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CLINICAL RESEARCH ARTICLE

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Self-reported PTSD is associated with increased use of MDMA in adolescents with substance use disorders

Lukas Andreas Basedow, Sören Kuitunen-Paul, Melina Felicitas Wiedmann, Veit Roessner and Yulia Golub

Department Of Child And Adolescent Psychiatry, Faculty Of Medicine, Technische Universität Dresden, Dresden, Germany

ABSTRACT

Background: Adolescent patients with a substance use disorder (SUD) often fulfil the criteria for a co-occurring post-traumatic stress disorder (PTSD). However, it is not clear if these dual-diagnosed adolescents present with unique levels of substance use and how their substance use relates to PTSD symptom clusters.

Objective: To investigate substance use in adolescents with co-occurring PTSD and SUD. Additionally, we explored how the use of specific substances is related to specific PTSD symptom clusters.

Method: We recruited n = 121 German adolescent SUD patients, in three groups: no history of traumatic events (TEs) (n = 35), TEs but not PTSD (n = 48), probable PTSD (n = 38). All groups were administered a trauma questionnaire and were asked to report their past-month substance use.

Results: Adolescents with probable PTSD and SUD report a higher frequency of MDMA use than adolescents with no PTSD and no TE (PTSD vs. noTE: U = 510.5, p = .016; PTSD vs. TE: U = 710.0, p = .010). The use of MDMA was more frequent in adolescents with avoidance symptoms (X^2 (1) = 6.0, p = .014). Participants report using substances at a younger age (PTSD vs. noTE: U = 372.0, p = .001; PTSD vs. TE: U = 653.5, p = .022) and PTSD symptom onset was on average 2.2 years earlier than first MDMA use (t (26) = −2.89, p = .008).

Conclusions: Adolescent SUD patients with probable PTSD are more likely to use MDMA than SUD patients without PTSD. The use of MDMA was associated with reported avoidance symptoms. The first age of MDMA use is initiated after PTSD onset. It is unclear whether the association of MDMA use with avoidance symptoms is due to efforts to reduce these symptoms or a result of regular MDMA use.

Auto-reporte de TEPT se asocia con un mayor uso de MDMA en adolescentes con trastornos por uso de sustancias

Antecedentes: Los pacientes adolescentes con un trastorno por uso de sustancias (TUS) a menudo cumplen los criterios para un trastorno de estrés postraumático concurrente (TEPT). Sin embargo, no está claro si estos adolescentes con diagnóstico dual presentan niveles únicos de consumo de sustancias y cómo su consumo de sustancias se relaciona con los conglomerados de síntomas del TEPT.

Objetivo: Investigar el uso de sustancias en adolescentes con concurrencia de TEPT y TUS. Además, exploramos cómo el uso de sustancias específicas se relaciona con grupos específicos de síntomas de TEPT.

Método: Reclutamos un n=121 pacientes adolescentes alemanes con TUS, en tres grupos: sin antecedentes de eventos traumáticos (no ETs) (n=35), ETs pero no TEPT (n=48), probable TEPT (n=38). A todos los grupos se les administró un cuestionario sobre traumas y se les pidió que informaran sobre su consumo de sustancias durante el mes anterior.

Resultados: Los adolescentes con probable TEPT y TUS informan una mayor frecuencia de uso de MDMA que los adolescentes sin TEPT y sin ETs (TEPT versus no ETs: U= 510.5, p= .016; TEPT versus ETs: U= 710.0, p=.010). El uso de MDMA fue más frecuente en adolescentes con síntomas de evitación (X^2 (1) = 6.0, p = .014). Los participantes informan que consumen sustancias a una edad más temprana (TEPT versus no ETs: U= 372.0, p= .001; TEPT frente a TE: U= 653.5, p= .022) y el inicio de los síntomas del TEPT fue en promedio 2.2 años antes del primer uso de MDMA (t (26) = −2.89, p = .008).

Conclusiones: Los pacientes adolescentes con TUS con probable TEPT son más propensos a usar MDMA que los pacientes con TUS sin TEPT. El uso de MDMA se asoció con el reporte de síntomas de evitación. La primera edad de uso de MDMA se inicia después del inicio del TEPT. No está claro si la asociación del uso de MDMA con los síntomas de evitación se debe a los esfuerzos por reducir estos síntomas o al resultado del uso regular de MDMA.

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关键词

不良生活事件; 摇头丸; 吸毒; 并发症; 成瘾; 创伤性应激; 自我给药

HIGHLIGHTS

- We investigated substance use in adolescents with substance use disorders.
- We observed increased MDMA use and a younger age of first substance use in participants with additional PTSD.
- Additionally, MDMA use was associated with the presence of specific PTSD symptoms.

CONTACT Lukas Andreas Basedow Lukas.basedow@ukdd.de Uniklinikum C.G.C. Dresden, Klinik für Kinder- und Jugendpsychiatrie, Fetscherstraße 74, Dresden 01307, Germany

Supplemental data for this article can be accessed here.

物质使用障碍青少年患者中自我报告的PTSD 与 MDMA 的使用增加有关
背景: 患有物质使用障碍 (SUD) 的青少年患者通常符合并发创伤后应激障碍 (PTSD) 的标准。然而, 尚不清楚这些双重诊断的青少年是否表现出独特的物质使用水平以及他们的物质使用与 PTSD 症状簇的关联。
目的: 考查 PTSD 和 SUD 并发青少年的物质使用情况。此外, 我们探索了特定物质使用如何与特定 PTSD症状簇相关。
方法: 我们招募了121 名德国青少年 SUD 患者, 分为三组:无创伤事件史组 (TE) (n = 35)、有TE但无 PTSD组 (n = 48)、可能 PTSD组 (n = 38)。所有组都完成了创伤问卷调查, 并被要求报告他们过去一个月的物质使用情况
结果: 与无 PTSD 和 无TE组 的青少年相比, 可能PTSD 和 SUD组的青少年报告的 MDMA 使用频率更高 (PTSD组 对比 无TE组:U = 510.5, p= .016; PTSD组 与 TE组:U = 710.0, p= . 010)。有回避症状的青少年更频繁地使用摇头丸 (X^2 (1) = 6.0, p= .014)。参与者报告在更小年龄使用物质 (PTSD组 对比 无TE组:U = 372.0, p= .001; PTSD组 对比 TE组:U = 653.5, p= .022) 并且 PTSD 症状的出现平均早于首次使用 MDMA 2.2 年 (t (26) = −2.89, p= .008)
结论: 与无 PTSD 的 SUD 患者相比, 患有可能 PTSD 的青少年 SUD 患者更可能使用 MDMA。使用摇头丸与报告的回避症状有关。首次使用MDMA 年龄是在 PTSD 发作后开始的。目前尚不清楚 MDMA 使用与回避症状的关联是由于努力减少这些症状还是定期使用 MDMA 的结果。

1. Introduction

Approximately one-third of adults who fulfil the criteria for a psychiatric disorder also fulfil diagnostic criteria for at least one co-occurring psychiatric disorder (Forman-Hoffman, Batts, Hedden, Spagnola, & Bose, 2018). Co-occurring psychiatric disorders present a challenge for mental health professionals in inpatient settings, which is reflected by the increased length of stay and medical costs observed in patients with multiple such disorders compared to patients with only one (Jansen, van Schijndel, van Waarde, & Van Busschbach, 2018).

One such pattern of co-occurring disorders is the co-occurrence of post-traumatic stress disorder (PTSD) and substance use disorders (SUDs). This co-occurrence is frequently observed in adolescents (Schulte & Hser, 2014), with 20–54% of adolescent SUD patients fulfiling PTSD criteria (Turner, Muck, Muck, Stephens, & Sukumar, 2004; Williams, Smith, An, & Hall, 2008). On the other hand, 30% of adolescent PTSD patients present with SUD (Essau, Conradt, & Petermann, 1999). The co-occurrence of PTSD and SUD in adolescents is associated with increased SUD severity (Basedow, Kuitunen-Paul, Roessner, & Golub, 2020), and often presents a situation that makes therapeutic care more challenging (Gielen, Havermans, Tekelenburg, & Jansen, 2012; Kuitunen-Paul, Roessner, Basedow, & Golub, 2020; Simmons & Suárez, 2016; Williams et al., 2008), i.e. through PTSD-associated flashbacks serving as a trigger for increased substance use.

While a number of possible explanations exist for this pattern of co-occurrence, three major hypotheses have emerged: i) SUD and PTSD may result from a common risk factor. Previous research has shown that both disorders have similar genetic and environmental factors that increase the chance of their occurrence (Xian et al., 2000). ii) Adolescents who engage in substance use may generally engage in more frequent high-risk behaviours (Baskin-Sommers & Sommers, 2006). This high-risk behavioural pattern may increase the chance of experiencing traumatic events (TEs), such as first-hand violence (Harford, Yi, & Grant, 2013), and subsequently developing PTSD (Glaesmer, Matern, Rief, Kuwert, & Braehler, 2015; Strom et al., 2012). iii) PTSD symptoms appear before a SUD is developed, and patients engage in substance use to cope with the PTSD symptoms, consequently developing a SUD (Dworkin, Wanklyn, Stasiewicz, & Coffey, 2018; Khantzian, 1997; McCauley, Killeen, Gros, Brady, & Back, 2012). This self-medication hypothesis has gained much empirical support (Chilcoat & Breslau, 1998; Sheerin et al., 2016) showing, for example, that one-fifth of PTSD patients use substances in an attempt to relieve PTSD symptoms such as hyperarousal, avoidance or intrusions (Leeies, Pagura, Sareen, & Bolton, 2010). Per definition, the self-medication hypothesis includes assumptions about the age of onset of PTSD and SUD namely, that SUD symptoms should develop following the PTSD symptoms. This pattern has been investigated and confirmed in previous studies, which showed that anxiety disorders (Slade, McEvoy, Chapman, Grove, & Teesson, 2015), conduct disorders (Guldager, Linneberg, & Hesse, 2012), and PTSD (Wu et al., 2010) predate future SUDs.

Even though the severity of adolescent SUD has been associated with a co-occurring PTSD (Basedow et al., 2020; Donbaek, Elklit, & Pedersen, 2014), little is known with regard to use of specific substances and PTSD symptomatology in adolescents. Based on the self-medication hypothesis, the specific subjective effects of different substances might be perceived as relieving symptoms, symptom neutral or leading to stronger symptoms. Accordingly, adolescents with SUD and PTSD might use different substances to achieve a subjective relief from different PTSD symptom clusters (SCs). Thus, a patient who experiences

strong hyperarousal symptoms might show a preference for substances with a relaxing effect, e.g. benzodiazepines, while a patient with avoidance symptoms might prefer stimulating substances, e.g. amphetamine. Previous studies in adults investigating how the use of psychoactive substances relates to the presence of specific PTSD symptoms reported conflicting results (Avant, Davis, & Cranston, 2011; Dworkin et al., 2018; Khoury, Tang, Bradley, Cubells, & Ressler, 2010; Tull, Gratz, Aklin, & Lejuez, 2010). For instance, the presence of avoidance symptoms has been associated with alcohol, benzodiazepine, cocaine, and cannabis use (Avant et al., 2011; Dworkin et al., 2018; Khoury et al., 2010; Tull et al., 2010). The question of specific substance use in a relation to distinct PTSD symptoms is particularly important for the development of targeted therapeutic interventions. However, no research so far could clarify these symptom-substance connections (Van Den Brink, 2015). Additionally, substance use and subsequent SUDs should have a later onset compared to the disorder that is medicated (Khantzian, 1997). This pattern has been shown previously for adult patients (Berenz et al., 2017), but not for adolescents. Furthermore, it is unclear if TEs alone might already predispose adolescents to increased substance use and SUD severity. While an association of TEs with SUD has been repeatedly suggested (Hari, 2005; Maté, 2008, 2012), previous research from our group has found similar levels of SUD severity between adolescents with TEs but not PTSD and adolescents without TEs (Basedow et al., 2020). It remains to be explored if similar differences are present concerning substance use.

We conducted this cross-sectional, exploratory study with two aims The primary goal was to investigate differences in frequency of substance use between subgroups of adolescent SUD patients (with a history of TEs and PTSD, with TEs but without PTSD, with no trauma exposure) and to explore the relationships between substance use frequency and the three PTSD SCs (intrusion, hyperarousal, avoidance). The secondary goal was to explore differences in age of first substance use and if age of first substance use differed from the onset of PTSD symptoms. Although previous research showed differences in SUD severity between those three groups (Basedow et al., 2020), the state of the literature did not support specific hypotheses regarding differences in substance use frequency.

2. Methods

2.1. Participants

Between November 2017 and November 2020, $n = 234$ treatment-seeking adolescents at a German outpatient clinic for adolescent substance abuse consented to participate in the study. From these participants, those who filled out the required questionnaires were selected, resulting in $n = 121$ (42% female) participants. These participants were divided into three groups based on whether they fulfilled PTSD criteria according to self-report ('PTSD'), reported a TE but did not fulfil PTSD criteria ('TE') or did not report any TE ('NoTE'). Detailed demographic information of the study sample can be found in Table 1.

Table 1. Sample description.

	Total	NoTE	TE	PTSD	Group comparison			
					Test statistic	*p*-value	$\alpha_{\text{Bonferroni-Holm}}$	Effect size
N (female)	121 (51)	35 (7)	48 (22)	38 (22)	X^2 (2) = 11.2	.004	.006*	$V = .30$
Mean age in years (SD)	15.9 (1.3)	15.7 (1.4)	15.9 (1.3)	16.2 (1.2)	F (118) = 1.3	.285		
	Number of participants divided by educational level (%) ($n = 35$ missing)				X^2 (10) = 10.3	.036	.008	$V = .21$
ISCED level 24	58 (48)	13 (37)	24 (50)	21 (55)				
ISCED level 25	7 (6)	4 (11)	0	3 (8)				
ISCED level 34	21 (17)	10 (29)	8 (17)	3 (8)				
	Number of participants divided by yearly income of parental household (%) ($n = 55$ missing)				X^2 (10) = 9.3	.507	.025	$V = .20$
Up to 10.000€	8 (7)	4 (11)	3 (6)	1 (3)				
Up to 20.000€	16 (13)	5 (14)	5 (10)	6 (16)				
Up to 30.000€	22 (18)	7 (20)	8 (17)	7 (18)				
Up to 45.000€	8 (6)	1 (3)	4 (8)	3 (8)				
More than 45.000€	12 (10)	8 (23)	2 (4)	2 (5)				
	Number of participants fulfiling criteria for a substance use disorder (%)							
Alcohol	31 (26)	6 (17)	14 (29)	11 (29)	X^2 (2) = 1.9	.395	.017	$V = .13$
Cannabis	49 (40)	12 (34)	23 (48)	14 (37)	X^2 (2) = 1.9	.393	.013	$V = .13$
MDMA	20 (17)	2 (6)	9 (19)	9 (24)	X^2 (2) = 4.5	.103	.010	$V = .20$
Amphetamine	7 (6)	1 (3)	4 (8)	2 (5)	X^2 (2) = 1.1	.565	.05	$V = .10$
Methamphetamine	16 (13)	0	8 (17)	8 (21)	X^2 (2) = 7.9	.020	.007	$V = .23$

*Statistically significant difference; *SD*, standard deviation; MDMA, 3-4,-methylendioxymethamphetamine; noTE, no traumatic experience group; TE, traumatic experience but no PTSD group; PTSD, post-traumatic stress disorder group; ISCED, International Standard Classification of Education; ISCED level 24, lower secondary education – general; ISCED level 25, lower secondary education – vocational; ISCED level 34, upper secondary education – general; differences in proportions (%) were tested via chi-square tests (corrected for multiple testing by Bonferroni-Holm procedure for eight tests) and differences in means were tested via ANOVA.

2.2. Materials

2.2.1. Traumatic events and PTSD

The University of California at Los Angeles Post Traumatic Stress Disorder Reaction Index for DSM-IV (UCLA RI-IV) (Steinberg, Brymer, Decker, & Pynoos, 2004), German version by (Ruf, Schauer, & Elbert, 2011), is a self-report questionnaire that screens for TEs and PTSD symptoms in adolescents. The instrument consists of a Criterion A section, in which patients select the TE that afflicts them the most from a list and indicate the traumatizing features of the event. The next section assesses the frequency of occurrence of PTSD symptoms during the past month (rated from 0 = none of the time to 4 = most of the time) and asks for the first age these symptoms were experienced with regard to the TE. The items map directly onto the DSM-IV intrusion (Criterion B), avoidance (Criterion C), and hyperarousal (Criterion D) SCs. Since the UCLA is a self-report questionnaire and does not include clinical judgment, we considered PTSD as probable and not as established, when all four criteria (Criterion A, B, C, & D) are present (Steinberg et al., 2004). Dependent variables (DVs) for this questionnaire were: age of first PTSD symptoms, probable presence of a PTSD, presence of a TE, and whether the criteria for the intrusion, avoidance, and hyperarousal SCs were fulfilled. In the current sample, internal consistency was good for criterion A and C (α = .82 and .81, respectively), and acceptable for criterion B and D (α = .77 and .76, respectively).

2.2.2. Substance use

The extent of substance use was assessed by clinical psychologists via a self-designed interview, asking specifically for the number of days each substance was used in the past month and at which age they started using the substance. DVs from this assessment were days of past-month tobacco, alcohol, cannabis, methylenedioxymethamphetamine (MDMA), and amphetamine (specifically 'speed', but not methamphetamine, cocaine or other stimulants) use, as well as the age of first tobacco, alcohol, cannabis, MDMA, and amphetamine use.

2.2.3. SUD diagnosis

The Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) (Sheehan et al., 2010) is a diagnostic interview used to evaluate the presence of psychiatric disorders. The interview contains diagnostic questions to assess the presence of 32 psychiatric disorders according to DSM-5 criteria. The DV of interest was the presence of a SUD according to DSM-5 criteria.

2.2.4. Sociodemographic information

The caregivers of our participants answered 36 questions from a self-designed questionnaire assessing socio-demographic data. We analysed the questions indicating age in years, gender, education level of the patient as well as yearly household income ('up to 10.000€', 'up to 20.000€', 'up to 30.000€', 'up to 45.000€', 'more than 45.000€'). Participants' educational levels were assessed according to the International Standard Classification of Education (ISCED) (UNESCO, 2012).

2.2.5. Procedure

Data collection was embedded into the standard diagnostic procedures at our outpatient clinic. During the first appointment, the extent of past-year substance use was assessed, the questionnaires were handed out, and participants as well as legal guardians gave written informed consent to the study. The study was conducted in accordance with the Declaration of Helsinki. All procedures were approved by the Institutional Review Board of the University Hospital C. G. Carus Dresden (EK 66,022,018). Participants were not financially compensated for their contribution.

2.2.6. Statistical analysis

All analyses were conducted with IBM SPSS Statistics for Windows, version 27.0 (IBM, Corp, 2020). Since our continuous DVs (number of days of tobacco, alcohol, cannabis, MDMA, and amphetamine use during previous month, age of first substance use) were all non-normally distributed across groups according the Shapiro–Wilk test (see Supplemental Table S1) we decided to use non-parametric tests for our group comparisons.

For the assessment of differences in socio-demographic characteristics between the three groups, we performed chi-square tests on the proportion of male and female participants, educational achievement, parental income and type of SUD. Age differences were assessed via an analysis of variance.

For our main research question, we conducted chi-square tests to compare the prevalence of each substance across the three groups (noTE, TE, PTSD). Additionally, we performed a Kruskal–Wallis omnibus test to determine if our three groups differed in the five continuous DVs variables. If any of the omnibus comparisons was significant, we performed Mann–Whitney U follow-up tests between all three groups. We used three Mann–Whitney U tests, limited to the TE and PTSD groups, to analyse if the presence of the three SCs (intrusion, avoidance, hyperarousal) was associated with the use frequency of substances whose prevalence differed between the groups.

For the analyses, related to our secondary research question we conducted a Kruskal–Wallis omnibus test and Mann–Whitney U follow-up tests to investigate

group differences in age of substance use onset. Additionally, we performed six paired sample t-tests to compare age of PTSD symptom onset with age of first substance use. The level of significance was set to $\alpha < 0.05$. To correct for Type 1 error through multiple testing we used the Bonferroni-Holm procedure (Holm, 1979) to assess significance of the chi-square tests, the non-parametric tests (Kruskal–Wallis, Mann–Whitney U) and the paired samples t-tests. Wherever we report *p*-values, we report the adjusted Bonferroni-Holm threshold for statistical significance ($\alpha_{\text{Bonferroni-Holm}}$) as well. Effect sizes were classified according to Cohen (1988) into small effects ($|d| \geq .20$, $|\eta^2| \geq .01$, $|V| \geq .10$), medium effects ($|d| \geq .50$, $|\eta^2| \geq .06$, $|V| \geq .30$), and large effects ($|d| \geq .80$, $|\eta^2| \geq .14$, $|V| \geq .50$).

3. Results

3.1. Sample description

The three groups did not differ in the distribution of SUD diagnoses, level of education, or parental income. Between the three groups only the proportion of female participants differed significantly (X^2 (2) = 11.2, $p = .004$, $\alpha_{\text{Bonferroni-Holm}} = .006$). The two gender groups did not differ in their age of first substance use ($U = 1608.50$, $p = .199$, $\alpha_{\text{Bonferroni-Holm}} = .01$) their past-month tobacco ($U = 1554.5$, $p = .101$, $\alpha_{\text{Bonferroni-Holm}} = .008$), alcohol ($U = 1580.00$, $p = .259$, $\alpha_{\text{Bonferroni-Holm}} = .017$), cannabis ($U = 1558.00$ $p = .215$, $\alpha_{\text{Bonferroni-Holm}} = .013$), MDMA ($U = 1656.00$, $p = .285$, $\alpha_{\text{Bonferroni-Holm}} = .025$), or amphetamine ($U = 169.00$, $p = .419$, $\alpha_{\text{Bonferroni-Holm}} = .05$) use. The types of traumas reported by our participants are displayed in Table 2. Most common were traumas related to violence (26%) and sexual abuse (22%).

3.2. Differences in substance use

We analysed differences in tobacco, alcohol, cannabis, MDMA, amphetamine use frequencies. While 13% of our sample fulfilled criteria for a methamphetamine use disorder, only $n = 2$ reported past-month use of methamphetamine, which is why we did not analyse methamphetamine use frequency. Furthermore, since none of our participants reported past-month use of cocaine, opioids, benzodiazepines or solvents we excluded these substances from the analyses as well.

The proportion of participants who had used MDMA in the last month differed between groups (X^2 (2) = 10.60, $p = .005$, $\alpha_{\text{Bonferroni-Holm}} = .010$, $d = .62$) with the probable PTSD group reporting the highest proportion of past-month MDMA users. No difference in the use of other substances could be identified. Furthermore, across all three groups participants differed significantly in terms of the number of days of MDMA use in the last month (H (2) = 9.9, $p = .007$, $\alpha_{\text{Bonferroni-Holm}} = .010$, $\eta^2 = .07$). The PTSD group had a higher past month frequency of MDMA use than the noTE group ($U = 510.5$, $p = .016$, $\alpha_{\text{Bonferroni-Holm}} = .025$, $\eta^2 = .04$) and the TE group ($U = 710.0$, $p = .010$, $\alpha_{\text{Bonferroni-Holm}} = .017$, $\eta^2 = .04$). The TE group did not differ from the noTE group in days of MDMA use in the past month ($U = 839.5$, $p = .992$, $\alpha_{\text{Bonferroni-Holm}} = .050$, $\eta^2 < .01$). Both differences constitute small effects. Mean scores, proportions and complete test results are displayed in Table 3, median scores and interquartile range (IQR) can be found in Supplemental Table S2.

3.3. Relationship between MDMA use and specific PTSD SCs

The past month frequency of MDMA use across the TE and PTSD groups was significantly higher in the group of participants fulfiling the avoidance criterion compared to those that did not ($U = 7.68$, $p = .008$, $\alpha_{\text{Bonferroni-Holm}} = .017$, $\eta^2 = .73$). For the other two SCs (intrusion, hyperarousal), no differences in frequency of MDMA use were detected, see Table 4. See Supplemental Table S3 for median and IQR values.

3.4. Age of onset of PTSD and substance use

Across all three groups participants differed significantly with medium-sized effects in terms of the age of their first substance use (H (2) = 11.3, $p = .003$, $\alpha_{\text{Bonferroni-Holm}} = .008$, $\eta^2 = .08$). The PTSD group had a lower age of first substance use than the noTE group ($U = 372.0$, $p = .001$, $\alpha_{\text{Bonferroni-Holm}} = .025$, $\eta^2 = .14$) and the TE group ($U = 653.5$, $p = .022$, $\alpha_{\text{Bonferroni-Holm}} = .017$, $\eta^2 = .06$), with the effect being

Table 2. Trauma types reported by participants in the TE and PTSD groups.

Trauma type	Total ($n = 121$)	TE ($n = 48$)	PTSD ($n = 38$)
Natural disaster (%)	11 (9)	10 (21)	1 (3)
Accident (%)	10 (8)	5 (10)	5 (13)
War (%)	3 (2)	0	3 (8)
Domestic violence vs. patient (%)	21 (17)	8 (17)	13 (34)
Domestic violence vs. others (%)	16 (13)	9 (19)	7 (18)
Non-domestic violence (%)	31 (26)	26 (54)	25 (66)
Sexual abuse (%)	27 (22)	12 (25)	15 (40)
Neglect (%)	16 (13)	5 (10)	11 (29)

TE, traumatic experience but no PTSD group; PTSD, post-traumatic stress disorder group.

Table 3. Mean scores and group comparisons.

	Total (n = 121)	NoTE (n = 35)	TE (n = 48)	PTSD (n = 38)	Group comparisons			
					Test statistic	p-value	$\alpha_{\text{Bonferroni-Holm}}$	Effect size
	Number of participants (%) having used the substance in the past month							
Tobacco	112 (93)	30 (86)	45 (94)	37 (97)	X^2 (2) = 3.8	.153	.013	V = .18
Alcohol	67 (55)	19 (54)	28 (58)	20 (53)	X^2 (2) = 0.3	.860	.05	V = .05
Cannabis	70 (58)	22 (63)	24 (50)	24 (63)	X^2 (2) = 2.0	.366	.025	V = .13
MDMA	19 (16)	3 (9)	4 (8)	12 (32)	X^2 (2) = 10.6	.005	.010*	V = .30
Amphetamine	9 (7)	1 (3)	3 (6)	5 (13)	X^2 (2) = 2.9	.232	.017	V = .15
	Mean number of days of substance use in the past month (SD)							
Tobacco	25.2 (9.7)	24.9 (10.6)	24.5 (9.9)	26.4 (8.8)	H (2) = 1.5	.468	.025	η^2 < .01
Alcohol	3.5 (6.4)	4.8 (8.2)	2.4 (3.9)	3.6 (7.1)	H (2) = 0.2	.890	.050	η^2 = .02
Cannabis	7.0 (9.7)	8.3 (10.6)	5.3 (7.9)	8.0 (1.6)	H (2) = 2.4	.297	.017	η^2 < .01
MDMA	0.33 (1.0)	0.14 (0.6)	0.29 (1.3)	0.54 (1.0)	H (2) = 9.9	.007	.010*	η^2 = .07
Amphetamine	0.49 (2.4)	0.23 (1.4)	0.7 (3.4)	0.47 (1.5)	H (2) = 2.7	.258	.013	η^2 = .01

* Statistically significant difference; *SD*, standard deviation; MDMA, 3-4,-methylendioxymethamphetamine; noTE, no traumatic experience group; TE, traumatic experience but no PTSD group; PTSD, post-traumatic stress disorder group; differences in proportions (%) were tested via chi-square tests and differences in means were tested via the Kruskal-Wallis procedure (both analyses corrected for multiple testing by Bonferroni-Holm procedure for five tests).

Table 4. Mann-Whitney U tests assessing associations between MDMA use and PTSD symptom clusters in TE and PTSD participants.

PTSD symptom cluster		N	Mean number of days of past month MDMA use (SD)	Group comparison			
				Test statistic	p-value	$\alpha_{\text{Bonferroni-Holm}}$	Effect size
Intrusion	present	62	0.38 (0.11)	U = 2.32	.184	.025	η^2 = .59
	not present	24	0.46 (0.35)				
Avoidance	present	43	0.52 (0.14)	U = 7.68	.008	.017*	η^2 = .73
	not present	43	0.28 (0.20)				
Hyperarousal	present	67	0.32 (0.10)	U = 0.13	.896	.050	η^2 = .51
	not present	19	0.68 (0.45)				

* Statistically significant difference; MDMA, 3-4,-methylendioxymethamphetamine; PTSD, post-traumatic stress disorder; differences were tested with Mann-Whitney U tests (corrected for multiple testing by Bonferroni-Holm procedure for three tests).

Table 5. Mean differences and test results for PTSD symptom onset and onset of substance use.

Difference from age of PTSD symptom onset	N	Mean difference in years (SD)	Test statistic	p-value	$\alpha_{\text{Bonferroni-Holm}}$	Effect size
First age of tobacco use	31	.07 (3.79)	t (30) = 0.95	.925	.050	d = .02
First age of alcohol use	32	−0.44 (3.58)	t (31) = −0.69	.494	.025	d = −.12
First age of cannabis use	33	−1.10 (3.72)	t (32) = −1.64	.111	.017	d = −.29
First age of MDMA use	27	−2.19 (3.93)	t (26) = −2.89	.008	.010*	d = −.56
First age of amphetamine use	16	−2.19 (3.25)	t (15) = −2.69	.017	.013	d = −.67

* Statistically significant difference; MDMA, 3-4,-methylendioxymethamphetamine; differences were tested via paired-t tests (corrected for multiple testing by Bonferroni-Holm procedure for five tests).

considered large and moderate, respectively. The TE group did not differ from the noTE group in their age of first substance use (U = 705.0, p = .206, $\alpha_{\text{Bonferroni-Holm}}$ = .050, η^2 = .02). All post hoc comparisons were controlled for multiple testing by applying the Bonferroni-Holm procedure for three tests. The age of PTSD onset was significantly lower than the age of first MDMA use (t (26) = −2.89, p = .008, d = −.56). All other differences were not significant (all p > $\alpha_{\text{Bonferroni-Holm}}$ corrected for five tests). Detailed tests results can be found in Table 5 and visual presentation of results in Supplemental Figure S1.

4. Discussion

In this study, we aimed to investigate if adolescent SUD patients with co-occurring probable PTSD are more likely to use specific substances than adolescent SUD patients without PTSD, and how the use of these substances relates to PTSD symptoms. We found that adolescent SUD patients with probable PTSD start using substances at an earlier age, are more likely to use MDMA, and use it more frequently than adolescents with a SUD and a history of TEs but no PTSD, or adolescents with only a SUD. Additionally, we observed that in adolescent SUD patients with TE history, the use of MDMA is associated specifically with the presence of the avoidance SC. Finally, we report that adolescents with a history of TEs start using MDMA after the first occurrence of PTSD symptoms.

The self-medication hypothesis posits that substance use and subsequent SUDs may be the result of an attempt to self-medicate co-occurring psychiatric disorders (Dworkin et al., 2018; Khantzian, 1997; McCauley et al., 2012). This hypothesis postulates that the preference for a specific substance may be the result of their ability to reduce acute symptomatology (Khantzian, 1997). In terms of co-occurring PTSD, the self-medication hypothesis implies that a co-occurring SUD occurs because the substance of choice has specific PTSD-symptom-relieving effects.

In fact, this pattern has been shown repeatedly in the context of alcohol use and PTSD, suggesting that after encountering TEs a common response is engaging in drinking to cope (Hawn, Cusack, & Amstadter, 2020; Wu et al., 2010).

In the context of the self-medication hypothesis, the increased use of MDMA in adolescents with co-occurring PTSD and SUD is not surprising. Since MDMA use in adolescents has been generally associated with a self-medication motive (Moonzwe, Schensul, & Kostick, 2011), and MDMA- assisted psychotherapy has recently been shown to reduce PTSD symptomatology (Thal & Lommen, 2018), adolescents in our sample with PTSD and SUD may show increased use of MDMA because it decreases their distress induced by the different PTSD SCs. Our results indeed show, that a higher prevalence of MDMA use is specifically related to the presence of the avoidance SC. Symptoms of the avoidance cluster include 'feeling of detachment' or 'restricted range of affect' which might be associated with MDMA use since MDMA has been shown to induce heightened empathy (Carlyle et al., 2019), increased pro-social behaviour (Borissova et al., 2020; Stewart et al., 2014) and is often used in social settings (McElrath & McEvoy, 2002). On the other hand, side effects of MDMA such as increased body temperature (Liechti, 2014) and increased blood pressure (Vizeli & Liechti, 2017) might explain why MDMA use is not associated with hyperarousal, since the increased activation of the sympathetic nervous system might exacerbate negative aspects of hyperarousal. Furthermore, acute detrimental effects of MDMA on memory (de Sousa Fernandes Perna et al., 2014; Kuypers & Ramaekers, 2005) could explain why the intrusion SC is not associated with its use: if memory is impaired, intrusive memories might also be suppressed. In light of the unique effects of MDMA it seems plausible that it is used by adolescents with a PTSD to reduce their avoidance-induced distress, and that this self-medication use might continue unchecked and eventually develop into a SUD.

This proposed association between MDMA use and avoidance symptoms might have clinical implications. As demonstrated by our results, a higher level of MDMA use might indicate the presence of other, untreated disorders such as PTSD. However, it is important to note that our results have little bearing on the discussion surrounding MDMA as an adjunct for PTSD therapy (Mitchell et al., 2021). Participants in our study received no psychotherapy and we have no way of assessing if their MDMA use has actually reduced PTSD symptomatology. This last point is especially important since the self-medication hypothesis is not entirely without fault. Lembke (2012) argues that the picture might be more complicated and that psychiatric symptoms not only contribute to substance use, but the reverse might also be possible: the use of psychoactive substances might lead to an increase in psychiatric symptomatology through the occurrence of withdrawal symptoms or adverse pharmacological effects.

Indeed, another explanation for our observed results could be that frequent MDMA use has negative psychopathological consequences that worsen subclinical PTSD symptoms, leading to a fully developed PTSD. This conclusion is supported by evidence showing that MDMA users show increased psychopathology in the Symptom Checklist-90-R compared to poly-substance users without MDMA use (Morgan, McFie, Fleetwood, & Robinson, 2002). Additionally, MDMA use has been associated with psychiatric symptoms such as depression (McGuire, 2000), prodromal psychotic symptoms (Wiedmann, Kuitunen-Paul, Basedow, Roessner, & Golub, n.d.) or depersonalization (McGuire, 2000; Thomasius, Schmolke, & Kraus, 1997) which often go hand in hand with PTSD (Auxéméry, 2018; Brady, Killeen, Brewerton, & Lucerini, 2000). Moreover, regular MDMA use might impair memory (Wunderli et al., 2017), disturb sleep (Schierenbeck, Riemann, Berger, & Hornyak, 2008) or diminish interest and excitement (Parrott, 2015) which could negatively influence the developmental process of PTSD. Finally, illicit MDMA use may further increase the risk of negative consequences, because of contamination with other psychoactive substances. For example, powder or pills sold as MDMA often contain synthetic cathinones (Oliver et al., 2019) with harsher side effects than MDMA (Karch, 2015; Papaseit et al., 2016). Nevertheless, we found that adolescents use MDMA on average two years after the first onset of PTSD symptoms, which is in line with research showing that adolescent MDMA use occurs later than mental health symptoms (Falck, Carlson, Wang, & Siegal, 2006). This pattern of symptoms first – use later, can be considered further support for the self-medication hypothesis, suggesting that adolescent PTSD patients discover MDMA in their adolescence, and start using more frequently and subsequently develop a SUD in an effort to reduce their symptoms. Additionally, our findings of an earlier age of first substance use in patients with co-occurring SUD and PTSD might indicate an early exploration of self-medication options.

Our results are unusual insofar as previous research has identified other substances to be associated with co-occurring PTSD and SUD and the avoidance SC. Specifically, adult alcohol use has been repeatedly associated with co-occurring PTSD and SUD (Hawn et al., 2020) and the presence of the avoidance cluster (Dworkin et al., 2018). However, this association is the result of comparing the level of symptoms between people who drink alcohol and people who do not. We, on the other hand, might not have found this

association because our sample consisted of adolescents drinking alcohol at elevated levels already. Considering that 55% of our sample had used alcohol in the past month, which is a prevalence rate three times higher than in the general German adolescent population (Orth & Merkel, 2020), our results might actually be in line with previous findings (Dworkin et al., 2018; Hawn et al., 2020). Other studies used similar research designs as Dworkin et al (2018) and concluded that levels of avoidance symptoms are higher in participants with regular use of opioids and benzodiazepines (Avant et al., 2011), as well as cocaine, cannabis, and alcohol (Khoury et al., 2010) compared to users with lower or no use. Apart from the issue expanded upon above, these studies all consisted of adult samples. Since adolescents show different patterns of use (Chen & Kandel, 1995) and use substances in different settings (Measham, Parker, & Aldridge, 1998) than adults they might tend to use different substances for self-medication as well. Additionally, our study included participants who used various substances in the past month, and MDMA emerged as a factor nonetheless, indicating that the MDMA use might be more relevant for patients with PTSD and SUD than other substances used at the same time.

4.1. Limitations

First, this study consists of cross-sectional, retrospective data, which means we cannot investigate how the use of psychoactive substances, especially MDMA, changes during the developmental course of a SUD or PTSD. Second, we based our calculations on past-month use of different substances, which represents only a snapshot of a participant's use history. Third, most of our measures, including our assessment of PTSD diagnosis, are based on self-report which might lead to social desirability or recall bias (Althubaiti, 2016), which could lead to an underreporting of substance use and the true proportion of substance use in this population to be larger. Additionally, this procedure might overestimate the proportion of PTSD diagnoses in our sample. Future research would be well advised to include standardized instruments and more long-term measures of use, e.g. the use over the past year, or lifetime exposure. Fourth, in assessing the age of PTSD symptom onset and substance use we could only include few participants, limiting the validity of our results regarding this topic and leading to our study having a low power to detect potential effects. Fifth, our sample consisted of a specific and limited convenience sample only including adolescent, treatment-seeking SUD patients. Therefore, we are not able to make any conclusion about the role MDMA use might play in adolescents with only a PTSD diagnosis. Sixth, because of the need to use non-parametric testing it was not possible to control for socio-demographic confounders during our main analysis. Fortunately, gender differences between the groups were not mirrored in our substance use outcomes. Finally, we conducted a large number of tests increasing our likelihood of reporting false-positive results. As a countermeasure, we only considered results to be statistically significant if they survived a correction with the Bonferroni-Holm procedure.

4.2. Conclusion

This study showed that adolescent SUD patients with co-occurring probable PTSD are more likely to have used MDMA in the past month, and use it in higher frequency, than adolescents with only a SUD, regardless of additional TE. This finding might reflect an attempt to self-medicate, specifically to deal with the SC of avoidance. On the other hand, the greater MDMA use might have facilitated the development of more severe avoidance symptoms. Independent of directionality, these results should be taken into account by clinicians encountering this highly vulnerable patient group. Particular care should be taken to comprehensively assess if substances (like MDMA) are used as a form of self-medication.

Authors' contributions

LAB analysed the data and wrote the manuscript. SKP participated in writing the manuscript, data analysis, and contributed to the discussion. MFW participated in writing the manuscript, and contributed to data interpretation and discussion. VR participated in writing the manuscript and contributed to discussion. YG designed the study, participated in writing the manuscript and contributed to discussion.

Data availability statement

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

Disclosure statement

SKP reports personal fees during the past 36 months from Mabuse Verlag, and a one-time lecture honoraria from a consortium of conference sponsors (Janssen-Cilag, Lilly Germany, Novartis Pharma, Pfizer Pharma). VR has received payment for consulting and writing activities from Lilly, Novartis, and Shire Pharmaceuticals, lecture honoraria from Lilly, Novartis, Shire Pharmaceuticals/Takeda, and Medice Pharma, and support for research from Shire Pharmaceuticals/Takeda and Novartis. He has carried out or is currently carrying out clinical trials in cooperation with the Novartis, Shire Pharmaceuticals/Takeda, Servier and Otsuka companies. The remaining authors declare that the research was conducted in the

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ORCID

Lukas Andreas Basedow http://orcid.org/0000-0003-4866-8686
Sören Kuitunen-Paul http://orcid.org/0000-0001-8224-6490
Melina Felicitas Wiedmann http://orcid.org/0000-0001-7250-4329
Veit Roessner http://orcid.org/0000-0002-1873-7081
Yulia Golub http://orcid.org/0000-0002-9191-5884

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