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

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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 (CB1); 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-
sub-categories (e.g., alcohol, opiates/opioids, THC, here retrieved have been systematically collected in peer-reviewed study; b) at least an abstract with estimated whether they provided data and independently extracted the data on ‘substance misuse in 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 alcohol 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-tetraidrocannabino (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-medicating 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 |
PTSD and substance misuse

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) focused 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 neuromodulatory systems allopregnanolone and pregnanolone (together termed ALLO) present with anti-stress and anti-noceptive properties. Reduced levels of neuromodulators 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 se, PTSD can result from exposure to extreme stress and is characterized by strong, associative memories for the traumatic events experienced. Some authors have suggested 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-acetyl-ethanolamines palmitoylthanolamid [PEA], oleoylthanolamide [OEA] and stearoylthanolamide [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-acetyl-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. Bakki 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 \( \kappa \)-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).

<table>
<thead>
<tr>
<th>Table 2. Overview of psychotropic medications available for PTSD treatment.</th>
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<tr>
<td>• SSRI s: some levels of efficacy</td>
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<tr>
<td>• SNRI s: some levels of efficacy</td>
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<tr>
<td>• Benzodiazepines: frequently prescribed; not recommended by guidelines</td>
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<tr>
<td>• Antipsychotics; quetiapine; aripiprazole</td>
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<tr>
<td>• Low potency THC: increasing levels of medical marijuana use in PTSD clients</td>
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<tr>
<td>• Opiates/opioids; high/very high prescription levels in PTSD clients; buprenorphine as a better treatment for chronic pain/PTSD clients</td>
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<td>• Topiramate for comorbidity with alcohol misuse</td>
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<td>• Propranolol: acute treatment to prevent memory consolidation</td>
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<td>• Oxytocin: acute treatment to prevent memory consolidation</td>
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<td>• MDMA-assisted psychotherapy</td>
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<td>• Ketamine to prevent memory consolidation</td>
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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-
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 consider 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).

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