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Substance use disorders and violence

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Abstract:

Substance use seems to be associated with increased prevalence levels of violent behaviour in both general population and psychiatric patients, with 'dual diagnosis' clients showing high rates of risky and criminal behaviour and worse therapy compliance. Cases of drug-related aggressiveness mostly involve a number of molecules, e.g. ethanol, stimulants, cannabinoids, opiates, benzodiazepines, synthetic cannabinoids and synthetic cathinones. Consumers of the virtually few hundreds, and up to a few thousands substances currently available may present to the emergency departments without providing information about the substances(s) ingested and it is likely that standard drug tests will show negative results. An appropriate treatment/management plan to cope with the related acute behavioural and psychopathological disturbances is here discussed. Because of the complex behavioural and medical toxicity issues associated with drug intake, raising awareness and education of health care professionals on drugs' health harms, interventions, harm reduction techniques, and referral pathways are here deemed of particular relevance.

Key words: aggression; cannabinoids; dual diagnosis; new psychoactive substances; NPS; psychoactive substances; substance use disorder; violence.

Introduction

The relationship between violence and substance use disorders (SUD) has been largely debated (Coomber et al, 2019), but recent changes in drug scenarios are likely to have complicated the situation (Schifano, 2018). To better understand the relationship between these two constructs, focus will be here first on briefly presenting a few relevant definitions.

Substance Use Disorder

SUD is a medical condition or state where the administration, consumption or other use of at least one substance/drug causes or contributes to some form of distress or impairment that has clinical significance for an individual. Several terms (e.g. drug abuse, drug dependence, drug addiction, and substance abuse) are used for referring to it (WHO, 2018a; APA, 2013). Different classes of substances may be involved, including: alcohol, opiates/opioids, psychedelic phenethylamines, dissociatives (i.e. phencyclidine, ketamine and derivatives); hallucinogens (i.e. cannabis and synthetic cannabinoids), hypnotic/sedatives (e.g. benzodiazepines), solvents/volatile substances and gases, stimulants (e.g. amphetamine-type substances, cocaine, synthetic cathinones, khat), and many others (Papaseit et al, 2014).

Violence; different natures of violence

The World Health Organization (WHO) describes it as "the intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment, or deprivation" (WHO, 2002). The nature of the relationship between substance use and violence can be very varied, with a range dimensions being included: suicide and self-abuse; child abuse; antisocial behaviour; sexual offences; and physical assault/manslaughter.

Suicide and self-abuse: Suicide represents the 18th cause of death, with up to 800,000 deaths per year (WHO, 2002; Nock et al., 2008; WHO, 2016; WHO, 2018b). Risk factors for suicide include previous suicide attempts, mental health problems, but also harmful use of alcohol and drug use (WHO, 2014). Notably, prevalence of risk factors for suicide has shown to be higher in drug users than in general population (Kwon et al., 2013; Pereira Morales et al., 2017). Suicide attempts are six times more frequent in individuals with alcohol or drug abuse than in no-users (Dragisic et al., 2015; Maloney et al., 2007), whilst completed suicide rates are higher in both men and women with substance abuse (respectively 2-3 times and 6.5-9 times higher) than in the general population (Oyefeso et al., 1999; Wilcox et al., 2004; Dragisic et al., 2015).

Self-abuse, including acts such as self-mutilation, self-poisoning and other self-harm practices (WHO, 2002), has been typically associated with history of mental health problems and substance use (McAllister, 2003; Skegg, 2005; McAllister, 2003), with a prevalence peak in women aged 14-17 years (Whitlock, 2010). Several studies have described a strong relationship between substance abuse (Pattinson and Kahan, 1983; Penn et al., 2003; Riala et al., 2009; Hughes et al., 2010; Moller et al., 2013).

Child abuse: Although estimating prevalence of child abuse has several problems (WHO, 2002; Theodore, 1999; Bross, 2000), their real occurrence may be more than 30 times higher than that identified by official reports (Stoltenborgh et al., 2011; Hillis et al., 2016). Indeed, a recent meta-analysis found that risk of child maltreatment increased with drug abuse and dependence severity, with the highest risk having been identified in parents with past-year dependence (Kepple, 2017). Moreover, children of drug abusers could get injured; be infected by HIV; or by other infections (Anda et al., 2010; Hillis et al., 2000). Conversely, adverse childhood experiences have been associated with a range of both psychopathological (Springer et al., 2003; Hillis et al., 2016) and substance abuse disorders in later life (Elwyn and Smith, 2013).

Antisocial behaviour: A relationship between substance use disorder and antisocial personality disorder (ASPD) is widely recognized (Ladd and Petry, 2003; Luk et al., 2016; Goldstein et al., 2007), with up to 14% substance users presenting comorbidity with ASPD (Casadio et al., 2016). These clients may present with high levels of polysubstance use, prevalence of sexual risky behaviour, mental and physical ill-health issues (Ladd and Petry, 2003; Westermeyer and Turas, 2005; Luk et al., 2016), aggression, violence, and serious criminal activity (Brooner et al., 1992; Žarkovic Palijan et al., 2009; Cottler et al., 1995). Interestingly, a recent study found preliminary evidence of a putatively genetic association between ASPD and use of alcohol and cannabis (Tielbeek et al., 2018).

Sexual offences: As with other types of violence, prevalence of sexual offences (WHO, 2002) is hard to estimate. Several surveys, both in US and Europe, found an incidence of rape of about 0.1% in males and 0.3-0.5% in females (Allrogen et al., 2016; U.S. Department of Justice, 2000; Jahromi et al., 2016; WHO, 2012; WHO, 2005;). However, cases notified to authorities can be representing generally the most violent expressions of this spectrum (i.e. rape and deaths related to sexual offences (Kaslow et al., 1998; Lopez-Castroman et al., 2013; Coker et al., 2000; Do et al., 2018; Holmes et al., 1996). Risk factors for being a sexual abuse victim include alcohol/drug use (WHO, 2002; Sutton et al., 2019). Individuals under alcohol or drug effects are perceived easier to force in unwanted sexual acts without using violence (Graham, 1996; Jewkes et al., 2011; WHO, 2012). Indeed, substance-intoxicated states could cause

disinhibition, misjudgement, but also aggressiveness and violent behaviours (WHO, 2002; Liakoni et al., 2018). Among the others, alcohol, cannabis and cocaine have been identified as the substances more associated with sexual violence events (Grisso et al., 1999; Crane et al., 2015; Parrott and Lisco, 2015; Liakoni et al., 2018). At times, assaulters could deliberately intoxicate the victim with alcohol or drugs, such as gamma-hydroxybutyrate (GHB; Corkery et al, 2015), ketamine (Schifano et al, 2008), flunitrazepam or other hypnotics (Giorgetti et al, 2017; Watts and Zimmerman, 2002).

Physical assault/manslaughter: It is largely accepted that substance use can be related in several ways with episodes of outward violence and aggression (Grisso et al., 1999; Room et al., 2005; Liakoni et al., 2018). The correlation between substance use and violent behaviours might be mediated by both a direct pharmacological effect of the index drug, but also by cognitive, social and dispositional factors (e.g. exposure to a dangerous environment or violence, childhood abuse, risk-taking personality traits) (Amore et al., 2008). There might be a tripartite relationship between violence and drug use. The first type is a 'psychopharmacological', dopamine-related (Schifano et al, 2015), violence in which the substance has a direct role in causing the harmful behaviour, either increasing aggressiveness and irritability or altering reality perception as during an induced psychotic episode (Goldstein, 1985; Žarkovic Palijan et al., 2009). The second is an 'economic' violence in which heavily dependent people commit assaults or homicides in order to obtain money for drugs (Golstein, 1985). The last is a 'systemic' violence that involves criminal organisations, drug trafficking, and street gang fights (Corkery et al, 2011; Heffernan et al., 1982; Goldstein, 1985; EMCDDA, 2018), although the proportion of drug-related homicides (DRH) remains unclear (EMCDDA, 2018; Akers 1992; Hohl et al. 2017). In a national report on deaths in England and Wales between March 2017 and March 2018, 44% of homicides were defined as 'drug-related', considering all the above-mentioned possible relationships (ONS, 2019).

Violence, mortality, and substance use; epidemiological issues

In order to characterise and measure the nature of violence associated with substance use, different types of data sources and information are required. However, the availability of these varies over both time and place.

Health and crime data can contribute to understand both non-fatal and fatal outcomes of violence associated with alcohol and substance use.

At a general level, mortality data can give some indication of the nature and extent of violence-related fatalities in a particular region or country, especially those treated as homicide, suicide and war-related deaths. They are capable to provide evidence of changes over time, identify 'at risk' groups, and differences between areas. Typically, such information is

obtained from medical death certificates. However, for more details it is necessary to either turn to special mortality registers (Corkery 2008; Corkery et al, 2014) or promote national confidential inquiries that try to access a variety of sources in order to get a complete picture (HQIP, 2017; HQIP, 2018).

Overall, the association between the occurrence of a violent death instance and a drug misuse intake episode may be direct or indirect. For example, a range of psychoactive substances can induce or trigger changes in mental states, including anxiety, depression, paranoia, psychosis and suicidal ideation (for a review, see Schifano et al, 2015). Indeed, stimulants appear to be particularly and directly implicated in suicides involving violent methods such as hanging and self-injuries (Schifano et al, 2012). Other classes of drugs including alcohol, GHB and natural cannabis are also commonly involved in suicides (Corkery et al., 2015). Conversely, for its effects in reducing inhibitions, impairing judgment and increasing reaction times, alcohol is often but indirectly involved in traffic-related deaths (Oyefeso et al., 2006) and accidental deaths for falling from heights, drowning, exposure to the elements (particularly hypothermia), and electrocution (Schifano et al., 2008; Corkery et al., 2012; Chiappini et al., 2015). Similarly, distorted perceptions of reality, particularly after the use of hallucinogens and dissociatives could indirectly cause death for falling from heights.

Dual diagnosis and violence

The coexistence of a mental illness and one or more substance-related disorders is indicated by the terms 'dual diagnosis' or 'co-occurring disorders' (EMCDDA, 2016; SAMSHA, 2014). Dual diagnosis may complicate the psychopathological clinical status; increase rates of: risky behaviours (e.g. promiscuous sexual behaviours); psychosocial impairment (e.g. unemployment, homelessness) and criminal behaviours; and determine poor outcomes with high drop-out and hospitalisation rates (EMCDDA, 2016). In 2014, 7.9 million adult past-year substance users (39% of the total) have been reported with the co-occurrence of a mental illness in the US (SAMSHA, 2014). In Europe, about 50% of substance users have been indicated as having both a substance use and mental health disorder (EMCDDA, 2016). Furthermore, in a sample of 374 psychiatric patients admitted over a year, almost one-third showed aggressive and violent behaviour in the month before admission; these episodes were associated with male sex, substance abuse, and positive symptoms (Amore et al, 2008).

Among people with a mental disorder, occurrence of SUD has been consistently shown to be a significant risk factor for aggression and violence (Gostin and Record, 2011; Latt et al., 2011; Soyka, 2000; Swanson et al., 1990; Volavka and Swanson, 2010; Zhuo et al., 2014). Moreover, a dual diagnosis condition has been established in 50-80% of forensic cases (Zarkovic Paljian et al., 2009).

Most frequently reported substances abused by psychiatric clients are alcohol, cannabis, stimulants, hallucinogens, sedatives, and opioids (Mueser et al., 1990; Soyka, 2000; Stompe et al., 2018), with most vulnerable categories including homeless men and prisoners (Erkiran et al., 2006; Soyka, 2000).

The coexistence of schizophrenia and SUD has a prevalence ranging from 10% to 70% (Erkiran et al., 2006). In schizophrenia, dual diagnosis, conditions violence seems more strongly related to both positive (e.g. persecutory delusions and bizarre behaviours), and negative symptoms (e.g. avolition-apathy, and social withdrawal; Swanson et al., 2006). Conversely, self-harm/suicide has been associated with presence of command hallucinations (Link and Stueve, 1994; Haddock et al., 2013; Maremmani et al., 2014).

A co-occurring substance abuse condition may increase the risk of violent behaviours and crimes in bipolar disorder as well (Fazel et al., 2010; Alniak, 2016). Risk factors for violence behaviours in this population are: younger age, male gender, low education level, and previous history of physical assault (Alniak, 2016). The presence of a bipolar spectrum diagnosis in heroin-addicted patients appeared to be associated with aggressive behaviours toward others (Maremmani et al., 2014).

Finally, in a sample of incarcerated women diagnosed with antisocial personality disorder, a SUD condition was highly prevalent, i.e.: alcohol dependence, 56.1%; opiate dependence, 48.8%; cocaine dependence, 61.0%; and associated with aggression and criminal behaviours (Lewis, 2011).

Specific substances of abuse and aggression

Cases of drug-related aggressiveness mostly involve a number of molecules, such as ethanol, stimulants, cannabinoids, opiates, benzodiazepines and a range of NPS (Anderson and Bokor, 2012; Ferner, 1996; Moore et al., 2010; Schifano et al., 2015). Conversely, polydrug consumption has been associated with higher number of physical and verbal aggressions compared with single drug abuse (Steele and Peralta, 2017). Overall, however, individuals who engage in substance use are more likely to be involved in several types of deviant behaviours (Osgood et al., 1988)

Substances of abuse intake and related neurobiological issues

The evidence of a relationship between violence and the use of a range of recreational drugs' ingestion has been suggested to be related to their association with increased dopamine levels (Schifano et al., 2015). Dopaminergic hyperactivity in the midbrain-striatum is thought to cause aberrant salience attribution (Miyata, 2019). Indeed, attribution of abnormally heightened salience to daily-life stimuli is considered to underlie the occurrence of persecutory delusions/psychosis and hence at

times facilitate the occurrence of 'defensive aggression'/violent behaviour (Ntounas et al, 2018).

On the other hand, ingestion of serotonergic compounds, including MDMA/ecstasy, have been related to several cases of aggressiveness, by inducing mania, disinhibition, akathisia, or serotonin syndrome, which might unleash violence episodes (Anderson and Bokor, 2012; Rouve et al., 2011; Wolkers et al., 2016). Numerous preclinical and clinical studies have suggested that serotonin (5-hydroxytryptamine or 5-HT) plays a critical role in modulating some dimensions of personality and behaviour (Wolkers et al., 2016), and its increase is involved in the risk of antidepressant-related acting out episodes, including suicides (Gillet et al., 2001). Finally, modulation of 5-HT neurotransmission by gamma-aminobutyric acid (GABA) and glutamate may be of critical significance in both suppression and escalation of aggressive behaviour (Miczek et al., 2015).

Alcohol

A causal link between alcohol and auto-/hetero-aggressive behaviours has recently been suggested, with a statistically significant increase of aggression occurrence at an alcohol level of 0.75 g/kg or higher (Kuypers et al., 2018). Alcohol may contribute to aggression by both decreasing the behavioural inhibitory activity of the frontal lobe region (Anderson and Bokor, 2012), and by dysregulating higher order cognitive capacities, leading to an increase in impulsive behaviours and overreactions (Kuypers et al., 2018). Considering accesses to the emergency departments related to violence, a history of chronic (mostly concurrent abuse of alcohol and cannabis) substance abuse may be identified in up to 1 out of 3 cases (Liakoni et al., 2018). In a recent systematic review about outward violence within the emergency department setting, reports of patient- or visitor-perpetrated violence ranged between 1 and 172 per 10,000 presentations. Alcohol and drug exposure was associated with nearly one in every two violent patient's behaviour (Nikathil et al., 2017). In the context of the emergency departments, not only alcohol intoxication but also alcohol withdrawal may be related with aggressiveness (Morgan, 2015).

Stimulants

Cocaine and amphetamines are often implicated in impulsive and aggressive behaviours, especially if ingested together with alcohol (Kuypers et al., 2018). This is possibly due to increase in self-confidence; assertiveness; impaired judgement and related paranoid ideation; disinhibition; hyperactivity; dysfunction of cognitive capacities of planning, lack of response inhibition; and emotional dysregulation (Kuypers et al., 2018; Gillet et al., 2001). Chronic effects could lead to a proper 'limbic dyscontrol syndrome', which is in turn related to limbic structures' changes in both noradrenalin and serotonin levels (Gillet et al.,

2001). Cocaine intake has been associated with violent behaviours, ranging from minor psychological aggressions to major physical acts, including murder and rape (Miller et al., 1991). In a cross-sectional study including 1,560 Brazilian young adults with lifetime use of crack cocaine, mortality was estimated at 20% and was typically related to drug-related murders and police confrontation (Narvaez et al., 2013).

Amphetamine users appeared to be significantly more agitated, violent and aggressive than patients with other toxicology-related emergency department presentations (Bunting et al., 2007). Amphetamine-type substances, including the 'ecstasy' (i.e. 3,4-methylenedioxymethamphetamine/MDMA)-group molecules, have been associated with aggressive and violent behaviours (Vaughn et al., 2015). Agitation and aggression were the main reported features in 48.2% of 2-(4-Iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25I-NBOMe; a psychedelic phenethylamine) toxicity cases in London nightclubs (Wood et al., 2015).

High dosage, long-term use, of stimulants is typically associated with intense psychotic symptoms, including delusions and hallucinations (Harro, 2015), which can drive either suicidal ideation or hetero-aggressiveness due to both high levels of DA increase but also the user's erroneous perception of danger (Fulde and Forster, 2015). Most troublesome adverse neuropsychiatric effects occur with h. Moreover, the persistent reduction in the serotonergic neurotransmission in abstinent users seems to contribute as well to increased levels of impulsivity and aggressive behaviours (Harro, 2015).

Cannabis

Despite the large body of related research, the strength of the association between marijuana use and aggression is still unclear (Ostrowsky, 2011; Smith et al., 2013). However, aggressiveness and chronic/heavy marijuana consumption may well be associated, due to changes in mood and behaviour during periods of both intoxication (Allsop et al., 2011; Budney and Hughes, 2006; Kouri et al., 1999) and abstinence (Smith et al., 2013). It is a reason of concern that daily use of marijuana during adolescence may determine the occurrence of neural connectivity impairment levels in the precuneus and fimbria of the hippocampus, together with a reduction of connectivity and inappropriate behaviour inhibition activity of the prefrontal cortex and in the subcortical regions (Volkow et al., 2014; Barthelemy et al., 2016). Indeed, early cannabis use has been implicated in criminal behaviour whilst being associated with both paranoid/suspicious ideation (Barthelemy et al., 2016) and maladaptive interpersonal functioning (Martinotti et al., 2017).

High levels of aggressiveness have been related with delta-9-THC high concentration cannabis, known to have potent psychotropic effects due to a strong agonist interaction with cannabinoid CB-1 receptors (Martinotti et al., 2017). Overall, endocannabinoid abnormalities in specific

psychopathological disorders have been reported, with preliminary evidence suggesting that the metabolizing endocannabinoids enzyme fatty acid amide hydrolase genetic polymorphisms are linked to antisocial personality disorder and impulsive/antisocial psychopathic traits (Kolla and Mishra, 2018).

Opioids

Despite opioids being central nervous system depressants, they have been associated with violent behaviours. Indeed, opioid withdrawal can lead to heightened aggression levels due to increased sensitivity to pain, feelings of anxiety and agitation, and sleep disruption. Furthermore, opioids may reduce inhibition and management of acting out behaviour, increasing the risk for violence (Schifano, 2005). Existing evidence suggests a strong link between opiates/opioids' drug use and involvement in crime, especially among individuals with frequent and problematic use of molecules such as: heroin (Hayhurst et al., 2017); new synthetic opioids/fentanyls (Schifano et al., 2019); but also prescribing molecules such as tramadol (El-Hadidy and Helaly, 2015).

Benzodiazepines

Whilst being typically prescribed for the treatment of anxiety, benzodiazepines, even at therapeutic dosages, have been associated with violence, irritability, and agitation (e.g. paradoxical reactions; Tae et al., 2014). These reactions are typically observed in polydrug users (Gillet et al., 2001), but also in the elderly (Reddy et al., 2018); and in individuals with pre-existing brain damage (Anderson and Bokor, 2012). This behavioural disinhibition may increase the risk of auto or hetero-aggression and acting out (Gillet et al., 2001; Saxon et al., 2010; Wallace and Taylor, 2009). Aggressive and hostile behaviours may be observed as well during the acute benzodiazepine withdrawal (Saxon et al., 2010).

New Psychoactive Substances (NPS): synthetic cannabinoids and synthetic cathinones

Although sharing some properties with THC, synthetic cannabinoids exhibit full cannabinoid CB-1 receptor agonist activity, are highly lipophilic and cross the blood-brain-barrier easily (Papanti et al., 2013). Effects could be unpredictable, with symptoms typically resembling cannabis intoxication, and including agitation, anxiety, irritability, hallucinations, cognitive impairment, and psychosis (e.g. 'spiceophrenia'; Papanti et al., 2013; Courts et al., 2016; Kolla and Mishra, 2018). In a sample of students, cannabinoid use was associated with physical outward violence; sexual risky behaviours, and physical fights (Clayton et al., 2017). Among synthetic cannabinoids, most reported compounds include JWH derivatives, XRL-11, ADB-PINACA, AM-2201, MAM-2201, and 5F-PB-22 (Armenian et al., 2017; Tournebize et al., 2015).

Toxicity of synthetic cathinones includes significant sympathomimetic effects similar to amphetamines, related to both a dose-dependent inhibition on the re-uptake of serotonin and dopamine and their affinity for serotonin 5-HT₂ and dopamine D₂ membrane transporters and receptors (Roberts et al., 2017). This stimulation could lead to psychotic episodes, agitation, aggression, and sometimes violent and bizarre behaviours (Capriola, 2013). Mephedrone is one of the most reported cathinones used in UK, and its consumption, alone or in combination with alcohol, could frequently induce these symptoms (Schifano et al, 2011; James et al., 2011). In a forensic setting, the synthetic cathinone 3,4-methylenedioxypyrovalerone (MDPV) was detected in blood and urine samples of 50 individuals involved in violent crimes, including bodily harm, robberies, homicides and acts of resistance. In many cases, subjects showed highly aggressive and violent behaviour with endangerment of self and others and/or psychotic symptoms; the risk for such behaviours rised with plasma concentrations of MDPV above 30 mg/L (Diestelman et al., 2018). Finally, mexedrone, a mephedrone derivative, was found in 11 of 305 patients who presented to an emergency department. All of them presented with agitation and 6 patients required sedation and/or physical restraint (Roberts et al., 2017).

Prevention and treatment issues

Prevention

Social and ecological factors (e.g. parental neglect, authoritarian parental figures, being bullied, antisocial peer culture) represent important risk factors for the emergence of violence, especially in the youngsters (Gilligan and Lee, 2004). Hence, early intervention on the parenting style, in terminating and preventing bullying and a healthy integration of peer, family, school and community bonds, could help to resolve some of these issues (Gillian and Lee, 2004). Also, violent neighbourhoods populated with gangs and drug dealers and easier access to weapons together with underemployment, high levels of transiency and overcrowding or unsafe housing constitute predisposing factors (Timmis, 2019; Gillian and Lee, 2004). Indeed, it has been shown that both neighbourhoods with positive processes (i.e. support, cohesion and involvement) and high-quality parenting (i.e. efficient monitoring, close relationship and warmth) reduce violent behaviour in children (Miller and Tolan, 2019).

There is a clear need for drug misuse prevention and intervention efforts at the population level, highlighting social context influences and promoting greater awareness of the health risks associated with drugs, considering as well daily tobacco and marijuana use (Oser et al, 2018). Prevention strategies should also be implemented in the emergency departments (ED), since individuals with mental disorders and substance misuse history who have been involved in serious violence episodes have visited EDs in the previous six months (Wang et al., 2019). Although prior

violence episodes may go under reported (Fond et al., 2019), appropriate history-taking and effective suicide risk assessment activities should be carried out (Wang et al., 2019). Provided that the severity of the subject's ill-health condition allows for time and space for such interventions, the administration of a range of structured violence risk assessment tools may help the clinician in understanding the likelihood for violent behaviour to occur. These tools include: the Dynamic Appraisal of Situational Aggression (DASA) (Kaunomäki et al., 2017); the Modified Overt Aggression Scale (MOAS) (Amore et al., 2008); and the Clinical Global Impression Scale (CGI-S) (Fond et al., 2019). The use of such tools has facilitated the development of tailored non-pharmacological and non-coercive interventions (Kaunomäki et al., 2017; Ogloff and Daffern, 2006) as practices such as seclusion and restraint have historically been associated to increased risk levels of violence (Khadivi et al., 2004).

Drug-related violence and aggressive behaviour; acute treatment and management issues

Consumers of misusing drugs may present to EDs without providing information about the substances(s) ingested and it is likely that standard drug tests will show negative results (Schifano et al, 2016). Conversely, it is problematic to draft a universally valid treatment/management plan to cope with the behavioural and psychopathological disturbances related to the intake of the virtually few hundreds (Schifano et al, 2015), and up to a few thousands (Schifano et al, 2018) substances currently available. Some clients may simply need reassurance, support, and medical monitoring. When a medication may be needed, given the complex/unknown pharmacology of the substances arguably ingested, benzodiazepines may be the agents of choice (for a thorough review, see Schifano et al, 2016). They may, however, need frequent re-dosing to achieve adequate sedative effect, and this may be a problem whilst in presence of alcohol. Benzodiazepines may be particularly useful for the treatment of the stimulant/synthetic cathinone-related agitation. Targeted treatment suggested includes intramuscular or intranasal midazolam, intramuscular lorazepam, or intravenous diazepam to control aggression and agitation. This approach may be useful as well to stop seizures (Guirguis et al, 2017).

Where patients cannot be controlled with benzodiazepines alone, propofol and/or antipsychotics may be considered, although drugs such as haloperidol, olanzapine, or ziprasidone can lower seizure thresholds, and contribute to dysrhythmias. In general, the use of atypical antipsychotics has shown good efficacy in containing episode of aggression in different cohort and different phases of illness (Mauri et al., 2011; Swanson et al., 2008). Indeed, although under-prescribed (Patchan et al., 2018), clozapine presents with a specific profile against aggression, which may not be linked to its antipsychotic properties (Volavka, 2013). Interestingly, the psychonauts' 'ideal trip terminator' (Valeriani et al,

2015) olanzapine (Kasinathan et al., 2016; Volavka and Citrome, 2011; Volavka, 2013) can be considered as well. Although often used in the acute treatment of aggression (Lindenmayer and Kotsaftis, 2000; Jones et al., 2011), efficacy of mood stabilisers in patients with dual diagnosis is controversial (Maremmani et al., 2010). Notably, in a study focused on prevention of relapse in alcohol-dependent patients, oxcarbazepine showed efficacy in dual diagnosis patients with high level of aggressiveness (Martinotti et al., 2007). Finally, the intake of serotonergic misusing drugs (e.g. phenethylamines, hallucinogens, NBOME compounds, etc.) may be associated with the occurrence of the serotonin syndrome, which is often associated with agitation, to be managed using both benzodiazepines and cyproheptadine (Schifano et al, 2016).

Maintenance therapy should be focused on the treatment of SUD more than on violent behaviour. In fact, medications prescribed in the treatment of opioid use disorder (e.g. buprenorphine and methadone) have been associated with reduction in prevalence of all crime (i.e. violent, nonviolent, and substance-related) categories in SUD individuals (Molero et al., 2018) whilst demonstrating efficacy in preventing both re-offending and re-incarceration (Hedrich et al., 2012; Chang et al., 2016). Moreover, methadone therapy has been related with a significant reduction in suicidal behaviour rates (Molero et al., 2018).

Longer term psychological approach

Staff training, with a focus on counselling and motivational interviewing (MI) is critical, especially for patients with comorbid polysubstance use disorder. MI was originally developed as a technique for motivating substance abusers to change (Miller and Rollnick, 1991). MI/brief intervention techniques have been proposed as well for the treatment of aggressive behaviour in dual diagnosis (McMurrin, 2009; López-Castro et al., 2019), including adolescent (Cunningham et al., 2012; Zatzick et al., 2014), populations albeit conflicting results have been reported (Steinauer et al., 2017).

Discussion and conclusions

The rapidly evolving drug scenario phenomenon represents a challenge for medicine, and especially so for emergency physicians and mental health professionals. Indeed, drug misuse intake is typically associated with the imbalance of a range of neurotransmitter pathways/receptors, and consequently with a significant risk of psychopathological disturbances and related violence occurrence (Schifano et al, 2015). Non adherence to prescribed medications appears linked to violent behaviours (Hedlund et al., 2017), hence patients' education and counselling should be carefully considered by clinicians. The effect of the combined intake of drug, including NPS, products, whether simultaneous or sequential, could be detrimental to individuals' health (Guirguis et al, 2017). In addition,

the limitations of the current detection tools highlight the existing need for efficient on-site screening and detection (Guirguis et al, 2017).

More adequate information and understanding of how and why violent substance-related episodes, including fatalities, do occur and eventual dissemination of timely statistics is here considered of paramount importance. Drug-related violent episodes should be recorded in sufficient detail for them to be identified, collated, and analysed by a central point. This large data set may improve treatment strategies and service provision, but also inform education and prevention strategies.

Vulnerable subjects, including both children/adolescents and psychiatric patients, may be exposed to a large number of pro drug web pages, from which anecdotal levels of knowledge related to both well-known and novel psychotropics are typically provided by the 'e-psychonauts' (e.g. drug fora/blog communities' members). Hence, future approaches should consider the role of web-based preventative strategies in targeting youngsters/vulnerable individuals at risk of approaching the drug market. Future studies should provide better levels of misusing drugs' clinical pharmacological-related knowledge, so that better tailored management/treatment strategies and guidelines can be made available. Finally, because of the complex behavioural and medical toxicity issues, raising awareness and education of health care professionals on drugs' health harms, interventions, harm reduction techniques, and referral pathways are here deemed of particular relevance (Guirguis et al., 2017).

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