RAP

Review article

Post-traumatic stress and substance misuse; neurobiological and clinical pharmacological correlates

Fabrizio Schifano[1]
Gabriele Duccio Papanti[1]
John Martin Corkery[1]
Laura Orsolini[1,2,3]

[1] Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, Herts, UK
[2] Neomesia Mental Health, Villa Jolanda Hospital, Jesi, Italy
[3] Polyedra, Teramo, Italy

Address for correspondence:
Laura Orsolini
Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit,
School of Life and Medical Sciences,
University of Hertfordshire
Hatfield, AL10 9AB, Herts, UK;
Villa Jolanda Hospital, Neomesia Mental Health,
Jesi, Italy;
Polyedra, Teramo, Italy
Tel.: (+39) 392 3244643
E-mail: laura.orsolini01@gmail.com

Abstract

In post-traumatic stress disorder (PTSD) clients, the use of drugs and alcohol may be used as a self-prescribed treatment to both avoid trauma reminders and cope with the related distress. Conversely, substance misuse 'per sé' might predispose to experience traumatic events. The present study aimed here at presenting an overview of most recent studies covering a range of issues relating to PTSD and substance misuse; namely: substances most frequently ingested by PTSD clients; neurobiological correlates; and treatment/management of these clients. Beyond the alcohol abuse/misuse, drugs most frequently misused are represented by opiates/opioids; sedatives; cannabis; and cocaine. PTSD-related khat misuse issues are here briefly discussed as well. From the neurobiological point of view, issues relating to amygdala and hippocampus dysfunction, with consequent altered levels of fear extinction/memory disruption, have been considered. Furthermore, PTSD may be characterized by imbalance of a range of neurotransmitter pathways, mainly cannabinoid-receptor (CB_1); serotonin; and oxytocin. Although there is currently no effective pharmacotherapy for PTSD, most clients may be regularly prescribed with antidepressants; anxiolytics/sedative-hypnotics; and antipsychotics. Due to the heterogeneity of PTSD phenotype, focusing on the symptoms/signs of the PTSD client would allow for more personalized treatment. Although more research is needed, the development of chemoprophylactic treatments, e.g., intervening pharmacologically after trauma to prevent the occurrence of PTSD seems particularly promising.

KEY WORDS: PTSD, post-traumatic stress disorder, addiction, drug misuse, stress, pharmacotherapy, recreational drugs.

Introduction and epidemiological issues

Post-traumatic stress disorder (PTSD) is a debilitating psychiatric disorder that develops following trauma exposure. It is characterized by four symptom clusters: intrusion, avoidance, negative alteration in cognitions and mood, and alterations in arousal and reactivity (1).

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (2), a PTSD should include the exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways: 1. Directly experiencing the traumatic event(s); 2. Witnessing, in person, the event(s) as it occurred to others; 3. Learning that the traumatic event(s) occurred to a close family member or close friend; 4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (criterion A). Contextually, after the traumatic event(s), a plethora of intrusion symptoms (e.g., intrusive distressing memories; recurrent distressing dreams; dissociative reactions; psychological distress at exposure to internal/external cues; etc.) have been reported (criterion B). Moreover, the subject may experience a persistent avoidance of stimuli associated with the traumatic event(s) (criterion C); negative alter-

ations in cognitions and mood (criterion D); marked alterations in arousal and reactivity (e.g. irritable behaviour; reckless or self-destructive behaviour; hypervigilance; exaggerated startle response, etc.) (Criterion E). The disturbance last more than 1 month and may cause a clinically significant distress or impairment in social, occupational or other significant areas of functioning (criterion F, G).

Although several risk factors have been implicated with the onset of a PTSD, it has been well documented that, once the disorder has established, it is likely a comorbidity with a drug misuse/abuse/dependence. According to cross-sectional studies of drug misusing inpatients, some 94% reported experiencing one or more PTSD criterion; 38.5% met criteria for current PTSD and 51.9% for lifetime PTSD (3). Indeed, the use of drugs and alcohol may be used as a self-prescribed treatment to avoid trauma reminders and to cope with the related distress as well. Conversely, a substance abusing lifestyle might predispose such individuals to experience traumatic events. According to Kline et al. (4) a third hypothesis postulates independent developmental pathways, starting from a shared aetiology, such as the trauma exposure itself.

The present study aimed here at presenting an overview of most recent studies covering a range of issues relating to PTSD and substance misuse; namely: substances most frequently ingested by PTSD clients; neurobiological correlates; and treatment/management of these clients.

Materials and methods

A comprehensive overview was carried out by using the PubMed/Medline database. FS and LO combined the search strategy of free text terms and exploded MESH headings for the topics of Post-traumatic stress and Substance Misuse. Secondary searches were performed using the reference list of included articles and relevant systematic reviews. All articles published without time and/or language restriction were selected. Working independently and in duplicate, two reviewers (FS and LO) read the papers and determined whether they provided data and independently extracted the data on 'substance misuse in post-traumatic stress subjects'. Disagreements were resolved by discussion and consensus with a third member of the team (DP). Data were collected using an *ad-hoc* developed data extraction spreadsheet. To be included in the present overview, studies were required to meet the following criteria: a) empirical and peer-reviewed study; b) at least an abstract with estimates and/or full results published in English; c) investigate subjects with concomitant substance misuse and post-traumatic stress disorder. All papers here retrieved have been systematically collected in sub-categories (e.g., alcohol, opiates/opioids, THC, cocaine and Khat) as following described.

Misusing substances most likely to be identified in PTSD clients

Alcohol

DiMaggio and Galea (5) reviewed and synthesized evidence from 31 population-based studies using Bayesian meta-analysis and meta-regression. Controlling for exposure, type of incident and time since the event occurred, 7.3% [95% credible interval (CrI) 1.1-32.5%] of a population can be expected to report increased alcohol consumption in the first 2 years following a terrorist event. According to DiMaggio and Galea (5), however, there is a 20% probability that the prevalence would be as high as 14%. Seal et al. (6) considered veterans' data in retrospective cross-sectional descriptive and multivariable analyses to determine the prevalence and independent correlates of alcohol (AUD) and drug (SUD) use disorders in 456,502 Iraq and Afghanistan veterans. Of those with AUD, SUD or both diagnoses, 55-75% also received PTSD or depression diagnoses. AUD, SUD or both diagnoses were 3-4.5 times more likely in veterans with PTSD and depression ($p < 0.001$). In confirming this, Kline et al. (4) found that baseline PTSD symptoms significantly increased the risk of screening positive for new onset al.cohol dependence, with the risk for AUD increasing by 9% for every unit increase in combat exposure (AOR=1.09; 95% CI=1.03-1.15. Finally, Calhoun et al. (7) examined the association of combat exposure, PTSD symptoms, binge drinking, in veterans (n=1087) and identified an overall 19% of frequent binge drinkers, with PTSD 'per se' being related to more frequent binge drinking episodes. Two hundred individuals (18-65 years) with chronic PTSD recruited to evaluate alcohol, cannabis and other illegal drugs use, reported a lifetime alcohol use disorder in 34.5% of sample, with current alcohol abuse disorder in 4% (8). Moreover, the Authors examined the role of lifetime alcohol diagnosis on dropout rate, by describing a significant effect (p=.001), with individuals with lifetime diagnoses of both alcohol and drug use being much more likely to drop out of treatment (55.3%) than were other individuals (26.5%; OR=3.42) (8).

Opiates/opioids

Meier et al. (9) aimed at determining prevalence rates of current co-occurring prescription opioid use problems and PTSD symptom severity among 573 new admissions to three addiction treatment units during 2011. Prescription opioid use was significantly associated with co-occurring PTSD symptom severity (OR: 1.42, $p<0.05$). Misuse of prescription opioids in combination with sedatives (OR: 3.81, $p<0.01$) or cocaine (OR: 2.24, $p<0.001$) were associated with PTSD severity.

Furthermore, Cochran et al. (10) carried out a cross-sectional survey in rural/urban community pharmacies with adult non-cancer patients. Some 164 patients completed the survey (87% response rate), re-

vealing positive screens for both prescription opioid misuse risk (14.3%), and PTSD (17.1%). A positive screen for PTSD increased odds (adjusted odds ratio =13.3; 95% CI, 3.48-50.66) for a positive opioid medication misuse risk score. In confirming this, Mackesy et al. (11) found that PTSD is a significant predictor of past year prescription opioid abuse (OR = 21.67 95% CI 2.46-190.75), and dependence (OR = 9.65, 95% CI 1.75-53.32).

THC

Trauma-exposed marijuana users with greater PTSD symptom severity may use delta-9-tetraidrocannabinolo (THC) to cope with negative mood issues, possibly because of a lower perceived capacity to tolerate emotional distress (12). From this point of view, PTSD is an approved condition for accessing medical cannabis in 5 US states at present. Bonn-Miller et al. (13) studied a convenience sample of patients (N=170) at a medical cannabis dispensary in California. Those with high PTSD scores were more likely to use cannabis to improve sleep. Consistent with prior research, this study found increased rates of coping-oriented use of cannabis and greater frequency of cannabis use among medical users with high PTSD scores compared with low PTSD scores.

Cocaine

Cocaine use appears to impact the risk of PTSD symptoms, especially in females. From this point of view, in collecting prevalence data on new admissions (n=573) to three addiction treatment agencies, Saunders et al. (14) found that patients with cocaine use disorders had a two-fold increased odds for a probable PTSD diagnosis, compared to patients without a cocaine use disorder (OR=2.19, 95% CI=1.49-3.22, $p < 0.001$). Furthermore, Vujanovic et al. (15) examined associations between distress tolerance and PTSD symptoms in a cocaine-dependent sample. Participants were comprised of 138 cocaine-dependent adults who endorsed trauma exposure. Results indicated that distress tolerance was significantly, incrementally (negatively) associated with PTSD symptom severity, contributing 6.8% of unique variance to the model ($p<.001$); notably, the overall model explained 44.8% of variance in PTSD symptomatology. A study examining relationships between PTSD symptom clusters and past-year SUD and/or AUD, suggested a strong relationship between cocaine use disorder and the hyperarousal symptom cluster among the subsample of individuals with concomitant AUD. The specific symptoms of irritability or angry outbursts and hypervigilance were significantly most severe in individuals with a cocaine use disorder than those without this disorder (16).

Khat

Increasing reports of cases of khat-related psychosis (17) have led to more familiarity with 'khat syndrome' and consequent concern being expressed about it. In part, this may be attributable to the influx of refugees to the EU/UK from war-torn countries such as Somalia, many of whom are suffering from PTSD and who use khat (18). Indeed, the stressful life situations which many of these individuals had escaped are self- medicated by means of khat (19).

PTSD neurobiological issues

From the neurobiological point of view (Table 1), PTSD can be conceived of as a trauma-induced mental disorder characterised by fear extinction dysfunction, a dysfunction associated with monoamines' turnover disruption (20), hence facilitating co-occurrence of PTSD with depressive/anxiety symptoms. Furthermore, the amygdala has been suggested to be hypersensitive in people with PTSD, with the oxytocin system having been implicated in amygdala reactivity, hence in modified stress responsivity. In this respect, Olff et al. (21) performed a series of functional magnetic resonance imaging (fMRI) studies in police officers with and without PTSD. They found significantly decreased bilateral amygdala reactivity towards emotional faces in PTSD patients compared to traumatized controls. Other studies (22) have found alterations of physiological stress pathways [e.g.

Table 1. Overview of neurobiological issues associated with PTSD occurrence.

- Issues relating to amygdala and hippocampus dysfunction; consequent altered levels of fear extinction/memory disruption
- Role of neuropeptide Y and neuroactive steroids (allopregnanolone; pregnanolone)
- Involvement of the following neurotransmitter pathways:
  - CB-1
  - Mu/delta opioid
  - NMDA
  - NA
  - GABA
  - Serotonin
  - Oxytocin

sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis] soon after trauma in individuals who have subsequently developed PTSD. In confirming the importance of the role of stress, Scioli-Salter et al. (23) focussed on the relationship between chronic pain and PTSD. They emphasized that those circuits that mediate emotional distress and physiological threat, including pain, converge. In particular, the neuropeptide Y and the neuroactive steroids allopregnanolone and pregnanolone (together termed ALLO) present with anti-stress and anti-nociceptive properties. Reduced levels of neuropeptide Y and ALLO have been implicated in the pathophysiology of both chronic pain and PTSD.

The role of the endocannabinoid (eCB) system has been suggested as being involved in PTSD-related processes as well. *Per sé*, PTSD can result from exposure to extreme stress and is characterized by strong, associative memories for the traumatic events experienced. Some Authors proposed as well to better investigate the role of traumatic memories too, in order to investigate the link between objective trauma to subjective ones (for more details, see Yoram Yovel's studies) (24). Furthermore, an elevated physical disease risk has been observed in PTSD, likely to be mediated by inflammatory processes (25). Preclinical studies (26) suggested that during acquisition and recall of aversive learning, eCBs prevent the expression and retention of inappropriate generalized/learned responses. Furthermore, the eCB system has been implicated in the regulation of the stress response and inflammatory processes as well. It has been suggested that modified eCB regulation can be expected in individuals with PTSD, but due to serum fluctuating levels of eCBs, only unconvincing/inconsistent results have typically been identified in the literature. On the other hand, these molecules are being accumulated in hair over time and thus may allow for a more reliable assessment. In considering this, Wilker et al. (25) investigated PTSD-associated differences in hair concentrations of endocannabinoids (N-acyl-ethanolamides palmitoylethanolamide [PEA], oleoylethanolamide [OEA] and stearoylethanolamide [SEA]) in 38 rebel war survivors from Northern Uganda suffering from PTSD and N=38 healthy rebel war survivors without current and lifetime PTSD. A significant group difference was observed for OEA, with PTSD patients showing reduced hair concentrations and regression analyses revealing strong negative relationships between all investigated N-acyl-ethanolamides and symptom severity of PTSD. Hence, Wilker et al. (25) concluded that reductions in eCBs' concentration might account for the increased inflammatory state as well as for the failure to extinguish fear memories observed in PTSD.

Following a different research pathway, Sadeh et al. (27) examined alterations in brain morphology and network connectivity associated with response inhibition failures and PTSD severity. They studied 189 trauma-exposed Operation Enduring Freedom/Operation Iraqi Freedom veterans (89% males, ages 19-62) presenting with a range of current PTSD severity. Overall, they identified reduction in cortical thickness in regions involved in flexible decision-making, emotion regulation and response inhibition and suggested that all these may contribute to impulse control deficits in PTSD. Furthermore, they suggested that PTSD occurrence may be facilitated by aberrant coupling between frontal regions and networks involved in selective attention, memory/learning, and response preparation. Along these lines of research, Wahlstrom et al. (28) recently examined the relationship between PTSD symptoms; emotion dysregulation; and physical aggression among incarcerated males with a history of methamphetamine use (N =60). PTSD symptoms ($p < .001$) were predictive of aggression and more specifically, those subjects characterized by larger levels of PTSD symptoms showed greater impulse control difficulties and more frequent aggressive behaviours (28).

Finally, other Authors have emphasized the role of sexual abuse in the pathogenesis of PTSD; Cusack et al. (29) studied 386 subjects with mental illness enrolled in a multisite (N=7) jail diversion project and found that history of sexual abuse was strongly associated with PTSD, which was in turn associated with both heavy drug use and heavy drinking.

Pharmacotherapy of PTSD

Current pharmacological treatment/management approach

From the clinical management point of view, PTSD treatment is often complicated by co-occurring conditions including pain, insomnia, brain injury, and other mental disorders (30). Although there is currently no effective pharmacotherapy for PTSD (29), Harpaz-Rotem et al. (32) explored overall pharmacological treatment of privately-insured PTSD subjects in the USA and found that some 60% of them received any psychotropic medication, mostly (74.3%) antidepressants; 73.7% anxiolytics/sedative-hypnotics; and 21.3% antipsychotics. Similarly, Mohamed et al. (33) considered records of psychotropics administered to VA patients diagnosed with PTSD (N=274,297) in 2004. Most veterans (89%) were prescribed antidepressants, 61% anxiolytics/sedative-hypnotics, and 34% antipsychotics (Table 2). Overall use seemed to be tailored to treatment of specific symptoms (e.g., insomnia, anxiety, nightmares, and flashbacks) rather than the PTSD itself.

Regarding antidepressants, multisite randomized clinical trials have noted some levels of efficacy of selective serotonin reuptake inhibitors (SSRIs), particularly sertraline (36) and escitalopram (37), and serotonin-norepinephrine reuptake inhibitors (SNRIs), particularly venlafaxine, for PTSD treatment (32-35). However, only 59% of those diagnosed with PTSD may respond to SSRIs (38).

Conversely, although most related clinical guidelines warn against routine benzodiazepine use, Hawkins et

al. (39) retrospectively studied 64,872 patients with a PTSD diagnosis during 2003-2010. Over time, long-term use in men and women increased from 15.4 to 16.4% and 18.0 to 22.7%, respectively. Comorbid psychiatric and alcohol use disorders were associated with a greater increase in long-term use of benzodiazepines. Among those prescribed benzodiazepines long-term, 47% were also prescribed opioids on a long-term basis. In confirming this, Bernardy et al. (30) aimed at assessing polysedative prescribing among veterans with PTSD over an 8-year period. In doing so, they accessed data from the National Department of Veterans Affairs (VA) and determined prescribing of benzodiazepines, hypnotics, atypical antipsychotics, opioids, and muscle relaxants. They found that in 2004 9.8% of veterans with PTSD concurrently received medications from three or more sedative classes and, by 2011, the prevalence of concurrent use involving three or more classes increased to 12.1%. Higher rates of prescribing were identified among women, rural residents, and younger adults. The most common combination was an opioid plus a benzodiazepine, taken concurrently by 15.9% of veterans with PTSD.

The concurrent use of opioids and benzodiazepines may be better understood if the relationship between chronic pain and PTSD is being considered. Indeed, specific circuits/neurobiological mediators/modulators that mediate emotional distress/PTSD and physiological threat, including pain, converge (24). From this point of view, Seal et al. (40) Article compared buprenorphine to other opioid medications in a retrospective cohort of 382 Iraq/Afghanistan veterans with PTSD, chronic pain, and substance use disorders. Twice as many veterans in the buprenorphine group (23.7%) compared to those in the opioid therapy group (11.7%) experienced improvement in PTSD symptoms (P=.001). Compared to veterans in the opioid therapy group, veterans receiving buprenorphine showed significant improvement in PTSD symptoms after 8 months, with increasing improvement up to 24 months (incidence rate ratio=1.79; 95% CI, 1.16–2.77; *P*=.009).

For those clients suffering from PTSD in comorbidity with AUD, topiramate might be a suitable option. Batki et al. (41) carried out a preliminary assessment of the efficacy and safety of this drug in reducing alcohol use and PTSD symptoms in veterans with both disorders in a prospective, placebo-controlled, pilot trial of flexible-dose topiramate in 30 veterans. Between-group analyses showed that topiramate reduced frequency of alcohol use and alcohol craving significantly more than placebo and tended to reduce drinking levels. Furthermore, drug treatment was also associated with decreased PTSD symptom severity and tended to reduce hyperarousal symptoms compared with placebo.

Clinical/management pharmacological options under investigation

According to Ragen et al. (31), the PTSD heterogeneity provides a challenge for discovering effective treatments for this disorder. There are several brain systems which may be considered for drug discovery purposes. In particular, drugs such as nabilone; d-cycloserine (42); morphine and norbinaltorphimine/nor-BNI (a highly selective κ-opioid receptor antagonist); 7,8-dihydroxyflavone, neurotrophins BDNF and FGF2; should aim at targeting systems such as cannabinoids (25), glutamate, opioids, and brain-derived neurotrophic factor, respectively (Table 2).

Future, novel, chemoprophylactic approaches, such as intervening pharmacologically after trauma to prevent the occurrence itself of post-traumatic distress, are being considered. Current evidence is suggestive for the pilot use of medications, such as propranolol (38), glucocorticoids, L-DOPA (42), and oxytocin, which may impact on early stress hormone levels and subsequent risk for post-traumatic distress (23).

Overall, to impact on specific aspects of fear extinc-

Table 2. Overview of psychotropic medications available for PTSD treatment.

- SSRIs: some levels of efficacy
- SNRIs: some levels of efficacy
- Benzodiazepines: frequently prescribed; not recommended by guidelines
- Antipsychotics; quetiapine; aripiprazole
- Low potency THC: increasing levels of medical marijuana use in PTSD clients
- Opiates/opioids; high/very high prescription levels in PTSD clients; buprenorphine as a better treatment for chronic pain/PTSD clients
- Topiramate for comorbidity with alcohol misuse
- Propranolol: acute treatment to prevent memory consolidation
- Oxytocin: acute treatment to prevent memory consolidation
- MDMA-assisted psychotherapy
- Ketamine to prevent memory consolidation

tion (e.g., acquisition, consolidation and retrieval), it has been suggested to consider a further range of neurotransmitter systems, including: serotonin, histamine, GABA, neuropeptides (neuropeptides Y and S); remaining targets (L-type-calcium channels, epigenetic modifications); together with their downstream signaling pathways (42).

Furthermore, MDMA-assisted psychotherapy for patients with chronic treatment refractory PTSD (TR-PTSD) is currently under investigation, with initial results showing levels of efficacy for this treatment approach (43).

To directly target trauma memories which may be associated with the PTSD pathogenesis, the use of ketamine, another drug being used recreationally, has been emphasized. Ketamine therapeutic potential has been recently valued for the management of both TR-PTSD (38) and complicated grief, an issue which may well be behind the PTSD complex clinical structure (44).

Finally, the use of transcranial magnetic stimulation (TMS) treatment has been advocated as well for the clinical management of TR-PTSD, especially if AUD, mild traumatic brain injury, and PTSD co-occur (45).

Substance- and alcohol-use disorders and PTSD; impact of addiction treatment* "per sé" *on PTSD outcomes

Coker et al. (46) collected data from 12,270 dually diagnosed veterans who sought treatment between 1993 and 2011; treatment in longer-term programmes, being prescribed psychiatric medication, and planned participation in meetings were all associated with slightly improved outcomes. Reductions in substance use measures were associated with robust improvements in PTSD symptoms and violent behaviour. Similarly, Manhapra et al. (47) assessed at intake and 4 months after discharge (N=22,948) dually diagnosed veterans, and found that attainment of abstinence at 4 months after treatment, irrespective of the substances abused, was strongly associated with improvement in PTSD symptoms, violence, suicidality and medical problems. Saunders et al. (48) evaluated the impact of medication-assisted treatment (MAT) and psychosocial therapies on treatment outcomes for patients with co-occurring opioid use disorders and PTSD, where MAT plus integrated cognitive-behavioural therapy (ICBT) was associated with more significant improvement in substance use. Finally, McGovern et al. (49) carried out, in 172 clients, a randomized controlled trial comparing the effect of ICBT, individual addiction counselling (IAC) and standard care on substance use and PTSD symptoms. Overall, ICBT produced more favourable outcomes on toxicology than IAC or standard care and showed a greater reduction in reported drug use than SC. Furthermore, recently more evidence come from randomized controlled trials in which the Eye Movement Desensitization and Reprocessing (EMDR) technique has been successfully administered to PTSD patients (50, 51), with only one study carried out on a sample of patients with substance use disorder and comorbid PTSD (52).

Conclusions

The body of research discussed here may offer levels of novel understanding relating to the neurobiology and neurochemistry of PTSD and related disorders. Indeed, the high levels of drug and alcohol misuse here reported in chronic PTSD clients are a reason of concern. One could conclude from here that the use of alcohol and/or opiates/opioids seems to be convincingly associated with the "core" of the PTSD symptomatology, e.g. coping with both stress and psychological suffering. Conversely, the increasing levels of medical prescription of marijuana in PTSD clients seem to be an intriguing issue, and issue better understood here whilst considering the importance of the eCB system in modulating stress levels and occurrence of PTSD itself (25, 26).

Overall, the exposure to traumatic life events often results in the occurrence of a plethora of post-traumatic symptoms which may in turns promote maladaptive and/or self-destructive behaviours, including substance misuse (53). However, although the causal mechanism linking trauma, substance misuse and psychological symptoms remains uncertain, psychoactive substances may be used to self-medicate the dysphoric mood, intrusive cognitions and somatic sequelae of trauma (54-56). The risk chain underlying self-medication of trauma symptoms may involve positive feedback loops between stress appraisal, emotion dysregulation, physiological arousal, compulsive behaviour, and palliative coping with substances (57). Prolonged or repeated stress activation subsequent to trauma exposure may lead to a chronic deviation of self-regulatory mechanisms from their normal mode of operation which may lead to heightened stress sensitivity, vulnerability to future stressors. Contextually, psychological stress and negative mood may evoke craving and addiction-related cognitive biases towards drug-related cues which may determine an increased motivation to acquire and consume drugs with is then sustained through negative reinforcement conditioning (58, 59).

Furthermore, due to the limited studies so far published, specifically focussing on the relationship/comorbidity between a PTSD and concurrent substance and/or alcohol use disorder, data here provided are unlikely to be generalized. Moreover, the present (more narrative than systematic) review owns limitations coming from the methodology and the heterogeneity of the studies here retrieved. Further research should be needed in this specific field of research.

In addition, due to the heterogeneity of the PTSD phenotype, focusing on the symptoms/signs of the PTSD client rather than on the PTSD categorical diagnosis "*per sé*" will allow for more personalized treatment, particularly for dissociative subtypes (60).

For example, several studies have supported internalizing and externalizing PTSD subtypes, by suggesting a higher rate of comorbid depression, panic, avoidance and suicidality for those with prominent internalization (e.g., high constraint and low positive emotionality) *vs* higher rates of substance use, aggression, impulsivity, delinquency and hypomania for those with a prominent externalizing subtype e.g., low constraint and high alienation) (61-66). Although more research is needed, particularly promising seemed here both the idea of chemoprophylactic treatments and of those approaches targeting PTSD relapse avoidance and facilitation of spontaneous recovery (67).

Finally, whilst considering the use of MDMA and ketamine one should also carefully considers the principle of "*primum: non nocere"* (e.g. first: do not harm), and takes into account the possible acute/long term effects of ingestion of these molecules (68, 69).

Acknowledgements

This paper was supported in part by grants of the European Commission (Drug Prevention and Information Programme 2014-16; contract no. JUST/2013/DPIP/AG/4823; *EU-MADNESS project*). Further financial support was provided by the EU Commission-targeted call on cross border law enforcement cooperation in the field of drug trafficking - DG Justice/DG Migrations and Home Affairs (JUST/2013/ISEC/DRUGS/AG/6429) *Project EPS/NPS* (Enhancing Police Skills concerning Novel Psychoactive Substances; NPS).

References

1. Lapiz-Bluhm MD, Peterson AL. Neurobehavioral Mechanisms of Traumatic Stress in Post-traumatic Stress Disorder. Curr Top Behav Neurosci. 2014;18:161-190.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Washington, D.C., American Psychiatric Press, 2013.
3. Reynolds M, Mezey G, Chapman M, Wheeler M, Drummond C, Baldacchino A. Co-morbid post-traumatic stress disorder in a substance misusing clinical population. Drug Alcohol Depend. 2005;77:251-258.
4. Kline A, Weiner MD, Ciccone DS, Interian A, St Hill L, Losonczy M. Increased risk of alcohol dependency in a cohort of National Guard troops with PTSD: a longitudinal study. J Psychiatr Res. 2014;50:18-25.
5. DiMaggio C, Galea S, Li G. Substance use and misuse in the aftermath of terrorism. A Bayesian meta-analysis. Addiction. 2009;104:894-904.
6. Seal KH, Cohen G, Waldrop A, Cohen BE, Maguen S, Ren L. Substance use disorders in Iraq and Afghanistan veterans in VA healthcare, 2001-2010: Implications for screening, diagnosis and treatment. Drug Alcohol Depend. 2011;116:93-101.
7. Calhoun PS, Schry AR, Wagner HR, Kimbrel NA, Dennis P, McDonald SD, Beckham JC, Dedert EA, Kudler H, Straits-Troster K. The prevalence of binge drinking and receipt of provider drinking advice among US veterans with military service in Iraq or Afghanistan. Am J Drug Alcohol Abuse. 2015 Aug 19:1-9. [Epub ahead of print]
8. Bedard-Gilligan M, Garcia N, Zoellner LA, Feeny NC. Alcohol, cannabis, and other drug use: Engagement and outcome in PTSD treatment. Psychol Addict Behav. 2018;32 (3):277-288. doi: 10.1037/adb0000355.
9. Meier A, Lambert-Harris C, McGovern MP, Xie H, An M, McLeman B. Co-occurring prescription opioid use problems and posttraumatic stress disorder symptom severity. Am J Drug Alcohol Abuse. 2014;40:304-311.
10. Cochran G, Rubinstein J, Bacci JL, Ylioja T, Tarter R. Screening Community Pharmacy Patients for Risk of Prescription Opioid Misuse. J Addict Med. 2015 Aug 17. [Epub ahead of print]
11. Mackesy-Amiti ME, Donenberg GR, Ouellet LJ. Prescription opioid misuse and mental health among young injection drug users. Am J Drug Alcohol Abuse. 2015;41:100-106.
12. Potter CM, Vujanovic AA, Marshall-Berenz EC, Bernstein A, Bonn-Miller MO. Posttraumatic stress and marijuana use coping motives: the mediating role of distress tolerance. J Anxiety Disord. 2011;25:437-443.
13. Bonn-Miller MO, Babson KA, Vandrey R. Using cannabis to help you sleep: heightened frequency of medical cannabis use among those with PTSD. Drug Alcohol Depend. 2014;136:162-165.
14. Saunders EC, Lambert-Harris C, McGovern MP, Meier A, Xie H. The Prevalence of Posttraumatic Stress Disorder Symptoms among Addiction Treatment Patients with Cocaine Use Disorders. J Psychoactive Drugs. 2015;47:42-50.
15. Vujanovic AA, Rathnayaka N, Amador CD, Schmitz JM. Distress Tolerance: Associations with Posttraumatic Stress Disorder Symptoms Among Trauma-Exposed, Cocaine-Dependent Adults. Behav Modif. 2016;40:120-143.
16. Dworkin ER, Wanklyn S, Stasiewicz PR, Coffey SF. PTSD symptom presentation among people with alcohol and drug use disorders: Comparisons by substance of abuse. Addict Behav. 2018;76:188-194. doi: 10.1016/j.addbeh.2017.08.019.
17. Corkery JM, Schifano F, Oyefeso A, Ghodse AH, Tonia T, Naidoo V, Button J. Review of literature and information on 'khat-related' mortality: a call for recognition of the issue and further research. Ann Ist Sup Sanita. 2011;47:445-464.
18. Bhui S, Abdi A, Abdi M, Pereira S, Dualeh M, Robertson D, Sathyamoorthy G, Ismail H. Traumatic events, migration characteristics and psychiatric symptoms among Somali refugees – preliminary communication. Soc Psychiatry Psychiatr Epidemiol. 2003;38:35-43.
19. Odenwald M, Hinkel H, Schauer E, Neuner F, Schauer M, Elbert TR, Rockstroh B. The consumption of khat and other drugs in Somali combatants: a cross-sectional study. PLoS Med. 2007;4:e341.
20. Lin CC, Tung CS, Liu YP. Escitalopram reversed the traumatic stress-induced depressed and anxiety-like symptoms but not the deficits of fear memory. Psychopharmacology (Berl). 2016 Jan 7.
21. Olff M, Koch SB, Nawijn L, Frijling JL, Van Zuiden M, Veltman DJ. Social support, oxytocin, and PTSD. Eur J Psychotraumatol. 2014;5:26513.
22. Ostrowski SA, Delahanty DL. Prospects for the pharmacological prevention of post-traumatic stress in vulnerable individuals. CNS Drugs. 2014;28:195-203.
23. Scioli-Salter ER, Forman DE, Otis JD, Gregor K, Valovski I, Rasmusson AM. The shared neuroanatomy and neurobiology of comorbid chronic pain and PTSD: therapeutic implications. Clin J Pain. 2015;31:363-374.
24. Yovell Y. From hysteria to posttraumatic stress disorder: Psychoanalysis and the neurobiology of traumatic memo-

ries. Neuro-Psychoanalysis. 2000;2:171-181.
25. Wilker S, Pfeiffer A, Elbert T, Ovuga E, Karabatsiakis A, Krumbholz A, Thieme D, Schelling G, Kolassa IT. Endocannabinoid concentrations in hair are associated with PTSD symptom severity. Psychoneuroendocrinology. 2016;67:198-206.
26. Reich CG, Mohammadi MH, Alger BE. Endocannabinoid modulation of fear responses: learning and state-dependent performance effects. J Psychopharmacol. 2008;22: 769-777.
27. Sadeh N, Spielberg JM, Miller MW, Milberg WP, Salat DH, Amick MM, Fortier CB, McGlinchey RE. Neurobiological indicators of disinhibition in posttraumatic stress disorder. Hum Brain Mapp. 2015;36:3076-3086.
28. Wahlstrom LC, Scott JP, Tuliao AP, DiLillo D, McChargue DE. Posttraumatic stress disorder symptoms, emotion dysregulation, and aggressive behavior among incarcerated methamphetamine users. J Dual Diagn. 2015;11:118-127.
29. Cusack KJ, Herring AH, Steadman HJ. PTSD as a mediator between lifetime sexual abuse and substance use among jail diversion participants. Psychiatr Serv. 2013;64:776-781.
30. Bernardy NC, Lund BC, Alexander B, Friedman MJ. Increased polysedative use in veterans with posttraumatic stress disorder. Pain Med. 2014;15:1083-1090.
31. Ragen BJ, Seidel J, Chollak C, Pietrzak RH, Neumeister A. Investigational drugs under development for the treatment of PTSD. Expert Opin Investig Drugs. 2015;24:659-672.
32. Harpaz-Rotem I, Rosenheck RA, Mohamed S, Desai RA. Pharmacologic treatment of posttraumatic stress disorder among privately insured Americans. Psychiatr Serv. 2008;59:1184-1190.
33. Mohamed S, Rosenheck RA. Pharmacotherapy of PTSD in the U.S. Department of Veterans Affairs: diagnostic-and symptom-guided drug selection. J Clin Psychiatry. 2008;69:959-965.
34. Davidson J, Baldwin D, Stein DJ, Kuper E, Benattia I, Ahmed S, Pedersen R, Musgnung J. Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial. Arch Gen Psychiatry. 2006;63(10):1158-1165.
35. Bernardy NC, Friedman MJ. Psychopharmacological strategies in the management of posttraumatic stress disorder (PTSD): what have we learned? Curr Psychiatry Rep. 2015;17:564.
36. Li W, Ma YB, Yang Q, Li BL, Meng QG, Zhang Y. Effect and safety of sertraline for treat posttraumatic stress disorder: a multicenter randomised controlled study. Int J Psychiatry Clin Pract. 2017;21(2):151-155. doi: 10.1080/13651501. 2017.1291838.
37. Qi W, Gevonden M, Shalev A. Efficacy and Tolerability of High-Dose Escitalopram in Posttraumatic Stress Disorder. J Clin Psychopharmacol. 2017;37(1):89-93. doi: 10.1097/JCP.0000000000000626.
38. Pradhan B, D'Amico JK, Makani R, Parikh T. Nonconventional Interventions for Chronic Post-Traumatic Stress Disorder (PTSD): Ketamine, Repetitive Trans-Cranial Magnetic Stimulation (Rtms) and Alternative Approaches. J Trauma Dissociation. 2015 Jul 10. [Epub ahead of print]
39. Hawkins EJ, Malte CA, Imel ZE, Saxon AJ, Kivlahan DR. Prevalence and trends of benzodiazepine use among Veterans Affairs patients with posttraumatic stress disorder, 2003-2010. Drug Alcohol Depend. 2012;124:154-161.
40. Seal KH, Shira Maguen, Daniel Bertenthal, Steven L Batki, Joan Striebel, Murray B Stein, Erin Madden, Thomas C Neylan. Observational Evidence for Buprenorphine's Impact on Posttraumatic Stress Symptoms in Veterans With Chronic Pain and Opioid Use Disorder. J Clin Psychiatry. 2016;10.4088/JCP.15m09893
41. Batki SL, Pennington DL, Lasher B, Neylan TC, Metzler T, Waldrop A, Delucchi K, Herbst E. Topiramate treatment of alcohol use disorder in veterans with posttraumatic stress disorder: a randomized controlled pilot trial. Alcohol Clin Exp Res. 2014;38:2169-2177.
42. Singewald N, Schmuckermair C, Whittle N, Holmes A, Ressler KJ. Pharmacology of cognitive enhancers for exposure-based therapy of fear, anxiety and trauma-related disorders. Pharmacol Ther. 2015;149:150-190.
43. Meyer JS. 3,4-methylenedioxymethamphetamine (MDMA): current perspectives. Subst Abuse Rehabil. 2013;4: 83-99.
44. Gowda MR, Srinivasa P, Kumbar PS, Ramalingaiah VH, Muthyalappa C, Durgoji S. Rapid Resolution of Grief with IV Infusion of Ketamine: A Unique Phenomenological Experience. Indian J Psychol Med. 2016;38:62-64.
45. Herrold AA, Kletzel SL, Harton BC, Chambers RA, Jordan N, Pape TL. Transcranial magnetic stimulation: potential treatment for co-occurring alcohol, traumatic brain injury and posttraumatic stress disorders. Neural Regen Res. 2014;9:1712-1730.
46. Coker KL, Stefanovics E, Rosenheck R. Correlates of improvement in substance abuse among dually diagnosed veterans with post-traumatic stress disorder in specialized intensive VA treatment. Psychol Trauma. 2016;8:41-48.
47. Manhapra A, Stefanovics E, Rosenheck R. Treatment outcomes for veterans with PTSD and substance use: Impact of specific substances and achievement of abstinence. Drug Alcohol Depend. 2015;156:70-77.
48. Saunders EC, McGovern MP, Lambert-Harris C, Meier A, McLeman B, Xie H. The impact of addiction medications on treatment outcomes for persons with co-occurring PTSD and opioid use disorders. Am J Addict. 2015;24:722-731.
49. McGovern MP, Lambert-Harris C, Xie H, Meier A, McLeman B, Saunders E. A randomized controlled trial of treatments for co-occurring substance use disorders and posttraumatic stress disorder. Addiction. 2015;110:1194-1204.
50. Regel S, Joseph S. Review of post-traumatic stress disorder: the management of PTSD in adults and children in primary and secondary care. Couns Psychother Res. 2007;7:129-130. doi: 10.1080/14733140701346156.
51. Flatten G, Gast U, Hofmann A, Knaevelsrud C, Lampe A, Liebermann P, et al. Posttraumatische Belastungsstörung: S3-Leitlinie und Quellentexte. Stuttgart: Schattauer; 2013.
52. Schäfer I, Chuey-Ferrer L, Hofmann A, Lieberman P, Mainusch G, Lotzin A. Effectiveness of EMDR in patients with substance use disorder and comorbid PTSD: study protocol for a randomized controlled trial. BMC Psychiatry. 2017;17(1):95. doi: 10.1186/s12888-017-1255-9.
53. Jacobsen LK, Southwick SM, Kosten TR. Substance use disorders in patients with posttraumatic stress disorder: A review of the literature. Am J Psychiatry. 2001;158:1184-1190.
54. Khantzian EJ. The self-medication hypothesis of substance use disorders: A reconsideration and recent applications. Harv Rev Psychiatry. 1997;4:231-244.
55. Leeies M, Pagura J, Sareen J, Bolton JM. The use of alcohol and drugs to self-medicate symptoms of posttraumatic stress disorder. Depression and Anxiety. 2010;27:731-736.
56. Robinson J, Sareen J, Cox BJ, Bolton JM. Role of self-medication in the development of comorbid anxiety and substance use disorders: A longitudinal investigation. Arch Gen Psychiatry. 2011;68:800.
57. Garland EL, Boettiger CA, Howard MO. Targeting cognitive-affective risk mechanisms in stress-precipitated alcohol dependence: An integrated, biopsychosocial model of

allostasis, automaticity, and addiction. Medical Hypotheses. 2011;76:745-754.
58. Field M, Powell H. Stress increases attentional bias for alcohol cues in social drinkers who drink to cope. Alcohol and Alcoholism. 2007;42:560-566.
59. Baker TB, Piper ME, McCarthy DE, Majeskie MR, Fiore MC. Addiction motivation reformulated: An affective processing model of negative reinforcement. Psychol Review. 2004;111:33-151.
60. Zoet HA, Wagenmans A, van Minnen A, de Jongh A. Presence of the dissociative subtype of PTSD does not moderate the outcome of intensive trauma-focused treatment for PTSD. Eur J Psychotraumatol. 2018 May 18;9(1):1468707. doi: 10.1080/20008198.2018.1468707.
61. Castillo DT, Joseph JS, Tharp AT, C'de Baca J, Torres-Sena LM, Qualls C, Miller MW. Externalizing and internalizing subtypes of post- traumatic psychopathology and anger expression. J Trauma Stress. 2014;27(1):108-111.
62. Forbes D, Elhai J, Miller M, Creamer M. Internalizing and externalizing classes in posttraumatic stress disorder: a latent class analysis. J Trauma Stress. 2010;23(3):340-349.
63. Miller MW, Greif JL, Smith AA. Multidimensional personality questionnaire profiles of veterans with traumatic combat exposure: externalizing and internalizing subtypes. Psychol Assess. 2003;15(2):205-215.
64. Miller MW, Kaloupek DG, Dillon AL, Keane TM. Externalizing and internalizing subtypes of combat-related PTSD: a replication and extension using the PSY-5 scales. J Abnorm Psychol. 2004;113(4):636-645.
65. Sellbom M, Bagby RM. Identifying PTSD personality subtypes in a workplace trauma sample. J Trauma Stress. 2009;22(5):471-475.
66. Wolf EJ, Miller MW, Harrington KM, Reardon A. Personality-based latent classes of posttraumatic psychopathology: personality disorders and the internalizing/externalizing model. J Abnorm Psychol. 2012;121(1):256-262.
67. Guina J, Baker M, Stinson K, Maust J, Coles J, Broderick P. Should Posttraumatic Stress Be a Disorder or a Specifier? Towards Improved Nosology Within the DSM Categorical Classification System. Curr Psychiatry Rep. 2017;19(10):66. doi: 10.1007/s11920-017-0821-7.
68. Schifano F. A bitter pill? Overview of ecstasy (MDMA; MDA) related fatalities. Psychopharmacol (Berlin). 2004; 173:242-248.
69. Schifano F, Corkery J, Oyefeso A, Tonia T, Ghodse AH. Trapped in the 'K-hole'; overview of deaths associated with ketamine misuse in the UK (1993-2006). J Clin Psychopharmacol. 2008;28:114-116.