TARGETING THE MISSING LINK: THE NEXUS OF EARLY PHASE PSYCHOSIS, SUBSTANCE MISUSE, AND ADVERSITY

by

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Dalhousie University is located in Mi'kma'ki,

the ancestral and unceded territory of the Mi'kmaq.

We are all Treaty people.

DEDICATION

This body of work is dedicated to Marian Kathryn Johnston, who inspired it all.

May you rest in peace, somewhere over the rainbow.

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ABSTRACT

Adverse events (AEs), such as bullying and child abuse, and substance misuse (SM) are each highly prevalent among people with psychotic disorders. However, there is limited information about the overlap of AEs and SM within psychotic disorders, especially among people in the early years of a psychotic disorder (i.e., early phase psychosis; EPP). Examining the overlap is important given that AEs and SM are each individually associated with mental health challenges. In Study 1, I conducted a systematic review of 57 studies assessing the nexus of psychotic disorders, SM, and AEs. Psychotic disorders and AEs were consistently associated, but the role of SM was less clear across studies. Most studies used general samples of people with psychotic disorders, rather than assessing by illness duration (e.g., EPP, chronic psychosis). Similarly, child abuse and cannabis/alcohol were the main foci of their respective literatures, limiting the scope of the information about the overlap between psychotic disorders, SM, and AEs. Risk of bias was moderate-high, with issues particularly identified with recruitment, design, and analyses. In Study 2, I surveyed young adults with EPP (N = 110) about their AEs and current SM. Psychosis commonly overlapped with SM and AEs, and SM rarely appeared in the absence of adversity. AEs and SM were individually highly prevalent (97% and 77%). When queried, 72% of participants acknowledged wanting to discuss their AEs with a mental health clinician. Study 3 trialed an adapted prolonged exposure intervention ('PE+') that targeted common mechanisms shared between psychosis, AE sequelae, and SM in a sample of young adults with EPP (N = 19). Across participants, there were clinically significant decreases in anxiety, depressive symptoms, and dissociation, and some improvements in experiential avoidance and sleep. Psychotic symptoms improved little, although they did not worsen, and SM had more variability, improving for some and worsening for others. My dissertation informs future development for AE-focused interventions for people with EPP by delineating the importance of the inclusion of SM and clarifying opportunities to meet the unique needs of this group.

LIST OF ABBREVIATIONS AND SYMBOLS USED

2SLGBTQ+	Two-spirit, lesbian, gay, bisexual, transgender, queer + individuals
α	Cronbach's alpha
Ω	Omega
AE(s)	Adverse event(s)/adversity
APA	American Psychological Association
BEAQ	Brief Experiential Avoidance Questionnaire
BHS	Beck Hopelessness Scale
CBT	Cognitive Behavioural therapy
CGI-I	Clinical Global Impression – Improvement of Illness
CGI-S	Clinical Global Impression – Severity of Illness
CI	Confidence interval
DBT	Dialectical Behaviour Therapy
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DUP	Duration of untreated psychosis
EMDR	Eye movement desensitization and reprocessing therapy
EPP	Early phase psychosis
ISTDP	Intensive short-term dynamic psychotherapy
M	Mean
MBD	Multiple baseline design
N	Sample size
NIH	National Institutes of Health
NSEPP	Nova Scotia Early Psychosis Program

p	p-value
PANSS	Positive and Negative Syndrome Scale
POC	People of Colour
PCL-5	Posttraumatic Stress Disorder Checklist-5
PD	Psychotic disorder(s)
PE	Prolonged Exposure therapy
PE+	Adapted Prolonged Exposure therapy
PLEs	Psychotic-like experience(s)
PTSD	Posttraumatic Stress Disorder
r	Correlation
R^2	Coefficient of determination
RCI	Reliable change index
RCT	Randomized controlled trial
SD	Standard deviation
SIP	Substance-induced psychosis
SM	Substance misuse
SOFAS	Social and Occupational Functioning Assessment Scale
SRS-3	Session Rating Scale-3
TALE	Trauma and Life Events checklist
TF-CBT	Trauma-focused cognitive behavioral therapy
TSC-40	Trauma Symptom Checklist-40
UID	Unreported illness duration

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Chapter 1. Introduction

Proneness-persistence-impairment model

Predicting the onset of a psychotic disorder (PD) is a challenging endeavour. Many early/prodromal symptoms are nonspecific (e.g., social withdrawal, sleep difficulties, poorer concentration; George et al., 2017; Velthorst et al., 2009) and psychotic-like experiences (PLEs) are more common among youth than most people expect (e.g., 17% of 9-12-year-olds; Kelleher et al., 2012). Less than one-third of individuals with nonspecific prodromal symptoms convert to a psychotic disorder (Hanssen et al., 2005). van Os and colleagues (2009) posited that one way to predict and understand psychosis conversion is through the lens of a psychosis proneness-persistence-impairment model. That is, some factors that make an individual prone to psychosis (e.g., genetics) may interact with environmental risk factors, which can result in PLEs that persist and eventually convert to psychotic symptoms. Many PLEs and positive psychotic symptoms (i.e., hallucinations, delusions) appear to be temporary. One study found lower rates of reported PLEs among adults (3%) than rates reported among the same individuals as adolescents (6%), while another study found a post-test probability of 8%. Although no individuals reported PLEs at baseline, 8% of individuals with a PLE at time 1 continued to experience PLEs at the two-year follow-up (Dhossche et al., 2002; Hanssen et al., 2005). Therefore, it is the persistence of PLEs, rather than their initial occurrence, that may signal a cause for concern.

The persistence of PLEs has been associated with an increased risk of developing a psychotic disorder (Welham et al., 2009). Following the onset of psychotic symptoms, their persistence can lead to impairment, with difficulties in functioning (e.g., attending work, school) becoming increasingly common as psychosis persists in duration (Hafeez & Yung, 2021). There are two environmental risk factors that may interact with genetic vulnerability for psychosis and have recently been an important area of research and clinical focus: substance use, specifically cannabis use, and past AEs. Researchers have observed an association between conversion to psychosis with a history of adversity, especially those with a history of sexual abuse (Bechdolf et al., 2010), and psychotic episodes triggered by substance use (i.e., substance-induced psychosis) appear to be related to a higher risk of later conversion to schizophrenia (Starzer et al., 2018). In addition to concerns about the development of a PD, AEs and substance use are associated with *maintenance* of psychotic symptoms once they have developed (Mackie et al., 2011; Morrison et al., 2003). In essence, these two environmental factors are important and worthy of empirical and clinical attention to aid in understanding their effects, both individually and together, in psychosis development and thus determining their potential roles as targets in mitigation strategies.

Adversity

Definition and operationalization

Life is full of stressors—such as daily difficulties, bad news, and challenging interactions. Yet for some individuals, the stressors in their lives

exceed the threshold for ‘everyday stressor’ and instead are better captured under the label ‘adversity’ or ‘adverse event’ (AE), which are terms that will be used interchangeably throughout this thesis. AEs are defined as “negative events that have occurred …. These events are outside the control of the [individual], have the potential to impede or alter normal development, and cause harm or the potential for harm along with stress and suffering” (Burgermeister, 2007, p.164). Examples of lifetime AEs include physical abuse, bullying, homelessness, and distressing hallucinations. The literature commonly employs an array of terms for AEs, such as trauma or traumatic life event (TLE; e.g., sexual abuse, assault), maltreatment (e.g., emotional neglect), stressful life events (SLEs; e.g., job loss), and stressful events, among others. Inconsistent definitions and operationalizations across studies have made interpretations and summaries challenging. For clarity, this thesis defined AEs as inclusive of traumatic events, in addition to broader events that do not meet the below criteria for ‘trauma’ according to the Diagnostic and Statistical Manual of Mental Disorders—Fifth edition text revision [DSM-5-TR] (American Psychiatric Association [APA], 2022)yet have similarly deleterious effects. Traumatic events are defined as experiences of “actual or threatened death, serious injury, or sexual violence” that are directly witnessed or experienced, or are experienced through indirect exposure (i.e., occupational exposure, event befalls loved one; APA, 2022).

Relationship of adversity with psychosis

AEs are considered a transdiagnostic risk factor for psychopathology (Albott et al., 2018); however, several studies have noted a significant

relationship between AEs and psychotic symptoms (Longden et al., 2016; Whitfield et al., 2005) and PDs, such as schizophrenia (Matheson et al., 2013a). A number of studies have found an elevated prevalence of AEs among individuals with PDs; some studies have reported prevalence rates exceeding 90%, with nearly 70% of participants reporting an AE independent of their psychotic illness (Picken & Tarrier, 2011; Tarrier & Picken, 2011). Elevated rates of PTSD are similarly observed among people with PDs (Aakre et al., 2014). A dose-response relationship has been reported between both the number of AEs and the frequency of AEs with psychosis. One study found that experiencing two AEs increased the likelihood of psychosis 3.37 times, while 3 AEs increased it to 7.42 times more likely, while 5 AEs increased the risk of experiencing psychosis 30.16 times (Shevlin et al., 2007). Another study examined the severity of the AE, specifically childhood abuse, and found that, compared to those who had never experienced childhood abuse, individuals who experienced 'moderate' abuse had an 11 times greater risk of experiencing psychosis, while those who experienced 'severe' abuse had a 48 times greater risk of experiencing psychosis (Janssen et al., 2004). The relationship between AEs and psychosis risk appears substantial, and the effects appear to go beyond the risk of onset. Bak and colleagues (2005) observed that individuals with a history of AEs may feel less able to cope with psychotic experiences, perceiving these events as uncontrollable, both of which may increase their distress. Additionally, there is evidence that dissociation may mediate the relationship between childhood maltreatment, especially neglect, and psychosis (Evans et al., 2015); this is

consistent with suggestions that dissociation is one of the mechanisms of psychosis development following AEs (Braehler et al., 2013). Much of the literature considered childhood AEs, especially childhood maltreatment, although it is also important to consider victimization in adulthood.

Theory of AE-focused treatment

Emotional processing theory (EPT) is one theorized mechanism of change for PTSD treatments (e.g., Prolonged Exposure, Trauma-Focused Cognitive Behavioural Therapy; Foa & McLean, 2016; McLean & Foa, 2011). EPT suggests that individuals experience a multi-component fear response: the stimuli provoking fear, the fear response (fight-or-flight response, e.g., rapid heartbeat), and meaning about both the stimuli and the fear response. This fear response becomes problematic when the fear structure is activated in harmless or safe situations. EPT posits that by activating fear structures, and then providing alternate experiences of feared stimuli or responses that compete with their initial fear response, reactions/meaning can be modified. In line with more recent work on learning, the focus is not on modifying previous associations or reactions, but rather generating new meaning and associations between previously feared stimuli or reactions and meaning. However, for this process to occur, the fear structure must be activated to incorporate these new experiences. That is why exposure is an effective treatment component in PTSD treatment (Foa & McLean, 2016) – it allows individuals to experience previously avoided stimuli or responses, and then aids participants to develop realistic, alternate beliefs that compete against previously developed beliefs (i.e., inhibitory learning;

Craske et al., 2016; Hofmann, 2008). Moreover, inhibitory learning is associated with a decrease in physiological reactivity, (i.e., the 'fight-or-flight' response is less easily triggered), which is associated with a positive treatment outcome in people with PTSD (Wangelin & Tuerk, 2015).

Substance misuse

Definition and operationalization

Short and colleagues (2013) found that among those with a schizophrenia-spectrum disorder, individuals were 1.9 times more likely to be victimized and 2.6 times more likely to experience violent victimization if they have a substance use disorder (SUD) than if they do not have an SUD. Compared to a community control group, people with a schizophrenia-spectrum disorder and an SUD have a 6.4 times greater chance of experiencing violent sexual victimization, when age and gender were controlled. These findings highlight the need to focus on substance misuse (SM) when considering PDs and AEs. SM is an umbrella term inclusive of risky or harmful use of substances (e.g., binge drinking), which also includes substance use disorders (SUDs; McLellan, 2017). SM is differentiated from substance use by its consequences – use may not have any adverse consequences, whereas misuse carries greater risks (e.g., to functioning, health).

Stress and coping model of substance misuse

Against a backdrop of other possible risk factors for substance use (e.g., temperament, social factors), the stress and coping model, also known as 'coping motives', posits that substance use may serve one or several functions,

such as affect regulation, distraction (e.g., from cognitions), or situation enhancement (Wills & Hirky, 1996). Coping style is theorized to increase or decrease the role of substance use in coping: active or problem-focused coping (e.g., planning, suppression of competing activities, seeking instrumental social support) is negatively associated with risk for substance use, while avoidant coping (e.g., denial, mental or behavioral disengagement) is positively associated with substance use, particularly at low levels of self-efficacy (Levin et al., 2007). Avoidant coping may worsen situations because of individuals' disengagement, further reducing any available social support, while the reverse is true for active coping. Cooper and colleagues (1992) tested models of alcohol use, finding support for a stressor vulnerability model. Stressful life events accounted for a significant amount of the total variance (35%) in alcohol use among men who engaged in avoidant coping and had positive expectancies of alcohol use (i.e., expected alcohol to help with negative emotions) and greater alcohol use problems were reported. The same effects were not observed among men low in avoidance coping or who had low positive expectancies for alcohol use, although similar effects were observed among women with positive expectancies for alcohol (greater alcohol use problems) with a smaller magnitude compared to men. Cooper and colleagues assessed whether negative affect mediated life stressors and alcohol misuse; analyses did not support mediation of the relationship between stressors and alcohol misuse, suggesting instead that stressors may increase negative affect, prompting increased alcohol use. Coping motives for substance use mediated the relationship between emotional and

physical abuse and SM in a sample of adolescents and young adults (Hogarth et al., 2019), even after controlling for gender and other non-substance use coping approaches. As discussed by Cooper and colleagues, using substances to cope can present problems for an individual given its strong relationship with problematic substance use (e.g., Poindexter et al., 2015). In summary, substance use may function as a coping strategy for life stressors, both small and large (e.g., AEs), and substance-related coping is related with negative outcomes.

Overlap of substance misuse with psychosis

There is a well-established relationship between psychosis and SM in the literature (Moore et al., 2007). Estimates of SUD rates in psychotic disorders can range from 40-70% (Addington & Addington, 2007; Ouellet-Plamondon et al., 2017), with one study finding a 62% SUD prevalence prior to early psychosis treatment (Lambert et al., 2005). A recent study at the Nova Scotia Early Psychosis Program (NSEPP) of SM in EPP found rates as high as 83% (Cookey et al., 2020). Alcohol and cannabis were most commonly misused (Cookey et al., 2020) , mirroring the findings of most studies of SM and PDs (E. Moore et al., 2012). Similar to AEs, cannabis use is predictive of psychotic symptoms in a dose-response fashion, with greater frequency of use predicting more psychotic symptoms (T. H. Moore et al., 2007; van Os et al., 2002), especially when individuals frequently use high-potency cannabis (Di Forti et al., 2014). Several research groups have found that cannabis use disorder (CUD) is associated with a younger age of onset of schizophrenia (Baudin et al., 2016; Large et al., 2011), and others have found that early onset of cannabis use was associated with the

onset of a PD (Arseneault et al., 2002), even after controlling for childhood PLEs. Others noted a differential relationship across gender: men who used multiple substances had a younger age of onset of psychosis than women (B. Arranz et al., 2015; Crocker & Tibbo, 2018). However, only two genders were examined, limiting the conclusions that can be drawn from this work. When considering the impact of specific substances, some researchers found that cannabis use predicted the severity of psychotic symptoms among people with a PD (van Nierop et al., 2013), and was commonly identified by individuals with PDs as the substance causing the most problems for them (E. Moore et al., 2012). Interestingly, previous work has also found that people with PDs may also experience positive and negative impacts of substance, even in small quantities, much more easily than people without PDs (e.g., Bizzarri et al., 2009; D'Souza et al., 2006; Knudsen & Vilmar, 1984).

The motives for use have been inconsistent across PD samples, with some studies highlighting enhancement motives (e.g., feeling good, getting high; Kolliakou et al., 2015),or coping with negative affect or stressors ('alleviation of dysphoria'; Kolliakou et al., 2011; Pencer & Addington, 2008) as the primary motives, with fewer recent studies finding support for the traditional 'self-medication' hypothesis (SMH; i.e., substance use to alleviate symptoms of illness, such as psychotic symptoms; (Bersani et al., 2002; Khantzian, 1987). The relevance of the traditional SMH to a PD population has been debated for many years. As highlighted above, much of the recent work examining substance use motives have supported enhancement motives or a modified SMH (Khantzian,

1997), which is inclusive of efforts to cope with illness symptoms (e.g., hallucinations) as well as coping with distressing thoughts, emotions, and physiological states by using substances (Waldrop et al., 2007).

Overlap with adversity

Similar to the evidence linking PDs and AEs, there is a plethora of evidence linking SM and AEs, with a particular focus on alcohol and cannabis misuse and AEs. In a Canadian sample, after adjusting for mood and anxiety disorders and demographic variables, child maltreatment (e.g., abuse, neglect) increased the odds of developing an SUD 1.4-2.6 times, with greater odds of developing an SUD among men (Afifi et al., 2012). Schalinski and colleagues (2015) observed greater membership to the alcohol dependency group among their participants with 'high' adversity (36%) compared to 'low' adversity (3%), while others have noted a relationship between child maltreatment and cannabis misuse (Oshri et al., 2011). The traditional and modified SMH have also been applied to the relationship between SM and AEs, with applications more specific to AE-related illness including efforts to cope with AE-related illness (e.g., physiological arousal in PTSD). In non-PD samples, the SMH has often been studied in the context of PTSD and alcohol misuse, and a recent systematic review of this relationship highlighted the methodological issues with this literature, such as poor operationalization of 'drinking to cope' (Hawn et al., 2020).

Early phase psychosis

The first few years of a PD is called early phase psychosis (EPP), and it is often defined as the first five years of a PD, which is inclusive of first-episode psychosis (FEP). Previous research has highlighted the importance of intervention within 3-5 years of illness onset to improve outcomes (Crumlish et al., 2009; Fowler et al., 2009). Previously, without intervention in this early stage, recovery rates were typically 20% or less (Jääskeläinen et al., 2013), although criteria for 'recovery' was stringent, requiring sustained symptomatic remission (i.e., recovery from psychotic symptoms) for at least two years, as well as sustained improvements to social and occupational functioning. In a meta-analysis examining first-episode psychosis (FEP) samples' rates of recovery and remission (i.e., 6 months without disorganization of speech or behaviour, or positive or negative symptoms; Caton et al., 2006), results indicated recovery for 37.9% of the included participants, and remission for 57.9% of participants (Lally et al., 2017). These rates, which were collected over an average of 7 years, suggest recent improvements to outcomes compared to those rates prior to early intervention. However, the focus on recovery has shifted from symptomatic recovery to functional recovery (i.e., returning to occupational or academic pursuits; Verma et al., 2012). In other words, EPP represents an important stage for intervention. Individuals in this stage of a psychotic disorder are often offered patient-specific early intervention services (e.g., medication, occupational therapy) to facilitate functional recovery from a psychotic illness. Evidence suggests that compared to treatment as usual, early intervention services in EPP

are associated with improved outcomes (e.g., reduced positive and negative symptom severity; Correll et al., 2018). Compared to individuals with chronic psychosis, people in EPP have experienced less illness burden, meaning their cognitive and affective functioning is less impacted (Lieberman et al., 2001) and developing interventions targeting this stage may impart greater benefit to individuals' recovery than interventions offered at a later stage. Although pharmacotherapy is typically the frontline intervention provided for psychotic symptoms, individuals in EPP often present to treatment with multiple other difficulties, such as SM, housing challenges, and a lack of social support. Considering the multitude of areas in which to intervene, choosing a treatment target is difficult. However, a theory that has been delineated and built upon in the literature may assist in developing treatment targets: network theory.

Network theory

Borsboom and colleagues (2011), and Borsboom and Cramer (2013) introduced network theory and analysis to psychopathology, illustrating the interconnected nature of the symptoms constituting the disorders listed in the DSM-5-TR (APA, 2022). Systems of symptoms, which are causally linked, were noted to maintain themselves through 'dynamic feedback loops' (Hardy et al., 2021, p.1), meaning that elements of the system served to strengthen connections between them. The relevance of this theory and associated analysis approach to psychosis was illustrated by Isvoranu and colleagues (2017), who mapped the associations between schizophrenia symptomatology for those with environmental exposures (i.e., AEs, urbanicity) and those with cannabis

exposure but no environmental exposures. For those with environmental exposures, there were strong links between paranoid ideation/psychoticism and interpersonal sensitivity; interpersonal sensitivity was in turn linked to depression, and depression unsurprisingly had a substantial link to anxiety. The structure of this psychosis-psychopathology model was similar for those without environmental exposures. However, the strength of the relationships between variables differed: the no-environmental-exposures model had a greater number of connections between variables, but these connections were weaker, whereas the connections in the environmental exposure model were fewer but more robust.

The focus of these network models are not diagnostic classifications but rather symptoms, meaning that network theory takes a transdiagnostic approach. It has been suggested that targeting one set of symptoms (AEs sequelae, e.g., dissociation, anxiety) within a constellation of mental health challenges can effect improvement on other, related symptoms (Goekoop & Goekoop, 2014). Hardy and colleagues (2021) extended network theory for psychosis by conducting a more focused examination of the networks connecting PTSD and psychosis, finding that AE-related beliefs (i.e., negative beliefs about self, the world) and hypervigilance were 'bridge' symptoms, linking psychosis and AEs. Network theory has only recently been applied to psychopathology, and even more recently to psychosis and AEs. However, the essence of the work thus far posits that models are transdiagnostic, that they examine mechanisms of development

and maintenance, and that targeting one element of the system may result in change to the entire system.

Limitations of prior work

The primary limitation of the literature in this field is the paucity of research examining the overlap between PDs, SM, and AEs, rather than only two of these three variables at a time, despite the strong relationships established between all three. Moreover, when these three variables are examined together, one variable functions as a primary variable of interest, while the other(s) are relegated to the background, which has prevented a thorough investigation of the overlaps between these variables. In addition, much of the literature focuses on chronic psychosis or 'people with psychotic disorders', meaning results specific to EPP are obscured. Furthermore, child abuse and cannabis/alcohol are the primary types of AEs and substances explored, seemingly at the expense of other types of AEs or substances that individuals can experience, although there may be other factors at play (i.e., lower incidence of other types of AEs, substances used).

Dissertation aims and hypotheses

The overarching aim of my dissertation was to review, investigate, and treat the nexus of PDs, SM, and adversity. There was a particular focus on EPP and its relationship with SM and AEs, given that EPP is comparatively less studied than other phases of psychosis.

Study 1 aims

The first study of my dissertation was a systematic review of the literature exploring the nexus, or three-way connection, between PDs, SM, and AEs. Most reviews in this area have focused on the relationships between two variables (e.g., PDs-SM; AEs-SM), neglecting the nuances of the inter-relations between these three variables. The aim of this systematic review was to understand factors affecting the PD-SM-AEs relationship, such as stage and type of PD (e.g., chronic psychosis), type of AE (e.g., sexual abuse), or type of substance (e.g., cocaine).

Study 2 aims

My second study addressed a similar limitation as study 1: the lack of inclusion of SM in PD-AE relationship research. However, this study focused on EPP and its overlap with SM and AEs, aiming to establish the proportion of individuals with EPP who have both SM and a history of AEs, as well as gathering information about whether people with this overlap were interested in discussing their AE experiences with mental health providers. I hypothesized: 1) More than 60% of the sample would have both a history of AEs and current SM, 2) PTSD symptoms would be highest amongst those who reported AEs before age 18, and 3) Over 50% of the sample with EPP, SM, and a history of AEs would be interested in speaking to a mental health professional about their AEs.

Study 2 was the foundation upon which I built an intervention study, Study 3. Study 2 had to be conducted first as it clarified whether participants were

interested in an intervention and what substances and AEs I could expect to treat, which helped to refine the intervention.

Study 3 aims

My third and final study, which was divided into two chapters in the thesis, tested an adapted prolonged exposure therapy protocol ('PE+'). Using a multiple-baseline design (i.e., a single-case experimental design), I recruited young adults in EPP with current SM and a history of distressing AEs, with at least one AE continuing to impact them (e.g., distress, flashbacks). This study helped to further the AEs intervention literature for people with PDs by developing and testing an AE-specific treatment that simultaneously addresses SM. This treatment targeted common mechanisms between psychosis, SM, and AEs, and observed whether targeting these mechanisms via an adversity-focused treatment would result in clinically significant changes in SM or psychotic symptoms. I hypothesized that PE+ treatment would result in clinically significant reductions in 1) negative psychotic symptoms (e.g., anhedonia), 2) adversity-related sequelae (e.g., anxiety, insomnia), 3) the frequency and quantity of SM, and 4) that all reductions would be maintained by 2-months post-treatment. Secondary hypotheses included: 1) clinically significant reductions in hopelessness and experiential avoidance, and 2) a global improvement in social and occupational functioning from pre-to-post PE+ therapy that would be maintained 2 months post-treatment.

Dissertation outline

Each study discussed above can be found in the subsequent chapters of this dissertation. Study 1 can be found in Chapter 2, transition chapter 1 (study 1

to 2) can be found in Chapter 3, Study 2 appears in Chapter 4, transition chapter 2 (study 2 to 3) is found in Chapter 5, the methods for Study 3 are discussed in Chapter 6, while Study 3 results can be found in Chapter 7. An overarching discussion of my dissertation's results, which includes theoretical and clinical implications, can be found in Chapter 8.

Chapter 2. A systematic review of the overlap between psychotic disorders, substance misuse, and a history of adversity.

The manuscript prepared for this study is presented below. Readers are advised that Victoria Patterson, under the co-supervision of Dr. Alissa Pencer and Dr. Philip Tibbo, was responsible for developing the research questions and search script, screening abstracts, reviewing full-text studies, and coordinating the activities of a second reviewer. Victoria wrote the initial draft of the manuscript, with support from her co-authors, and received and incorporated feedback from all co-authors. The manuscript is under review at *Schizophrenia Research*. The full reference for this manuscript is:

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Abstract

Objectives: This systematic review aimed to examine the relationship between AEs, PDs, and SM, and associations with stages of a PD.

Methods: We conducted a systematic search of six databases to identify eligible studies published between 2000 and 2023, in addition to forward and backward searches. Inclusion criteria included a diagnosed PD, a lifetime history of an AE, and SM. Both longitudinal and cross-sectional designs were included, but high-risk and prodromal studies were excluded.

Results: This review included 57 reports of the possible 16,215 articles found during the search. The prevalence rate of AEs often exceeded 75%, while SM was estimated to exceed 40%. Individuals with a PD, SM, and a history of adversity exhibited poorer functional outcomes, lower rates of remission of psychotic symptoms, and increased rates of PTSD symptoms and diagnoses relative to people without SM and AEs. There were greater rates of adversity among those with a PD and SM compared to those with only a PD. The temporal ordering of events was unclear given that few studies reported age of onset for all events.

Conclusions: There appears to be an association between PDs, SM, and AEs, and these variables may impact outcomes and risk for people with PDs. However, the cross-sectional nature of the data, power issues, inconsistent measurement, and a lack of diversity limit the possible causal conclusions that can be drawn from this body of literature.

Keywords: PDs, adversity, substance use, comorbidity, review

Introduction

SM, inclusive of SUDs, is commonly found among individuals with PDs (e.g., schizophrenia), with prevalence rates ranging from 40 to 80% (Cantor-Graae et al., 2001; Cookey et al., 2020; Hunt et al., 2018; Lambert et al., 2005). SM is associated with a younger age of illness onset and a longer duration of untreated psychosis (DUP; Large et al., 2011, 2014). Moreover, SM has been linked to poorer functional outcomes and greater symptom severity among people with PDs (Talamo et al., 2006). In addition, SM is theorized to be both a risk factor (Seid et al., 2021; Walsh et al., 2003) and coping strategy for managing the sequelae of AEs (e.g., child abuse, assault; Wills & Hirky, 1996). Previous work has found that the often-reciprocal relationship between SM and AEs can result in the maintenance of both SM and AE-related challenges (e.g., PTSD).

More recently, the relationship between AEs and PDs has become an important area of focus. Several studies have found elevated prevalence rates of AEs among people with PDs (e.g., 70-90%; Compton et al., 2004; Schalinski et al., 2015), elevated rates of PTSD (Tarrier & Picken, 2011) and findings of early life AEs being associated with worse PD outcomes (e.g., more severe positive symptoms; Gairns et al., 2015; Janssen et al., 2004; Jones et al., 2019). There is increasing evidence that AEs and SM are separate factors that influence both the onset and outcomes of PDs, and the bidirectional relationships between AEs/SM and PDs may maintain PD symptoms. Yet, the nexus of these three variables has not yet been the focus of a systematic review.

Previous systematic reviews have primarily focused on the association between childhood maltreatment (e.g., abuse, neglect) and psychosis. An earlier review evaluated the existing evidence, noting methodological issues (Bendall et al., 2007) while others focused on examining child maltreatment prevalence rates in PDs (Matheson et al., 2013b) and the mediators and moderators of the relationship between adversity and psychosis (Williams et al., 2018). More recently, a systematic review examining childhood trauma among those with first-episode psychosis (Vila-Badia et al., 2021) found an elevated incidence of maltreatment compared to controls. These reviews indicate a significant relationship between adversity and psychosis, yet the scope of evidence is limited given the narrow focus on child maltreatment and schizophrenia samples. As a result, a broader diversity of AEs is neglected, including those AEs occurring during adulthood. Moreover, psychosis samples rarely include substance-induced psychosis (SIP), despite a high prevalence of SIP in early intervention services (Caton et al., 2005). Two systematic reviews published in 2020 examined substance use in the context of the relationship between childhood adversity and psychosis. Sideli et al., 2020) reviewed 12 articles that predominately examined cannabis as a moderator or mediator between childhood adversity and psychosis. One study found evidence of both direct and indirect effects of AEs on psychosis, with cannabis acting as a partial mediator (van Nierop et al., 2014), while others found that cannabis did not mediate AEs and psychosis (Goldstone et al., 2011, 2012). There were contrasting results among studies examining multiplicative and additive interactions between

cannabis and childhood AEs on the risk of developing psychotic symptoms; some found evidence for an additive (Harley et al., 2010) and multiplicative interaction (Houston et al., 2008), while others did not (Baudin et al., 2016; Morgan et al., 2014). However, this review was limited by strong cannabis focus. Setién-Suero and colleagues (2020) summarized 23 articles investigating the relationships among childhood AEs, PDs, and substance use; however, their review was not focused exclusively on the three-way overlap between variables, preventing an in-depth exploration of the relationships among these variables. Moreover, their search was more circumscribed in terms of included study designs and databases searched, leading to a smaller review sample.

Given the existence of several high-quality systematic reviews focused on the two-way overlaps between PDs, SM, and AEs (e.g., Bendall et al., 2007; Hunt et al., 2018), it is important to carry out an in-depth review of the overlap between these three variables and gain an understanding of factors affecting this relationship. The aims of this systematic review were to take a contemporaneous approach to examining whether the relationship between PDs, SM, and AEs varied depending on:

1) Stage and type of PD (e.g., EPP, SIP)
2) Substance type (e.g., cannabis, cocaine)
3) Type of adversity (e.g., sexual abuse, being unhoused)

Methods

Search procedure

A systematic review of the literature was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Page et al., 2021). This review was prospectively registered on PROSPERO (CRD42020142485). We searched six databases in November 2019, including PubMed, PsycINFO, CINAHL, Web of Science, Scopus, and Embase, and the search results were updated in June 2023. We searched broadly for words indicating adversity (e.g., trauma, abuse) 'AND' PDs (e.g., 'psychosis', 'schizo*') 'AND' SM (e.g., 'cocaine', 'substance abuse') using branched logic. Reference lists of all included studies were searched to ensure completeness. Full details of the search terms are available in our PROSPERO registration.

Inclusion and exclusion criteria

Included studies must have met all criteria within the same study: 1) participants had to have a diagnosis of a non-affective PD (e.g., schizophrenia, SIP) [ICD F20-F29], 2) at least one lifetime AE (e.g., homelessness, child abuse) was measured in the study sample, 3) author-defined SM (e.g., SUDs, problematic use) was measured in the study sample, and 4) the article was written in English or French. Lastly, 5) the article must have been published between the years 2000 and 2023, given our contemporaneous focus.

Exclusion criteria included: 1) animal models, 2) studies of mental illness that did not analyze PDs separately, 3) affective psychosis (either as primary cohort or within study sample; separate subsamples of people with psychotic

disorders examined in a larger study of mental illness were included), 4) ultra-high risk, prodromal, or family high-risk population samples, or 5) AEs were only measured using chart notes. Chart notes often severely underrepresent the proportion of individuals who have experienced adversity (Read & Fraser, 1998) and are not considered a valid method of ascertaining exposure to adversity. The exception to this rule was police records – studies solely focused on criminal victimization were included.

Data extraction and analytic plan

Study selection was conducted according to the described eligibility criteria. Two independent reviewers (VP and AH) screened titles and abstracts from all identified reports and examined articles for eligibility in their full text format. Data from the following domains were extracted: participant information (e.g., demographics, symptoms), psychosis (e.g., disorder, stage), SM (e.g., frequency of misuse, substance type), adversity (e.g., type, timing), methods (e.g., measures), results, theorized relationship between three variables of interest, and information about the temporal timing of the relationship, if available. Inter-rater reliability for abstract screening was 0.42, and full-text screening was 0.61; the primary cause of the substantial disagreements among reviewers was one reviewer being over-inclusive of articles. Overall, the disagreements were resolved by being over-inclusive, especially at the abstract screening stage.

Assessment of risk and bias

In line with PRISMA recommendations, a component approach was used to assess included studies for risk of bias in place of use of less robust methods (e.g., checklists, questionnaires; Liberati et al., 2009). The quality of included articles was evaluated using the Effective Public Health Practice Project's (EPHPP) quality assessment tool for quantitative studies. Previous research has demonstrated the validity (Deeks et al., 2003; Thomas et al., 2004) and reliability (Armijo-Olivo et al., 2012) of the EPHPP tool in healthcare contexts. The EPHPP quality assessment tool was adapted by Williams and colleagues (2018) to assess the potential for bias in studies examining mediators and moderators between adversity and psychosis, and we adopted their modified version to assess study quality and potential for bias in six domains: (1) selection bias, (2) study design, (3) confounders, (4) data collection methods, (5) withdrawals and dropouts, and (6) analyses. Each domain and the study overall were assigned a 'strong', 'moderate', or 'weak' rating by two independent reviewers (VP and BS). Overall strong ratings were assigned to studies with no weak ratings, moderate ratings to studies with one weak rating, and weak ratings to studies with two or more weak ratings. Following independent evaluation, reviewers met to discuss discrepant ratings and reach a consensus on domain and overall ratings.

Results

Fifty-seven studies met full inclusion criteria and were included in the review (see Figure 1). These reports generally focused on child abuse and

primarily examined alcohol and cannabis as the main substances of interest (see Table 1).

Adversity

Amongst the included studies, several focused on childhood AEs only (43.9%; 25/57), especially physical and sexual abuse, 22.8% focused on AEs that only occurred during adulthood (13/57), and 31.6% examined AEs across the lifespan (18/57). Two reports (3.5%) did not report the timing of AEs. The estimates of rates of childhood AEs ranged from 9.2% (sexual abuse only) to 80%; the prevalence of victimization in adulthood ranged from 5.6% (violent criminal victimization) to 48% (Buchanan et al., 2023; Dolan et al., 2012; Fitzgerald et al., 2005; Honkonen et al., 2004; Larney et al., 2009); and the rate of lifetime AEs ranged from 48.5% to 100% (Aakre et al., 2014; Gearon et al., 2003a; Hassan et al., 2016; Hassan & De Luca, 2015; Karsinti et al., 2015; K. Mueser et al., 2004; Ng et al., 2016; Picken et al., 2010; Picken & Tarrier, 2011; C. Ramsay et al., 2011; Resnick et al., 2003; Rosenberg et al., 2007; Schalinski et al., 2015a; Steel et al., 2011; Tarrier & Picken, 2011; Widing et al., 2022; Yousef et al., 2022). Thirteen of the seventeen studies reporting on the lifetime prevalence of AEs estimated a rate of 75% or higher (Aakre et al., 2014; Gearon et al., 2003a; Hassan & De Luca, 2015; K. Mueser et al., 2004; Ng et al., 2016; Picken et al., 2010; Picken & Tarrier, 2011; C. Ramsay et al., 2011; Resnick et al., 2003; Rosenberg et al., 2007; Steel et al., 2011; Tarrier & Picken, 2011; Yousef et al., 2022). Eleven studies measured PTSD, with estimates ranging from 5% to 70% (Aakre et al., 2014; Birgenheir et al., 2014; Černý et al., 2018;

Grella, 2003; Hassan & De Luca, 2015; Larney et al., 2009; K. Mueser et al., 2004; Ng et al., 2016; Picken & Tarrier, 2011; Resnick et al., 2003; Temmingh et al., 2021). Nine of the eleven studies found prevalence rates exceeding 10% (Aakre et al., 2014; Birgenheir et al., 2014; Černý et al., 2018; Grella, 2003; Larney et al., 2009; K. Mueser et al., 2004; Ng et al., 2016; Picken & Tarrier, 2011; Resnick et al., 2003). One study assessed 81 care coordinators' knowledge of their patients' trauma history. The results revealed that these professionals had limited knowledge of their patients' history of adversity. While none of the patients had a recorded diagnosis of PTSD in their chart, approximately 12.7% met criteria for PTSD (Picken et al., 2010).

Substance misuse

Most studies examined alcohol (66.7%; 38/57) and cannabis (57.9%; 33/57), while other substances were less of a focus (36.8%; 21/57). Other studies did not report details of examined substances (43.8%; 25/57).

The estimates of SM ranged from 6.4% to 87% (Aakre et al., 2014; Alli et al., 2019; Amani et al., 2022; Ascher-Svanum et al., 2010; Birgenheir et al., 2014; Buchanan et al., 2023; Dolan et al., 2012; Gearon et al., 2001, 2003a; Hassan & De Luca, 2015; Honkonen et al., 2004; K. Mueser et al., 2004; Resnick et al., 2003; Rosenberg et al., 2007; Schalinski et al., 2015a; Scheller-Gilkey et al., 2004a; Swartz et al., 2006; Temmingh et al., 2021; Widing et al., 2022; Yousef et al., 2022), with twelve of twenty studies reporting a prevalence exceeding 40.0% (Aakre et al., 2014; Alli et al., 2019; Amani et al., 2022; Ascher-Svanum et al., 2010; Dolan et al., 2012; Gearon et al., 2001, 2003a; Hassan & De Luca, 2015;

Rosenberg et al., 2007; Scheller-Gilkey et al., 2004a; Temmingh et al., 2021; Yousef et al., 2022). Rates of alcohol misuse ranged from 4.3% to 70.0%, and the prevalence of cannabis misuse ranged from 7.0% to 57.0% (Arranz et al., 2018; Baudin et al., 2016; Compton et al., 2004; Dennison et al., 2021; Houston et al., 2008; Karsinti et al., 2015; Korchia et al., 2022; Larney et al., 2009; Ramsay et al., 2011; Steel et al., 2011; Tarrier & Picken, 2011; Temmingh et al., 2021; Tiles-Sar et al., 2023).

Integrated evidence

Most of the included reports focused on samples without any information on psychotic illness duration (31.6%, 18/57) or mixed samples (i.e., multiple stages of psychosis in one sample; 28%, 16/57). The remaining studies focused on EPP (i.e., illness duration ≤ 5 years; 15.8%, 9/57), chronic psychosis (i.e., onset ≥ 10 years; 15.8%, 9/57), and SIP disorders (8.8%; 5/57). The results of each of these groupings is reported below. One report included both a sample with SIP and a group with EPP; this report was grouped with the SIP studies above given there were so few EPP patients in the sample.

Unreported illness duration (UID)

Fourteen of the eighteen retrospective studies used cross-sectional designs to examine AEs and SM among people with PDs, while four used a case-control design and one used a cohort design. The collective *N* of these studies is 63,021 (range = 40 to 24,959). Eleven of the eighteen studies focused solely on samples of individuals with schizophrenia and/or schizoaffective disorder, and alcohol was the most studied substance. Most studies examined

AEs in only one phase of life, i.e., childhood (seven studies), or adulthood (six studies).

There was an elevated prevalence of AEs among individuals with PDs with higher incidence rates of childhood AEs found among those with both a PD and SM (e.g., 75%; Scheller-Gilkey et al., 2002); AEs seem to increase the likelihood of SM in people with schizophrenia (Rosenberg et al., 2007). A study of veterans seeking substance use services (*n* = 24,959) found that physical or sexual abuse predicted the onset of PDs and SM, with men at increased risk of developing an SUD (P. C. Ouimette et al., 2000). However, only a small proportion of their sample met criteria for a PD (*n* = 29; 0.001% of total sample), limiting conclusions. Sexual abuse and cannabis use were examined in a PD sample in a couple of studies with contrasting findings: one found that early cannabis use rather than sexual abuse drove the risk of psychosis development (Houston et al., 2008; Ng et al., 2016), while another found that sexual abuse was the primary risk factor, regardless of the presence of cannabis use (Yousef et al., 2022). Two studies investigating homelessness among people with PDs found a significant relationship between homelessness and both psychotic symptom severity and SM (Scheller-Gilkey et al., 2004), while another study suggested that SM was an important contributor to homelessness (Fuller-Thomson & Hollister, 2016a; van Nierop, Bak, De Graaf, et al., 2016). Four studies measuring PTSD among people with PDs reported more severe and frequent symptoms of PTSD (Sin & Spain, 2017) and higher rates of SUDs and psychiatric hospitalizations than participants without PDs (Debell et al., 2014).

Results were mixed regarding the prevalence of PTSD. One study found the highest prevalence of PTSD among people with mood disorders (Hasan et al., 2020), while the other found the highest rates among women with both a PD and SUD.

AEs and SM were risk factors for violence perpetration in schizophrenia (Amani et al., 2022); however, four studies noted more elevated risk for victimization than perpetration. Victimization risk was more than two times greater for individuals with a PD (Černý et al., 2018; Larney et al., 2009), especially women with a PD; the latter group had higher prevalence of physical victimization compared to both women and men without a PD (Černý et al., 2018). Two studies examined the relationship between SM and victimization, finding that PDs and psychostimulant use increased victimization risk (Larney et al., 2009); yet a large study of outpatients (*n* = 1,208) posited that SM only increased the odds of *violent* victimization (e.g., assault; Schomerus et al., 2008) but did not increase the odds of any victimization (e.g., burglary).

Mixed samples

Thirteen of the sixteen retrospective studies used cross-sectional designs to examine AEs and SM among people with PDs, while two used a case-control design and one used a cohort design. The collective *N* of these studies was 6,946 (range = 49 to 1,724). Six studies examined the relationship between SM and AEs. Although two studies found an association between SM and AEs (Baudin et al., 2016; Temmingh et al., 2021), there were no significant differences in the proportion of individuals meeting criteria for an SUD between

those with and without a history of AEs (Baudin et al., 2016) or PTSD (Tarrier & Picken, 2011). Another study similarly found no significant differences in rates of SM between the victimized and non-victimized groups (Fitzgerald et al., 2005). Two outpatient studies compared SM and AEs between different diagnostic groups. The first compared individuals with schizoaffective disorder (depressive subtype; SA-D) to a group with schizophrenia; SA-D was positively associated with child abuse and alcohol dependence in both the univariate and multivariate analyses (Dennison et al., 2021). This study also made use of two replication samples, the only study to attempt to further support their conclusions via replication. However, replication analyses did not find associations between SA-D and alcohol use or child abuse. The second study compared two PD groups (unspecified PDs, primary PDs) to a third group with mood disorders and found no significant differences in the prevalence of childhood AEs between any groups, but described greater cannabis use in the two PD groups relative to the mood disorders group (Widing et al., 2022).

Three studies investigated correlates of violent victimization in adulthood. Results suggested an association between SM and violent victimization in one (Honkonen et al., 2004), but two other reports using the same dataset found that violent victimization was neither predicted by scores on a SM measure (Dolan et al., 2013) nor was violent victimization associated with more severe psychotic symptoms (Dolan et al., 2012). In contrast, childhood AEs were associated with more severe psychotic symptoms (Baudin et al., 2016; Schalinski et al., 2015a) and a study of individuals with PDs, AEs, and comorbid psychopathology (e.g.,

depressive, anxious symptoms) found this sample had more severe psychotic symptoms, lower functioning, and were more likely to have comorbid SM (van Nierop, Bak, De Graaf, et al., 2016) than individuals with PDs who do not have a history of AEs. Although there were no statistically significant differences in PTSD prevalence between those with and without auditory hallucinations, those with PTSD reported greater frequency and intensity of hallucinations than those without PTSD (Steel et al., 2011). Studies investigating correlates of adversity found that psychotic illness and stressful illness-related events (e.g., hospitalization) can contribute to PTSD following illness onset (Picken & Tarrier, 2011), and childhood abuse, especially emotional abuse, was a predictor of suicide attempts with high lethality. Although a large proportion of the group who had attempted suicide also had a history of SM (41%) relative to the proportion with an SM history in the group who had not attempted suicide (25%), SM was not a significant univariate predictor of suicide attempts (Alli et al., 2019).

Chronic samples

Seven of the nine studies used cross-sectional designs, while two used a cohort design. The collective *N* was 3,614 (range = 47 to 1,460). One study compared three clinical groups: individuals with mood disorders and SM, PDs and SM, and a PD-only group. Higher rates of lifetime abuse were found among those with mood disorders but SM was only associated with current emotional abuse in the PD-SM group (Gearon et al., 2001). However, the sample size of this study was small for a three-group design, limiting conclusions (*n* = 80). SM and sexual abuse were significantly associated with PD treatment resistance,

even after adjusting for confounders (e.g., age of onset of a PD; Hassan & De Luca, 2015), and recent homelessness and higher positive psychotic symptoms were both predictors of SM in a multivariate model (Swartz et al., 2006).

Four studies examined PTSD and correlates in outpatients. Two studies reported greater PTSD symptom frequency and severity (Scheller-Gilkey et al., 2004), and an elevated proportion of a substance-using sample of women with PDs (Gearon et al., 2003a) met criteria for PTSD (46%) compared to schizophrenia-only samples (30%) and SM only samples (30-37%). The other two studies provided support for the hypothesis that in people with PDs, PTSD is associated with lower functioning and more severe psychotic symptoms (Ng et al., 2016; Resnick et al., 2003). However, reductions in victimization risk are associated with improvement in participants' overall functioning (Buchanan et al., 2023).

EPP samples

Four of the nine studies used a cross-sectional design, while two used a cohort design, and three used a case-control approach. The collective *N* was 2,355 (range = 18 to 1,119). Violence exposure and environmental adversity were associated with cannabis use escalation and greater cannabis use (Pauselli et al., 2018) and cannabis use was related to elevated rates of AEs (Compton et al., 2004; Ramsay et al., 2011), Another study found a contrasting result, with SM weakening the association between childhood AEs and premorbid adjustment, with the authors suggesting little relationship between SM and AEs (Kilian et al., 2017).

Two studies followed EPP samples over three years and compared outcomes to those of a control group. Both studies found greater cannabis use and childhood AEs in their patient groups (e.g., >80%; Arranz et al., 2018). The first study investigated variability in fractional anisotropy (Domen et al., 2019), a measure of brain connectivity, in people with PDs. They found that those who had the greatest exposure to cannabis or childhood AEs exhibited a pronounced decline in fractional anisotropy over time compared to siblings and control participants (i.e., community members with no family history of PDs). There was a dose-response negative association between childhood AEs and group at follow-up, indicating that greater AE exposure was associated with lower whole brain connectivity, and interactions between cannabis use, childhood AEs, and group at follow-up and when examining change from baseline to follow-up. Compared to controls and siblings, patients who experienced 'high' levels of AEs and had 'heavy' cannabis use had the most significant reductions in fractional anisotropy over time. The second study (Arranz et al., 2018) aimed to determine predictors of PD onset; childhood AEs accounted for a significant proportion of the variance (R^2 Nagelkerke = 0.44 with demographics and AEs, 0.26 with demographics only), and the inclusion of cannabis and tobacco use slightly improved the demographics-AE prediction model (R^2 Nagelkerke = 0.49; $p <$ .000). Another study found that, at the three-year follow-up, childhood AEs had a negative relationship with social functioning, and contrary to expectations, weekly cannabis use was associated with better social functioning (Tiles-Sar et al., 2023). Cannabis may have acted as a facilitator for social interactions.

Substance-induced psychosis

Three of the five studies used a cross-sectional design, while two used a case-control approach. The collective *N* was 954 (range = 37 to 601). Primary PDs (*n* = 19) were compared to a cannabis-induced psychosis sample (*n* = 18) and there were no significant differences in cannabis use problems or number of lifetime AEs (Woolridge et al., 2022) but the small sample limits conclusions that can be drawn. In a study of cocaine-induced psychosis, AEs and psychotic symptoms were not related, but AEs were related the age of onset of cannabis use (Karsinti et al., 2015). In terms of correlates, lifetime abuse (i.e., emotional, physical, and/or sexual) was associated with suicidal ideation among individuals with substance-induced psychosis, while lifetime physical abuse was associated with suicide attempts (Palma-Álvarez et al., 2023).

Two studies of highly controlled samples examined methamphetamine-induced psychosis (Yui et al., 2000, 2004). Results indicated flashbacks of the psychotic symptoms occurred during mild stressors in the ‘flashbackers’ group, which the authors posited may sensitize individuals’ noradrenergic system, although other explanations may be possible (e.g., noradrenergic system was sensitized by methamphetamines). However, both studies made use of an inappropriate control group composed of both methamphetamine-naïve individuals and individuals who used methamphetamines.

Temporality of events

Most studies did not discuss age of onset (e.g., age at which AEs occurred; 91.2%; 52/57), which makes temporal inferences difficult. Five studies

did posit at least a partial order of events; AEs appear first in the order (Ramsay et al., 2011; Shevlin et al., 2009), while others posit that psychosis may be the last of the three events to appear, with AEs and SM predicting psychosis (S. Arranz et al., 2018; Houston et al., 2008; Karsinti et al., 2015). However, these studies had small samples and several AEs were examined, making it difficult to establish a temporal order for AEs generally and to compare results across studies.

Risk of bias

Twenty-nine studies (50.9%) were rated as 'weak', primarily due to issues with measurement and possible recruitment bias (see Supplemental materials, Table 1). When there was a lack of clarity, studies were marked as 'weak', which may explain the elevated risk of bias reported here compared to recent similar systematic reviews (e.g., Alameda et al., 2021; Setién-Suero et al., 2020; 4.3%, 0% high risk of bias). Twenty-four (42.1%) studies with 'moderate' risk of bias had fewer instances of measurement and recruitment bias, and four longitudinal studies (7.0%) were considered to have low risk of bias, meaning they were rated as 'strong' studies. Few studies received 'strong' ratings for analyses; studies were obligated to report a sample justification (e.g., power analysis) and describe their variables to receive such a rating.

Discussion

The evidence supports the hypothesis that the nexus between PDs, SM, and AEs is broadly and specifically associated with negative health outcomes and represents a common occurrence. There were higher rates of both AEs and

SM among people with EPP and the catch-all category of UID, but rates of AEs and SM were higher among people with mood disorders r than chronic psychosis. Mixed samples reported similar levels of AEs between PDs and mood disorder samples, yet elevated rates of SM in PDs. Across stages of PDs, there were elevated rates of PTSD (12-70%; (Ng et al., 2016; Picken & Tarrier, 2011; Tarrier & Picken, 2011), yet, despite prevalence rates much higher than those in the general population (6.8%; Kessler et al., 2005), PTSD is often undiagnosed in individuals with PDs (de Bont et al., 2015). In both mixed and chronic samples, people with PDs and PTSD had more severe positive psychotic symptoms, but only UID studies examined the further overlap with increased substance use and relationships between SM and PD onset. Given the substantial literature covering the PTSD-SUD comorbidity (e.g., Kramer et al., 2014; Stewart, 1996; Stewart & Conrod, 2003), it is surprising that more studies did not examine this link in PDs.

Studies of UID and mixed samples both found a relationship between SM and violent victimization in adulthood, but interestingly, SM did not significantly predict victimization nor was SM associated with more severe psychotic symptoms, which contrasts with the more severe positive symptoms and SM observed with childhood AEs. In essence, an earlier onset of AEs can result in greater symptom severity across domains, possibly due to brain alterations (e.g., HPA axis changes; Berens et al., 2017). However, it is interesting that SM does not appear to predict victimization, given that a recent, large study found that victimization is common among those with SM (Seid et al., 2021). However, few

studies focused on the SM-victimization link among people with PDs, and more research is needed to gain a more fulsome picture of these relationships.

Homelessness was a consequence of SM and greater psychotic symptom severity in UID samples but was a predictor of SM in chronic psychosis samples, along with more severe positive psychotic symptoms. There were also differences among other predictors—studies with UID samples could not establish whether sexual abuse or cannabis was a stronger predictor of psychosis, but AEs alone appeared to account for much of the variance of PD development in EPP samples, with SM adding little above and beyond the AEs-only model. Finally, mixed samples and SIP samples both found that abuse predicted suicidal ideation and attempts although mixed samples examined childhood AEs, while SIP samples examined lifetime AEs. SM was not identified as a predictor of suicidal ideation or attempts in either group.

Most studies focused on child abuse to the exclusion of other types of AEs (e.g., psychotic phenomena), and the same substances are reviewed time and time again (alcohol and cannabis), preventing an understanding of the relations between substances like cocaine and methamphetamines with AEs and PDs. Moreover, SM is often included in studies of PDs and AEs in a cursory manner, resulting in insufficient exploration of its relationships with AEs and SM. Future studies are advised to take a broad view on both AEs and SM, and explore the relationship between SM, symptoms of PDs, and AEs in greater depth.

Many of the results of this review align with previous systematic reviews examining childhood AEs and psychosis (Bendall et al., 2007; Varese et al.,

2012) and PTSD and psychosis (Dallel et al., 2018); however, the examination of the relationships between SM with PDs and AEs provides additional information about how these variables often overlap and interact. Nonetheless, many of the critiques levied in previous reviews of childhood trauma and psychosis continue to apply to the current state of this literature. Bendall and colleagues (2007) noted three issues in their review fifteen years ago that remain true of the evidence included here: 1) primary use of cross-sectional study designs, 2) varying terminology and measurement of AEs, and 3) issues with statistical power. Few studies used control groups, preventing causal conclusions, and five studies did not attempt to control for any confounders (Amani et al., 2022; Birgenheir et al., 2014; Larney et al., 2009; Picken et al., 2010; Steel et al., 2011). There was a lack of cohesion with respect to operationalization and measurement of both AEs and SM across the literature—unified definitions and measurement approaches would help to advance discussions in this field. As mentioned above, few studies used power analyses, which is especially problematic given that many studies used large-N analyses (e.g., logistic regression) with small samples.

Limitations

The present review has several clear limitations. The period studied (2000-2023) spans three versions of the DSM: DSM-III-R (APA, 1987), DSM-IV-TR (APA, 2000), and DSM-5 (APA, 2013). As a result, the definitions of SUDs/SM, PDs, and PTSD vary across studies, meaning that measurement would also differ, rendering comparisons more challenging. The second limitation

is language–included studies were restricted to English and French, limiting the scope of the evidence. Third, the review articles are very concentrated in North America, with 47.3% (27/57) using American or Canadian samples; conclusions may be less generalizable to countries with dissimilar societal structures. In addition, few studies included women, non-binary, Middle Eastern, Asian, and Black people, meaning that samples may not be representative of the societies in which they are conducted. Moreover, many trials resulted in multiple reports; if bias was introduced during recruitment, it could result in bias on a wider scale than within a single report. Finally, Berkson's bias (Berkson, 1946), which suggests that the presence of two or more clinical issues (e.g., psychosis) may bias the representativeness of a sample, and prompt individuals to seek out treatment, leading to their overinclusion in clinical research or treatment.

Clinical implications

The 57 studies of this review provide a strong rationale for the consideration of SM and AEs simultaneously when working with people with PDs. Some studies suggested that over 33% of patients with PDs have clinically significant PTSD symptoms (Steel et al., 2011) and others have posited that due to the exclusive focus on psychotic symptoms in psychosis intervention programs, up to 96% of patients with PDs could be undiagnosed and untreated for PTSD (de Bont et al., 2015; Ng et al., 2016). Not only should clinicians regularly inquire about both AEs and SM, but they should also consider how the presence of all three variables may be related to risk and outcomes (Yousef et al., 2022). The evidence suggests that the point of focus should not be on the individual

variables, but rather the interactions between them (Scheller-Gilkey et al., 2004a). Several studies have already suggested that evidence-based trauma-focused interventions for people with PD are needed (Fuller-Thomson & Hollister, 2016; van Nierop, Bak, de Graaf, et al., 2016) and treatment development has been underway over the last decade. However, the evidence is limited and treatments often do not consider SM (Sin & Spain, 2017). The results of this review begin to provide support for the inclusion of SM and its interactions with psychotic symptoms and AE sequelae within interventions for people with PDs, especially given the strong evidence of SM's independent relationships with AE sequelae (e.g., connections between alcohol use and PTSD; Debell et al., 2014) and psychotic symptoms (e.g., cannabis and hospitalization rates; Hasan et al., 2020). Future studies should focus on developing or modifying interventions targeting the overlaps between PDs, SM, and AEs.

Tables

Table 1.1.1. Studies examining adverse events (AEs) and substance misuse (SM) among people with psychotic disorders (PDs)

Study	N	Assessment tools 1. AEs 2. Psychosis 3. SM	Sample	1. Timing of adversity 2. Type of adversity	1. Type of PD 2. Duration	Substances
Aakre et al., 2014[a]	117	1. CAPS-SZ, TLEQ 2. SCID, PANSS 3. SCID	Women outpatients with an SUD, depression and an SUD, or an SUD and a psychotic disorder	1. Lifetime 2. Childhood sexual or physical abuse; trauma in adulthood (e.g., traumatic loss, assault)	1. Schizophrenia, schizoaffective 2. Not reported	Alcohol, cocaine, opiates, sedatives, polysubstance

Alli et al., 2019	49	1. CTF-SF 2. MINI DSM-IV, chart review 3. MINI DSM-IV	Patients with a psychotic disorder	1. Childhood 2. Sexual, emotional, physical abuse; emotional and physical neglect	1. Schizophrenia spectrum disorders 2. Mixed sample	Not reported
Amani et al., 2022	60	1. Not reported 2. Not reported 3. Not reported	Forensic patients with a psychotic disorder	1. Childhood 2. Sexual, psychological, physical abuse; death of parent(s)	1. Schizophrenia 2. Not reported	Cannabis, alcohol, stimulants, cocaine, polysubstance use
Arranz et al., 2018	207	1. CTQ-SF, Holmes-Rahe 2. OPCRIT DSM-IV 3. Authors' interview	Outpatients with a psychotic disorder	1. Childhood 2. Sexual, emotional, physical abuse; emotional and physical neglect	1. Psychotic disorders 2. EPP	Cannabis

Ascher-Svanum et al., 2010	609	1. QOLI – Victimization subscale 2. PANSS 3. Not reported	Outpatients with psychotic disorders	1. Adulthood 2. Violent and non-violent criminal victimization	1. Schizophrenia, schizoaffective, schizophreniform 2. Not reported	Alcohol, cannabis, cocaine
Baudin et al., 2016	366	1. CTQ 2. PANSS 3. SCID	Patients with a psychotic disorder	1. Childhood 2. Sexual, emotional, physical abuse; emotional and physical neglect	1. Schizophrenia, schizoaffective 2. Mixed sample	Cannabis
Birgenheir et al, 2014	20,722	1. Not reported 2. Not reported 3. Not reported	Veterans with a psychotic disorder	1. Not reported 2. Events meeting criterion A of PTSD in DSM-IV	1. Schizophrenia 2. Not reported	Not reported
Buchanan et al., 2023[b] CATIE trial	1,179	1. MCVI 2. PANSS 3. SCID	Outpatients with a	1. Adulthood	1. Schizophrenia 2. Chronic psychosis	Alcohol, cannabis, cocaine

			psychotic disorder	2. Physical or sexual assault; assault with a weapon		
Černy et al., 2018	316	1. SCID PTSD module: DSM-IV, CECA-Q, MCVI 2. MINI 3. MINI, AUDIT, DUDIT	Patients with a psychotic disorder	1. Lifetime 2. Physical or sexual abuse; physical assault	1. Schizophrenia 2. Not reported	Alcohol, 'drugs'
Compton et al., 2004	18	1. CTQ-SF 2. SCID: DSM-III 3. SCID: DSM-III	Black inpatients with a psychotic disorder	1. Childhood 2. Sexual, emotional, physical abuse; emotional and physical neglect	1. Schizophrenia, schizophreniform, or schizoaffective 2. EPP	Cannabis
Dennison et al., 2021	1,724	1. CLEQ 2. OPCRIT: ICD-10, SAPS, SANS	Outpatients with a	1. Childhood 2. Death of a caregiver, friend,	1. Schizophrenia or schizoaffective (depressive type)	Cannabis, alcohol, 'other substances'

		3. OPCRIT: ICD-10; case notes	psychotic disorder	sibling; parental separation; incarceration or hospitalization of a caregiver; 'other events'	2. Mixed sample	
Dolan et al., 2012[c]	92	1. Police database 2. VBPTS – Positive, Negative subscales 3. DAST	Male outpatients with a psychotic disorder	1. Adulthood 2. Non-violent and violent criminal victimization	1. Schizophrenia, schizoaffective, schizophreniform 2. Mixed sample	Alcohol, 'drugs', polysubstance use
Dolan et al., 2013[c]	94	1. Police database, MCVI 2. VBPTS 3. DAST, file review	Male outpatients with a psychotic disorder	1. Adulthood 2. Non-violent and violent criminal victimization	1. Schizophrenia, schizoaffective, schizophreniform 2. Mixed sample	Alcohol, 'drugs'

Domen et al., 2019	258	1. CTQ-SF 2. PANSS 3. CIDI	Outpatients with a psychotic disorder and their first-degree relatives	1. Childhood 2. Sexual, emotional, physical abuse; emotional and physical neglect	1. Schizophrenia, schizophreniform, schizoaffective, psychotic disorder NOS, brief psychotic disorder 2. EPP	Alcohol, cannabis, 'other drugs'
Fitzgerald et al., 2005 SCAP study	347	1. QOLI, author-made instrument 2. PANSS 3. CAGE, author-made instrument	Inpatients and outpatients with a psychotic disorder	1. Adulthood 2. Non-violent and violent victimization	1. Schizophrenia, schizophreniform, schizoaffective 2. Mixed sample	Alcohol, 'drugs'
Fuller-Thomson & Hollister, 2016	101	1. Author-made measure of three ACEs	Community members with a	1. Childhood 2. Witnessing parental domestic violence,	1. Schizophrenia 2. Not reported	Alcohol, 'drugs'

		2. Self-reported schizophrenia diagnosis 3. CIDI	psychotic disorder	physical and sexual abuse		
Gearon et al., 2001	80	1. ASI 2. SCID: DSM-IV, PANSS 3. ASI, IDTS, SMQ	Outpatients with a psychotic disorder	1. Childhood 2. Emotional, physical, and sexual abuse	1. Schizophrenia or schizoaffective 2. Chronic psychosis	Cannabis, cocaine, heroin, sedatives, polysubstance
Gearon et al., 2003[a]	54	1. TLEQ, CAPS 2. SCID: DSM-IV, file review 3. SCID: DSM-IV	Women outpatients with a psychotic disorder	1. Lifetime 2. Sexual or physical abuse, domestic violence, assault, traumatic loss, serious illness, etc.	1. Schizophrenia or schizoaffective 2. Chronic psychosis	Alcohol, cannabis cocaine, opioids

Grella, 2003	400	1. SCID: DSM-IV PTSD module, author-made questionnaire 2. SCID: DSM-IV 3. SCID: DSM-IV	Outpatients in treatment programs for substance use	1. Not reported 2. Events meeting criterion A of PTSD in DSM-IV	1. Schizophrenia, schizoaffective, psychosis NOS 2. Not reported	Alcohol, amphetamines, cannabis, cocaine, opioids, sedatives
Hachtel et al., 2019	69	1. CTQ, LQoLP 2. File review [SANS, BPRS] 3. ASSIST	Male outpatients with a psychotic disorder	1. Lifetime 2. Sexual, emotional, physical abuse; emotional and physical neglect; physical or sexual assault, other victimization in adulthood	1. Schizophrenia, schizoaffective, drug-induced psychosis 2. EPP	Alcohol, amphetamines, cannabis, cocaine
Hassan et al., 2016	361	1. CTQ 2. SCID: DSM-IV	Outpatients with a	1. Childhood	1. Schizophrenia, schizoaffective	Alcohol, cannabis, 'other drugs'

		3. Not reported	psychotic disorder	2. Sexual, emotional, physical abuse; emotional and physical neglect	2. Chronic psychosis	
Hassan & De Luca, 2015	186	1. SLESQ, CTQ 2. SCID: DSM-IV 3. Not reported	Outpatients with a psychotic disorder	1. Lifetime 2. Sexual, emotional, physical abuse; emotional and physical neglect; life-threatening illness or accident, sudden loss of loved one, assault	1. Schizophrenia, schizoaffective 2. Mixed sample	Alcohol, 'drugs'
Honkonen et al., 2004	666	1. Authors' interview 2. PANSS 3. File review, authors' interview	Patients with a psychotic disorder	1. Adulthood 2. Non-violent and violent victimization	1. Schizophrenia 2. Mixed sample	Alcohol, 'drugs'

Houston et al., 2008[d]	5,877	1. CIDI – sexual trauma questions (PTSD module) 2. CIDI : DSM-III 3. CIDI : DSM-III	Community members with a psychotic disorder	1. Childhood 2. Sexual molestation, rape	1. Schizophrenia, schizophreniform, schizoaffective, delusional disorder, atypical psychosis 2. Not reported	Cannabis
Karsinti et al., 2015	144	1. CTQ 2. SAPS-CIP 3. Not reported	Outpatients in treatment programs for substance use	1. Childhood 2. Sexual, emotional, physical abuse; emotional and physical neglect	1. Substance-induced psychotic disorder (stimulants) 2. SIP	Alcohol, cannabis, cocaine, opiates
Kilian et al., 2017	129	1. CTQ-SF 2. SCID: DSM-IV 3. Urine screening test, SCID-IV	Inpatients and outpatients with a psychotic disorder	1. Childhood 2. Sexual, emotional, physical abuse; emotional and physical neglect	1. Schizophrenia, schizophreniform, schizoaffective 2. EPP	Cannabis, methamphetamine, methaqualone

Korchia et al., 2022	561	1. CTQ 2. SCID: DSM-IV, PANSS 3. SCID: DSM-IV	Outpatients with a psychotic disorder	1. Childhood 2. Sexual, emotional, physical abuse; emotional and physical neglect	1. Schizophrenia, schizoaffective 2. Not reported	Alcohol, cannabis
Langlois et al., 2021[e]	247	1. CTQ-SF, TEC, Perceptions of Parental Nurturance, Perceptions of Parental Harsh Discipline 2. SCID: DSM-IV 3. LSUR	Inpatients and outpatients with a psychotic disorder	1. Childhood 2. Sexual, emotional, physical abuse; emotional and physical neglect; natural disaster, traumatic injury, etc.	1. Non-substance induced schizophrenia spectrum disorders 2. EPP	Alcohol, cannabis
Larney et al., 2009	105	1. TSQ, authors' questionnaire	Unhoused substance-using adults	1. Adulthood 2. Physical assault, homelessness	1. Schizophrenia or other psychotic disorder	Alcohol, benzodiazepines,

		2. Authors' quesionnaire 3. Authors' questionnaire	with a psychotic disorder		2. Not reported	cannabis, heroin, psychostimulants
Mueer et al., 2004	782	1. SAEQ, PCL, modified CTS2 2. SCID: DSM-IV, chart review 3. DALI	Outpatients with a psychotic disorder	1. Lifetime 2. Sexual and physical abuse; sexual and physical assault, homelessness	1. Schizophrenia, schizoaffective 2. Not reported	Alcohol, 'drugs'
Ng et al., 2016	125	1. HTQ 2. SCID: DSM-IV, PANSS, chart review 3. Not reported	Outpatients with a psychotic disorder	1. Lifetime 2. Exposure to war, assault, torture, sexual assault, homelessness, etc.	1. Schizophrenia 2. Chronic psychosis	Alcohol, 'drugs'

Odell & Commander, 2000	39	1. Authors' questionnaire 2. Life Chart Schedule, file review 3. SCID: DSM-IV	Unhoused outpatients with a psychotic disorder	1. Adulthood 2. Homelessness	1. Schizophrenia 2. Not reported	Alcohol, 'drugs'
Opler et al., 2001	391	1. Authors' interview 2. SCID: DSM-III, PANSS 3. SCID: DSM-III	Inpatients and outpatients with a psychotic disorder	1. Adulthood 2. Homelessness	1. Schizophrenia, schizoaffective 2. Not reported	Not reported
Ouimette et al., 2000	24,959	1. ASI 2. File review 3. ASI, file review	Veterans with a substance use disorder	1. Childhood 2. Sexual and physical abuse	1. Schizophrenia spectrum disorder 2. Not reported	Not reported

Palma-Álvarez et al., 2023	601	1. EuropASI 2. Authors' questionnaire 3. EuropASI	Outpatients with a substance use disorder	1. Lifetime 2. Physical, sexual, emotional abuse	1. Substance-induced psychotic disorder 2. Substance-induced	Alcohol, benzodiazepines, cannabis, cocaine, opioids
Pauselli et al., 2018[e]	247	1. TEC, NDS 2. SCID: DSM-IV 3. LSUR, CEQ	Inpatients with a psychotic disorder	1. Childhood 2. Sexual, emotional, physical abuse; emotional and physical neglect, life-threatening illness or accident, sudden loss of loved one, assault, etc.	1. Non-substance induced psychotic disorders 2. EPP	Alcohol, cannabis
Picken et al., 2010[f] MIDAS trial	110	1. PDS, ITQ 2. Chart review 3. SCID: DSM-IV	Outpatients with a psychotic	1. Lifetime 2. Sexual, emotional, physical abuse;	1. Schizophrenia, schizophreniform,	Alcohol, amphetamines,

			disorder and SUD	emotional and physical neglect; life-threatening illness or accident, sudden loss of loved one, assault, psychotic experiences, hospitalization for psychosis, etc.	schizoaffective, psychosis NOS 2. Mixed sample	cannabis, crack cocaine, heroin
Picken & Tarrier, 2011[f] MIDAS trial	110	1. PDS, CAPS-S 2. File review, PANSS 3. SCID: DSM-IV	Outpatients with a psychotic disorder and SUD	1. Lifetime 2. Sexual, emotional, physical abuse; emotional and physical neglect; life-threatening illness or accident, sudden loss of loved one, assault,	1. Schizophrenia, schizophreniform, schizoaffective, psychosis NOS 2. Mixed sample	Alcohol, amphetamines, cannabis, crack cocaine, heroin

				psychotic experiences, hospitalization for psychosis, etc.		
Ramsay et al., 2011	61	1. CTQ-SF, TEC 2. SAPS, SANS 3. LSUR, SCID : DSM-IV	Inpatients with a psychotic disorder	1. Lifetime 2. Sexual, emotional, physical abuse; emotional and physical neglect; life-threatening illness or accident, sudden loss of loved one, assault, etc.	1. Non-substance induced schizophrenia spectrum disorders 2. EPP	Alcohol, cannabis
Resnick et al., 2003	47	1. THQ-R, CAPS 2. SCID: DSM-IV, PANSS 3. Not reported	Outpatients with a psychotic disorder	1. Lifetime 2. Sexual, and, physical abuse; life-threatening illness or	1. Schizophrenia, schizoaffective 2. Chronic psychosis	Alcohol, ‘drugs’

				accident, sudden loss of loved one, sexual assault, natural disaster, etc.		
Rosenberg et al., 2007	569	1. SAEQ, PCL, modified CTS2 2. SCID: DSM-IV, chart review 3. DALI SCID: DSM-IV, chart review	Outpatients with a psychotic disorder	1. Lifetime 2. Sexual and physical abuse, domestic violence, foster care, parental separation/divorce, parental mental illness, parental death	1. Schizophrenia, schizoaffective 2. Not reported	Alcohol, ‘drugs’
Schalinski et al., 2015	62	1. MACE interview 2. PANSS 3. Not reported	Inpatients with a psychotic disorder	1. Childhood 2. Peer emotional, physical violence; parental emotional, physical abuse,	1. Non-substance induced schizophrenia spectrum disorders 2. Mixed sample	Alcohol, ‘drugs’

				sexual abuse, domestic violence, physical neglect		
Scheller-Gilkey et al., 2002	40	1. Modified CTES, Davidson PTSD scale 2. SCID: DSM-III 3. ASI, urine screen, SCID: SM-III	Outpatients with a psychotic disorder	1. Childhood 2. Death of a family member, sexual or physical abuse, exposure to violence, major illness or injury, disasters, etc.	1. Schizophrenia, schizoaffective 2. Not reported	Alcohol, cannabis, cocaine
Scheller-Gilkey et al., 2004	122	1. Modified CTES, Davidson PTSD scale 2. PANSS 3. ASI, urine screen, salivary alcohol test	Outpatients with a psychotic disorder	1. Childhood 2. Death of a family member, sexual or physical abuse, exposure to violence, major illness or injury, disasters, etc.	1. Schizophrenia, schizoaffective 2. Chronic psychosis	Alcohol, cannabis, cocaine

Schomerus et al., 2008 EuroSC study	1,208	1. Lehman QoLI interview 2. SCAN: DSM-IV 3. SCAN: DSM-IV	Outpatients with a psychotic disorder	1. Adulthood 2. Non-violent and violent victimization	1. Schizophrenia 2. Not reported	Alcohol, 'drugs'
Shevlin et al., 2009[d] NCS study	5,868	1. CIDI – sexual trauma questions (PTSD module) 2. CIDI : DSM-III 3. CIDI : DSM-III	Community members with a psychotic disorder	1. Childhood 2. Sexual molestation, rape	1. Schizophrenia, schizophreniform, schizoaffective, delusional disorder, atypical psychosis 2. Not reported	Cannabis
Steel et al., 2011 MIDAS study	110	1. PDS 2. Chart review, PANSS, PSYRATS 3. SCID: DSM-IV	Outpatients with a psychotic disorder	1. Lifetime 2. Sexual, emotional, physical abuse; emotional and physical neglect; life-threatening illness or accident, sudden loss	1. Schizophrenia, schizophreniform, schizoaffective, psychosis NOS 2. Mixed sample	Alcohol, amphetamines, cannabis, ecstasy, heroin

				of loved one, assault, psychotic experiences, hospitalization for psychosis, etc.		
Swartz et al., 2006[b] CATIE trial	1,460	1. Authors' interview 2. SCID: DSM-IV, PANSS 3. Hair assay, urine screen, ADUS, collateral report, SCID: DSM-IV	Individuals with a psychotic disorder	1. Lifetime 2. Physical and sexual abuse; homelessness, non-violent and violent victimization	1. Schizophrenia 2. Chronic psychosis	Not reported
Tarrier & Picken, 2011[e]	110	1. PDS 2. File review, PANSS	Outpatients with a	1. Lifetime 2. Sexual, emotional, physical abuse;	1. Schizophrenia, schizophreniform,	Alcohol, amphetamines,

MIDAS study		3. SCID: DSM-IV	psychotic disorder	emotional and physical neglect; life-threatening illness or accident, sudden loss of loved one, assault, psychotic experiences, hospitalization for psychosis, etc.	schizoaffective, psychosis NOS 2. Mixed sample	cannabis, crack cocaine, heroin
Temmingh et al., 2021 SAX study	1,420	1. SCID: DSM-IV PTSD module, DSM-IV psychosocial and environmental problems 2. SCID: DSM-IV 3. SCID: DSM-IV	Black inpatients and outpatients with a psychotic disorder	1. Lifetime 2. Sexual, physical abuse, death of family member, discrimination, homelessness, unsafe neighbourhood, neglect, etc.	1. Schizophrenia, schizoaffective 2. Mixed sample	Alcohol, cannabis, methamphetamine, methaqualone, 'other'

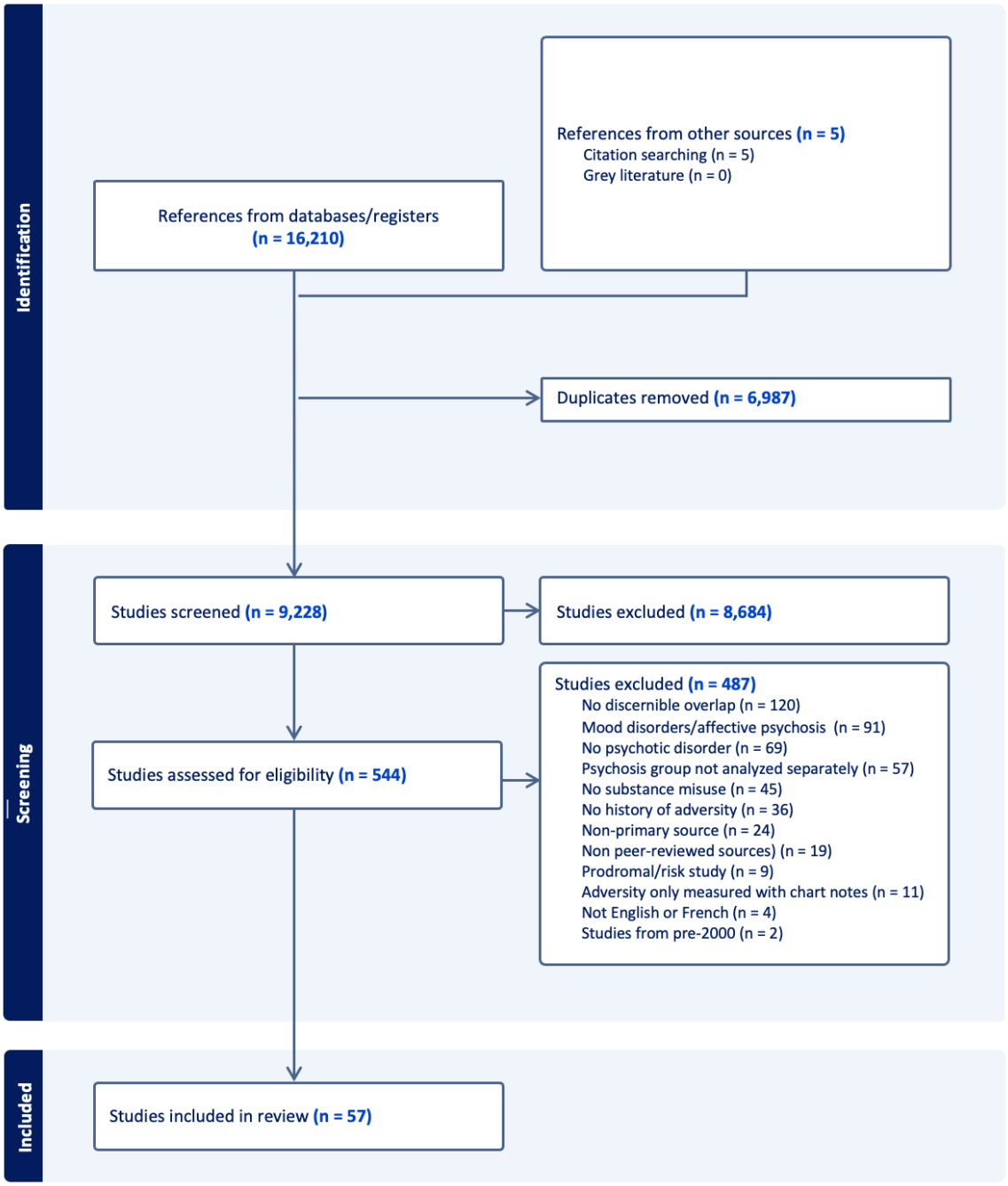
Tiles-Sar et al., 2023 GROUP study	1,119	1. CTQ 2. Not reported 3. CIDI	Outpatients with a psychotic disorder	1. Childhood 2. Sexual, emotional, physical abuse; emotional and physical neglect	1. Schizophrenia, schizoaffective, unspecified psychotic disorder 2. EPP	Alcohol, cannabis
van Nierop et al., 2016 GROUP study	GROUP study = 532	1. CTQ 2. CASH/SCAN, PANSS 3. CIDI	Outpatients with a psychotic disorder	1. Childhood 2. Sexual, emotional, physical abuse; emotional and physical neglect	1. Non-affective psychotic disorder 2. Mixed sample	Not reported
Widing et al., 2022 TOP study	1,099	1. CTQ-SF 2. SCID: DSM-IV 3. AUDIT, DUDIT, SCID: DSM-IV	Outpatients with a psychotic disorder	1. Childhood 2. Sexual, emotional, physical abuse; emotional and physical neglect	1. Schizophrenia, schizophreniform, schizoaffective, psychotic disorder not otherwise specified 2. Mixed sample	Cannabis, 'other substances'

Woolridge et al., 2022	37	1. BTQ-R 2. BPRS 3. CUDIT-R, NIDA checklist	Outpatients with a psychotic disorder	1. Lifetime 2. Sexual, physical abuse; life-threatening illness or accident, sudden loss of loved one, assault, exposure to war zone, natural disaster	1. Cannabis-induced psychotic disorder, schizophrenia-spectrum disorder 2. SIP, EPP	Cannabis
Yousef et al., 2022	165	1. ACE-IQ 2. SCID: DSM-5, PANSS 3. SCID: DSM-5, ASI-5, urine drug screen	Outpatients with a psychotic disorder	1. Childhood 2. Sexual, emotional, physical abuse, physical and emotional neglect, peer aggression, domestic violence, societal violence,	1. Schizophrenia 2. Mixed sample	Cannabis, tramadol

				jailed family members, etc.		
Yui et al., 2000	86	1. Authors' interview 2. File review, 'structured interview' 3. Not reported	Incarcerated women with a psychotic disorder	1. Adulthood 2. Distressing flashbacks	1. SIP (methamphetamine) psychotic disorder 2. SIP	Methamphetamine
Yui et al., 2004	86	1. Authors' interview 2. File review, 'structured interview' 3. Not reported	Incarcerated women with a psychotic disorder	1. Adulthood 2. Distressing flashbacks	1. SIP (methamphetamine) psychotic disorder 2. SIP	Methamphetamin

Figures

Figure 7.7.1. PRISMA flow diagram of study selection for this systematic review



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Chapter 3. Transition to study 2

Overview of Study 1: Findings and Implications

Study 1 was a systematic review examining the nexus of PDs, SM, and AEs in the existing literature published from 2000-2023. Results indicated that these three variables overlap, and the literature appeared to hint at reciprocal relationships among these variables (e.g., AEs are a risk factor for psychosis and can worsen psychosis symptom severity, which may increase risk for AEs). Interestingly, this literature was primarily composed of mixed-stage samples, meaning that it was impossible to discern whether there were unique patterns of AEs and substance use by stage of a PD. My results shed light on a pattern in the literature: there is a plethora of convincing evidence of the strong relationship between AEs and psychosis (Varese et al., 2012), psychosis and SM (Cantor-Graae et al., 2001), but there is much less consensus on the role of SM in the relationship between AEs and psychosis. At times, although highly prevalent, SM appeared to be of minimal importance (e.g., Fitzgerald et al., 2005), while at other times, substances played a key role (e.g., Gearon et al., 2003). However, a complicating factor in this review was that substance use was often examined in a cursory manner when AEs were also examined in a PD population; studies rarely focused on the three-way co-occurrence, but rather the respective occurrence, of these difficulties. Moreover, at times substance use was examined, while SM was the focus of other studies. Cannabis and alcohol are the most widely accepted and used substances in North American culture, which explains their focus in the research, however, because of this focus, we know

less about what other substances are used when AEs are present. Moreover, tobacco is another commonly used substance among people with PDs; however, we chose to focus on substances which have more functional impact on people with PDs. Non-abuse AEs were also much less explored, especially with regards to illness-related AEs and those events that would not meet the criterion A of a DSM-5 (APA, 2013) PTSD diagnosis, but are still impactful (e.g., bullying, discrimination). The inconsistency in measurement across the literature made it challenging to achieve the objective of assessing how exactly the PD-SM-AEs relationship is impacted by specific stages of psychosis, substances, and AE type. Across the literature, the most common AE measurement approach was to focus on childhood, neglecting adulthood and similarly neglecting potential psychosis-related AE events (e.g., hospitalization, police contact during illness). Therefore, there is a gap in knowledge about the lifetime picture of AEs among individuals with PDs, especially those in EPP, a period during which mitigation strategies could have the most profound impact. However, a questionnaire was developed by Carr and colleagues (2018), the Trauma and Life Events (TALE) checklist that importantly examines lifetime AEs in people with PDs, including psychosis-related events; the TALE was tested in an EPP sample as part of a psychometric analysis. Although a newer instrument, this measure, which was highlighted by a recent review as the only lifetime AE measure to include psychosis-related AEs (Airey et al., 2023), may facilitate a better measurement of AEs in an EPP population.

Planning for Study 2: Challenges

Within the trauma literature, there has been a shift towards using a polyvictimization lens (Finkelhor et al., 2011, 2009), which suggests that experiencing multiple *types* of AEs (e.g., sexual abuse, neglect, assault) leads to the development of difficulties (e.g., low self-esteem, learned helplessness) in a dose-response fashion (i.e., as AEs increase in number, difficulties proportionally increase). Polyvictimization does not consider chronicity of events or type of perpetrator (e.g., family, stranger). However, the effect of AEs have also been examined using a 'complex trauma' lens, examining the impact of early AEs perpetrated within the caregiving system (Cook et al., 2005). Regardless of the theoretical underpinnings of the examination, the research is clear: a greater number of AEs carries a greater risk for broad difficulties including more psychopathology, disordered relationships, and challenges with self-regulation (e.g., McLaughlin & Lambert, 2017; Steine et al., 2017). These concepts have only recently been recognized and explored in an EPP population, meaning there are still several gaps remaining. It is yet unclear whether polyvictimization is common throughout the EPP population and if so, what is the overlap with SM in this group. This is the crux of the research question I wanted to answer with Study 2: what is the overlap of SM and AEs in an EPP population? Likewise, I was especially interested in understanding the role of SM further – is SM predicted by AE age of onset and number of AEs, as would be in keeping with the stress and coping model of SM (Wills & Hirky, 1996)? Is there a difference in SM between those with and without a history of AEs? Several studies of mixed

samples did not find differences in substance use between those with and without a history of AEs, but this was unexplored in an EPP sample. Although tobacco use was not a substance of interest in Study 1, given its lesser impact on psychotic symptoms and individual functioning, it would be interesting to gauge its prevalence in an EPP sample with AEs and ascertain whether the rates differ from PD samples without reported AEs (e.g., Myles et al., 2012).

I developed six hypotheses, pre-registered a statistical analysis plan, gathered questionnaires, including the TALE, and planned to move ahead with these analyses. My aim for Study 2 was to explore the substances and AEs common to this group, examine their experiences with disclosure of AEs, and gain a better understanding of the overlap between EPP, SM, and AEs.

This study was launched in January 2020, and thus the pandemic affected recruitment due to restrictions in place at the start of the pandemic in the health care settings. However, to mitigate the impact of recruitment challenges, I partnered with the Early Psychosis Intervention Program (EPIP) in Saskatchewan and the EPIP clinic was added as a second site to this survey project. In addition to my recruitment challenges, the pattern of results, which are delineated in the next chapter, made much of my statistical analysis plan impossible. After exploring many alternative analyses, searching for options capable of analyzing my zero-inflated data that had a negative binomial distribution with a midsize sample, I was forced to shift directions and analyze the hypotheses I could, leaving several behind for the future when I had more power as most small-n techniques had violated assumptions.

Study 2, as outlined in the next chapter, examined the overlap between SM and AEs among patients of an early intervention for psychosis clinic and provides incremental value to the literature and clinicians alike by providing information about the pattern of overlap, barriers to disclosure of AEs, and whether individuals in EPP with SM and a history of AEs want to discuss their AEs in a healthcare setting.

Chapter 4. Lifetime adversity among individuals with early phase psychosis and comorbid substance misuse

The manuscript prepared for this study is presented below. Readers are advised that Victoria Patterson, under the co-supervision of Dr. Alissa Pencer and Dr. Philip Tibbo, was responsible for developing the research questions, obtaining ethics approval, pre-registering the study, recruiting participants, as well as collecting and analyzing data. Victoria wrote the initial draft of the manuscript, with support from her co-authors, and received and incorporated feedback from all co-authors. The manuscript has not yet been submitted for review.

Abstract

Background: Adverse events (AEs) and substance misuse (SM) are rarely examined together among people in early phase psychosis (EPP), although both are frequently examined in isolation given their high prevalence rates in this population. As a result, we do not know the frequency of this three-way overlap. Moreover, AEs are often limited to childhood abuse and do not often include illness-related events (e.g., threatening hallucinations), and information about disclosure of AEs has not been examined in an EPP population. We aimed to gain a better understanding of the overlap between these three variables in addition to gaining more information about adversity within this group.

Methods: We surveyed 110 individuals aged 16-35 years with EPP about SM, lifetime AEs, disclosure of AEs, and PTSD symptoms.

Results: Nearly all participants (97.2%) had experienced at least 1 AE (*M* = 8), suggesting polyvictimization, and over 22% of the sample met or exceeded the cutoff for PTSD on a self-report measure. Over 77% of participants had SM, most commonly alcohol orcannabis and they often used more than one substance (*M* = 2.7). Approximately 76.2% of participants had EPP, SM, and a history of at least 1 AE. Most participants (78.7%) had disclosed their AEs to another person, and 72.7% would like to speak to a mental health professional about their experiences.

Conclusions: Adverse events and substance misuse commonly co-occur in EPP, and these results have important clinical ramifications for assessment and treatment in an EPP population.

Keywords: Psychotic disorders; adversity; substance misuse; disclosure; comorbidity

Introduction

The onset and progression of psychotic disorders are oftentimes intertwined with adverse events (AEs) and substance misuse (SM; Conus et al., 2010; deRuiter et al., 2013; Hunt et al., 2018; Kilcommons & Morrison, 2005). AEs are uncontrollable negative experiences that "cause harm or the potential for harm along with stress and suffering" (Burgermeister, 2007) e.g., child abuse, discrimination), while SM is the problematic use of drugs and alcohol that interferes with day-to-day functioning (Arseneault et al., 2002; van Os et al., 2002). Many studies have examined the co-occurrence of two of these three variables (e.g., psychosis and SM; AEs and SM); however, there is a general lack of consensus regarding the frequency of the overlap between these three variables.

In line with the psychosis proneness-persistence-impairment model of psychotic disorders (van Os et al., 2009), AEs have been found to be one of the most substantial risk factors related to the onset of a psychotic disorder (PD), as well as one of the greatest predictors of negative clinical outcomes (e.g., suicide risk; Bailey et al., 2018; Conus et al., 2010). Previous research has estimated that at least 50-80% of individuals with chronic psychosis (i.e., 10+ years with a psychotic disorder) have experienced an AE prior to psychosis onset (Larsson et al., 2013; Read et al., 2005), which is similar to some estimates of AEs in the general population (e.g., 27-80.1%; Akyuz et al., 2005; Elliott, 1997; Frans et al., 2005). Estimates of AE prevalence are similarly elevated in early phase psychosis (EPP; first five years of a psychotic disorder), with AE prevalence

ranging between 30-96% (Bendall et al., 2007; DeTore et al., 2021; Gearon et al., 2003; Neria et al., 2002; Ramsay et al., 2011; Varese et al., 2012). Some studies found that more than 25% of their sample experienced five or more AEs (Trauelsen et al., 2015), which appears elevated compared to control participants who experienced 2-3 AEs (Briere et al., 2015).

Similar to AEs, SM is associated with psychosis onset and is present in more than 60% of persons experiencing psychosis (Conus et al., 2010; Cuffel et al., 1993; Lambert et al., 2005). SM has been shown to lead to more negative functional and symptomatic outcomes in psychosis, such as increased hallucinations and delusions, lower remission rates, and a reduced ability to function in work and school environments (Abdel-Baki et al., 2017; Gonzalez-Pinto et al., 2011; Lambert et al., 2005). In addition, the frequency and quantity of use necessary to be considered 'misuse' may be lower in people with PDs given the greater impact on symptoms, risk of relapse, and functioning (Drake et al., 1989; Kavanagh et al., 2002). Among EPP populations, SM has been found to be significantly elevated compared to chronic psychosis populations, with more than 80% of EPP program patients misusing cannabis and/or alcohol at program entry (Cookey et al., 2020; Ouellet-Plamondon et al., 2017). However, EPP often occurs during emerging adulthood (i.e., age 18-25; Arnett, 2007), which is a period marked by higher substance use, even in the general population. Notably, longitudinal and cross-sectional studies have found that more frequent substance use in EPP is associated with increased positive symptoms (e.g., hallucinations) and poorer social functioning compared to less frequent use, suggesting a dose-

response relationship between SM and clinical outcomes in psychosis (Cookey et al., 2020; Linszen et al., 2004; Wade et al., 2007).

SM is commonly comorbid with psychotic disorders and a history of AEs (Buckley et al., 2009). Psychotic episodes occur more frequently among those who use cannabis and have a history of adversity (Harley et al., 2010; Konings et al., 2012). Cannabis appears to have a greater effect on the risk of developing a psychotic disorder when individuals have also experienced frequent AEs throughout their lives (Konings et al., 2012). Although there appears to be a multifaceted relationship between psychosis, AEs, and SM, the overlap between all three variables has yet to be explored extensively. Compared to chronic psychosis populations, EPP patients appear to have a higher rate of SM (Cookey et al., 2020; Schofield et al., 2001) and a similar rate of AEs (Braehler et al., 2013). However, there has been little research to date on the overlap between all three variables in individuals with EPP. Given that previous research has already established elevated rates of SM and AEs in people with psychotic disorders independently, the logical next step is to explore simultaneously the prevalence of both SM and AEs among people with EPP.

Previous studies have suggested that AEs may precede SM (Lo & Cheng, 2007), while SM typically precedes psychosis (Zammit et al., 2002); yet, it is unknown whether AEs typically appear before or after the onset of a psychotic disorder, or whether they commonly occur at multiple time points. There is also a gap in knowledge about the types of AEs experienced by those in EPP. Psychotic experiences are infrequently categorized as an AE, even though

Beattie and colleagues (2009) found that 45% of their sample experienced moderate to severe symptoms of posttraumatic stress disorder (PTSD) related to their positive psychotic symptoms (e.g., hallucinations) and events surrounding their first admission to a psychiatric hospital. Another study noted that individuals in EPP were twice as likely to report a history of bullying compared to controls (Trotta et al., 2013). Yet, very few studies of AEs in EPP include bullying, despite the general adversity literature reporting its high frequency and detrimental impact on development (Arseneault, 2018), at times finding effects on par with an interpersonal trauma (Idsoe et al., 2021). Furthermore, it would be beneficial to understand whether individuals in EPP disclose their AEs experiences, the barriers that may prevent disclosure, and whether they would be interested in discussing their experiences with a mental health clinician. To further optimize outcomes in EPP in those with SM, it is imperative to have a better understanding of the overlap of a broader range of AEs which will help inform developments of psychotherapy options for these young adults.

Aims and hypotheses

The overarching goal of this project is to gather information about the nexus of EPP, SM, and AEs. Our specific aims are as follows: 1) Establish the proportion of people with EPP who have both SM and a history of AEs and gather information about types of AEs and substances used; and 2) determine whether people with EPP are interested in psychological support for difficulties related to AEs and what barriers may prevent them from accessing treatment.

This study's three specific hypotheses are as follows: 1) More than 60% of the sample will have both a history of AEs and current SM, 2) PTSD symptoms will be highest amongst those who report AEs before age 18, and 3) Over 50% of the sample with EPP, SM, and a history of AEs will be interested in speaking to a mental health professional about their AEs.

Methods

Participants and setting

Participants recruited for the study were patients at the Nova Scotia Early Psychosis Program (NSEPP) in Halifax, Nova Scotia, or the Early Psychosis Intervention Program (EPIP) in Saskatoon, Saskatchewan. The NSEPP has approximately 300 EPP patients in the program at a time (M_{age} = 26.39, SD = 4.79). The EPIP has approximately 55 active patients at a time (M_{age} = 24.8, SD = 4.25). Inclusion criteria included: 1) Aged 16-35 years, 2) diagnosis of a primary psychotic disorder within the past 5 years [ICD F20-29], and 3) fluent in English. We were attempting to establish the rate of AEs and SM in this sample; therefore, participants were not required to use substances or have a history of AEs to participate.

Measures and procedures

Participants reported demographics (i.e., age, gender, sexual orientation, race) and completed three questionnaires related to AEs. The Trauma and Life Events checklist (TALE; Carr et al., 2018) was used, a 21-item questionnaire asking participants if any of 20 listed events had occurred, when, whether they were repeated, and which events are still affecting them now. Scores could range

from 0-20; higher scores indicated more lifetime AEs. The second measure was the 8-item version (Price et al., 2016) of the PTSD Checklist-5 (PCL-5; Blanchard et al., 1996), which screens for PTSD symptoms. Response options are on a 5-point scale ranging from 'Not at all' (0) to 'Extremely' (4). A cut score of 19 was suggested to detect PTSD, as this score maximizes sensitivity at 83% with sensitivity at 39%. The five-item author-compiled Disclosure and Interest in Treatment (DIT) scale was used to ask participants about their experiences disclosing their adversity history (i.e., to whom, helpfulness of disclosure), interest in speaking to a mental health clinician about their AEs, and the barriers to speaking to a clinician.

To establish rates of SM, we administered three questionnaires. The full length versions of all SM questionnaires have been validated for use with people with EPP (Cassidy et al., 2008; Hides et al., 2009; Humeniuk et al., 2008). The two-item Alcohol, Smoking, and Substance Involvement Screening Test – Frequency and Concern (ASSIST-FC; McRee et al., 2018; WHO ASSIST Working Group, 2002) was used to examine current substance use frequency (i.e., past 3 months), as well as asking about expressed concerns about the participant's substance use. Scores can range from 0-12 for each substance; alcohol scores ≥6 and non-alcohol scores ≥2 indicated SM. The 3-item Alcohol Use Disorders Identification Test – Alcohol consumption version (AUDIT-C; . Bradley et al., 2003; Bush et al., 1998) assessed alcohol use in the past year. Total scores can range from 0-12 with scores of ≥4 indicating hazardous drinking (K. A. Bradley et al., 2003; Bush et al., 1998). The 10-item version of the Drug

Abuse Screening Test (DAST; Skinner, 1982) was used to categorize individuals' level of substance use; scores ranged from 0-10. Individuals were categorized into the following categories based on their DAST-10 total score (Skinner, 1982): 'No misuse' (0), 'Low misuse' (1-2), 'Moderate misuse' (3-5), 'Substantial misuse' (6-8), or 'Severe misuse' (9-10).

All participants completed the TALE and PCL-5, followed by the ASSIST-FC, AUDIT-C, and DAST-10 questionnaires but only NSEPP participants completed the DIT survey. The study was approved by the Nova Scotia Health Research Ethics Board (REB #1025128), the IWK Health Research Ethics Board (REB #1025492), and the University of Saskatchewan's Behavioural Research Ethics Board in Saskatchewan (REB#565).

Data analysis

Study hypotheses and analytic approach, including power analyses and test assumptions, were preregistered, and can be found here: https://osf.io/4m5j3. Analyses were conducted using *R* (R Core Team, 2022) version 4.2.1. Preregistered a priori power analyses suggested that we needed a sample of $N = 200$ to run all planned analyses. Our sample of $N = 110$ was too small for the planned large-*N* analyses (e.g., logistic regression), and, after reviewing the distributions, conducting the Shapiro-Wilks test, overdispersion test (Cameron & Trivedi, 1990), and assessment for zero inflation (Hartig, 2022), we concluded that our data was zero-inflated and overdispersed given that all three tests rejected the null hypothesis. We required the use of a zero inflated negative binomial regression (Campbell, 2021). However, given our lack of power to carry

out this analysis, and the fact that smaller-*N* analyses (e.g., *t*-tests, Mann-Whitney U) were inappropriate given assumption violations, we tested three of the originally planned six hypotheses using descriptives and calculated confidence intervals (CIs) for each proportion.

Results

Participants

Figure 1 outlines the participant recruitment process, and Table 1 delineates the demographic information for this sample of 110 participants. Although many participants were members of majority groups, 57% of the sample were part of a marginalized group on the basis of race, gender, and/or sexual orientation.

Adversity and substance misuse

Nearly all participants (97.2%, 95% CI 92, 99) experienced at least one lifetime AE on the TALE (*M* = 8, *SD* = 3.8; range 0-17); approximately 40% of the sample experienced 10 or more AEs (see Table 2). Over 91% of the sample experienced their first AE during childhood, with the average age of first AE occurrence at age 7 (SD = 4.7; range = 0-17) and adult onset of AEs occurred at an average age of 20.6 (SD = 3.6). The mean age of first lifetime AE occurrence was in childhood (*M* = 8.1 years, SD = 5.9). Approximately 58% of participants still experience the impact of at least 1 AE (see Table 4); the median rating of current AE impact was 4 (SD = 3.6; range 0-10), suggesting “some” effects. Scores on the abbreviated PCL-5 suggested “some” difficulties, on average (*M* =

11.84, SD = 8.47; range 0-32); 22.7% (95% CI 15.9, 31.4) of the sample (*n* = 25) scored at or above the cutoff suggestive of PTSD.

Many participants used at least one substance; alcohol and cannabis were the most common. Approximately 77.2% of the sample engaged in any SM (drug or alcohol), while drug-related SM in this sample was 67.3% (95% CI 68.5, 85.3), with most individuals engaging in substantial levels of drug misuse, while just over half the sample engaged in alcohol misuse. Of the 77.2%, 46.3% of the sample had both drug and alcohol-related SM, 20.9% had drug-only SM, and 10.0% had alcohol-only SM. Table 2 illustrates the endorsed AEs and SM details. See Supplemental Materials for details on substance prevalence.

Overlaps

See Figure 2 for information on the co-occurrence of EPP, SM, and AEs. Much of this sample had EPP, SM, and AEs (76.3%, 95% CI 67.6, 83.3), although 20.9% (95% CI 14.3, 29.4) had AEs and EPP without SM. SM rarely appeared without AEs (0.9%, 95% CI 0.1, 4.9), and both SM and AEs were absent for a small proportion of the sample 1.8%, 95% CI 0.5, 6.3). Table 4 illustrates the specific overlaps between AEs and SM; illness-related AEs appear to overlap substantially with SM. For those who use substances, moderate levels of SM were the most common across AEs. The AEs with the greatest proportion of participants meeting criteria for severe SM on the DAST-10 included: assault by a stranger, acting in ways that put you in danger or were strange/embarrassing, and unusual experiences that were distressing or made you feel unsafe.

Disclosure and interest in treatment

Of those who reported experiencing an AE on the DIT scale, 72.7% (95% CI 60, 78.7) would like to speak to a mental health professional about their AEs. Of those who did not want to discuss their AEs with a mental health professional, the following reasons were endorsed: do not want to speak about AE (45.8%), a reason not listed here (e.g., feels unnecessary now; event was “not that bad”; 29.2%), they did not want people to know AE occurred (26.3%), no time (16.7%), distrust therapists (12.5%), or discussing AE would be too upsetting (12.5%). Participants could endorse multiple options.

Most participants (78.2%) previously disclosed their AE; the receiver of the disclosure was often a MH professional (72.8%), family member (67%), or friend (61.4%). Less commonly, disclosures were made to medical professionals (32.9%) or others (8.6%; e.g., church members). Most individuals who disclosed experienced the disclosure as helpful (73.2%; 95% CI 46.9, 66.8). When disclosures were perceived as unhelpful, this happened because other problems were discussed instead of disclosure (5.6%), the participant didn’t like/agree with the recipient of the disclosure (4.2%), the participant was not able to discuss what they wanted to (2.8%), they didn’t discuss difficult event at all (2.8%), or they distrusted disclosure recipient (2.8%).

Discussion

The study used a retrospective cross-sectional between-subjects design to study AEs and SM within a sample of individuals within EPP. As anticipated, SM and AEs were common amongst this EPP sample, but, most importantly, EPP,

SM, and AEs overlap often (76.3%), with SM rarely occurring in the absence of AEs. Nearly a quarter (22%) of our sample met the cutoff suggestive of PTSD, and more than half of those with a history of both AEs and SM reported wanting to speak to a mental health professional about their AEs.

The present study was one of the few to illustrate the AE-SM overlap in an EPP population and to consider a broader range of AEs, including those AEs specific to a psychotic illness (e.g., distressing hallucinations). When examining substances, tobacco use appears slightly lower among people with EPP (e.g., 50-61%; Myles et al., 2012) than among those with chronic psychosis (e.g., 70-80%; Poirier et al., 2002). In a study of chronic psychosis and SM (Ng et al., 2016), rates of SM were similar to this study, which is surprising given that SM often declines over time following admission to treatment (Abdel-Baki et al., 2017). However, fewer AEs were endorsed (*M* = 4) and PTSD (12%), in that prior study (Abdel-Baki et al., 2017) potentially explained by the fact that neither illness-related AEs nor childhood-specific AEs (e.g., bullying) were considered. When compared to a sample that did consider illness-related events (Picken & Tarrier, 2011), a similar overall prevalence of AEs (>90%) and PTSD levels was observed, yet the mean number of AEs was almost double in our sample (8 vs. 4.3), potentially due to the fewer items on their measure vs the TALE (16 vs 20 items). In an EPP sample, Carr and colleagues (Carr et al., 2018) similarly found that psychosis and bullying were among the most reported AEs, although sexual abuse was the event affecting our participants most now, in contrast to their sample most affected by hospitalization and treatment.

Individuals with psychosis are regularly screened out from treatment trials for adversity (R. Bradley et al., 2005; Ronconi et al., 2014), and no AE-focused intervention has yet been adapted specifically for people with EPP and SM. Yet, over 70% of our sample wanted to speak to a clinician about AEs, a finding supported by several qualitative studies examining disclosure of and treatment for AEs (Campodonico et al., 2022; Tong et al., 2017). Tong and colleagues (2017) reported similar barriers to treatment; participants often did not want to talk about their AEs, or did not want to discuss the event for fear that it would be too upsetting, a common barrier to engaging in AE-focused treatment. Participants in our study appeared more concerned about someone else knowing that they experienced a particular AE, potentially indicating a role for self-conscious emotions commonly associated with AEs (e.g., shame, guilt; Lee et al., 2001).

This study and others found that people with EPP often experience a multitude of AEs (Bonoldi et al., 2013; Schalinski et al., 2015b) and they have a higher prevalence of PTSD than the general population (Berry et al., 2013; Brady et al., 2003; Gairns et al., 2015). They also have high rates of SM (Hartz et al., 2014; Kavanagh et al., 2004), which is the second most common exclusion criteria for AE-focused research trials (Leeman et al., 2017; Ronconi et al., 2014). In essence, treatment for the nexus of these variables remains a research and clinical gap because these symptoms cause both impairment and distress (Baudin et al., 2016), and can bidirectionally increase symptom severity (Bailey et al., 2018; Nathan & Lewis, 2021). Treatments must be able to address illness-

related AEs, given their high prevalence, high recurrence, and adverse long-term impacts. Additionally, treatment must be capable of addressing the issues related to SM in this population (e.g., cravings, links to AEs and psychosis), which is not part of traditional AE-focused therapies. Yet, treatment guidelines suggest integrated treatment (i.e., one provider, one treatment approach) as the first-line approach (Cragin et al., 2017; Kavanagh et al., 2002), necessitating that a single clinician be well-versed in EPP, SM, and AEs sequelae (e.g., dissociation) in order to treat the links between these challenges. Moreover, an intervention provided during EPP may be most beneficial because individuals may have improved chances of recovery compared to engaging in treatment once psychosis has become chronic and further comorbid psychopathology develops (e.g., PTSD; Braehler et al., 2013; Crumlish et al., 2009; Lieberman et al., 2001).

Strengths & limitations

This study has several strengths. The clearest strength is the breadth of AEs explored in an EPP population, notably the inclusion of illness-related AEs. These events are often omitted, which precludes clinical intervention development, given the lack of knowledge in this area. Yet, results suggest that these events should be included given their frequency and continued impact on participants. Another clear strength is the greater sexual and gender diversity than reported in many similar samples; 32.7% of our sample was part of the of LGBTQIA+ community, significantly exceeding the expected 6.8% prevalence observed in a large case-control study (Post et al., 2021). The experiences of LGBTQIA+ people with psychotic disorders are rarely examined, despite their

greater representation in psychotic samples (Bolton & Sareen, 2011). Although the nature of the event was not reported, over 41% of our sample reported discrimination, which may imbue minority stress effects.

There are several limitations to our findings. This data is cross-sectional, thereby precluding any causal connections given that we cannot determine directionality of effects. In addition, given the overlap between psychotic disorders and PTSD symptoms, it is difficult to completely differentiate these symptoms into one category or another without the use of diagnostic instruments and clinical judgement. As well, criterion A of a DSM-5 (APA, 2013) PTSD diagnosis was not evaluated in this context. Therefore, future studies should attempt to replicate these results using clinical diagnostic instruments. In addition, given that psychosis-related AEs, particularly item 15 of the TALE ('unusual experiences that made you feel in danger or distress'), are both an AE and a psychotic symptom, there is conflation between a predictor and an outcome. Moreover, the item includes both distress, which is common among individuals experiencing psychosis (Kelleher et al., 2015), and the sense of being in danger, which is uncommon. Distress and feelings of being in danger therefore cannot be separated and results for this item should be considered with this caveat in mind. Finally, much of the sample included men and White individuals, limiting the generalizability of this information to other genders and races.

Conclusions and future directions

The results of this study illustrate the importance of assessing and treating both SM and AEs in an EPP population, given their common overlap and high

prevalence. Moreover, asking about AEs is critical, given that many individuals with EPP wish to discuss these experiences, and focusing on a broad range of AEs that includes illness-related experiences (e.g., hospitalizations) seems particularly important. In addition, PTSD symptoms were quite elevated among this group. SM was typically at a moderate or substantial level, and alcohol, tobacco, and cannabis were the most used substances. These results may facilitate the tailoring of an AE-focused intervention for people with EPP, which should consider the role of SM, especially given that SM is not typically part of AE-focused treatment (e.g., trauma-focused cognitive-behavioural therapy, prolonged exposure). Future studies should also consider exploring AE sequelae (e.g., dissociation, depression, anxiety) in an EPP-SM-AEs population, as these challenges were not explored in this study, and they remain a gap in the literature. Furthermore, future studies should assess the relative age of onset of psychosis, SM, and AEs to establish the temporal ordering of experiences to determine which variables are risk and maintenance factors in this group.

Tables

Table 2.1.1. Participant demographics

	Participants *N* = 110
Age (years), *M* (SD)	25.3 (4.2)
Race, *%, n*	
White	66.3% (73)
Black	10% (11)
Indigenous	8.2% (9)
Asian	5.5% (6)
Multiracial	4.5% (5)
Arab	1.8% (2)
Latinx	1.8% (2)
Race not listed	1.8% (2)
Gender, *%, n*	
Man	69.1% (76)
Woman	22.7% (25)
Non-binary	8.2% (9)
Sexual orientation, *%, n*	
Heterosexual	68.2% (75)
Bisexual	12.7% (14)
Gay/Lesbian	7.2% (8)
Pansexual	5.5% (6)

Queer	1.8% (2)
Asexual	1.8% (2)

Note: Additional gender options were offered; only those used are reported. 6% of participants were transgender.

Table 2.1.2. Adverse event (AE) prevalence and age of occurrence

	%, n *M (SD)*[a]	Age of first occurrence *M* (SD)	Recurrence *%, n*	Still affected now *%, n*
TALE Interpersonal events	4.6 (2.5)[a]			
Bullying/harassment	72.7% (80)	11.9 (6)	90.0% (72)	10.0% (8)
Someone close to you insulting/humiliating you	50.0% (55)	13.7 (7.7)	83.6% (46)	25.4% (14)
Witnessing physical violence/verbal aggression at home	43.6% (48)	7.6 (4.4)	72.9% (35)	14.6% (7)
Stranger being physically violent/aggressive towards you	41.8% (46)	16.5 (6.5)	58.7% (27)	10.9% (5)
Discrimination	41.0% (45)	14.9 (6.5)	88.9% (40)	13.3% (6)
Feeling unsafe, unloved, or unimportant during childhood	41.0% (45)	8.3 (4.3)	82.2% (37)	13.3% (6)
Someone close to you being violent/aggressive towards you	40.0% (44)	12.3 (6.5)	68.1% (30)	15.9% (7)
Temporary separation from caregiver (e.g., foster care)	39.0% (43)	12.1 (6.4)	46.5% (20)	11.6% (5)
Permanent separation from caregiver	32.7% (36)	15.0 (8.3)	38.9% (14)	27.7% (10)
Sexual assault/abuse since age 16	25.5% (28)	20.2 (4.2)	57.1% (16)	20.8% (5)
Sexual assault/abuse before age 16	21.8% (24)	8.8 (4.7)	62.5% (15)	39.3% (11)

Physical neglect during childhood	6.4% (7)	9.7 (4.3)	57.1% (4)	0.0% (0)
Exposure to war	3.6% (4)	4.25 (7.8)	50.0% (2)	25.0% (1)
TALE Illness events	2.26 (1.2)[a]			
Unusual experiences (e.g., hearing voices) that made you feel distressed or unsafe	80.0% (88)	21.2 (6.1)	72.7% (64)	18.2% (16)
Acting in ways that put you in danger, or were strange/embarrassing	57.2% (63)	18.9 (4.5)	69.8% (44)	14.3% (9)
Contact with mental health services that involved threatening/upsetting events	52.0% (57)	22.7 (5)	47.3% (27)	24.6% (14)
Any other contact with health or justice services that was upsetting or frightening	37.2% (41)	19.6 (5.1)	43.9% (18)	17.1% (7)
TALE Other AEs	1.5 (0.9)[a]			
Sudden/unexpected change in circumstances	47.2% (52)	14.2 (7.4)	55.8% (29)	9.6% (5)
Accidental/non-interpersonal events (e.g., fire)	31.0% (34)	16.5 (6.4)	61.8% (21)	20.5% (7)
Other events not listed above (e.g., homelessness)	37.2% (40)	17.5 (7.4)	40.0% (16)	32.5% (13)

Table 2.1.3. Substance use prevalence and co-occurrence

Number of substances used, *M (SD)*	2.7 (1.5)
AUDIT-C, *M* (*SD)*	4.15 (3.2)
Substance use in past 3 months, %, *n*	
Alcohol	72.2% (80)
Tobacco	61.8% (68)
Cannabis	54.5% (60)
Hallucinogens	14.5% (16)
Cocaine	12.7% (14)
Sedatives	8.2% (9)
Amphetamines	6.4% (7)
Opioids	4.5% (5)
Inhalants	1.8% (2)
Other	4.5% (5)
Use of 2+ substances	52.8% (58)
Use of 3+ substances	20.9% (24)
Non-alcohol SM level %, *n*	
Low-or-none	32.7% (36)
Moderate	28.2% (31)
Substantial	29.1% (32)
Severe	10.0% (11)
Alcohol misuse %, *n*	56.4% (62)

Table 2.1.4. Overlap of substance misuse and lifetime AEs experienced by participants

Event	Level of drug misuse				Total % with AE and SM
	Low-to-no	Moderate	Substantial	Severe	
1. Exposure to war	0.9% (1)	1.8% (2)	0.01% (1)	0.0% (0)	2.7%
2. Loss/permanent separation from caregiver (e.g., death)	6.3% (7)	9.0% (10)	12.7% (14)	4.5% (5)	30.9%
3. Temporary separation from caregiver (e.g., being put in care)	10.0% (11)	10.0% (11)	14.5% (16)	4.5% (5)	33.6%
4. Sudden/unexpected move or change in circumstances	11.8% (13)	13.6% (15)	16.3% (18)	5.4% (6)	39.1%
5. Bullying/harassment	21.8% (24)	20.9% (23)	22.7% (25)	7.2% (8)	57.3%
6. Discrimination	12.7% (14)	10.0% (11)	13.6% (15)	4.5% (5)	31.8%
7. Someone close to you insulting/humiliating you	10.0% (11)	14.5% (16)	18.2% (20)	7.2% (8)	44.5%

8. Someone close to you being violent/aggressive towards you	12.7% (14)	8.2% (9)	11.8% (13)	7.2% (8)	33.6%
9. Witnessing physical violence/verbal aggression at home	16.4% (18)	13.6% (15)	8.2% (9)	5.5% (6)	33.6%
10. Stranger being physically violent/aggressive towards you	13.6% (15)	12.7% (14)	10.9% (12)	10.0% (11)	33.6%
11. Feeling unsafe, unloved, or unimportant during childhood	14.5% (16)	9.0% (10)	13.6% (15)	3.6% (4)	30.9%
12. Physical neglect (e.g., insufficient food) during childhood	1.8% (2)	0.01% (1)	1.8% (2)	1.8% (2)	4.5%
13. Unwanted sexual contact since 16th birthday	6.3% (7)	4.5% (5)	9.0% (10)	1.8% (2)	16.3%
14. Unwanted sexual contact before 16th birthday	5.5% (6)	6.3% (7)	10.9% (12)	2.7% (3)	20.0%
15. Unusual experiences (e.g., hearing voices) that were distressing or made you feel in danger	26.4% (29)	20.9% (23)	24.5% (27)	8.2% (9)	62.7%

16. Acting in ways that put you in danger, or are strange/embarrassing	15.5% (17)	13.6% (15)	19.0% (21)	9.0% (10)	48.2%
17. Contact with mental health services that involved threatening/upsetting events	19% (21)	10.0% (11)	16.3% (18)	6.3% (7)	40.9%
18. Any other contact with health or justice services that was upsetting or frightening	8.2% (9)	10.0% (11)	13.6% (15)	5.5% (6)	30.9%
19. Any other events that were accidental/non-interpersonal (e.g., fire)	10.0% (11)	7.2% (8)	10.0% (11)	3.6% (4)	25.5%
20. Other events not listed above (e.g., homelessness)	10.9% (12)	11.8% (13)	9.0% (10)	4.5% (5)	30.0%

Note: Percentages represent % of total sample. Participants could endorse more than one event. The levels of drug misuse do not include alcohol. The % of individuals with AEs and SM include both drugs and alcohol.

Figures

Figure 2.1.1. Participant recruitment flow

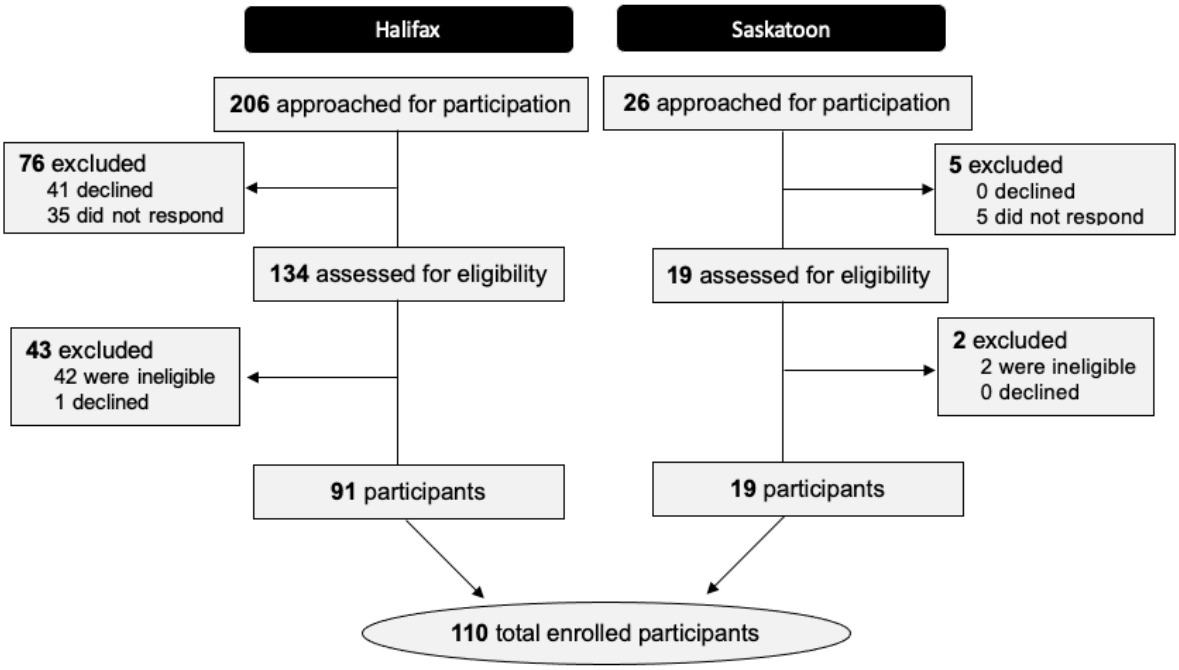
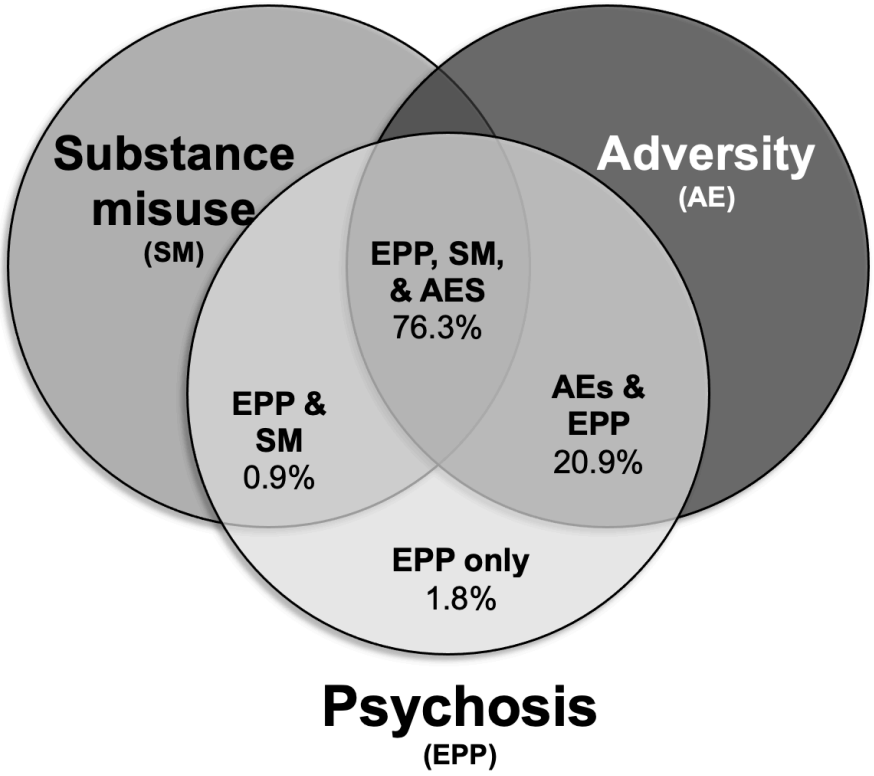


Figure 2.1.2. The co-occurrence of SM and AEs with EPP



Note. AE-only and SM-only groups are not possible given that all participants have EPP.

Supplemental Table 2.1.5. Substance use co-occurrences for people who uses substances (*n* = 98)

Multi-substance use	%, *n*
Use of 2+ substances	59.2% (58)
Use of 3+ substances	23.5% (23)
Use of 4+ substances	14.3% (14)
Use of 5+ substances	6.1% (6)
Use of 6+ substances	4.1% (4)
Use of 7+ substances	-
Use of 2+ substances[a]	80.6% (79)
Use of 3+ substances[a]	44.9% (44)
Use of 4+ substances[a]	20.4% (20)
Use of 5+ substances[a]	14.3% (14)
Use of 6+ substances[a]	6.1% (6)
Use of 7+ substances[a]	4.1% (4)

Note. [a]Includes tobacco as a substance

Supplemental Table 2.1.6. Patterns of substance co-occurrence for people who use substances (*n* = 98)

	Tobacco	Alcohol	Cannabis	Cocaine	Amphetamines	Inhalants	Sedatives	Hallucinogens	Opioids	Other
Tobacco	-	-	-	-	-	-	-	-	-	-
Alcohol	49.0%	-	-	-	-	-	-	-	-	-
Cannabis	40.9%	44.5%	-	-	-	-	-	-	-	-
Cocaine	11.8%	12.7%	11.8%	-	-	-	-	-	-	-
Amphetamines	5.4%	6.3%	5.4%	4.5%	-	-	-	-	-	-
Inhalants	1.8%	1.8%	1.8%	1.8%	1.8%	-	-	-	-	-
Sedatives	7.2%	7.2%	5.4%	2.7%	2.7%	1.0%	-	-	-	-
Hallucinogens	10.9%	12.7%	12.7%	4.5%	2.7%	1.0%	2.7%	-	-	-
Opioids	4.5%	4.5%	4.5%	1.8%	1.8%	1.8%	1.8%	2.7%	-	-
Other	2.7%	4.5%	2.7%	1.8%	1.0%	1.8%	0.0%	1.8%	1.0%	-

Chapter 5. Transition to study 3

Overview of Study 2: Findings and Implications

My findings indicate that AEs and SM commonly appear among those with EPP. The expansive literature examining the AE-PD and SM-PD relationships have showcased the pervasive issues with comorbid psychopathology, functioning challenges, and difficulties with recovery (e.g., Bendall et al., 2012; de Jager et al., 2021; Large et al., 2014; Rosenberg et al., 2007; Schenkel et al., 2005; Vila-Badia et al., 2021). Previous studies noted that those with a history of AEs often experience delays in treatment (Ng et al., 2016), reflected in arriving to treatment later and subsequently more ill (Veru et al., 2022). Similarly, other studies found that people with AEs and SM appear to require higher doses of antipsychotics (Hassan & De Luca, 2015) and may experience a diminished recovery from psychosis. The specific PD-SM-AEs literature has just begun to illustrate the difficulties associated with this nexus (e.g., more severe psychotic symptoms, poorer functioning; Christy et al., 2023), which are likely as or more severe than the challenges associated with the overlap of two of these three variables.

However, despite the findings reported in the previous chapter and in other literature, there remains both a research and clinical care gap with regards to the treatment of the overlap between EPP, SM, and AEs. Few treatment options exist, and this is partially attributable to a commonly held fear among clinicians: fear of symptom exacerbation when addressing AEs. Becker et al. (2004) surveyed 217 psychologists about using exposure therapy and contraindications

for its use for individuals with PTSD; more than 85% of surveyed clinicians believed that a PD was an appropriate contraindication for the use of exposure techniques. Several studies have found evidence of this same concern among clinicians across countries (e.g., Chadwick & Billings, 2022; Gairns et al., 2015; van den Berg et al., 2016). Despite clinician concerns, more than 70% of Study 2 EPP patients wanted to speak to a clinician about their AEs, suggesting that this issue represents a likely frustrating gap for patients, who are left with few treatment options and potentially little access to treatment. Interestingly, the early evidence for AE-focused treatment in PDs has been conducted among those with chronic psychosis (e.g., van den Berg et al., 2015), and only a few, temporary symptom exacerbations have been observed (van den Berg, de Bont, et al., 2016), suggesting that this significant clinical fear may not be supported by evidence in a PD population.

Planning for Study 3

The first step to treating the challenges delineated above and in the literature was to choose an intervention approach. The choice of intervention was a crucial decision since the literature is still in its infancy, limiting the evidence upon which to build an intervention. A Canadian study provided preliminary evidence for the use of trauma-focused Acceptance and Commitment Therapy (ACT) in a group format (Spidel et al., 2019) and several studies examined the outcomes of Trauma-Focused Cognitive Behavioural Therapy (TF-CBT) among people with PDs (Mueser etal., 2008; Mueser et al., 2015; O'Driscoll et al., 2016; Steel et al., 2017). Although both seemingly efficacious approaches for

addressing AE sequelae among people with PDs, ACT has more limited evidence with regards to adversity-focused treatment and the group format appeared more practically challenging to implement given difficulties with disengagement observed in the PD population, which are notably higher when SM is present (Doyle et al., 2014; Stowkowy et al., 2012). TF-CBT was highlighted as potentially too cognitively taxing for people with PDs who may be more ill (O'Driscoll et al., 2016) and Cognitive Processing Therapy (CPT), which is similar to TF-CBT, may have the same issue. Cognitive burden is likely to present as an even larger barrier among people in EPP, making both treatments a less efficacious choice than behaviourally focused treatments. The other possible treatment options were Eye Movement Desensitization and Reprocessing (EMDR) therapy and Prolonged Exposure (PE), two exposure-heavy approaches. Given the fact that the cognitive impacts of a PD (e.g., working memory, executive function deficits; Sharma & Antonova, 2003) are a concern, an exposure-focused approach may permit the exploration of AEs with less of a cognitive burden on the participant that may occur with a more cognition-focused treatment, such as CBT. Although both EMDR and PE have preliminary evidence supporting their use among people with PDs (e.g., van den Berg et al., 2015), I focused on the treatment approach with the strongest evidence base supporting its efficacy in the general population using the APA treatment guidelines (American Psychiatric Association, 2017), to guide my decision to choose PE.

Study 2 results highlighted that polyvictimization is typical for those with EPP, SM, and AEs, suggesting that the treatment of choice must be capable of treating multiply victimized people. Although PE is a single-AE treatment, requiring the choice of an 'index' AE and focusing on that event for the duration of treatment, there is evidence that PE remains an appropriate choice for this group, although treatment may require a greater number of sessions (Coffey et al., 2003; J. A. Morrison et al., 2014). When considering the role of SM in treatment, other intervention studies (e.g., de Bont et al., 2016) have found support for the network approach to mental health challenges, outlined by Goekoop and Goekoop (2014), meaning that targeting one set of symptoms (e.g., psychotic symptoms) within a constellation of mental health challenges can improve other symptoms (e.g., anxiety); similarly, one set of symptoms can exacerbate other symptoms, meaning parts of a psychopathology system may interact with other parts, thereby improving or worsening the constellation of symptoms overall. As a result, the focus became the treatment of AE sequelae, while operating under the assumption that by changing one part of the network of symptoms, other facets of the network (e.g., psychosis and SM) would be affected as well. The focus of treatment was AE sequelae more broadly, meaning treatment outcomes were inclusive of PTSD symptoms but not exclusive to PTSD symptoms. The research suggests that individuals exposed to 'complex trauma' often experience a wide range of psychopathology (e.g., anxiety, depressive symptoms, PTSD symptoms; Courtois, 2004); therefore, a wide range of outcomes were monitored during treatment. In addition to choosing treatment

outcomes, I hypothesized two mechanisms of change on which to focus and measure throughout treatment: hopelessness and experiential avoidance.

The two aims of the treatment study explored in Chapter 6 were to test the overarching hypothesis of whether targeting AE sequelae results in changes to AE sequelae, psychotic symptoms, and SM, in addition to examining the outcomes of an AE-focused treatment applied to an EPP-SM group for the first time.

Chapter 6. A multiple baseline trial of adapted prolonged exposure psychotherapy (PE+) for individuals with early phase psychosis, comorbid substance misuse, and a history of adversity: A study protocol

The manuscript prepared for this study is presented below. Readers are advised that Victoria Patterson, under the co-supervision of Dr. Alissa Pencer and Dr. Philip Tibbo and in collaboration with Dr. Sherry Stewart and Dr. Joel Town, was responsible for developing the study protocol, including designing the treatment elements, establishing an analysis plan, publishing the clinical trial preregistration, writing the treatment manual, and drafting the study protocol manuscript. She received and incorporated feedback from all co-authors. The manuscript underwent peer-review and required two rounds of revisions, which Victoria led, prior to the manuscript's acceptance in *Frontiers in Psychology – Psychopathology* on November 8th, 2022. The full reference for this manuscript is:

Patterson, V. C., Tibbo, P. G., Stewart, S. H., Town, J., Crocker, C. E., Ursuliak, Z., ... & Pencer, A. (2022). A multiple baseline trial of adapted prolonged exposure psychotherapy for individuals with early phase psychosis, comorbid substance misuse, and a history of adversity: A study protocol. *Frontiers in Psychology*, *13*. Doi: 10.3389/fpsyg.2022.1012776

Abstract

Background: Adversity is prevalent among people with psychotic disorders, especially those within the first five years of a psychotic disorder, called early phase psychosis. Although adversity can lead to many negative outcomes (e.g., posttraumatic stress symptoms), very few treatments for adversity-related sequelae have been tested with individuals with psychotic disorders, and even fewer studies have specifically tested interventions for people in early phase psychosis. Furthermore, people who misuse substances are commonly excluded from adversity treatment trials, which is problematic given that individuals with early phase psychosis have high rates of substance misuse. For the first time, this trial will examine the outcomes of an adapted 15-session prolonged exposure protocol (i.e., PE+) to observe whether reductions in adversity-related psychopathology occurs among people with early phase psychosis and comorbid substance misuse.

Methods: This study will use a multiple-baseline design with randomization of participants to treatment start time. Participants will complete baseline appointments prior to therapy, engage in assessments between each of the five therapy modules, and complete a series of follow-up appointments two months after the completion of therapy. Primary hypothesized outcomes include clinically significant reductions in 1) negative psychotic symptoms measured using the Positive and Negative Syndrome Scale, 2) adversity-related sequelae measured using the Trauma Symptom Checklist-40, and 3) substance use frequency and overall risk score measured with the Alcohol, Smoking, and Substance

Involvement Screening Test. We also anticipate that clinically significant reductions in hopelessness and experiential avoidance, measured with the Beck Hopelessness Scale and Brief Experiential Avoidance Questionnaire, the theorized mechanisms of change of PE+, will also be observed. A secondary outcome is a hypothesized improvement in functioning, measured using the Clinical Global Impression and Social and Occupational Functioning Assessment scales.

Discussion: The results of this treatment trial will contribute to the advancement of treatment research for individuals in early phase psychosis who have current substance misuse and a history of adversity, and the findings may provide evidence supporting reductions in hopelessness and experiential avoidance as mechanisms of change for this treatment.

Trial registration: Clinicaltrials.gov, NCT04546178; registered August 28, 2020, https://clinicaltrials.gov/ct2/show/NCT04546178?term=NCT04546178&draw=2&rank=1

Introduction

Adversity, which can be defined as the experience of a negative life event that was stressful, uncontrollable, and either was or could have been harmful (Burgermeister, 2007), encompasses both traumatic events (e.g., child abuse) and non-life-threatening events with a similarly negative impact (e.g., discrimination). Adversity exposure is a significant individual influence on the onset of psychosis and clinical outcomes (Conus et al., 2010; Janssen et al., 2004; van Os et al., 2009; Varese et al., 2012). The psychosis proneness-persistence-impairment model (van Os et al., 2009) states that psychological mechanisms, many of which are common outcomes of adversity exposure (e.g., dissociation, external locus of control), can sensitize an individual at risk for psychosis, resulting in the emergence and persistence of psychotic symptoms. Previous studies have found high rates of adversity exposure among young adults in early phase psychosis (EPP; i.e., first five years of a psychotic illness) ranging from 30 to 96% (Bendall et al., 2007; DeTore et al., 2021; Gearon et al., 2003; Neria et al., 2002; Ramsay et al., 2011; Trauelsen et al., 2015; Üçok & Bıkmaz, 2007; Varese et al., 2012), with a mean of four lifetime adverse event exposures (Gearon et al., 2003a; Steel et al., 2011). Adversity exposure is associated with delays in accessing treatment for psychosis (Veru et al., 2022), experiencing more severe psychotic symptoms (Bailey et al., 2018), and a slower recovery during treatment for psychosis (Aas et al., 2016). Experiencing both adversity and EPP is associated with the development of comorbid psychopathology (e.g., depression, post-traumatic stress disorder; Trauelsen et

al., 2015), including the development of substance misuse (Khoury et al., 2010; Phillips & Johnson, 2001).

Substance misuse (SM), defined as the problematic use of drugs and alcohol that interferes with functioning, represents another major individual influence on psychosis onset and clinical outcomes (Nathan & Lewis, 2021; National Collaborating Centre for Mental Health (UK), 2008). This is another broad term that encompasses but is not limited to substance use disorders (SUDs), as well as including substance use that is harmful (e.g., binge drinking) but does not meet criteria for an SUD (McLellan, 2017). Similar to the proneness-persistence-impairment model above, the stress and coping theory of SM (Wills & Hirky, 1996) posits that psychological mechanisms (e.g., self-efficacy) may play a role in the development and maintenance of SM. Estimates of SM prevalence among individuals with EPP exceed 80% (Cookey et al., 2020; Ouellet-Plamondon et al., 2017), which is remarkably elevated when compared to the 50% prevalence rate among people who have been living with psychosis for over ten years (i.e., chronic psychosis (Rosenberg et al., 2007). Cannabis and alcohol are the most commonly misused substances among people with EPP, with estimated prevalence rates of 70% and 62% (Cookey et al., 2020), and nearly 25% of those in EPP engage in polysubstance misuse (i.e., misuse of 2 or more substances; Ouellet-Plamondon et al., 2017).

SM is associated with more negative outcomes related to the psychotic disorder (Lambert et al., 2005), including increased hallucinations and delusions, lower recovery rates, and lower functioning (Abdel-Baki et al., 2017; González-

Pinto A et al., 2011). Individuals with SM, psychosis, and a history of adversity also report more distressing hallucinations (Steel et al., 2011), a higher likelihood of developing PTSD (Gearon et al., 2003c), and an increased risk of victimization in adulthood (Seid et al., 2021; Walsh et al., 2003). In summary, adversity and SM are highly prevalent among individuals with EPP, they may play a role in psychosis onset, and they are associated with negative outcomes that have a significant impact on the individual level.

Benefits of adversity-specific treatment in EPP

Psychological treatments may be especially effective for people with EPP, a history of adversity, and SM. This type of treatment can target adversity-related sequelae that trigger and maintain psychosis and SM (e.g., avoidance, dissociation). In addition, treatment can target common comorbid psychopathology (e.g., depression, anxiety) that may be lowering functioning (Scheller-Gilkey et al., 2004b), causing distress, and lowering the quality of life.

There is some evidence that psychological interventions targeting adversity-related sequelae delivered to individuals with psychotic disorders may improve long-term outcomes for both psychosis and adversity-related psychopathology (e.g., improved quality of life, increased remission rates; Crumlish et al., 2009; van den Berg et al., 2016), especially for those with a substantial history of adversity (Kilian et al., 2020). Furthermore, compared to individuals with chronic psychosis, young adults in EPP may be able to better engage in and benefit from an adversity-focused psychological intervention

because they have not yet sustained the same degree of biological and psychological burden of a long-term psychotic illness (Lieberman et al., 2001).

Importantly, young adults with EPP want treatment for difficulties related to adversity. Australian individuals in EPP discussed their experiences receiving an adversity-focused intervention (Tong et al., 2017), noting that a desire for change was a major motivating factor for participants to initiate and continue to participate in the intervention. Although the participants reported that the intervention was distressing, they also experienced relief and found it beneficial overall (Tong et al., 2017). Participating in an adversity-focused intervention can also help to foster insight into factors leading to the development and maintenance of psychosis (e.g., avoidance), which can aid in recovery (Halpin et al., 2016).

Despite the perceived benefits of participating in an adversity-focused intervention, people with psychosis are routinely excluded; psychosis is the most common exclusion criteria for adversity-specific treatment trials, used in over 90% of trials (Ronconi et al., 2014). Additionally, the few studies that have examined the effects of adversity-focused treatment among people with psychosis primarily focused on individuals with chronic psychosis or included individuals in different phases of a psychotic disorder. Consequently, little is known about treatment effects specifically among people with EPP.

Adversity-specific treatments for people with psychotic disorders

Steel and colleagues (2017) conducted a randomized controlled trial (RCT) of cognitive restructuring for PTSD in individuals with schizophrenia. This

treatment did not significantly improve either PTSD or psychotic symptoms – the authors suggested that cognitive restructuring on its own was insufficient and that exposure, an efficacious therapeutic component (see Foa & McLean, 2016 for a review), may be needed to effect clinically significant change. More recently, a trauma-focused CBT for psychosis trial with an exposure component (TF-CBTp; Keen et al., 2017) found that individuals with a psychotic disorder and a complex trauma history experienced improvements in depressive symptoms, anxiety, delusions, PTSD symptoms, and well-being following therapy, although hallucination frequency did not change. Qualitative results highlighted the utility of an integrated approach to treating psychotic symptoms and adversity sequelae. Taken together, these findings suggest that exposure may be needed to effect clinically significant symptom change.

Prolonged Exposure (PE) therapy is an evidence-based form of cognitive behavioural therapy that includes a significant exposure component. PE is one of the most rigorously studied treatment options for people with a psychotic disorder and a history of adversity. An RCT of adults with chronic psychosis and PTSD (mean age = 41) compared PE and EMDR to a waitlist control group (van den Berg et al., 2015). This study found that, compared to the waitlist control group, the PE group experienced a significant reduction in PTSD symptoms and greater rates of PTSD diagnosis remission, even when participants had a dissociative subtype of PTSD (van Minnen et al., 2016). PE therapy also appeared to significantly reduce paranoia and depressive symptoms and improve functioning (de Bont et al., 2016). Grubaugh and colleagues (2017) replicated these results

among veterans with a psychotic disorder and PTSD (mean age = 46.8). Most participants who completed at least eight PE treatment sessions experienced PTSD symptom remission by the end of treatment. In short, PE therapy appears to effectively reduce psychopathology in individuals with chronic psychosis.

Although some work examines PE treatment among people with psychosis and a history of adversity, there are no PE treatment trials that have included individuals with a psychotic disorder, history of adversity, and SM. In fact, SUDs (previously specified as 'substance dependence') are the second most common exclusion criteria for adversity-focused treatment trials, after psychosis, meaning that many individuals with EPP have likely been excluded from previous PE treatment research due to the high rates of substance misuse (a term inclusive of SUDs) among those with EPP. A better understanding of the impact of SM on adversity treatment effects and the effects of adversity-focused treatment on SM may help optimize adversity-focused treatment for individuals with psychotic disorders.

Treatments for adversity-related sequelae in people with EPP with SM

Given the existing evidence supporting the efficacy of PE among people with chronic psychosis, adapting a PE protocol for people in EPP with SM may be the optimal path forward. People with EPP are often younger (M_{age} = 22.83 years; Cookey et al., 2020) than those with chronic psychosis (M_{age} = 41.2 years; van den Berg et al., 2015), and people with EPP may be in a better position to benefit from treatment compared to those with chronic psychosis because they have not yet sustained the same degree of biological and psychological burden

of substance misuse or a long-term psychotic illness (Lieberman et al., 2001). An adapted PE protocol must be capable of addressing common adverse events experienced by people with EPP (e.g., restraint during hospitalization for psychosis; Carr et al., 2018), accounting for the links between AE sequelae and both psychosis and SM. As well, protocols must adhere to treatment recommendations for AE sequelae in EPP. Cragin and colleagues (2017) interviewed 49 early psychosis treatment experts about suggested clinical treatment guidelines for people with psychotic disorders and comorbid adversity-related sequelae. An integrated treatment approach (i.e., one clinician treating both types of disorders at the same time) was endorsed as a first-line approach by experts more often (85.4%) than other possible approaches (e.g., sequenced—psychosis first (41.7%), parallel (31.3%)). Experts also recommended the following treatment elements: anxiety or stress management, psychoeducation, meditation or mindfulness, cognitive restructuring, interpersonal effectiveness, emotion-focused interventions, and case management. Exposure was rated as a second-line intervention, despite prior evidence that exposure seems necessary for clinically significant symptom change (Foa & McLean, 2016; Taylor et al., 2003). This finding likely speaks to clinicians' hesitancy to recommend adversity-specific exposure treatments for people with psychotic disorders, given a common fear amongst clinicians of exacerbating psychotic symptoms through AE cue exposure (Cragin et al., 2017). More recently, a systematic review of intervention studies for psychotic disorders and trauma (Bloomfield et al., 2020) suggested that future treatments should

include many third-wave elements or strategies (Hayes, 2004), such as emotion regulation, psychological acceptance, interpersonal skills, attachment work, strategies to manage dissociation, and trauma memory reprocessing. The review findings indicated that although several studies used an 8-session protocol, future trials should include more sessions to potentially increase the magnitude of treatment effects (Spidel et al., 2019; van den Berg et al., 2015). Overall, the literature supports the use of an integrated treatment approach that uses most core elements of a standard PE protocol with the addition of third-wave strategies and an increased treatment length.

Aims and hypotheses

The specific aim of this project will be to address the identified treatment gap in early intervention care by applying an adapted PE therapy protocol, called PE+, to a younger EPP population with a history of adversity and current substance misuse. We plan to 1) establish the impact of PE+ on the severity of psychotic symptoms, substance misuse, adversity-related symptoms (e.g., anxiety) and 2) discern whether clinically significant change occurs between sessions 8 and 15, which if true would provide support for the argument that longer treatment duration results in significant symptom change in this cohort. We hypothesize that PE+ treatment will result in clinically significant reductions in 1) negative psychotic symptoms (e.g., anhedonia), 2) adversity-related sequelae (e.g., anxiety, insomnia), and 3) the frequency and quantity of SM, and 4) that all reductions will be maintained by 2-months post-treatment. We also anticipate clinically significant reductions in hopelessness and experiential avoidance, the

theorized mechanisms of change of PE+. In terms of secondary outcomes, we hypothesize that participants will experience a global improvement in social and occupational functioning from pre-post PE+ therapy that will be maintained 2 months post-treatment.

Methods

Design, randomization, and blinding

This study will use a multiple-baseline design (MBD; Kratochwill et al., 2010), a type of single-case experimental design ideal for stringently examining intervention effects. MBDs are AB designs, meaning they have a baseline ('A' phase) and intervention ('B' phase), and they do not repeat phases, given that behavioural interventions cannot be rescinded after application. Notably, MBDs temporally stagger intervention start time across participants, thereby creating a control group composed of each participant's pre-intervention scores. Participants will be randomized to a two, three, or four-week baseline condition, thereby staggering the intervention start times; participants will be randomized to a treatment start time using a random sampling/assignment generator (www.randomizer.org). Randomization is used to increase internal validity and minimize bias by preventing participants from being assigned to a treatment start time based on need or symptom severity, especially given that participants are recruited from an outpatient clinic (Kratochwill & Levin, 2010). Randomization order will be delivered using sequentially ordered sealed envelopes that will be opened at the time of randomization. Randomization breakdown s as follows: 2-week delay (40%), 3-week delay (25%), 4-week delay (35%).

Participants and setting

The study will take place at the Nova Scotia Early Psychosis Program (NSEPP), an early psychosis clinic with approximately 250 active patients that is located within a Canadian academic psychiatric hospital in Halifax, Nova Scotia. Most patients are young adults; the mean age of individuals entering the program is 23 years. Individuals must meet the following criteria to participate in the study:

Inclusion criteria

1. Current patient at the NSEPP for the duration of the study;
2. Aged 19-35 years;
3. Diagnosis of a primary psychotic disorder (i.e., schizotypal disorder, delusional disorder, brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder, substance/medication-induced psychotic disorder, other specified schizophrenia spectrum or other psychotic disorder, or unspecified schizophrenia spectrum or other psychotic disorder);
4. Diagnosis of a primary psychotic disorder within the past 5 years; participants must not surpass this 5-year diagnostic window while enrolled in the study;
5. Have experienced 1 or more negative, distressing lifetime adverse events (e.g., child abuse, discrimination) listed on the Trauma and Life Events (TALE) checklist that are currently affecting the participant;
6. At least one score within the “moderate” or “high” risk range for any substance (excluding tobacco products) on the World Health

Organization's Alcohol, Smoking and Substance Involvement Screening Test (WHO ASSIST); and

7. Speaks and understands English

Exclusion criteria

1. Aged 36 and older;
2. Aged 18 and younger;
3. Scoring in the 'high risk' range for cocaine use on the WHO ASSIST[1], suggesting significant misuse;
4. Participant does not speak or understand English;
5. Current involuntary inpatient admission in a hospital or under a Community Treatment Order;
6. Documented, diagnosed intellectual disability; and/or
7. Currently participating in any intervention designed to change substance use or treat adversity-related sequelae (e.g., other clinical trials, psychological therapy)

Measures

Eligibility

The TALE checklist (Carr et al., 2018) is a yes/no scale that asked participants which of the listed events they have experienced in their lifetime (e.g., traumatic entry into care), whether these events occurred more than once,

[1] High cocaine use may be too treatment-interfering and prevent meaningful treatment gains given its significant impact on executive functions (Fernández-Serrano et al., 2010); therefore, individuals with high levels of cocaine use were excluded.

and at what age(s) the event(s) occurred. Additionally, participants were asked whether any adverse events experienced are currently affecting them in any way and to what degree (0, “Not at all” to 10, “Extremely”). The TALE was created as a measure of adverse events specifically for individuals with psychosis, and psychometrics suggest good test-retest reliability (r= .90, p <.001), adequate convergent validity with the Trauma History Questionnaire (r= .69, p < .001), and moderate construct validity in terms of correlations with Trauma Symptom Questionnaire outcomes (r= .37, p = .02). The WHO ASSIST (WHO ASSIST Working Group, 2002), an 8-item interview, will be used to measure substance use frequency, urge to use, substance-related difficulties in functioning, and challenges with substance use reduction. Responses are made on a 5-point scale (“Never” to “Daily or almost daily”) and scores can range from 0-39 for each substance-specific subscale, with higher scores indicating greater substance misuse. The total score for each substance will be used as an indicator of substance misuse. When used with individuals with first-episode psychosis, the WHO ASSIST was significantly correlated with a measure of alcohol use (r= .53, p < .001) and substance dependence (r = .44, p < .001), and it had appropriate internal consistency ratings for the total score ($M_{Cronbach\ alpha}$ = .90) and substance-specific subscales ($M_{Cronbach\ alpha}$ = .79, SD = .08; (Hides et al., 2009; Humeniuk et al., 2008).

Primary and secondary outcome measures

Primary

The primary outcome measures were psychotic symptoms, adversity-related sequelae, and substance misuse. Adversity-related sequelae was the core outcome we were targeting; however, we were also interested in whether it was possible to use an integrated treatment approach that also would effect change on both psychotic symptoms and substance misuse. Psychotic symptoms were measured with the use of the Structured Clinical Interview – Positive and Negative Syndrome Scale (SCI-PANSS; Kay et al., 1987), a semi-structured clinical interview measuring both positive and negative symptoms of psychosis. We used the total score for each of the positive and negative scales; each total score could range from 7 to 49 with higher scores indicating greater positive or negative symptoms. In an early psychosis sample, the SCI-PANSS positive and negative scales had appropriate internal consistency ($a_{Positive\ scale}$ = .89; $a_{Negative\ scale}$ = .90). The Trauma Symptom Checklist-40 (TSC-40; Elliott & Briere, 1992) measured adversity-related sequelae (e.g., depression, insomnia). Response options ranged from 'Never' (0) to 'Often' (3). We used the total score and the subscale scores (i.e., dissociation, anxiety, depression, sleep disturbance, sexual problems, sexual abuse trauma index). Total scores could range from 0 to 120, with higher scores indicating the presence of greater psychopathology; subscale score ranges varied by construct. Several studies have used the TSC-40 with people with psychotic disorders (Pec et al., 2014; Spidel et al., 2019) although psychometrics have not been computed with this

population. Studies with non-psychosis populations have estimated strong reliability for the TSC-40 total score (W = .93; Rizeq et al., 2020). Substance misuse was measured using the WHO ASSIST, described within the 'Eligibility measures' section above.

In addition to the above outcomes, we also measured changes to hypothesized treatment targets that may function as mechanisms of symptom maintenance: 1) experiential avoidance, and 2) hopelessness. The Brief Experiential Avoidance Questionnaire (BEAQ; Gámez et al., 2014) is a 15-item measure of experiential avoidance; we used the overall score on this measure as an indicator of avoidance. Response options were on a 6-point scale ranging from 'Strongly disagree' (1) to 'Strongly agree' (6). Total scores could range from 15-90 with higher scores indicating higher experiential avoidance. Across three groups (i.e., students, patients, community), internal consistency was estimated to be good ($M\alpha$= .84). Hopelessness was measured with the 20-item Beck Hopelessness Scale (BHS; Beck et al., 1974). Response options were true/false, and we used the total score on this measure as an indicator of hopelessness. Scores could range from 0 to 20, with higher scores indicating greater hopelessness. In a chronic psychosis population, BHS total score internal consistency (α = .85) and subscale internal consistency ($\alpha_{\text{Negative expectations}}$ = .84; $\alpha_{\text{Loss of motivation}}$ = .81) were considered good (Kao et al., 2012).

Secondary

Functioning was measured using the Social and Occupational Functioning Assessment Scale (SOFAS; Morosini et al., 2000), a single-item clinician-

reported instrument. Ratings ranged from ‘Persistent inability to maintain minimal personal hygiene/unable to function without harming self or others or without considerable external support’ (1-10) to ‘Superior functioning in a wide range of activities’ (91-100); lower scores indicated greater impairment in functioning. The Clinical Global Impression – Severity of Illness (CGI-S; Guy, 1976) measured the clinician’s judgement of the severity of the participant’s symptoms of mental illness at this time and the Clinical Global Impression – Improvement of Illness (CGI-I; Guy, 1976) measured the clinician’s judgement of the degree of improvement from baseline. The CGI-I and -S served as additional measures of functioning that differed from the SOFAS in that the former provided global estimates of illness severity and improvement, respectively. We used the total severity score of the CGI-S, which ranged from ‘’Normal, not ill at all’ (1) to ‘Among the most extremely ill’ (7), and the total improvement score of the CGI-I, which ranged from ‘Very much improved’ (1) to ‘Very much worse’ (7). Higher scores indicated more severe symptoms on the CGI-S and symptom worsening on the CGI-I. Symptom measures do not necessarily provide information about impairment; therefore, the SOFAS were used to estimate symptom impairment, and the CGI-S was used as a global rating of severity, given its holistic view of participant symptoms (i.e., accounts for all symptoms, rather than specific symptom domains).

The PTSD Checklist-5 (PCL-5; Price et al., 2016; Weathers et al., 1993) is a shortened 8-item version of the PCL screened for PTSD symptomatology (e.g., intrusive thoughts, negative beliefs) and functioned as a treatment progress

monitoring tool. All items were rated on a 5-point scale ranging from 'Not at all' (0) to 'Extremely' (4), and the total score could range from 0 to 32 with higher scores indicating greater PTSD symptomatology. In a community sample, the total score internal consistency for the 8-item PCL-5 measure was high (α = .90; Price et al., 2016). A recent study of the 20-item version of the PCL-5 (Penney et al., 2021) found that this measure had appropriate psychometrics amongst people with psychosis, although the factor structure did differ amongst this group; no analyses of the psychometrics of the abbreviated 8-item PCL-5 measure have been completed to date with people with psychotic disorders.

A measure of therapeutic alliance, the Session Rating Scale – 3 (SRS-3; Duncan et al., 2003), was administered following each therapy session to account for fluctuations in the therapist-participant relationship on assessment scores. This 4-item assessment tool measured the patient's perception of the therapeutic relationship, goals and topics covered in session, therapist approach/method, and the therapy session overall for each session. Participants placed the SRS-3 directly in a sealed envelope; therapists did not have access to this information during therapy. Total scores could range from 0 to 40 with higher scores indicating greater therapeutic alliance.

Intervention

This study's psychotherapeutic intervention, PE+, consisted of a 15-session course of weekly 90-minute sessions of adapted PE therapy. The primary theoretical 'active ingredient' of PE+ is exposure (i.e., imaginal, in vivo; see Figure 1), an effective therapeutic component with substantial evidence

supporting its efficacy in treating a variety of mental health challenges, including PTSD and anxiety disorders (see Foa & McLean, 2016 for a review). PE+ used PE's theoretical framework, emotional processing theory, which posits that by repeatedly exposing an individual to feared stimuli (e.g., thoughts, feelings, objects) related to their adverse experience(s), they may generate alternate beliefs and associations with that experience and associated stimuli that may result in a less threatening perspective on the initially feared situation. The American Psychological Association's (APA) treatment guidelines for CBT therapies for PTSD recommend 4 to 16 sessions of treatment (American Psychological Association, 2017); while fewer sessions might be viewed as more efficient and less costly, several studies testing psychological interventions for adversity-related psychopathology among people with psychosis found that both researchers and participants believed eight sessions was too few (de Bont et al., 2016; Spidel et al., 2019). Therefore, a treatment duration on the longer end of the APA treatment guidelines (i.e., 15 sessions) was selected for the current study.

Treatment was divided into five modules; each module consisted of three sessions. The modules were as follows: 1) psychoeducation about adversity, SM, and the interplay of both with psychosis; 2) emotion identification and regulation; 3) imaginal exposure and identifying thoughts and beliefs, 4) in vivo exposures, and 5) planning for termination and maintenance. Module 1 involved an intake interview that included a suicide risk assessment, followed by psychoeducation about the short and long-term effects of adversity, and the relationship of

adversity with psychosis and SM. Psychoeducation formed the foundation upon which the participant could then start to build connections between these experiences within their own life, culminating in a joint case conceptualization at the end of this module. Participants began discussing their adverse experiences at the end of this first module. Module 2 was focused on aiding participants to develop or enhance their emotional identification and regulation skills, to help participants effectively process their past experiences. Skills included mindfulness (e.g., nonjudgmental observation), cognitive restructuring (e.g., check the facts), and distress tolerance (i.e., Temperature, Intense exercise, Paced breathing, Paired muscle relaxation) adopted from Dialectical Behavior Therapy (DBT; Linehan, 2014). Modules 3 and 4 were the imaginal and in vivo exposure modules. Participants began imaginal exposure in the first session of module 3 and in vivo exposures began the first session of module 4; both types of exposures continued until the end of treatment (i.e., imaginal exposure across 9 sessions, in vivo exposure across 6 sessions). Exposure (i.e., imaginal, in vivo) is the core therapeutic ingredient of PE+ treatment, resulting in its greater use across sessions. Imaginal exposures became more targeted over time to focus on the most difficult moments of past adverse experiences. Module 5 consisted of relapse prevention strategies, including identifying helpful aspects of treatment, a final joint case conceptualization, and discussions of preventing symptom relapse. Throughout therapy, participants were encouraged to practice and further develop the emotional regulation and distress tolerance skills learned in the second module, and participants were asked to listen to recordings of in-

session imaginal exposure throughout modules three-five. Homework adherence was rated at the beginning of every session by participants' therapist. All session protocols and materials were reviewed and discussed during the design phase of the study with the research team's patient partner (SL); her expertise was used to modify clinical procedures to improve feasibility for potential participants (e.g., reduction of between-session imaginal exposures).

The study therapists were three senior PhD students in Clinical Psychology with 3-5 years of clinical experience who had completed training in PE therapy. Training involved the completion of an online PE certification through PEWeb (http://pe.musc.edu/) and completing and reviewing roleplays of PE treatment elements (e.g., imaginal exposure) as a group over the course of four months. Study therapists worked under the supervision of a clinical psychologist, AP, who has over 20 years of experience providing evidence-based treatment, including CBT for psychosis and substance misuse, and PE for PTSD. Therapists participated in weekly supervision with AP to discuss session challenges, ethical issues, and treatment fidelity. In addition, study therapists received monthly group-based psychodynamic supervision, using video-review of treatment tapes, to identify and formulate participant dissociative processes from an integrative perspective. Prior to delivering treatment, all therapists completed a two-hour video-based training to supplement supervision. This was provided by JT, a clinical psychologist with over 15 years of experience and expertise in intensive short-term dynamic psychotherapy (ISTDP) and psychotherapy research. The rationale for the inclusion of this additional training and supervision

was the necessity to identify and address dissociative processes as they occurred as dissociation could interfere with treatment effects. Study therapists also conducted study assessments, although no therapist acted as an assessor for the same participant they were treating; therapists were blinded to assessment results during treatment. Any instances of unblinding were to be reported in the publication of trial results.

Treatment fidelity monitoring

As part of the National Institutes of Health's (NIH) Behaviour Change Consortium, Bellg and colleagues (2004) outlined a series of strategies to enhance treatment fidelity in treatment studies. These strategies facilitate the five elements of treatment fidelity: 1) treatment adherence, 2) therapist competence, 3) treatment differentiation, 4) treatment receipt, and 5) treatment enactment. We used the NIH Behaviour Change Consortium framework of treatment fidelity to assess treatment fidelity within this trial using both direct (e.g., review of videotaped therapy sessions) and indirect (e.g., questionnaires, adherence checklists) assessment strategies (see Appendix A for a full description of study treatment fidelity strategies).

We used a study manual with manualized treatment sessions to ensure equivalent delivery across participants, and therapists were trained in all treatment and assessment components together to ensure standardized training across clinicians. Therapists participated in training that included a significant role-playing and videotape review component to ensure therapist competence was achieved before beginning treatment delivery. Following the completion of all

therapy sessions, 10% of therapy session videos were randomly selected for adherence review by two independent raters experienced in psychotherapy delivery. Video reviewers used a predetermined checklist of session components to rate videos with each item score ranging from ‘0’ (did not include) to ‘2’ (complete inclusion); session scores had to total at least 80% of the total possible score based on the predetermined elements for that session to be considered adherent. There is little agreement in the field about what constitutes an appropriate benchmark for within-session treatment adherence. However, a previous study found that the mean session adherence rate for therapists was approximately 80%, which was considered highly adherent (Huppert et al., 2001). We will adopt a similar standard, especially given that treatment fidelity checklists are detailed, thereby creating a conservative standard for adherence. The video review process was supervised by a licensed clinical psychologist, AP, who provided training during this study. In addition, therapists were provided with weekly supervision, including video review, to minimize therapist drift.

Procedure

All new NSEPP patients are routinely asked whether they consent to being contacted for research purposes, with approximately 80% agreeing to be contacted. Patients can self-refer to the study or, with their consent, their NSEPP clinician can refer them. Potential participants were screened with the WHO ASSIST (Hides et al., 2009; WHO ASSIST Working Group, 2002) and the Trauma and Life Events checklist (TALE; Carr et al., 2018). See Table 1 for measure information, see Figure 2 for procedure details. If the individual was

eligible for the study, they participated in a consent appointment with study research staff that involved discussing the study and asking participants to sign an informed consent form, followed by either scheduling their baseline assessment for a future date or completing a baseline appointment immediately following the consent process. Baseline assessments included four self-report instruments, the BEAQ, BHS, PCL-5, and TSC-40, in addition to several clinician-administered measures, such as the SCI-PANSS, which was used to assess psychotic symptoms, and the CGI-I and -S, along with the SOFAS, which assessed illness severity, symptom change, and functioning, respectively. Demographic information related to participants' age, gender, race, ethnicity, and sexual orientation was also collected; these variables were critical to collect as participants from a marginalized community (e.g., 2SLGBTQ+) may have had different experiences than those who are not a part of marginalized groups. This assessment was followed by 1-3 brief follow-up assessments, depending on the randomization to start time (i.e., 2-,3-, or 4-week delay between initial interview and therapy) to establish a symptom baseline. The participant's treatment start time, determined by randomization, was communicated to the participant at the baseline interview. The participant also participated in an assessment prior to beginning the intervention. The BHS, BEAQ, and TSC-40 were administered, in addition to the completion of the SOFAS, CGI-I and -S, WHO ASSIST, and SCI-PANSS. After each therapy session, participants completed the SRS-3 to account for the influence of fluctuations in the therapist-participant relationship on assessment scores, and after each therapy module

(i.e., 3 sessions each), current symptoms and SM were assessed using the instruments above (i.e., BEAQ, BHS, TSC-40, PCL-5, WHO ASSIST). Psychotic symptoms were reassessed using the SCI-PANSS after the final session of treatment had been completed. There were also two follow-up sessions 2-months post-intervention to assess maintenance of therapeutic gains using all the same instruments as at the baseline assessment; each assessment session took approximately 75 minutes. Participants were also asked for their feedback on how to further optimize PE+ therapy for use with patients with EPP in the future and this feedback was reported and can be used to optimize this treatment in the future. All participants were informed that they could discontinue their study participation at any time, and that if psychotic symptoms were to worsen significantly, they would be referred to their clinician in the early psychosis program for an appointment.

Data analysis

The goal of this intervention study was to determine the effect of PE+ therapy on psychotic symptoms, substance misuse, adversity-related illness (e.g., PTSD), and functioning. Therefore, the desired outcomes of the analyses were the significance of symptom change and its maintenance over time. Given the small projected study sample size, it was determined that inferential statistics would not be appropriate. As a result, it was not possible to compute a power analysis; however, a sample of ~20 participants is typical for studies using the MBD based on previously published studies using this design (Frueh et al., 2009). Instead of inferential statistics, the Reliable Change Index (RCI; Jacobson

& Truax, 1991) was used to classify participants' post-intervention score category: recovered (i.e., met criteria for clinical change), improved (i.e., have statistically significant change but not large enough to be considered a full recovery), unchanged (i.e., no change over time), and deteriorated (i.e., significant worsening of symptoms over time). We calculated the numerical criteria needed to assess symptom change using previously published means and standard deviations of the measures we were using (e.g., SCI-PANSS, TSC-40 scores; see clinical trial registration statistical plan at clinicaltrials.gov). The change criterion being used was moderate, meaning clinically significant change was defined as participants' post-intervention assessment scores falling between the scores of a healthy population and a mentally ill population. This criterion was the most realistic given that we were aiming to treat a multitude of psychological symptoms rather than a single symptom domain (e.g., PTSD symptoms). We used the RCI to assess whether clinically significant change occurred in 1) hopelessness and avoidance scores, 2) negative psychotic symptoms (e.g., anhedonia), 3) frequency and quantity of substance misuse, and 4) functioning scores, with gains in all symptom domains maintained at 2 months-post treatment.

Discussion

The results of this novel adaptation study have the potential to further treatment research by determining whether PE+ contributes to clinically meaningful symptom change for individuals with EPP who are experiencing adversity-related mental health challenges and substance-use related issues.

This study had several strengths. PE has been studied within individuals with psychotic disorders; however, adaptations of treatment for those in EPP have not yet been tested. Furthermore, no previous treatment studies have specifically recruited individuals with comorbid SM and directly measured the effect of PE on SM. The inclusion of SM within this study provides a necessary and novel contribution to the literature, whilst the focus on an EPP population extends the existing body of knowledge of adversity-focused treatment in psychotic disorders. The study intervention took place within a comprehensive early intervention service with an embedded research program; recruiting participants from this service and delivering the PE+ intervention within an existing clinical setting helped enhance the 'real-world applicability' of this study's results, given that this treatment is meant to be delivered in an early intervention service. Moreover, the integration of this treatment within an existing early intervention service aided with recruitment by using direct clinician referrals as well as providing a built-in safeguard for participants by allowing follow-up clinical care with clinicians for those participants who may experience psychotic symptom deterioration or relapse. A significant strength of this study was the inclusion of a patient partner on the research team; their experience increased the breadth of the team's expertise and allowed for the patient perspective when creating the treatment protocol and designing treatment materials. Finally, randomization and comprehensive measures of treatment fidelity helped support the internal validity of the empirical findings of this study.

Despite this study's many strengths, there were several limitations to its findings. There was no requirement for participants to meet criteria for a PTSD diagnosis to receive the PE+ intervention, which introduced variability into the results. Participants had to present with SM and a history of AEs and ongoing distress related to the AE, but their symptom presentation could vary. This approach was appropriate for an initial adaptation of this therapeutic approach. In addition, recruitment processes were not standardized, meaning there could have been bias introduced via clinician referral. All efforts were made to approach every eligible person; however, some eligibility criteria could not be assessed without an interview; therefore, some potential eligible participants may have been missed.

In conclusion, the results of this study may provide support for the use of an adapted PE protocol to treat adversity-related mental health challenges among individuals with early-phase psychosis and current substance misuse, a common clinical presentation, and provide a tailored treatment option for this group of affected individuals in the future. This treatment might help improve long-term outcomes of individuals within early intervention services, reduce the high burden of comorbid psychopathology, and improve social and occupational functioning within this group. Finally, this trial may provide evidence of the promise of this intervention thereby stimulating further research using larger samples and more rigorous designs (e.g., RCT).

Tables

Table 3.1.1. Measures for PE+ study

Variable	Measure	Items	Timepoints	Report type
Adversity occurrence	TALE (Carr et al., 2018)	21	Eligibility assessment, post-therapy follow-up 1	Self-report
Substance misuse	WHO ASSIST (WHO ASSIST Working Group, 2002)	8	Baseline assessment, Assessments 1-6, Post-therapy follow-ups 1-2	Clinician-administered
Positive and negative psychotic symptoms	SCI-PANSS (Kay et al., 1987)	109[a]	Baseline assessment, Assessment 1, Assessment 6, Post-therapy follow-up 1	Clinician-administered
Adversity-related symptoms	TSC-40 (Elliott & Briere, 1992)	40	Baseline assessment, Baseline follow-ups 1-3, Assessments 1-6, Post-therapy follow-ups 1-2	Self-report
Experiential avoidance	BEAQ (Gámez et al., 2014)	15	Baseline assessment, Baseline follow-ups 1-3, Assessments 1-6, Post-therapy follow-ups 1-2	Self-report

Hopelessness	BHS (Beck et al., 1974)	20	Baseline assessment, Baseline follow-ups 1-3, Assessments 1-6, Post-therapy follow-ups 1-2	Self-report
Social and occupational functioning	SOFAS (Morosini et al., 2000)	1	Baseline assessment, Baseline follow-ups 1-3, Assessments 1-6, Post-therapy follow-ups 1-2	Clinician report
Illness severity	CGI-S (Guy, 1976)	1	Baseline assessment, Assessment 1, Assessment 6, Post-therapy follow-up 1	Clinician report
Improvement of illness	CGI-I (Guy, 1976)	1	Assessment 1, Assessment 6, Post-therapy follow-up 1	Clinician report
PTSD symptoms	PCL-5 (Price et al., 2016; Weathers et al., 1993)	8	Baseline assessment, Baseline follow-ups 1-3, Assessments 1-6, Post-therapy follow-ups 1-2	Self-report
Therapeutic alliance	SRS-3 (Duncan et al., 2003)	4	Therapy sessions 1-15	Self-report

[a]Positive and negative SCI-PANSS items only

Figures

Figure 3.1.1. PE+ treatment components, target mechanisms, and clinical outcomes

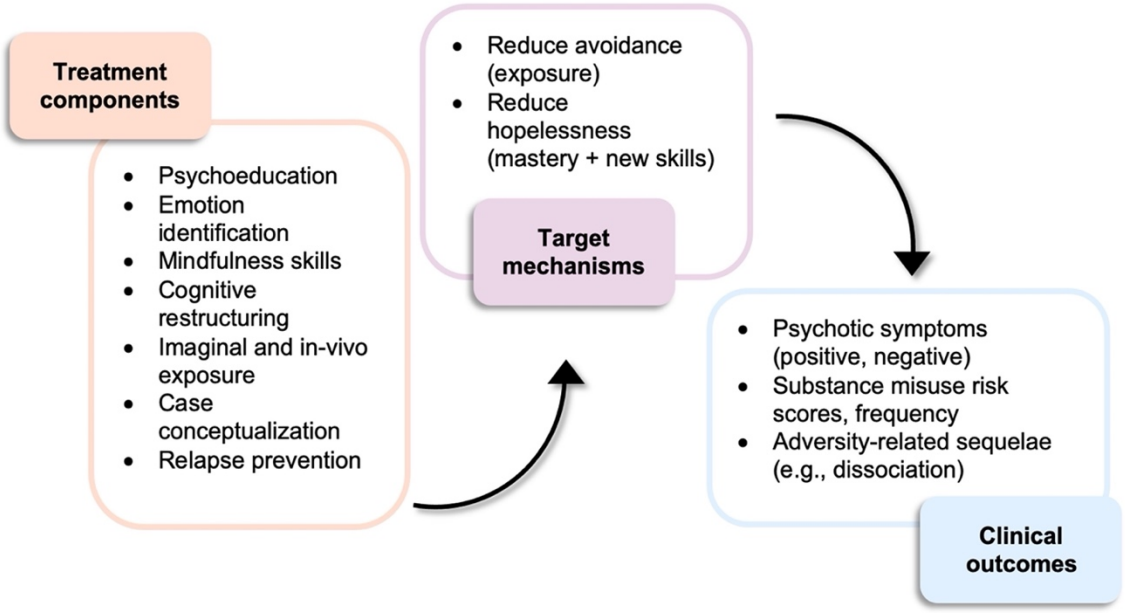
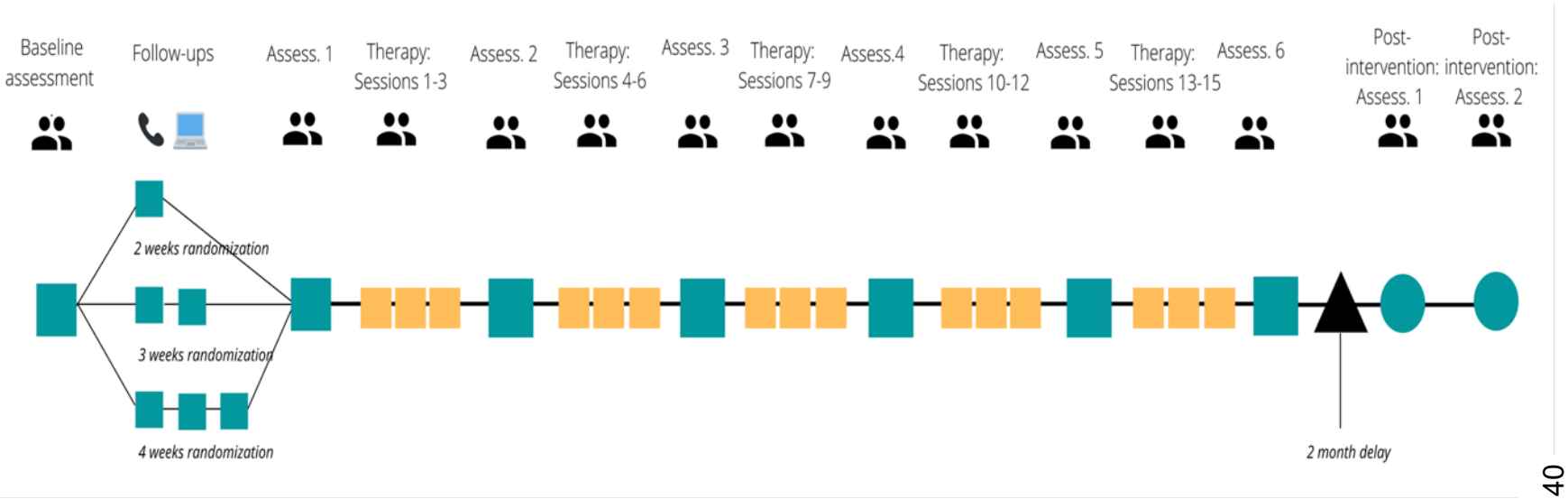


Figure 3.1.2. PE+ study procedures



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Chapter 7: Outcomes of an adapted prolonged exposure psychotherapy for people with early phase psychosis, substance misuse, and a history of adversity: The PE+ trial

The manuscript prepared for this study is presented below. Readers are advised that Victoria Patterson, under the co-supervision of Dr. Alissa Pencer and Dr. Philip Tibbo and in collaboration with Dr. Sherry Stewart and Dr. Joel Town, was responsible for designing the study, developing the study protocol and research hypotheses, gaining ethical approval, collecting the data, preparing the data for analyses, and interpreting study results. Victoria wrote the initial draft of the manuscript and received and incorporated feedback from all co-authors. She submitted the manuscript to *BMC Psychiatry* for peer review. The current reference is as follows:

Patterson, V. C., Tibbo, P. G., Stewart, S. H., Town, J., Crocker, C. E., Ursuliak, Z., Lee, S., Morrison, J., Abidi, J., Dempster, K., Alexiadis, M., Henderson, N., & Pencer, A. (under review). Outcomes of an adapted prolonged exposure psychotherapy for people with early phase psychosis, substance misuse, and a history of adversity: The PE+ trial. Submitted to *BMC Psychiatry*.

Abstract

Background: Several adversity-focused treatment trials have reported improvements to adversity sequelae (e.g., PTSD symptoms) and decreases in psychotic symptoms among individuals with psychotic disorders. Yet, no trials have examined the impact of adversity-focused treatment on substance use or examined the outcomes among an early phase psychosis population. These gaps in both the research literature and clinical practice have resulted in less knowledge about the outcomes of adversity-focused treatment at this stage of psychotic illness, including the impact on substance use.

Methods: The outcomes of an adapted prolonged exposure protocol (PE+) among an early phase psychosis population were examined using a multiple-baseline design. Nineteen adults with a psychotic disorder, current substance misuse, and a history of adversity were recruited from an early psychosis program. Participants were randomized to treatment start time and participated in a 15-session course of PE+ therapy. Ten assessments were completed focusing on primary outcomes (i.e., adversity sequelae, negative psychotic symptoms, substance misuse) and secondary outcomes (i.e., functioning, hopelessness, experiential avoidance). The Reliable Change Index (RCI) was used to establish whether there were clinically significant changes to primary or secondary outcomes.

Results: Half or more of treatment completers experienced clinically significant changes to most domains of adversity sequelae. However, no participants experienced improvements in negative psychotic symptoms, and substance

misuse had more variables outcomes across participants. In terms of secondary outcomes, functioning and experiential avoidance were improved for several participants, while hopelessness decreased for only one participant. Participants reported high satisfaction with the PE+ treatment and exposure and coping skills were rated as the most helpful elements of treatment.

Conclusions: Reductions in adversity sequelae were observed following PE+ treatment, suggesting that adversity-focused treatment may be beneficial for an early psychosis population. Yet, few positive changes to psychotic symptoms or substance use were observed. Further integrating treatment strategies for psychosis and substance use into PE+ may be required to effectively treat the links between psychosis, adversity sequelae, and substance use. Future studies should make efforts to integrate substance use strategies into adversity treatment trials for people with psychotic disorders.

Trial registration: Clinicaltrials.gov, NCT04546178; registered August 28, 2020, https://clinicaltrials.gov/ct2/show/NCT04546178?term=NCT04546178&draw=2&rank=1.

Keywords: Prolonged exposure; early phase psychosis; adversity; substance misuse; cognitive-behavioural therapy

Introduction

Previous studies have found more negative outcomes for those individuals with psychotic disorders (PDs) and a history of adverse events (AEs), both in terms of course of illness (e.g., more distressing hallucinations, greater risk of suicide) (Hassan et al., 2016; Steel et al., 2011) and treatment outcomes (e.g., fewer treatment goals met, slower improvement; Aas et al., 2016; Jones et al., 2019). In addition, several studies have suggested that psychosis itself can function as an AE for individuals with PDs (Bak et al., 2005; Bendall et al., 2012; Mueser et al., 2010; Tarrier & Picken, 2011), resulting in similarly poor outcomes. Due to the significant impacts of AEs on illness course and treatment, there has been a consistent call in the literature to develop adversity-focused interventions for people with PDs and a history of AEs to improve outcomes for this group (Gairns et al., 2015; Ng et al., 2016; Schalinski et al., 2015a). However, substance misuse (SM) is a very common comorbid issue for people with PDs and a history of AEs, with quite elevated prevalence rates (Cantor-Graae et al., 2001). Yet, SM is rarely considered in the presence of AEs, despite its similarly deleterious impact on psychotic symptoms and outcomes of treatment (Archie & Gyömörey, 2009) and relationship with AEs sequelae (e.g., PTSD symptoms, depressive symptoms). Taken together, the above literature, along with recent preliminary clinical guidelines for adversity-focused treatments for people with PDs (Cragin et al., 2017), suggest the need for an integrated psychological treatment capable of simultaneously addressing AE sequelae, SM, and psychotic symptoms.

Several studies have examined the efficacy of an AE-focused treatment, prolonged exposure (PE), in a PD population. PE, an evidence-based intervention for PTSD, uses exposure to reduce avoidance of both internal and external AE reminders with the aim of reducing distress and increasing functioning (Foa et al., 1991; Foa & McLean, 2016; Powers et al., 2010). However, the evidence has thus far focused almost exclusively on people with chronic psychosis rather than early phase psychosis (EPP; i.e., first 5 years of a psychotic disorder), and SM outcomes have rarely been considered (Wood et al., 2023). Moreover, a recent study examining unmet clinical needs in early psychosis programs across five countries highlighted the necessity of developing tailored adversity-focused treatments for people with EPP (Wood et al., 2023), suggesting a gap in both the research literature and clinical practice.

The current study aimed to examine the outcomes of an adapted PE protocol, called 'PE+', and observe whether specifically targeting AE sequelae results in clinically significant changes in SM/psychotic symptoms. Our primary outcomes were reductions in AE sequelae, psychotic symptoms, and SM. Our secondary outcome was related to functioning; we hypothesized an improvement in social and occupational functioning. We hypothesized that there would be a decrease in hopelessness and experiential avoidance (the theorized mechanisms of change of PE+ treatment), as well as decreases in negative psychotic symptoms, SM, and AE sequelae, all of which would be maintained at follow-up 2 months post-treatment.

Methods

Design

The protocol of this study, which includes a detailed discussion of the methodology and intervention components, was published previously (see Patterson et al., 2022; Chapter 5). The PE+ study used a multiple baseline design, which included a 2–4-week baseline measurement period functioning as a control against which to compare the measurements collected during and post-intervention (Kratochwill & Levin, 2010; Kratochwill et al., 2010). Participants were randomized to either the 2-week delay, 3-week delay, or 4-week delay condition. Following the baseline period, participants engaged in five three-session 'modules' of therapy, each focused on a different therapeutic ingredient (e.g., imaginal exposure). After each module, individuals participated in a brief assessment. Therapists were blinded to assessment results during treatment. After the sixth assessment was complete, immediately following treatment completion, there was a 2-month delay after which participants returned for two follow-up assessment appointments to examine maintenance of therapeutic gains.

Participants

All patients were recruited from the Nova Scotia Early Psychosis (NSEPP), an early intervention program for psychosis located in Halifax, Nova Scotia, Canada. The inclusion criteria for the study were as follows: 1) aged 19 to 35 years old, 2) diagnosis of a schizophrenia spectrum disorder within the last 5 years, 3) SM within the last 3 months (i.e., 'moderate' or higher score on the

World Health Organization's Alcohol, Smoking, and Substance Involvement Screening Test (WHO ASSIST) measure; WHO ASSIST Working Group, 2002), 4) have experienced 1+ AEs that continue to affect their life (i.e., affected ≥5 out of 10 on the Trauma and Life Events (TALE) questionnaire) (Carr et al., 2018), and 5) speaks and understands English.

Individuals could not participate if they met any of the exclusion criteria: 1) Age outside of specified age range (i.e., ≤ 18 years, ≥ 36 years,), 2) Scoring in the 'high risk' range for cocaine use on the WHO ASSIST, 3) does not speak English, 4) current involuntary admission or under a Community Treatment Order (due to concerns about voluntariness), 5) a diagnosed intellectual disability, or 6) current participation in an intervention to change SM or treat AE sequelae.

Measures

The three primary outcome measures included the Trauma Symptom Checklist-40 (TSC-40; Elliott & Briere, 1992), Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), and the WHO ASSIST (WHO ASSIST Working Group, 2002). The TSC-40 was used to establish whether adversity sequelae improved[2]. The PANSS was used to assess change in both positive and negative psychotic symptoms over time; the general psychopathology scale items were not collected to reduce participant burden. The WHO ASSIST was both an eligibility measure and outcome measure of SM, assessing risk for substance-use related harm. The Beck Hopelessness Scale (BHS; Beck et al., 1974; Kao et

[2] Although an abbreviated 8-item version of the PCL-5 was also used within this study and results are reported below, the PCL-5 was considered a secondary measure because it is specific to PTSD symptoms, whereas the TSC-40 is a broadband measure assessing various domains of psychopathology relevant to AEs (e.g., anxiety, depression).

al., 2012) measured hopelessness, while the Brief Experiential Avoidance Questionnaire (BEAQ; Gámez et al., 2014b), measured experiential avoidance. The Social and Occupational Functioning Assessment Questionnaire (SOFAS; Morosini et al., 2000) measured functioning, the Clinical Global Impression – Severity (CGI-S) and CGI – Improvement (CGI-I; Guy, 1976) examined symptom severity, and the 8-item PTSD Checklist for DSM-5 (PCL-5; Price et al., 2016; Weathers et al., 1993) assessed PTSD symptoms. The TSC-40 and PCL-5 were administered at baseline, across all six assessments, and the 2-month post-therapy follow-up assessments, while the WHO ASSIST and SOFAS were administered at the same time points except the second post-therapy follow-up assessment. The PANSS and CGI were administered at assessments one and six, and at the first follow-up assessment.

In the context of treatment fidelity, specifically treatment receipt and enactment, participants were asked to answer two questions (see Table 2) about how difficult it was to understand the information presented in sessions and how helpful this treatment was in achieving the goals they set at the beginning of treatment from “Extremely Difficult” (0) to “Extremely Easy” (10). In addition, participants were asked how easy it was to use the skills they learned in therapy from “Extremely Difficult” (0) to “Extremely Easy” (10) and how often they used these skills, ranging from “Never” (0) to “Almost Every Day or Every Day” (10). Finally, the Satisfaction with Therapy subscale of the Satisfaction with Therapy and Therapist Scale – Revised (STTS-R); Oei & Green, 2008) was administered; participants were asked six questions about their satisfaction with treatment (e.g.,

treatment needs were met) ranging from “Strongly disagree” (1) to “Strongly agree” (5). Total scores could range from 0-30, with higher scores indicating greater satisfaction.

Procedure

Participants were recruited through the NSEPP from November 2021 until November 2022. Interested individuals completed an eligibility screening appointment either via telephone or in person at the clinic, after which a baseline appointment was scheduled if they were eligible. During that baseline appointment, individuals received their randomization status (i.e., 2-, 3-, or 4-week delay) via a sealed envelope (see Figure 1 for participant recruitment flow). Study therapists were blinded to assessment results during treatment; there were no instances of unblinding.

Treatment

As a part of typical clinical care at the EPP clinic, participants worked with a nurse and a psychiatrist for medication management, and had access to occupational therapy support, but they were not receiving any psychological therapy. The PE+ treatment is an adaptation of the evidence-based PE therapy for PTSD. PE+ involved fifteen weekly 90-minute sessions divided into five three-session modules; the first module involved psychoeducation about AEs, SM, and psychosis, and how the three influence one other, followed by a second module of adapted Dialectical Behaviour Therapy (DBT) skills (Linehan, 2014) material regarding emotion identification and regulation and distress tolerance skills (i.e., **T**emperature, **I**ntense exercise, **P**aced breathing, **P**aired muscle relaxation;

TIPP). The next two modules were focused on imaginal and in vivo exposures, respectively; the imaginal exposures were initiated in module three (i.e., session 7 of 15) and were continued until the end of therapy, while in vivo exposures were initiated in module four (session 10 of 15) and continued until the final session. The fifth and final module consisted of relapse prevention skills. Participants were instructed to select one AE, typically the 'worst' event, to focus on from the start of treatment until the end.

Supervision and fidelity monitoring

Study therapists were senior PhD students with 3-5 years' experience, and prior experience with PDs and AEs. The study therapists completed over 16 hours of training prior to delivering the PE+ intervention, including clinical roleplays of PE skills, and feedback on intervention skills, in addition to completing a didactic PE course. Therapists participated in weekly group supervision and ad hoc supervision as needed with a registered psychologist (AP) during the study, and they received periodic supervision from another registered psychologist (JT) regarding dissociation management.

Each therapy session was recorded and scored against the author-adapted treatment adherence checklist for that session based on treatment adherence checklists for traditional PE (Sherrill et al., 2020). Ten percent of all sessions were randomized for inclusion in treatment adherence ratings carried out by two independent coders; sessions were randomized for inclusion by module and therapist. The adherence rating lists were conservative, and any departure from the manualized treatment (e.g., missing session agenda, insufficiently detailed

recaps of previous sessions, shorter session length) was considered a lapse in adherence.

Data Analysis

We took a stringent intent-to-treat (ITT) approach to data analysis, including all participants who were randomized in the results, regardless of whether they completed therapy. Inferential statistics were not deemed appropriate given the small sample size and our focus on clinically significant change (CSC) rather than statistically significant changes. We used the Reliable Change Index (RCI; Jacobson & Truax, 1991) to assess change from baseline— all metrics used to establish the degree of required change can be found at clinicaltrials.gov (NCT04546178). The categories of change are CSC (i.e., full recovery), improved (i.e., partial recovery), no change (i.e., no significant change from baseline), or deterioration (i.e., significant negative change from baseline). Quantitative data pertaining to treatment fidelity (i.e., treatment enactment, receipt) were gathered from participants and descriptives were computed for the quantitative data, along with qualitative feedback about participants' experiences in treatment.

Results

Participants

Nineteen individuals with a psychotic spectrum disorder participated in the PE+ study (see Table 1). Although the majority of participants had a diagnosis of schizophrenia and were either White or men, 42% of the sample were members of the 2SLGBTQ+ community given their gender or sexual orientation.

Participants commonly misused cannabis (100%) and alcohol (53%), although participants used 2.3 substances on average (SD = 1.3, range 1-6). SM at baseline was as follows: cocaine (37%), hallucinogens (26%), sedatives (26%), amphetamines (16%), inhalants (5%), and other substances (5%). Inhalants and opioids were grouped under 'other substances' given their low frequency throughout the study. Participants experienced a multitude of different AEs; the AEs most commonly experienced by participants, by category, was as follows: bullying and being put down/humiliated by someone close to the participant (84%; interpersonal AEs), terrifying psychotic symptoms (79%; psychosis-related AEs), and experiencing illness/disaster (e.g., house fire; 42%; non-interpersonal AEs).

Four participants dropped out during the baseline period (i.e., pre-therapy), and three participants dropped out during treatment. Five participants reported dropping out due to changes in life circumstances (e.g., moving, change in work hours), and two did not disclose their reasons. Of those who dropped out during treatment, two participants completed at least half of treatment, while the other participant completed only six sessions before dropping out. The sample of treatment starters was n = 15, and there were n = 12 treatment completers.

Symptom outcomes

Table 2 lists the baseline, post-therapy, and follow-up symptom measurements. When reviewing individual changes using the RCI (see Figure 2), a pattern emerges. Most participants (83%) experienced an amelioration in overall AE-related psychopathology (improvement or CSC) on the TSC-40 by

follow-up (Δmeans = 20.9), with 58% achieving CSC. The course of improvement was often one involving temporary improvements or deteriorations on an upward trajectory. Symptoms appeared to consistently improve after Module 3, the imaginal exposure-focused module. When examining specific domains of the TSC-40 results (see Figure 3), half or more of the participants achieved CSC on dissociation and anxiety, and just under 50% achieved CSC on the depressive symptom domain. However, the courses across participants varied significantly–dissociation had a similar pattern to the TSC-40 total score, increasing and returning to baseline before increasing again, whereas anxiety and depressive symptoms stayed consistent once an amelioration had occurred, although there were more early deteriorations from baseline observed at assessment 1 compared to dissociation and TSC-40 total scores. Sleep appeared to improve little, deteriorating or remaining unchanged for most participants. The results of the abbreviated PCL-5 also suggested improvement; 58.3% of participants achieved CSC by follow-up. Participants who experienced improvements in PCL-5 scores typically maintained those improvements over time. The PANSS positive symptoms (Δmeans = 5.8) improved for two participants (16.7%) and that change was maintained at follow-up, but there were no changes to negative psychotic symptoms for any participants. In terms of the proposed mechanisms, only one participant experienced improvement to hopelessness (8%), although there was clinically significant improvement to experiential avoidance for a third of treatment completers (*n* = 4), despite somewhat limited change to group means from baseline (Δmeans = 8.9).

Group-level alcohol scores did not appear to vary substantially at follow-up (Δmeans = 1.4), but on an individual level, four participants experienced ameliorations to their alcohol use by follow-up (50%), although only one met criteria for CSC (12.5%). However, four participants experienced increases in alcohol use scores (deteriorations) throughout the study, although these increases were temporary for three participants; the fourth maintained the increase at follow-up. Similarly, four participants experienced increases in cannabis scores (26.7%); two participants maintained the increased use by the follow-up period (16.7%), one returned to their baseline score (8.3%), and one experienced improvement (8.3%). The cannabis group mean marginally shifted (Δmeans = 2.5). Although not used as frequently as cannabis or alcohol, there was an amelioration to hallucinogen use by follow-up for 71% of the sample of treatment completers who used hallucinogens (*n* = 5), while no changes were observed to cocaine or sedative scores at any time, and a brief amelioration was observed for one participant using amphetamines before they returned to their baseline score.

Treatment fidelity and therapeutic alliance

Inter-rater reliability for treatment videos was strong; kappas ranged from 0.83 to 0.93 across modules (*M* = 0.88, SD = .04). The overall mean adherence rating was 82% (SD = 15%), considered adherent(Huppert et al., 2001). Table 3 lists all quantitative treatment fidelity ratings. Participants reported that the information presented in treatment was easy to understand and apply to their everyday lives. The average frequency of skill use (e.g., exposure) was reported

to be moderate, ranging from occasional use to every day, suggesting appropriate levels of treatment enactment overall. At follow-up, participants reported a similar frequency of skill use, with only one participant reporting a reduction in skill use frequency since ending treatment. Completion of between-session tasks (i.e., participant homework) was monitored throughout treatment to assess treatment enactment. Participants at least partially completed homework in 89% of sessions, and 50% of all sessions included completion of all homework. Differences between therapists on ratings of overall therapeutic alliance with clients were minor [range: 36.2 – 38.3], as were differences in ratings between modules [range: 35.2 – 38.6]. Overall, ratings of therapeutic alliance were high, suggesting a strong alliance between therapists and participants in this study.

Participant feedback

Feedback was quite consistent across participants. When asked about the most helpful element of treatment, several treatment completers noted that exposure, although difficult, was the most helpful aspect of treatment (41.7%; 5/12). However, participants also remarked that coping strategies alone (DBT skills, e.g., check the facts, TIPP; Linehan, 2014) (25%; 3/12) and both exposure and coping strategies (25%; 3/12) were the most helpful treatment components. One participant did not respond. It is noteworthy that during an open-ended request for feedback on the therapist, therapy, and research study experience, 50% of treatment completers (6/12) remarked on the vital role that their therapist played in treatment, highlighting how helpful it was that their therapist had a

nonjudgmental approach and made efforts to understand their experience. Table 3 describes the quantitative study feedback; overall, participants were very satisfied with the PE+ treatment.

When asked how this treatment approach could be adapted to better meet the needs of those who may need it in future, treatment completers consistently mentioned increasing the number of sessions (75%; 9/12). Some participants (16.7%; 2/12) wanted more emphasis on psychotic symptoms, given the links between their AEs and psychosis, as well as additional skills to cope with hallucinations. These participants discussed the importance of being able to discuss the interconnections between their AEs and their psychotic symptoms, especially when the AE occurred during or was a psychotic episode.

Discussion

Primary outcomes of PE+ included improvements across most domains of AEs sequelae (i.e., dissociation, depressive symptoms, anxiety) including PTSD symptoms, no changes to negative psychotic symptoms, and 16.7% (2/12) participants experienced clinically significant improvements in substance use by follow-up. However, 40% (6/15) did achieve temporary improvements in SM during the study, although they were not maintained by follow-up. Several participants had substance use deteriorations, often occurring early in treatment before returning to baseline, and deteriorating again during imaginal exposure module (Module 3). However, no deteriorations in psychotic symptoms were observed. Our hypotheses were not supported with regards to improvements to psychotic symptoms or substance use, but improvements in AE sequelae (i.e.,

anxiety, dissociation, depressive symptoms, PTSD symptoms) by follow-up did support hypotheses.

In terms of secondary outcomes, treatment starters experienced some improvements in experiential avoidance (33%) and functioning (46.7%), although only 33% of the sample maintained functioning improvements at follow-up. Few changes to hopelessness were observed (6.7%); less than half the sample experienced significant change, meaning that hypotheses for experiential avoidance, hopelessness, and functioning were not supported. Only two participants (13.3%) experienced improvements in positive psychotic symptoms by follow-up. Participants were satisfied with the quality of treatment and found the PE+ treatment helpful to achieve their goals, which aligns with previous participant experiences with adversity-focused treatments (Tong et al., 2017). Participants noted that primarily exposure and but to a lesser extent emotion-focused skill-building were the most helpful elements of treatment.

Several other adversity-focused treatment trials also observed improvements to AE-related sequelae consistent with our results. Keen and colleagues (2017) reported that 63% of their participants with psychotic symptoms achieved CSC to AE sequelae during their longer protocol (median number of sessions = 41), while van den Berg and colleagues (2015) found that more than 56% of their participants with chronic psychosis no longer met criteria for PTSD by the 6-month follow-up assessment after the end of their 8-session treatment. It was unclear whether the improvements to AEs sequelae found in these previous studies would translate to an EPP population; however, our

findings suggest that similar improvements can be expected. In contrast, there were fewer improvements to positive psychotic symptoms in the PE+ study than in other studies, where small effects were found in pre-to-post analyses, although negative symptoms remained unchanged in some trials (Brand et al., 2018). However, other approaches had reported changes to negative symptoms following intervention (e.g., Kim et al., 2010; White et al., 2011), which prompted our focus on negative rather than positive symptoms. However, no other study focused exclusively on an EPP sample, instead using predominately chronic or mixed-duration samples who were typically at least 10-15 years older than those usually in EPP. It is noteworthy that no deteriorations in psychotic symptoms were observed during the PE+ trial. Although previous adversity-focused trials among people with chronic psychosis similarly observed few psychotic symptom exacerbations (van den Berg, de Bont, et al., 2016), a consistent barrier to the delivery of adversity-focused treatments among patients with psychotic disorders is clinician fear of psychotic symptom exacerbation (Gairns et al., 2015). The PE+ trial results may provide clinicians with more confidence that adversity-focused treatments appear to be safe for people with EPP, although patients may benefit from substance use monitoring throughout treatment.

To our knowledge, this is the first adversity-focused treatment trial for people with EPP, and the first to integrate and measure SM over time. Current clinical guidelines for addressing AEs with people with psychotic disorders (Cragin et al., 2017) suggest integrated treatment with one clinician addressing psychosis and AEs sequelae simultaneously. We suggest extending these

guidelines to include substance use challenges as well and adopting an integrated approach to treatment for psychosis, SM, and AEs. We hypothesized that by targeting AE-related symptoms, we might indirectly improve all symptom domains (e.g., psychosis, SM) given that SM may function as a coping mechanism for AE sequelae, as suggested by the stress and coping model of SM (Wills & Hirky, 1996), and AE sequelae may be maintaining psychotic symptoms through shared mechanisms (e.g., dissociation). Our results do not appear to support this hypothesis and, indeed, SM deteriorated in several cases, suggesting an alternative approach may be needed. Rather than targeting one domain, it may be more helpful to take a fully integrated approach, incorporating psychosis-specific treatment strategies from Cognitive Behavioural Therapy for Psychosis (CBTp; Beck et al., 2011), and integrating SM strategies with PE+, in a similar way as with the Concurrent Treatment of PTSD and SUDs using Prolonged Exposure (COPE; Back et al., 2014) protocol. A more integrated approach may allow a greater focus on treating the links that may be maintaining these challenges (e.g., cannabis use to reduce anxiety caused by PTSD which worsens auditory hallucinations). A comprehensive review of the PTSD-alcohol misuse literature (Stewart, 1996) highlighted this issue, noting that single-focus treatment for PTSD or alcohol misuse appeared to be insufficient, and that integrated treatment may be more efficacious as it considers both the links between difficulties and the separate impact of each difficulty on an individual's life.

In our sample, SM was more frequently unchanged or worsened than improved, suggesting even more direct targeting of substance use may be required to change use in a group with psychosis and a history of AEs, especially because PE treatment in non-psychosis populations did not result in SM increases (Peirce et al., 2020). Participants also expressed benefiting from the coping strategies module, which is a stabilization module, suggesting its acceptability among participants. However, other trials have found positive effects without stabilization. Brand and colleagues suggested that the acceptability and efficacy of a stabilization phase should be examined; although acceptable to our participants, no changes to psychopathology scores were observed following this phase.

A significant strength of the PE+ trial is the comprehensive treatment fidelity approach. We created and reported a thorough treatment fidelity plan, including a treatment manual, therapist training, video coding for adherence, and measures of both treatment receipt and enactment. This robust approach is not always used (Borrelli et al., 2005; Perepletchikova et al., 2007). Although comprehensive, we suggest future studies explore the psychometrics of our adapted fidelity checklists. In addition, we tested the PE+ embedded within an early psychosis program, meaning that it was tested in the environment in which it would be delivered in the future, which increases the ecological validity of PE+. The two limitations of these results involve sample size and limited diversity of race and culture (although there was substantial sample diversity on sexual orientation and gender identity). Given the preliminary nature of this study, a

small sample was appropriate; however, generalizing these results to a larger sample may present challenges, especially if the program structure differs from the standard approach to care detailed above. Moreover, the racial and cultural diversity of this sample was limited; few ethnicities were represented in this sample and the majority of participants reported that their race was White. This may make generalizing PE+ results to other races and cultures more difficult.

Conclusions and future directions

In conclusion, PE+ treatment appeared to be helpful for AEs sequelae but was less effective at improving psychotic symptoms and substance misuse. However, importantly, psychotic symptoms did not worsen despite the exposure component. Participants found PE+ to be helpful and noted that exposure and coping skills were the most helpful elements of treatment. A few participants believed that treatment did not focus enough on psychotic symptoms. Further work needs to be done to establish an effective, integrated treatment capable of addressing the links between psychotic symptoms, SM, and AEs sequelae. Integrating more substance use treatment strategies (e.g., coping with cravings) and increasing the focus on treating psychotic symptoms in PE+ may be a more beneficial approach. Such a 'PE++' approach could be developed from the current intervention and be piloted before bringing this expanded adversity-focused approach to a full randomized controlled trial (RCT). Moreover, future studies should explore a longer treatment duration; AE-focused treatment studies with people with PDs have consistently found that protocols using 8-15 sessions are too short (Spidel et al., 2019; van den Berg et al., 2015). Lastly, future

adversity-focused treatment trials should include adolescents in their early psychosis samples to understand whether adversity sequelae improvements observed with young adults will generalize to a younger age group.

Tables

Table 4.1.1. Participant demographics at baseline

	Participants *N* = 19
Age, *M* (SD)	24.9 (3.6)
Race, %	
Black	10.5% (2)
Multiracial	10.5% (2)
White	74.0% (14)
Unknown	5.0% (1)
Gender, %	
Non-binary	26.3% (5)
Man	52.6% (10)
Woman	21.0% (4)
Sexual orientation, %	
Asexual	5.2% (1)
Bisexual	5.2% (1)
Gay/Lesbian	10.5% (2)
Heterosexual	57.9% (11)
Pansexual	15.8% (3)
Queer	5.2% (1)
Number of months at NSEPP, *M* (SD)	24.0 (23)
Diagnosis, % (n)	

Brief Psychotic disorder	5.2% (1)
Psychotic disorder not otherwise specified (NOS)	15.8% (3)
Schizophrenia	57.9% (11)
Schizoaffective	15.8% (3)
Substance-induced psychotic disorder	5.2% (1)
AEs, *M* (SD)	
Lifetime AEs	11.8 (2.5)
Interpersonal AEs	7.2 (2.9)
Psychosis-related AEs	2.5 (0.9)
Non-interpersonal AEs	1.4 (0.7)

Note: NSEPP = Nova Scotia Early Psychosis Program (NSEPP); AEs = Adverse Events

Table 4.1.2. Mean clinical scores at baseline, post-treatment, and follow-up

	Baseline *N* = 19	**Post-therapy** *N* = 12	**2-month follow-up** *N* = 12
PCL-5 (8-item)	17.8 (5.9)	10.1 (6.4)	8.5 (6.1)
BEAQ	54.7 (10.2)	49.1 (12.5)	50.5 (11.6)
BHS	7.1 (5.1)	5.0 (4.6)	4.5 (4.6)
TSC-40 total score	45.2 (17.5)	31.1 (20.8)	24.7 (16.4)
TSC-40 - Anxiety	8.5 (5.0)	5.1 (4.2)	4.2 (3.4)
TSC-40 - Depression	10.8 (3.9)	7.3 (5.8)	5.7 (4.2)
TSC-40 - Dissociation	9.1 (3.7)	6.8 (4)	5.4 (2.6)
TSC-40 - Sleep	7.3 (4.4)	5.6 (4.6)	4.6 (4.2)
PANSS positive symptoms,	18.1 (5.6)	12.8 (0.3)	12.2 (2.8)
PANSS negative symptoms	14.8 (3.4)	13.3 (3.7)	15.2 (6.2)
SOFAS	57.0 (9.3)	67.7 (13.1)	69.5 (13.6)
CGI-S	3.8 (0.9)	3.2 (0.9)	3.5 (1.2)
WHO ASSIST			
Alcohol	12.3 (7.2)	11.5 (8.8)	10.0 (8.9)
Cannabis	21.8 (9.8)	19.5 (10.7)	3.5 (9)
Cocaine	9.0 (7.6)	6.5 (0.5)	3.5 (0.5)
Amphetamines	5.8 (4.3)	6.0 (3)	3.0 (0)
Inhalants	6.0 (0)	-	-
Sedatives	5.3 (2.2)	4.5 (1.5)	4.0 (2)

Hallucinogens	6.7 (4.1)	6.0 (0)	2.7 (0.9)
Opioids	3.0 (0)	-	2.0 (0)
Other substances	6.0 (0)	-	2.0 (0)

Note. PCL-5 = PTSD Checklist 5; BEAQ = Brief Experiential Avoidance Questionnaire; BHS = Beck Hopelessness Scale; TSC-40 = Trauma Checklist 40; PANSS = Positive and Negative Syndrome Scale; SOFAS = Social and Occupational Functioning Assessment Scale; CGI-S = Clinical Global Impression – Severity scale; WHO ASSIST = Alcohol Smoking, Substance Involvement Screening Test. The WHO ASSIST scores are only calculated for those who use each substance. A dash indicates that substance was not used by any participants.

Table 4.1.3. Participant receipt and enactment and participant opinions about treatment (*n* = 12)

	***M* (SD)**
Post-treatment receipt and enactment	
How easy was it to understand the information presented in sessions?	8.6 (1.6)
How easy was it to use the skills you learned in the therapy sessions in your day-to-day life?	7.0 (2.0)
On average, how often did you use the skills you learned?	6.6 (2)
How helpful was this therapy in helping you to achieve the goals you set at the beginning of treatment?	7.5 (1.2)
Overall, how difficult was it to do this therapy?	6.4 (2.2)
2-month follow-up receipt and enactment	
Since ending therapy 2 months ago, how easy has it been to use the skills you learned in the therapy sessions in your day-to-day life?	6.4 (2.2)
Since ending therapy 2 months ago, how often have you used the skills you learned?	6.6 (1.2)
Satisfaction with Therapy	
I am satisfied with the quality of therapy I received	4.6 (0.5)
My needs were met by the therapy	4.5 (0.5)
I would recommend this therapy to a friend if they needed it	4.4 (0.7)
I would come back to the clinic for this therapy if I needed help	4.5 (0.7)

I am now able to deal more effectively with my problems	4.0 (0.9)
I was able to focus on what was of real concern to me in therapy	4.3 (0.9)

Note. These items were administered to the completer sample (*n* = 12). Receipt and enactment ratings were rated from 0 to 10 and participant ratings of treatment ranged from 0 to 5; higher ratings indicated greater frequency of skill use, ease of understanding, agreement, etc.

Figures

Figure 4.1.1. Participant recruitment information

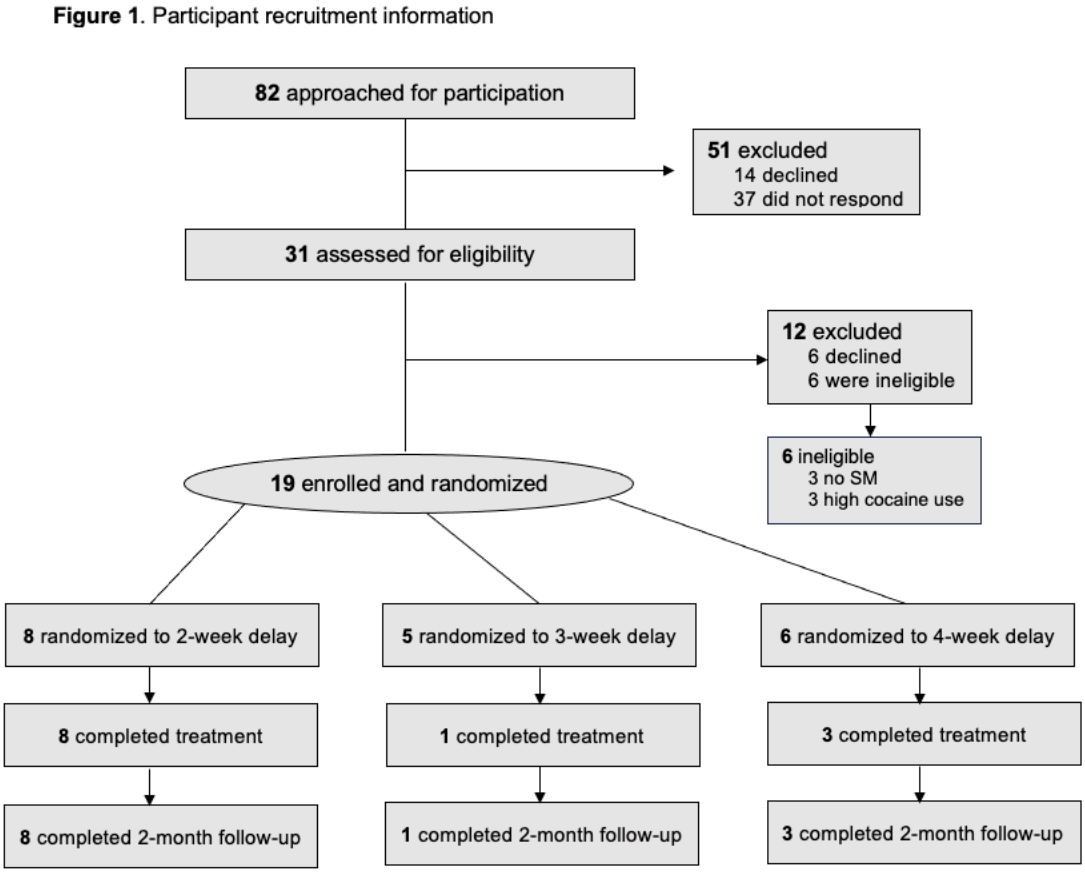
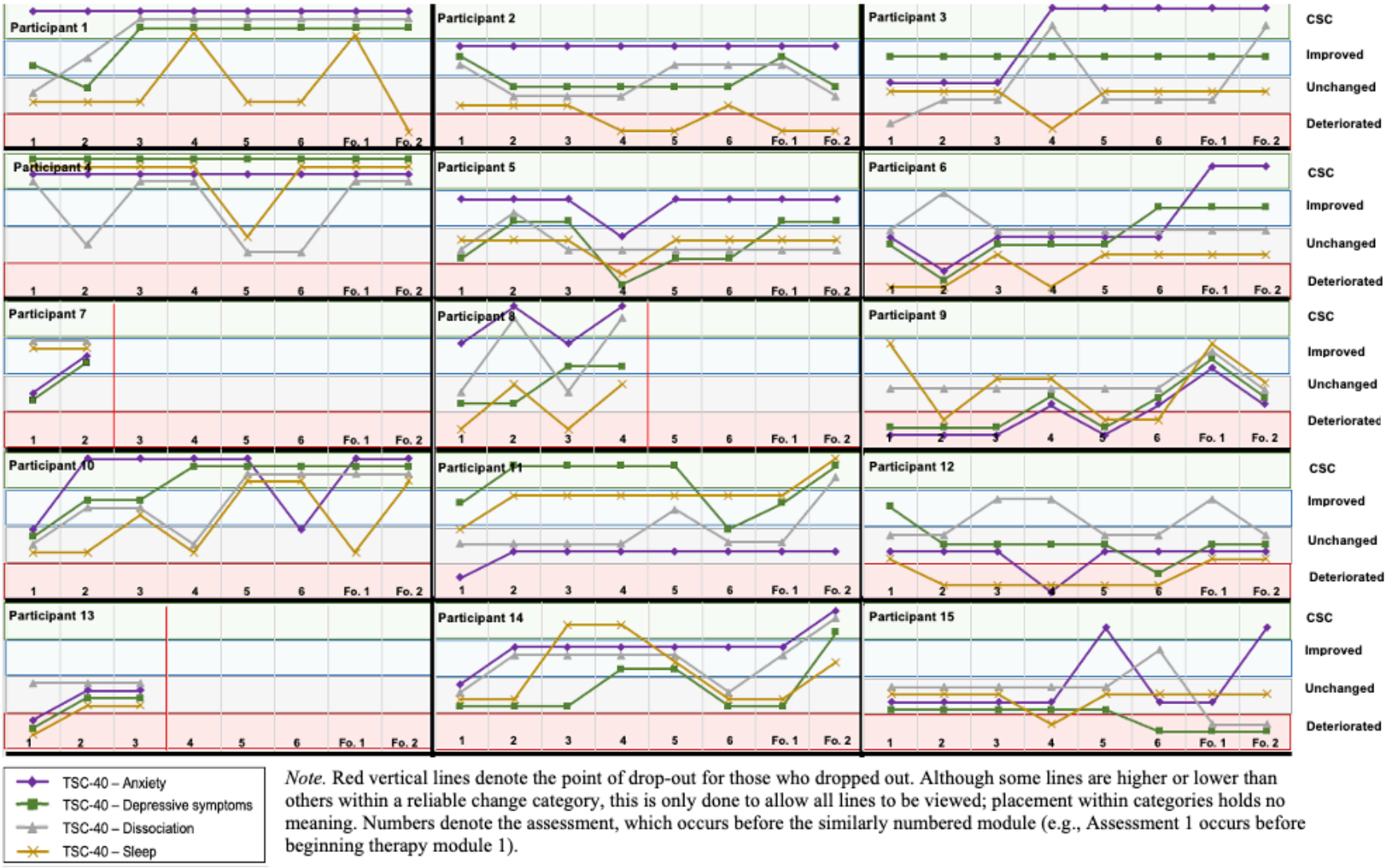


Figure 4.1.2. RCI scores for primary outcomes (TSC-40 total, alcohol, cannabis) and positive psychotic **symptoms**

Note. Red vertical lines denote the point of drop-out for those who dropped out. Although some lines are higher or lower than others within a reliable change category, this is only done to allow all lines to be viewed; placement within categories holds no meaning. Numbers denote the assessment, which occurs before the similarly numbered module (e.g., Assessment 1 occurs before beginning therapy module 1).

Figure 4.1.3. RCIs for TSC-40 subscales (anxiety, depressive symptoms, dissociation, sleep) across PE+ treatment



Note. Red vertical lines denote the point of drop-out for those who dropped out. Although some lines are higher or lower than others within a reliable change category, this is only done to allow all lines to be viewed; placement within categories holds no meaning. Numbers denote the assessment, which occurs before the similarly numbered module (e.g., Assessment 1 occurs before beginning therapy module 1).

Acknowledgements

Ethics statement

The studies involving human participants were reviewed and approved by Nova Scotia Health Research Ethics Board (REB#1025608). The participants provided their written informed consent to participate in this study.

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Chapter 8. General Discussion

The overarching aim of my dissertation was to review, explore, and treat the nexus of early EPP, SM, and AEs. In service of that goal, I built a linear program of three research studies that ultimately aimed to advance the knowledge base of psychosocial interventions treating adversity sequelae (e.g., dissociation, PTSD symptoms) among people with early phase psychosis and substance misuse. In the following sections, I will summarize, integrate, and position my findings within the broader literature, as well as discuss the theoretical and clinical implications of my dissertation. Lastly, I will delineate the strengths and limitations of my research and outline possible future directions.

Summary

In Study 1, as described in Chapter 2, I reviewed the extant literature examining PDs, SM, and AEs. Against a background of elevated rates of AEs, review findings highlighted both broad and specific links to negative health outcomes for individuals experiencing this three-way overlap. Additionally, a dearth of evidence examining this overlap by phase of psychosis was identified, with significant gaps for EPP and substance-induced psychosis. The relationship between SM and AEs was often unexplored, with SM occupying a background role in analyses. Examination of AEs and SM were both limited, with a circumscribed focus on child abuse and alcohol and cannabis; few other AEs or substances were examined. Critically, several methodological issues were flagged, such as a lack of power analyses, inconsistent definitions, and predominately cross-sectional evidence. Despite these issues, the evidence

underscores the importance of considering both SM and AEs when examining the complex relationships between PDs, SM, and AEs.

In Study 2, described in Chapter 4, I employed a retrospective cross-sectional between-subjects design to examine the prevalence of the overlap between EPP, SM, and AEs. There was a substantial overlap (>60%) between EPP, SM, and AEs, with SM rarely appearing in the absence of AEs, although the reverse was not true. The most endorsed AEs were distressing psychotic symptoms (80%), bullying (72.7%), and acting in dangerous, strange, or embarrassing ways (57.2%), while the most used substances were tobacco, alcohol, and cannabis. Almost a quarter of participants (22%) exceeded the screening cutoff score of a PTSD measure, suggesting ongoing psychopathology at a potentially clinical level. Nearly three-quarters of participants who experienced an AE would like to speak to a mental health professional about their AE. The results emphasize the importance of asking about a broad spectrum of AEs and substances, as results indicated that many people with EPP are polyvictims and use multiple substances.

The third and final study of my dissertation, discussed in Chapters 6 and 7, utilized a multiple-baseline design to examine the outcomes of an adapted Prolonged Exposure (‘PE+’) protocol among young adults with EPP, SM, and a history of AEs. Most individuals used multiple substances and experienced an average of 11 lifetime AEs. Treatment outcomes for AE sequelae indicated significant clinical change, while psychotic symptoms generally did not significantly improve, although no deteriorations were observed. SM had a more

variable pattern of outcomes, with some improvements and some deteriorations. Study results suggest the potential effectiveness of PE+ for addressing adversity sequelae in an EPP population; however, treatment protocol refinements may be required to effectively address the complex psychopathology observed in this high-AE, high-SM population.

Theoretical implications

The integration of evidence across all three studies suggests gaps in understanding the role of SM in the EPP-AEs relationship. SM was inconsistently associated with AEs throughout the literature, although prevalent among those with PDs. Similarly, SM was elevated in an EPP sample, and rarely appeared in isolation from AEs, yet intervention outcomes indicated that SM at times increased in the face of improvements to AEs sequelae. It is possible that this inverse relationship between AE sequelae and SM could be explained by the stress and coping model (Wills & Hirky, 1996); as AE-related fear structures are activated, individuals use substances to disengage and inhibit inhibitory learning, preventing emotional processing. However, this pattern of results was inconsistent across participants, suggesting additional processes which require further research to explore in depth. Konkolÿ Thege and colleagues (2017) found a similar pattern in the literature of non-treatment seeking individuals: SM was inconsistently associated with AEs. Given that both improvements and deteriorations were observed across participants in Study 3, there appears to be a relationship between AEs and SM, although it did not appear to be dependent on the severity of psychopathology (e.g., psychotic symptom severity),

functioning, or gender. It is possible that SM serves multiple functions within the EPP-SM-AEs relationship and may also depend on the substance, which may explain the variable pattern of results. Coping motives (e.g., relief from physiological arousal due to AE sequelae) may predict the use of substances in some instances (e.g., alcohol-PTSD link; Grosso et al., 2014), while other instances of use may be better explained by enhancement motives (i.e., facilitate or enhance positive affect). A study of adults with PDs found elevated rates of both coping and enhancement motives (Spencer et al., 2002). In addition, a recent study of AE cues and cannabis use among individuals exposed to an AE (Atasoy et al., 2023) suggested that individuals with greater symptoms of PTSD may use cannabis to cope with both PTSD related symptoms as well as general negative affect. Together these theories may explain my findings – individuals who use substances to cope with negative affect may have experienced a decrease in use, yet PE+ treatment was not designed to impact enhancement motives for SM, or to address trauma-cue elicited craving. Future intervention work should endeavour to understand the function of SM throughout AE-focused treatment, assessing the specific motives for use prior to, during, and following treatment.

Emotional Processing Theory (EPT) appears to be similarly applicable to individuals in EPP as with non-PD populations. Furthermore, the use of EPT is likely to address bridge symptoms between AEs and psychosis highlighted by Hardy et al. (2021), which could be maintaining both AEs sequelae and psychosis. In terms of maintenance mechanisms, hopelessness did not appear

to decrease substantially, despite the decreases in AEs symptoms (i.e., dissociation, depressive symptoms, anxiety, PTSD symptoms), suggesting other mechanisms may be more prominent in this process.

Clinical implications

As discussed, many clinicians are hesitant to ask individuals with PDs about AEs (Lothian & Read, 2002), and AE-focused treatments are rarely offered to people with PDs. This hesitancy to offer treatment for AEs may be partially due to a lack of evidence base supporting their use in a PD population given the heavy exclusion of people with PDs from AE-focused treatment research (Ronconi et al., 2014). Although there are a multitude of barriers which perpetuate the hesitancy to discuss AEs with people with PDs, one of the most significant factors is the clinician belief that psychotic symptoms must be completely stabilized (Gairns et al., 2015), which is especially relevant for an EPP population who is often still attempting to find and maintain stability of symptoms. Moreover, there is a common fear of destabilization of psychotic symptoms among clinicians (van den Berg, van der Vleugel, et al., 2016). This fear of destabilization may further prevent clinicians from recommending their patients engage in exposure-based adversity-focused treatments, despite recent promising evidence, including from this dissertation, that exposure-based interventions are effective for treating AEs sequelae among people with PDs and a history of AEs. Moreover, recent results from 110 early psychosis programs across five countries (Wood et al., 2023) indicated significant barriers to adversity-focused assessment and treatment (i.e., siloed mental health care

approach, a lack of AE-specific training, and forced-choice case conceptualization (i.e., psychosis or adversity as primary issue)). Taken together, the clinical implications of my work are twofold.

First, the implementation of AE-focused clinical interventions in early psychosis programs are unlikely to be successful if practical limitations (i.e., no standard practice for assessing AEs, clinician hesitancy to discuss AEs) persist. Clinicians in early psychosis programs infrequently receive training related to adversity, and even less frequently do they receive training on adversity within the context of psychosis (Gairns et al., 2015; Wood et al., 2023). Yet, clinician responses to disclosures are critical; prior work indicated that the average time to next AE disclosure after receiving a poor response (i.e., disbelief) was seven years (Ahrens, 2002). Offering clinician training related to AE-focused treatment may be a beneficial first step; a Dutch study (van den Berg, van der Vleugel, et al., 2016) found significant decreases in harm expectancies and significant increases in therapist-rated credibility of AE-focused treatments following theoretical and technical training in PE and EMDR, and clinicians continued to use these approaches at the 2-year follow-up. Providing psychoeducation to clinicians helps decrease their concerns about harms of exposure therapy; however, training may be helpful.

Second, as practical barriers to AE-focused assessment and treatment are addressed, early psychosis programs could move towards a model of integrated care inclusive of psychosis, AEs, and SM. As discussed, clinicians suggested an integrated model of care (Cragin et al., 2017), meaning one clinician provides

care for psychosis, SM, and AE sequelae, rather than single-diagnosis models, which are the current favoured approach in many early psychosis programs. In addition, AE-focused treatments designed for use with a polyvictimized population ('complex trauma') with moderate-to-substantial misuse of multiple substances should be implemented. Given the complexities faced by this population, treatment should be expected to exceed the typical 10-12 sessions; the National Institute for Health and Care Excellence (NICE) guidelines suggest a minimum of 16 sessions of CBTp for psychosis (National Institute for Health and Care Excellence, 2015), but the strongest positive outcomes were observed after more than 20 sessions (Sarin et al., 2011). It can be inferred that treatment duration is likely to be similarly lengthy among those with EPP, SM, and AEs. The results of Study 3 and prior work (e.g., Spidel et al., 2019; van den Berg et al., 2015) has consistently found that treatment duration of 15 sessions or less is too short.

Strengths and limitations

Each study has its own strengths and limitations, discussed within their respective chapters; however, this dissertation also has global strengths and weaknesses, which will be discussed here.

Sample

Studies 2 and 3 recruited participants from a hospital-based early psychosis program, ensuring that participants meet criteria for a psychotic disorder. In addition, recruitment was inclusive of schizophrenia spectrum disorders, meaning that individuals who may not be included in schizophrenia-

only samples (e.g., schizophreniform disorder) were included. This approach to diagnostic inclusion is likely more reflective of real-world composition of early psychosis programs (Leuci et al., 2020), thereby increasing the generalizability of findings to other clinical samples. In addition, both Study 2 and 3 recruited several understudied subgroups of people with EPP: trans, gender-diverse, and queer individuals. Interestingly, trans, gender diverse (i.e., identifying outside the binary, moving fluidly across genders, or not identifying with any gender; Tan et al., 2020), and queer (e.g., bisexual, lesbian) people may be overrepresented in EPP clinics, potentially due to hypothesized minority stress effects (Meyer, 1995). Previous work found rates of schizophrenia spectrum disorders that were more than three times higher among trans individuals than cisgender individuals (Dragon et al., 2017), and approximately double among bisexual women and gay men (Bolton & Sareen, 2011) compared to heterosexual women and men. Despite these elevated prevalence rates, these groups are underrepresented in research. Therefore, their inclusion here strengthens the findings of Study 2 and especially Study 3, given that these groups may be overrepresented in samples seeking adversity-focused intervention due to their adverse identity-related experiences (Livingston et al., 2019). Although different, I also took an inclusive approach to Study 1, the systematic review. I searched across six databases, screening over 16,000 abstracts to ensure a thorough search resulting in an inclusive sample of studies examining the nexus of PDs, SM, and AEs.

The core limitations of the samples included in this dissertation are the lack of systematic recruitment procedures, limited gender and racial diversity,

and the possibility of Berkson's bias. In Studies 2 and 3, participants were approached in a non-systematic manner; study staff and clinicians approached clinic patients about study participation; however, not all clinic participants were approached. It is possible that the most severely ill patients were included less frequently given the difficulties contacting those without a mobile device, or fixed address with access to a telephone or computer, although significant attempts were made to include individuals who were unhoused given their underrepresentation in research yet overrepresentation in psychosis clinics (Ayano et al., 2019). Similarly, Black, Indigenous, and People of Colour (POC) were less often included, with White people constituting the largest racial group. As discussed throughout this thesis, the low racial and cultural diversity limits the generalizability of these findings. As mentioned in Study 1, Berkson's bias may affect representativeness of the samples studied throughout this thesis, and results may not generalize to those with only two of the three variables of interest studied here. However, given that the results are intended to generalize to those individuals with PDs-SM-AEs, the issue may be limited in its magnitude. Finally, the small sample found in Study 3, although appropriate for a pilot study, limits the scope of these findings. Individual changes (e.g., job loss, relationship breakup) would have had a more significant impact on assessment findings given this small sample; results should be considered with this caveat in mind.

Research design

The multiple-baseline design (MBD) of Study 3 represents an appropriate experimental design choice for a small-N study (Smith & Little, 2018), because it

is well-suited to examining individual rather than group-mean change. The individual view of clinically important change is important in a pilot intervention to determine whether a larger study is justified, and suggest areas that may need modification in future iterations (Conn et al., 2010). The rigour of the MBD design was primarily due to randomization to treatment start time and a baseline control group. Randomization to treatment start point (i.e., randomized phase start-point designs) is used to increase internal validity in an MBD and safeguard against biased enrollment (e.g., enrolling more ill participants first), and the participants functioned as their own control group, increasing the rigour of this small-N study. Furthermore, Study 3 met six of the seven 'gold standards' for treatment outcome studies outlined by Foa and Meadows (1997): clearly defined target symptoms, blind evaluators, adequately trained assessors, manualized, replicable, and specific treatment, unbiased assignment to treatment, and evaluation of treatment adherence. Another strength of Study 3 was the partnership with a patient who joined the research team. Previous work exploring patients' perspectives on AE-focused therapy in EPP highlighted the importance of patient choice and control over their treatment (Tong et al., 2017). The first step towards that reality is ensuring patients have opportunities to create and tailor evidence-based interventions to meet their needs. The work of the patient partner and their invaluable perspective permeated the phases of PE+ study, from conception to the first draft manuscript, and increased the feasibility of treatment engagement for the PE+ study participants.

Conversely, there were several methodological shortcomings of the work presented here. Although MBDs are a rigorous small-N design, a balance was struck between rigor and feasibility in Study 3, given the frequent challenges with recruitment and retention of EPP samples in research (Walta et al., 2022). MBD guidelines (Kratochwill et al., 2010) suggest the use of six or more phases with at least three time points per phase. The PE+ study has three phases with a minimum of two time points. However, the repetition of assessments during baseline and treatment would meet criteria, even if the follow-up assessments do not meet the minimum time point criteria. In addition, to reduce participant burden and minimize drop-out, several measures were not collected during the PE+ baseline, namely the PANSS and the WHO ASSIST. Collecting this data on multiple occasions would have provided a more stable baseline comparison point to which later results could be compared rather than only collecting this information upon study enrollment, immediately before and after treatment, and at follow-up. Finally, the one 'gold standard' element of treatment outcome studies outlined by Foa and Meadows that was not met was the use of valid and reliable measures. They recommended both diagnostic and self-report measures, however, no diagnostic measures were used in the PE+ study (Study 3).

Measurement

A significant strength of this dissertation is its transparency. All studies were pre-registered: Study 1, a systematic review, was pre-registered ahead of the review process on PROSPERO, an international prospective register of

systematic reviews, Study 2 analyses were pre-registered on the Open Science Framework (OSF) website, and Study 3 was pre-registered prior to data collection on clinicaltrials.gov. Previous research suggested that pre-registration can act as a safeguard against 'p-hacking', as well as safeguarding against the longstanding issue known as 'HARKing' (Hypothesizing After Results are Known) (Kerr, 1998), wherein exploratory analyses are presented as confirmatory analyses. Pre-registration may increase confidence in researchers' results and the field of psychology, especially given the recent replication crisis in much of psychology (Nelson et al., 2018; Open Science Collaboration, 2015). Hindsight bias (i.e., believing events were more predictable than they were) and selective reporting may also be reduced by pre-registration, thereby minimizing overall bias in published reports (Logg & Dorison, 2021). Relatedly, another common issue in the literature is the use of insufficiently powered analyses. Although there has been increased attention on this issue and steps have been taken to remedy it (e.g., a priori power analyses, confidence intervals), many published studies are underpowered, which may artificially increase effect sizes (Maxwell, 2004). This issue was also highlighted in my systematic review—of the 57 studies included, fewer than 5 included power analyses (<9%). A strength of Study 2 was the thorough analysis plan, inclusive of power analyses for all planned analyses, even though it wasn't possible to carry out several of the planned analyses due to a lack of power. It was important to follow best practices and ensure that only accurate results are introduced in the literature base

examining EPP-SM-AEs given its early stages and the importance of building upon a solid foundation to further future research.

In terms of measurement limitations, the use of previously unvalidated measures (i.e., DIT, PE+ treatment fidelity checklists) is a limiting factor of the conclusions of Studies 2 and 3. Psychometric analyses ensure that conclusions based on measures (e.g., questionnaires) are reflective of the constructs intended to be measured (i.e., valid) and conclusions are stable across time (i.e., reliable). A psychometric analysis of the DIT measure would strengthen the conclusions of Study 2, and, assuming strong psychometric properties, the DIT could be used to identify opportunities for the introduction of an AE-focused intervention in EPP programs. In addition, one questionnaire was modified for repeated use – the WHO ASSIST was modified for monthly use instead of trimonthly use. This modification has similar limitations to the use of unvalidated questionnaires in that reliability and validity may be affected.

Future directions

Although each of the three studies contained suggestions for future directions, there are numerous possible directions for future work that can build on the results outlined throughout this dissertation.

The impact of the EPP-SM-AEs overlap

One of the aims of Study 2 was to compare AEs among those with and without SM; this goal was thwarted due to power issues. Future work should aim to understand and compare AEs (e.g., prevalence rates, types of AEs) alongside a greater focus on psychopathology. The occurrence of adversity does not imply

a lasting negative impact; the multifinality of outcomes of AEs indicate that some individuals who experience AEs do not experience clinical levels of psychopathology (Haskett et al., 2006). However, many individuals do experience either transient or lasting impacts (e.g., Bick & Nelson, 2016). A limitation of this dissertation is the lack of evidence to support the negative impact of the EPP-SM-AEs overlap; however, prior work has examined negative outcomes for both AEs and SM, suggesting this negative impact is present. Nevertheless, more direct evidence of both a high prevalence of the EPP-SM-AEs overlap as well as a strong negative impact would provide a stauncher justification for investment in adversity-focused treatments for these individuals. Tomassi and colleagues (2017) posited that those with a PD who have a history of AEs and use substances may represent a distinct group; future work could test this hypothesis using a latent class analysis (LCA; e.g., Weller et al., 2020). Using a larger sample, an LCA could establish profiles/classes delineated by AEs and SM, and class associations with severity of psychopathology could be observed.

Temporality of EPP-SM-AEs

No studies included age of onset for psychosis, substance use, and AEs within Study 1, although temporality can be inferred based on previously published literature. However, like the possible future work delineated in the section above, reporting onset of EPP, SM, and AEs within one study would enable researchers to delineate temporality and map psychopathology onset. Prior work suggests temporality matters; individuals who were classified as

polyvictims in early childhood (age 0-5) had high continuity of polyvictim status for the remainder of childhood (Dierkhising et al., 2019), and those who experienced polyvictimization status in early childhood or those classified as 'persistent polyvictims' (i.e., polyvictimization across all stages of childhood) had the worst outcomes of internalizing and externalizing symptoms. Therefore, examining not only occurrence of any AEs, but also polyvictimization status may be important. The literature would suggest that the ordering of events is AEs-SM-EPP however it is yet unclear what proportion of the time SM precedes AEs, or AEs follow EPP. Furthermore, comparing outcomes for those with a SM-EPP-AEs ordering versus those with an AEs-EPP-SM/AEs-SM-EPP ordering could provide information leading to treatment personalization for treatment of psychosis (e.g., CBTp, medication) and adversity-focused treatment, assuming these outcomes differ. In addition, this approach could provide a greater understanding of the optimal age at which to intervene, if early adulthood is too late.

Modification of PE+

I hope to conduct future work pertaining to the PE+ protocol. My future approach will attempt to remedy the measurement shortcoming by making use of a diagnostic instrument at baseline (i.e., the Structured Clinical Interview for DSM-5, SCID-5; First et al., 2015) to assess whether loss of diagnosis occurs during and following treatment, in addition to the use of symptom-specific measures. This broad diagnostic instrument could examine PTSD, as well as depressive and anxiety disorders. Although categorical diagnoses do not

represent the most important treatment target, diagnostic information would provide germane information about treatment impact. Additionally, future research could compare treatment outcomes (e.g., psychotic symptoms, adversity sequelae, substance use frequency and quantity) of highly integrated treatment (i.e., CBTp + PE+ with more SM interventions) to PE+ as-is and compare both outcomes to a TAU condition (i.e., unmodified PE). This approach could be fruitful in delineating the importance of integrating SM and psychosis-specific interventions within an adversity-focused intervention. Another avenue to explore is the effect of PE+ within participants who have experienced different index events. It would be important to establish whether adversity-focused interventions can successfully treat psychosis-related PTSD; outcomes compared by index events could be integrated into the proposed comparison of treatment protocol groups above. Finally, it will be important to explore whether adversity-focused interventions have differential outcomes (i.e., by gender, race) to better understand who benefits most from treatment, and opportunities for future treatment personalization. Future samples could extend age criteria to include adolescents with EPP to examine whether treatment outcomes seen in adults with EPP would translate to youth samples.

Maintenance mechanisms

As mentioned above, future work is needed to clarify maintenance mechanisms of the EPP-SM-AEs nexus. Study 3 examined experiential avoidance and hopelessness as maintenance mechanisms, however little change was observed. Future work should test these mechanisms in a larger

sample. Other posited mechanisms include an external locus of control, dissociation, negative schemas, and stress sensitivity (Gibson et al., 2016). Negative schemas and hypervigilance linked psychosis to PTSD in a network analysis (Hardy et al., 2021); together, these findings suggest that maintenance mechanisms of PTSD symptoms (e.g., negative world beliefs, hypervigilance) may continue to be relevant in the context of EPP and SM and should be tested directly. However, future work should endeavour to examine maintenance mechanisms such as higher emotional reactivity or stress sensitivity, both of which include a strong physiological component, potentially delineating the role of SM in the EPP-AEs relationship. Heightened emotional reactivity was proposed by McLaughlin and Lambert (2017) as a possible explanatory mechanism for post-AE psychopathology. In summary, maintenance mechanisms remain an important focus for future work.

Conclusions

Standard treatment for psychotic disorders often involves treating psychotic symptoms in isolation; however, this approach misses important contributors to treatment outcomes. My dissertation demonstrated that the overlap of psychotic disorders, substance misuse, and adversity represents an understudied area in the literature with many important gaps. I found elevated rates of SM, AEs, and overlap between both SM and AEs within an early psychosis population, and most of these participants wanted to discuss their AEs with a mental health clinician. When given the opportunity to undergo AE-focused treatment, young adults with EPP appeared to benefit from treatment with

regards to AE sequelae, although treatment generally did not significantly improve psychotic symptoms or substance misuse. Participants identified exposure and coping skills as the most helpful treatment elements.

My dissertation provides some insight into the clinical presentation of EPP with SM and AEs and offers preliminary evidence for the outcomes of adversity-focused treatment in a younger population of people with psychotic disorders. Together, my findings provide some groundwork for future intervention work to build on to clarify treatment mechanisms and improvement of treatment outcomes for vulnerable individuals experiencing not only the onset of a psychotic disorder, but also grappling with the impacts of AEs and the ramifications of substance use.

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Appendix A. supplemental materials for PE+ study

Treatment fidelity

Definition

Treatment fidelity, an umbrella term, refers to the collection of strategies to 'monitor and enhance the reliability and validity of behavioural interventions […] and ensure a research study reliably and validly tests a clinical intervention" . Treatment fidelity is critical when evaluating interventions, especially new interventions – without ensuring the treatment was delivered as intended, effects cannot be attributed to this treatment (Perepletchikova et al., 2007). Previous studies have delineated the various elements that comprise treatment fidelity (Bellg et al., 2004; Perepletchikova et al., 2007) and found the following elements: 1) treatment adherence (i.e., therapist adherence to treatment protocol), 2) therapist competence (i.e., therapist skill level), and 3) treatment differentiation (i.e., critical differences between treatment approaches; Moncher & Prinz, 1991). More recently, intervention scholars have argued that it is insufficient to only measure treatment fidelity in the context of testing a behavioural intervention – researchers must also assess treatment receipt (i.e., how easily a participant can understand information and skills learned in treatment) and treatment enactment (i.e., degree to which participants use information/skills learned in treatment). Treatment receipt is the foundation upon which treatment enactment is built – without an understanding of the information received during treatment, participants cannot apply the information or skills learned (Rixon et al., 2016). This study will examine all five facets of treatment

fidelity and dissemination to ensure that PE+ is a valid and reliably delivered intervention to treat the negative outcomes of adversity amongst individuals with early phase psychosis and substance misuse.

Treatment fidelity plan for PE+ study

Treatment fidelity will be assessed using a multi-pronged approach involving two overarching types of methods: 1) direct assessment, which includes direct review of videotaped therapy sessions, and 2) indirect assessment, which includes questionnaires and adherence checklists (e.g., SRS-3).

Treatment fidelity across stages of treatment

As part of the NIH Behaviour Change Consortium (BCC), Bellg and colleagues (2004) outlined a series of strategies to enhance treatment fidelity in treatment studies. These strategies facilitate the five elements of treatment fidelity: 1) treatment adherence, 2) therapist competence, 3) treatment differentiation, 4) treatment receipt, and 5) treatment enactment. The BCC framework of treatment fidelity will be used to assess treatment fidelity within this study.

Design

Design as it relates to treatment fidelity means ensuring that the study design allows the testing of connections between the variables of interest and the psychological interventions. In this case, it means delineating the theoretical foundation of PE+ (i.e., emotional processing theory), ensuring that the specific interventions (e.g., imaginal exposure, post-exposure processing) are related to this theory, and the design ensures equivalent intervention dose across

participants. Kaderavek and Justice (2010) suggested the use of a standardized treatment study manual to facilitate consistency across providers and provide a model for treatment delivery.

Supplemental Table 5.1.1. PE+ treatment fidelity plan: Design

Goal	Recommended strategies	PE+ implementation
Ensure same treatment dose	• Provide a fixed number of sessions with fixed duration to all participants	• All participants are asked to participate in 15 sessions, a fixed number of sessions, with a fixed duration of 90 minutes each
	• Record deviations of sessions length	• The length of all sessions is reported within the clinical session note
	• Use a scripted treatment manual	• Each session has an outline and scripted sections to increase similarity between therapists
	• Monitor homework completion	• All homework completion is tracked and quantified within the clinical session note template

	• Provide specialized training to providers to deal with different types of patients equally	• PE+ therapists were trained by multiple trainers to ensure skills are present to manage different presentations of adversity sequelae
	• Ensure the theoretical foundation of the treatment is clearly delineated and the interventions are connected to the theory	• PE+ is based on the theoretical foundation of Prolonged Exposure (PE), which uses the framework of Emotional Processing Theory (EPT) – this theory is summarized in the PE+ study manual

Provider Training

Provider training is important when examining treatment fidelity – equivalent training across providers ensures consistency across therapeutic sessions and participants. Furthermore, training ensures therapists possess the necessary skills to competently deliver treatment.

Supplemental Table 5.1.2. PE+ treatment fidelity plan: Provider training

Goal	Recommended strategies	PE+ implementation
Standardize training	• Train providers together and use same instructors for all providers	• All therapists were trained together when learning PE+ -related

		interventions (e.g., imaginal exposures) from Dr. Pencer, a registered psychologist, and how to assess and intervene when participants are displaying dissociative phenomena from Dr. Town, a registered psychologist
	• Use standardized training manuals/materials/provider resources	• The study manual contains standardized session plans, handouts, and resource documents
	• Use structured practice and role-playing	• Therapists engaged in a biweekly clinical skills practice session, which included role-plays to practice specific clinical skills (e.g., post-session processing) and mock

		assessment scoring over the course of 5 months
	• Design training to allow for diverse implementation styles and experience levels of providers	• Providers are all PhD students in Clinical Psychology and training accounted for all levels of experience and study procedures allow for some flexibility in implementation style
Ensure provider skill acquisition	• Score provider adherence according to an a priori checklist	• All sessions were scored immediately after the session by the therapist to establish whether all elements were fully completed, partially completed, or not completed and why. An a priori cut-off score of 80% of each session's total was used to

		determine whether a session was considered acceptably adherent to the session protocol
Minimize "drift" in provider skills	• Conduct weekly supervision	• Group supervision will be offered on a weekly basis to therapists to troubleshoot challenges, review case conceptualization, and
	• Allow providers easy access to project staff for questions about the intervention	• Group supervisor is also co-PI, and PI is one of the therapists, meaning therapists have easy access to both individuals for questions regarding the intervention and study procedures
Accommodate providers differences	• Monitor differential drop-out rates	• Drop-outs will be examined by randomization status (i.e., 2-,3-, or 4-week

		delay) and provider assignment (i.e., to which therapist they are assigned)
	• Use regular debriefing meetings	• Debriefing meetings will be available to therapists when needed

Delivery of Treatment

Supplemental Table 5.1.3. PE+ treatment fidelity plan: Delivery of treatment

Goal	Recommended strategies	PE+ implementation
Control for provider differences	• Assess participants' perceptions of provider warmth and credibility via self-report questionnaire and provide feedback to interventionist and include in analyses	• Therapists were evaluated by their clients following each session using the Session Rating Scale 3 (SRS-3) – this measure examines the therapeutic relationship, sessions goals and topics, approach/method, and provides an overall rating. Therapists did not review this feedback during the study to minimize participant

		bias; however, participants were asked to give their therapists feedback midway through the course of therapy.
	• Conduct a qualitative interview at end of study	• Participants are asked about their perception of their therapist by their assessor following the final treatment session – also asked to discuss their perception of what their therapist did that was helpful vs. unhelpful
Reduce differences within treatment	• Use a scripted intervention protocol and treatment manual	• PE+ manual was always accessible to therapists and all sessions had a clear outline and scripted sections
Ensure adherence to treatment protocol	• Randomly monitor audiotapes for both protocol adherence and nonspecific treatment effects	• Following the completion of all therapy sessions, 10% of videos were randomly selected for adherence review ○ Two (2) independent reviewers, one of whom was Victoria Patterson

(study PI), reviewed a random sample consisting of 10% of the videos (i.e., 30 videos amounting to 45 hours total); several videos from each therapist were reviewed. VP did review her own therapy session tapes, however, if there were rating differences, the second coder's rating was always adopted to minimize bias.

- The two raters reviewed videos against a predetermined checklist of session elements – scores include 'did not include (0)', 'partial inclusion (1)', and 'complete inclusion (2).' Session scores must total

		at least 80% of the total possible score based on the predetermined elements for that session to be considered adherent (e.g., a total score of 16 out of 20 is considered adherent, whereas 14 of 20 is not). o This rating procedure will be supervised by Dr. Pencer, an expert in psychotherapy, psychosis, adversity, and substance misuse.
• After each encounter, have provider complete a behavioural checklist of intervention components delivered	• Adherence checklists were filled out by therapists following each session, which also enabled the reporting of session protocol deviations	

Minimize contamination between conditions	• Use treatment-specific handouts, presentation materials, manuals • Supervise therapists frequently	• All handouts, materials, and the manual were treatment-specific to PE+ • Therapists received weekly supervision

Receipt of Treatment

The ability to understand treatment information and skills represents an important element of treatment fidelity. This element allows participants to effectively utilize information gained and permits an accurate measure of fidelity – participants cannot use information they do not understand. Within this study, measuring treatment receipt means checking for comprehension, tracking homework completion, and using strategies to maximize comprehension (e.g., summarizing).

Supplemental Table 5.1.4. PE+ treatment fidelity plan: Receipt of treatment

Goal	Recommended strategies	PE+ implementation
Ensure participant comprehension/participant	• Have providers review homework or self-monitoring logs	• Therapists reviewed homework tasks

ability to use cognitive skills		near the beginning of each session to solidify learning, correct any misconceptions or misunderstandings, and scaffold content. In addition, homework completion was tracked to help measure adherence as an indirect measurement of comprehension
	• Use scripts that prompt providers to paraphrase/summarize content	• Every session began with a summary of the previous

		session's content, and paraphrasing/summarizing was encouraged throughout treatment to facilitate learning and build rapport
	• Have providers monitor and give feedback on practice sessions	• Participants were taught a series of emotion-focused coping skills throughout the early modules of the treatment, and therapists were instructed to provide feedback on skill utilization to

	maximize effectiveness.

Enactment of Treatment Skills

Enactment scaffolds well onto treatment receipt – participants may understand the information and skills learned, but if they are not used, treatment will minimally affect behaviour and/or outcomes. Tracking the extent of use of treatment skills provides information on treatment enactment.

Supplemental Table 5.1.5. PE+ treatment fidelity plan: Enactment of skills

Goal	Recommended strategies	PE+ implementation
Ensure participant use of cognitive skills	• Use self-report regarding achievement of goals	• The post-therapy feedback questionnaire included items such as "How helpful was this therapy in helping you achieve the goals you set at the beginning of treatment?" and followed a discussion of goal review during the final module of therapy

	• Discuss ongoing use of skills with participants	• Participants discussed their skill use throughout treatment with their therapist and troubleshooted issues throughout to minimize barriers to skill use
Ensure participant use of behavioural skills	• Monitor frequency of sessions	• Session frequency was recorded, as were deviations from the study protocol delineating a schedule of weekly therapy appointments
	• Observe in vivo interactions	• Therapists observed participants' familiarity with treatment skills to establish use
	• Assess with questionnaires	• Participants completed a feedback measure pot-therapy that asked about frequency of use of skills learned/used in treatment