al., 2017), offender violence, severity of sexual acts, and physical injury (Brown et al., 2009; Zinzow et al., 2010). Inconsistent associations have been found between symptom severity and demographic characteristics such as age, education, and ethnicity (Ullman and Filipas, 2001), as well as relationship to the perpetrator (Resick, 1993).

Another predictor of symptom severity even for those without prior history of substance abuse is substance use proximal to, or during an assault. Previous findings indicate reported use of psychoactive substances at the time of assault by 33–73% of rape victims seeking care in a hospital based setting (Kilpatrick et al., 2007; McCauley et al., 2013; Resnick et al., 2013). Women whose assaults included both incapacitation due to substance use or administration and forcible rape, as compared to those experiencing only substance related or forcible rape tactics, reported highest prevalence of PTSD, major depression, and alcohol abuse (Zinzow et al., 2012b), disorders that are highly comorbid with psychotic disorders (Buckley et al., 2008).

The current study aims to examine the associations between demographics, sexual assault severity characteristics and substance use with the course of schizophrenia using epidemiological catchment area study design of adult sexual assault victims. It was hypothesized that experience of drug and/or alcohol facilitated sexual assault and higher assault severity would increase the likelihood of psychiatric hospital readmissions.

2. Methods

Data on all individuals received from 2000 to 2010 at the Center for Care of Sexual Assault Victims at Wolfson Medical Center, the largest medical center for sexual assault victims in the country, were merged with the Israel National Psychiatric Hospitalization Case Registry that contains all nation-wide lifetime psychiatric hospitalizations of schizophrenia (birth to 6 years post-assault).

2.1. Ethics

The Institutional Review Board at the University of Haifa and the Helsinki Committee at Wolfson Medical Center approved the merger

of the study data sources. Both approving bodies waived the requirement of written informed consent. Data were linked at the Ministry of Health using as common unique national identification numbers. Then the identification numbers were encrypted and passed to the researchers to ensure participant anonymity and confidentiality.

2.2. Sexual assault victim registry

The study was conducted at the Center for Care of Sexual Assault Victims at Wolfson Medical Center, the largest medical center for sexual assault victims in Israel (The Knesset Research and Information Center, 2017). This center provides sexual assault care that covers the catchment area for the entire central region of Israel (a total population of approximately 4,000,000) (Central Bureau of Statistics, 2017). Data were collected on all 2147 persons (approximately 0.05% of the catchment area of central Israel) treated from 1st October 2000 to 1st July 2010. Each victim who arrived at the center was examined by a gynecologist trained to treat sexual assault victims, and was interviewed on intake by a social worker, a forensic medical doctor specialist, and a policeman/woman. During the interview, this information was entered directly into the hospital sexual assault registry, and covers demographic, drug use and assault information.

Information for each victim was documented in a dedicated computerized standardized data collection form. Demographic data were collected on sex, birth year, age of arrival at the center, and marital status (coded as single or other). The number of assailants was coded as one or over one. Means of subdual refers to the means of victim subdual before and/or during the assault. It was classified 'physical' if force was used (i.e. presence of a weapon, attempted strangulation, holding, kick) or 'other' if physical means were not used (i.e. social pressure, verbal threats). Extreme violence was defined as present if the victim suffered from physical injuries that required (non-psychological) medical treatment beyond the center. The sexual act was categorized into vaginal penetration or other (including anal, oral and/or other orifices). Alcohol use shortly before or during the sexual assault was coded as present or absent. Drug use was classified in the same way. The immediacy of arrival was indexed by whether or not care at the center was given within 24 h of the time of the attack. The temporal order of events was based on first lifetime date of psychiatric hospitalization and date of arrival at the center. The categories derived were: assault center then psychiatric hospitalization; psychiatric hospitalization then assault center; and co-occurrence within the same year.

2.3. Ascertainment of schizophrenia

2.3.1. The National Psychiatric Case Registry (NPCR)

Psychiatric care in Israel is freely available by law to all *de-jure* residents (Levav and Grinshpoon, 2004). The NPCR was established in the 1950's and consists of all nation-wide inpatient admissions to mental hospitals or psychiatric units of general hospitals. Research has found that the NPCR captures almost all people with schizophrenia (Weiser et al., 2012b). By mandate, all inpatient psychiatric settings submit information on all admissions and discharges to the Health Information Division, Ministry of Health. That division verifies reporting compliance, updating diagnostic coding schemes and information consistency. The registry information is comprised of admission and discharge dates, and the respective ICD-10 diagnoses by a certified psychiatrist. To ascertain schizophrenia, the last registry discharge or admission of schizophrenia was used. Validation research has shown that the last diagnosis of schizophrenia in the NPCR registry has acceptable sensitivity and specificity when assessed against research diagnosis (Weiser et al., 2005b), and is longitudinally reliable (Rabinowitz et al., 1994). This approach was adopted in prior studies (Davidson et al., 1999; Levav et al., 2007; Levine et al., 2016; Levine et al., 2014; Weiser et al., 2000).

2.4. Statistical analyses

Age of onset of schizophrenia was computed by taking the date at first psychiatric admission less birth date and using the mean as a categorical variable (age of 23). Birth year was also categorized by the mean (1979). To quantify the association between the study covariates defined in the hospital sexual assault registry (above) with the course of psychiatric re-hospitalizations in the psychiatric case registry, recurrent events Cox models were computed. Hazard Ratios (HR) were computed from models as the primary analysis applying standard statistical guidelines (Therneau, 2000), indexing re-hospitalization risk. HR values where the associated 95% confidence intervals cross the unity indicate a non-statistically significant result. The primary analysis was computed for the total population with schizophrenia and sexual assault.

Two sensitivity analyses were computed like the primary analysis. First, analysis was recomputed restricted to women only, since females are more likely to be victims of sexual assault than males (Tolin and Foa, 2006) and their responses to trauma exposure differ from males' responses (Read et al., 2001). This model differed from the primary analysis in that sex was not a covariate. Second, analysis was recomputed among women for whom schizophrenia preceded arrival at the sexual assault center. This model differed from the primary analysis in that temporal precedence of arrival was not a covariate. Thus, sensitivity analyses were recomputed twice for the primary analysis, adjusting for a potential confounding by gender or onset timing.

3. Results

In total, 2147 persons were treated from October 2000 to July 2010 at the Center for Care of Sexual Assault Victims, Wolfson Medical Center. Among these persons, the source population consisted of 117 (5.5%) individuals with a psychiatric hospitalization for schizophrenia from birth to 6 years after the sexual assault.

The source population was comprised of a majority of females ($n = 105$, 89.7%) and predominantly with a diagnosis of schizophrenia before or during the same year of arrival at the sexual assault center ($n = 105$,

89.7%; of whom 84% were females, $n = 88$). Schizophrenia onset after admission to the center was diagnosed in 12 persons (10.3% of the study population, 0.6% of all persons who attended the Center). Drug use was present in 24 (20.5) and absent in 93 (79.5%) of the study sample. Table 1 shows the sample characteristics of the source population.

Recurrent events Cox regression showed that the risk of psychiatric hospitalization was statistically significantly ($p < 0.05$) increased by: being single (HR = 1.38, 95% CI range 1.04, 1.83) compared to other marital status and presence of drug use shortly before or during the sexual assault (HR = 1.33, 95% CI range 1.02, 1.75) compared with absence of drug use. That risk decreased by being born after 1979 compared to being born before 1979 (HR = 0.44, 95% CI range 0.3, 0.64). Also, temporal order of schizophrenia onset and arrival at the center showed that the risk of psychiatric hospitalization was increased for those with schizophrenia diagnosed before arrival at the center (HR = 2.10, 95% CI range 1.32, 3.33), and co-occurrence of schizophrenia onset and assault in the same year (HR = 2.40, 95% CI range 1.24, 4.64) compared to arrival at the center then the onset of schizophrenia.

Results of sensitivity analyses replicated among females only (for descriptive statistics and detailed regression results see Table 2) and among females with the onset of schizophrenia prior to sexual assault (see Table 3) compared with the primary analysis with one exception. Among the total source population and among females with the onset of schizophrenia prior to sexual assault, single status was statistically significant, whereas among females in general, single status was not statistically significant.

4. Discussion

The current study examines association between adult sexual assault and the course of schizophrenia in an epidemiological catchment study of sexual assault survivors followed from birth to 6 years post-assault. Specifically, we tested substance use and sexual assault severity characteristics involvement in the course of schizophrenia, based on psychiatric re-hospitalizations.

Table 1

Re-hospitalization rates according to demographic factors, sexual assault severity, and timing: analysis of total population.

Covariate	Category	N	Percent	Annual re-hospitalization rate		Risk of re-hospitalization	
				Mean	95% CI range	HR	95% CI range
Sex	Female	105	89.74	1.18	1.27–1.08	Reference	
	Male	12	10.26	0.74	0.92–0.55	0.66	1.10–0.39
Birth year	After 1979	55	47.01	1.79	1.59–2.0	Reference	
	Before 1979	62	52.99	0.79	0.72–0.86	0.44	0.30–0.64
Marital status	Other	35	29.91	0.73	0.63–0.84	Reference	
	Single	82	70.09	1.34	1.22–1.46	1.38	1.04–1.83
Immediacy of arrival	Other	33	28.21	0.92	0.79–1.05	Reference	
	Within 24 h	84	71.79	1.21	1.10–1.32	1.21	0.93–1.57
Number of assailants	One	27	23.08	1.45	1.20–1.70	Reference	
	Over one	90	76.92	1.03	0.95–1.11	0.94	0.73–1.20
Alcohol use	Absent	91	77.78	1.00	0.92–1.08	Reference	
	Present	26	22.22	1.65	1.35–1.65	0.89	0.69–1.15
Drug use	Absent	93	79.49	1.01	0.93–1.10	Reference	
	Present	24	20.51	1.72	1.39–2.05	1.33	1.02–1.75
Means of subdual	Other	50	42.74	1.29	1.12–1.47	Reference	
	Physical	67	57.26	1.03	0.94–1.11	1.04	0.7–1.40
Sexual act	Other	47	40.27	1.16	1.00–1.31	Reference	
	Vaginal	70	59.83	1.11	1.01–1.20	1.08	0.84–1.28
Extreme violence	Absent	85	72.65	1.11	1.00–1.22	Reference	
	Present	32	27.35	1.18	1.05–1.32	1.22	0.97–1.53
Age of onset (schizophrenia)	Over 23	45	38.46	0.79	0.69–0.89	Reference	
	Under 23	72	61.54	1.32	1.20–1.44	0.87	0.63–1.20
Age attended center	27 or over	67	57.26	1.01	0.92–1.09	Reference	
	Under 27	50	42.74	1.40	1.20–1.59	0.62	0.45–0.86
Temporal order	Center then hospitalization	12	10.26	0.51	0.34–0.68	Reference	
	Hospitalization then center	97	82.91	1.19	1.10–1.29	2.10	1.32–3.33
	Same year	8	6.84	1.00	0.72–1.28	2.40	1.24–4.64

Note. HR: hazard ratio; CI: 95% confidence interval range. Statistically significant values of the HR ($p < 0.05$) are underlined for clarity.

Table 2
Re-hospitalization rates according to demographic factors, sexual assault severity, and timing: analysis of females only.

Covariate	Category	N	Percent	Annual re-hospitalization rate		Risk of re-hospitalization	
				Mean	95% CI range	HR	95% CI range
Birth year	After 1979	48	45.71	1.90	1.67–2.13	Reference	
	Before 1979	57	54.29	0.82	0.74–0.90	0.38	<u>0.26–0.57</u>
Marital status	Other	33	31.43	0.80	0.69–0.91	Reference	
	Single	72	68.57	1.38	1.25–1.51	1.28	0.96–1.71
Immediacy of arrival	Other	29	27.62	0.92	0.78–1.06	Reference	
	Within 24 h	76	72.38	1.27	1.15–1.39	1.20	0.90–1.62
Number of assailants	One	25	23.81	1.53	1.26–1.79	Reference	
	Over one	80	76.19	1.06	0.97–1.15	0.91	0.71–1.17
Alcohol use	Absent	82	78.1	1.04	0.95–1.12	Reference	
	Present	23	21.9	1.75	1.42–2.07	0.91	0.71–1.16
Drug use	Absent	83	79.05	1.06	0.97–1.15	Reference	
	Present	22	20.95	1.76	1.41–2.10	<u>1.32</u>	<u>1.01–1.74</u>
Means of subdual	Other	43	40.95	1.42	1.22–1.62	Reference	
	Physical	62	59.05	1.04	0.94–1.13	1.04	0.76–1.43
Sexual act	Other	36	34.29	1.31	1.12–1.51	Reference	
	Vaginal	69	65.71	1.10	1.00–1.19	1.03	0.81–1.30
Extreme violence	Absent	77	73.33	1.15	1.04–1.27	Reference	
	Present	28	26.67	1.23	1.08–1.38	1.21	0.97–1.51
Age of onset (schizophrenia)	Over 23	39	37.14	0.88	0.76–0.99	Reference	
	Under 23	66	62.86	1.33	1.20–1.46	0.84	0.60–1.17
Age attended center	27 or over	60	57.14	1.07	0.97–1.16	Reference	
	Under 27	45	42.86	1.41	1.20–1.61	<u>0.56</u>	<u>0.40–0.79</u>
Temporal order	Center then hospitalization	10	9.52	0.54	0.35–0.73	Reference	
	Hospitalization then center	88	83.81	1.25	1.14–1.35	<u>1.96</u>	<u>1.23–3.12</u>
	Same year	7	6.67	1.00	0.71–1.29	<u>2.09</u>	<u>1.12–3.92</u>

Note. HR: hazard ratio; CI: 95% confidence interval range. Statistically significant values of the HR ($p < 0.05$) are underlined for clarity.

The current study results show that the prevalence of schizophrenia in sexual assault survivors seeking care in a hospital based setting is 5.5%. That is almost 10 times higher than among the general population, estimated about 3–8 per thousand (Simeone et al., 2015). This is in line with prior research indicating that people with severe mental illnesses are particularly vulnerable to violence and victimization (Fortugno et al., 2013; Khalifeh et al., 2015; Khalifeh et al., 2016). Our results, based on professional clinical diagnosis, self-report and physical examination shortly after the assault is of special interest, as most research on violence and mental illness is based on self-reports and is focused on

violence perpetrated by people with psychotic disorders (Choe et al., 2008; Maniglio, 2009).

Schizophrenia onset after admission to the Center was diagnosed in 0.6% of all victims. This finding may suggest that exposure to adult sexual assault is linked to the onset of psychosis in some individuals. Recent research based on retrospective self-reported traumatic life events timing and severity suggested that adult traumatic events alone could be linked to psychosis independently of childhood adversity (Mansueto and Faravelli, 2017). Nonetheless, a majority of the literature suggests that severe trauma can be the consequence of prodromal

Table 3
Re-hospitalization rates according to demographic factors, sexual assault severity, and timing: analysis of females with schizophrenia diagnosed before arriving at the center.

Covariate	Category	N	Percent	Annual re-hospitalization rate		Risk of re-hospitalization	
				Mean	95% CI range	HR	95% CI range
Birth year	After 1979	37	42.05	2.12	1.85–2.39	Reference	
	Before 1979	51	57.95	0.86	0.78–0.95	<u>0.47</u>	<u>0.32–0.70</u>
Marital status	Other	28	31.82	0.79	0.67–0.91	Reference	
	Single	60	68.18	1.51	1.37–1.66	1.38	1.01–1.88
Immediacy of arrival	Other	27	30.68	0.92	0.78–1.06	Reference	
	Within 24 h	61	69.32	1.40	1.26–1.53	1.23	0.91–1.67
Number of assailants	One	18	20.45	1.93	1.57–2.29	Reference	
	Over one	70	79.55	1.08	0.98–1.17	0.88	0.68–1.14
Alcohol use	Absent	71	80.68	1.06	0.97–1.15	Reference	
	Present	17	19.32	2.22	1.80–2.65	1.04	0.82–1.31
Drug use	Absent	69	78.41	1.12	1.02–1.22	Reference	
	Present	19	21.59	1.90	1.51–2.28	<u>1.34</u>	<u>1.03–1.74</u>
Means of subdual	Other	37	42.05	1.47	1.26–1.69	Reference	
	Physical	51	57.95	1.11	1.00–1.22	1.17	0.82–1.67
Sexual act	Other	29	32.95	1.52	1.29–1.75	Reference	
	Vaginal	59	67.05	1.10	1.00–1.21	0.97	0.75–1.25
Extreme violence	Absent	65	73.86	1.25	1.12–1.38	Reference	
	Present	23	26.14	1.24	1.08–1.39	1.14	0.89–1.46
Age of onset (schizophrenia)	Over 23	29	32.95	1.01	0.87–1.16	Reference	
	Under 23	59	67.05	1.35	1.21–1.48	0.83	0.58–1.18
Age attended center	27 or over	55	62.5	1.07	0.97–1.17	Reference	
	Under 27	33	37.5	1.78	1.50–2.06	<u>0.65</u>	<u>0.47–0.90</u>

Note. HR: hazard ratio; CI: 95% confidence interval range. Statistically significant values of the HR ($p < 0.05$) are underlined for clarity.

dysfunctional behavior, and that adverse childhood experiences precede sexual or other victimization as well as severe psychopathology in adulthood in most individuals (Gibson et al., 2016; Korkeila et al., 2010; Ports et al., 2016). Women with schizophrenia seem particularly at risk for this repetition of trauma (Darves-Bornoz et al., 1995). In the current study we were unable to ascertain or rule out the role of childhood trauma in the development of psychotic symptoms, since such information is unavailable in both registries. Moreover, the extent to which it is possible to extend the current study results based on adulthood sexual assault to childhood is unknown. Therefore, further research is needed to elucidate the relationship between adulthood sexual assault and psychosis course adjusting for childhood adversity.

Of the 12 characteristics investigated, five were associated with a poorer course of schizophrenia; three of which were socio-demographic ones. The course of schizophrenia was significantly associated with single status, younger age (being born after 1979) and sexual assault at older age (attending the center over age 27). Prior diagnosis of psychosis was also associated with recurrent hospitalizations. This is consistent with general psychiatric research that showed a prototypical deterioration course among individuals diagnosed at younger age (Rabinowitz et al., 2006), as well as more frequent hospitalizations in single individuals with schizophrenia (Nyer et al., 2010).

Sexual assault severity characteristics (e.g. number of assailants, means of subdual, penetration type, offender violence and physical injury of the victim) as well as immediacy of seeking help, that were previously found to be associated with poorer outcomes in other disorders such as PTSD, major depression and SUD (Brown et al., 2009; Pinsky et al., 2017; Zinzow et al., 2010), disorders that are highly comorbid with psychotic disorders (Buckley et al., 2008), had a null association with a poorer course of schizophrenia in the current study. Early meta-analysis (Weaver and Clum, 1995) and more recent studies (Frazier, 2003; Koss et al., 2002; Startup et al., 2007), also indicated that such sexual assault severity measures have small to moderate effect sizes in predicting psychological distress, whereas subjective factors (e.g. self-blame, perceptions of controllability, life-threat or safety) had more adverse effects on mental functioning. Several models have been suggested concerning the association between stressful life events and psychosis. Affective dysregulation, heightened stress sensitivity, information processing biases, external attribution orientation, negative self-schemas, and dissociative tendencies have been proposed as tentative psychosocial mechanisms involved in the relationship between trauma and psychosis (Gibson et al., 2016). Bio-environmental models imply that trauma may influence critical processes of brain development, change immuno-inflammatory processes, disrupt synaptic plasticity and connectivity and interact with genetic vulnerability or shape gene expression via epigenetic mechanisms thereby triggering psychosis onset or worsening psychosis course and outcomes (Misiak et al., 2017). Future research is warranted to examine the lifetime likelihood of a diagnosis and course of psychosis associated with such subjective measures of adult sexual assault severity.

The current study results showed that drug use shortly before or during the sexual assault was significantly associated with a worse course of schizophrenia. A tentative explanation is that psychoactive substances acutely affect sexual arousal, risk taking, and disrupt cognitive processes such as attention, planning and decision-making. Certain drugs may also alter the perception of danger cues or initiation of cues that inhibit aggressive behaviors, as well as reaction to emotions, intentions and behaviors (Peterson et al., 1990; Simons et al., 2016; Testa and Livingston, 2009; Testa et al., 2000). Psychoactive substances may sustain and even exacerbate psychopathology and maladaptive functioning, e.g. dysregulate dopamine release that hardwire psychotic beliefs thereby increase misattribution of salience to stimuli involved in paranoia and hallucinations (Howes and Murray, 2014). Drug induced neurochemical changes may also interact with brain stress-response mechanisms involved in psychosis, such as neuroinflammation processes, endocannabinoid signaling and the aforementioned

dopaminergic system (Howes et al., 2017; Mizrahi, 2016), to trigger relapse following the assault. Psychoactive substance use is linked to increased victim self-blame and maladaptive coping, as well as negative social reactions to sexual assault disclosure (Peter-Hagene and Ullman, 2016; Ullman et al., 2007), which in turn are related to psychological distress (Gutner et al., 2006).

Drug use may also be a symptom of SUD. SUD comorbidity in major psychosis has a lifetime prevalence of 47–48.3% (Altamura et al., 2011). Individuals with co-occurring schizophrenia and SUD, when compared to individuals with a single diagnosis, have worse overall clinical outcomes (De Witte et al., 2014; Volkow, 2009) and tend to experience high rates of interpersonal victimization (Brunette and Drake, 1997; de Waal et al., 2018; Gearon et al., 2003). Unfortunately, neither the sexual assault victim registry nor The National Psychiatric Case Registry (NPCR) contains a validated SUD diagnosis, even though both registries are the largest in their kind in the nation. Moreover, despite evidence that some drugs, notably cannabis, can exacerbate psychotic symptoms and hospitalization (Arranz et al., 2018; Morgan and Gayer-Anderson, 2016; Thomsen et al., 2018), no information on the type of drug used or the pattern of drug usage (acute vs. chronic) is available. This limits conclusions regarding the pattern of drug use, which requires future investigation.

4.1. Limitations

Several limitations that are known caveats of registry-based research should be considered. First, psychiatric re-hospitalizations were used as an indirect measure of clinical exacerbation and the course of schizophrenia. However, psychiatric hospitalizations are consistently treated as a proxy outcome measure of psychotic disorders course (Addington et al., 2010; Tarricone et al., 2014). Moreover, this limitation is balanced by the extensive follow-up period, the accurate hospitalization dates made available by these multi-site country-wide data and former studies that support the validity, specificity, sensitivity and reliability of the diagnoses in this data registry (Rabinowitz et al., 1994; Weiser et al., 2005a; Weiser et al., 2012a). This registry enabled the establishment of a temporal order of assault/illness without relying on biased self-reports.

Second, findings may not be generalizable to all victims of sexual assault. Only a subgroup of rape victims seek post-assault medical care and they are more likely to indicate specific post-assault health concerns and to report the incident to police (Ullman, 2007; Zinzow et al., 2012a). Nonetheless, this subgroup includes all individuals treated at the largest medical center for sexual assault victims in the country during 10 years. As this center provides sexual assault care for the central region of Israel (a population of approximately 4,000,000), this is an epidemiological catchment study. Moreover, data provided is based on both objective physical indicators of sexual assault and various self-reported assault measures, collected mostly within 24 h of assault, thereby reducing reliance on retrospective self-report that may represent delusional beliefs and memory deficits.

Third, owing to a lack of such information in either registry, this study did not rule out confounding by childhood neglect, abuse or the quantity of stressful life events. In addition, no data on the type of drug used or the pattern of drug use (acute vs. chronic, severity), SUD diagnosis or genetic vulnerability to SUD or schizophrenia were analyzed, as no such information is available in the registries. The study data consists of ICD diagnostic codes and not specific symptoms. Therefore, it was not possible to examine specific symptoms dimensions that have been suggested to better conceptualize the phenomenology of psychosis than diagnosis (Ajnakina et al., 2016; Costello, 1992; van Os et al., 1999). Thus, the current study results do not generalize to specific symptoms. Future research is warranted to examine the effects of sexual assault on specific psychotic symptoms. Nonetheless, the current study data comprised of the NPCR that enables a lifetime follow-up of the course of schizophrenia, based on valid and reliable clinical diagnoses

(Rabinowitz et al., 1994; Weiser et al., 2005a; Weiser et al., 2012a). Future research using more in depth drug assessments as well as urinalysis would be appropriate to adjust for these factors. Causal inference is not possible from observational epidemiologic study data such as the current. However, an experiment to separate cause and effect for sexual assault would be unethical. Hence, these longitudinal data offer an optimal alternative.

4.2. Implications

Several clinical implications for prevention and intervention should be considered. First, drug use must be assessed and addressed systematically in sexual assault survivors with schizophrenia seeking care in a hospital-based setting, to help identify high-risk individuals. Second, facilitated referral for dual diagnosis integrated treatment in addition to counseling at the time of admission to post-assault medical services may be advisable for some survivors. Implementation of screening, brief intervention, and referral to treatment (SBIRT) approaches targeting substance abuse should be considered, as they were found to be effective within emergency department populations (Madras et al., 2009) and within non-psychiatric sexual assault victims seeking medical care (Blow et al., 2010; Boudreaux et al., 2009). Interventions aimed to promote protective factors toward remission should also be considered (Cheng et al., 2016; Ruggeri et al., 2015). Third, education about substance use as an assault tactic and vulnerability factor for re-hospitalization of people with psychotic disorders might be helpful for reducing risk behavior and victims' self-blame (Resnick et al., 2013; Testa and Livingston, 2009). These recommendations are relevant among assault survivors given the vast literature that show that victims of crime are likely to be victimized repeatedly during their life span (Classen et al., 2005; Messman-Moore and Long, 2003; Ruback et al., 2014) and that victimization is associated with poorer quality-of-life and greater treatment resistance among psychiatric patients (Mueser et al., 2002; Neria et al., 2005).

4.3. Conclusions

This catchment area study of sexual assault victims showed that a poorer course of schizophrenia was significantly associated with victims' single status, younger age, sexual assault at an older age and previous diagnosis of psychosis. The only situational assault severity characteristic that predicted long-term deleterious illness course was substance use shortly before or during the sexual assault. This suggests that persons who use drugs and previously were diagnosed with schizophrenia or developed schizophrenia after the sexual assault should be targeted for intensive interventions to prevent an exacerbated course of the disorder. Future studies are warranted to examine the mechanisms of acute versus chronic drug use in adult sexual assault victims with schizophrenia, accounting for prior adverse childhood experiences. Implications of the current study results for prevention, assessment, treatment formulation and implementation are underscored by the result that drug use and abuse patterns are associated with an exacerbated course of schizophrenia, yet is often not ascertained in psychiatric assessments (Elklit and Shevlin, 2010).

Role of the funding source

The present study has been partially supported by the Israel Anti-Drug Authority (IADA) awarded to Dr. S. Rabinovitz and Mrs. K. Goldman. IADA had no involvement in study design, in the collection, analysis and interpretation of data; in preparation, review, approval of the manuscript or in the decision to submit the paper for publication.

Conflict of interest

In unrelated work, Dr. Levine has received research support, and/or consultancy fees and/or travel support from F. Hoffmann-La Roche, Shire Pharmaceuticals, Eli Lilly and Maccabi Healthcare Services. The remaining authors report no conflict of interest.

CRediT authorship contribution statement

Sharon Rabinovitz: Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing - original draft, Writing - review & editing. **Keren Goldman:** Conceptualization, Investigation, Project administration, Writing - review & editing. **Paula Rosca:** Writing - review & editing, Resources. **Julia Barda:** Data curation, Writing - review & editing. **Stephen Z. Levine:** Methodology, Formal analysis, Writing - review & editing.

CRediT authorship contribution statement

Sharon Rabinovitz: Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing - original draft, Writing - review & editing. **Keren Goldman:** Conceptualization, Investigation, Project administration, Writing - review & editing. **Paula Rosca:** Writing - review & editing, Resources. **Julia Barda:** Data curation, Writing - review & editing. **Stephen Z. Levine:** Methodology, Formal analysis, Writing - review & editing.

Acknowledgements

The authors would like to thank Inna Pugachova, Health Information Division, Ministry of Health, Jerusalem, Israel for her kind assistance in facilitating data access.

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