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"Purple Drank" (Codeine and Promethazine Cough Syrup): A Systematic Review of a Social Phenomenon with Medical Implications

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ABSTRACT

In the early 1990s, several studies reported the misuse of codeine and promethazine hydrochloride cough syrup. Since then, the combination of this pharmaceutical, together with sprite or alcohol, known on the streets as "purple drank" or "lean", has become a popular drug among rap singers who promote its tranquilizing and euphoric effects through their music and videos. This review examines the "purple drank" phenomenon, taking into consideration its clinical and social implications. The study was conducted using PubMed, Scopus, and Web of Science as search engines, applying several inclusion and exclusion criteria and the string "Purple AND drank", resulting in 138 records. Seven papers that met our criteria were found. The risk of bias assessment, when applicable, was also considered, resulting in a low level of risk. Epidemiological data highlighted a heterogeneous diffusion of the misuse of this mixture, which is not exclusively linked to a specific type of user (African-American teenagers, athletes, and rappers), as previously reported in American newspapers and in the social media. New digital tools should be taken into consideration for further social and medical evaluations of this phenomenon.

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Purple Drank; codeine abuse; promethazine abuse; social subgroups; opioids

Introduction

Purple Drank and social media

Purple Drank (PD), also known as "*Syrup*" or "*Lean*", is not entirely new to the market. It was used in Texas during the 60's and it became the "drug of the poor" during the 90's (Elwood 2001) because it was easily available and not costly. The phenomenon widely expanded in the 90's especially among teenagers, mainly because of the emphasis it was given by American rappers in the lyrics of their songs (Agnich et al. 2013). Above all, this drug became popular among African-Americans in the greater Southern region of the United States. The abuse became even more widespread thanks to a new form of hip-hop music flourishing at that time in Houston called *screw*, created by DJ Screw. Hence, in Texas, the abuse of Purple Drank became a public health problem (Elwood 2001).

Today, there is a high interest in the role that mass media play in relation to dangerous behaviors and drug abuse (Ferrence 2001). Data related to drug use, obtained from social media, were analyzed in order to tackle various issues such as new trends, changes in the use of harmful substances, social behavior and cultural aspects of drug abuse (Kim et al. 2017). Yet, how can mass media influence individual perception of behaviors considered at risk? Gabriel Tarde, a French sociologist, in his book "*Laws of Imitation*" argues that proximity leads to imitation, causing a ripple effect in which "inferiors" imitate "superiors." Subsequently, such imitation can lead to assimilation, in a sort of "conquering epidemic" (Djellal and Gallouj 2014). Albert Bandura, a Canadian-American social-psychologist, drawing on Tarde's theory, conceived the Social Learning Theory, positing that people learn from each other through observation, imitation and modeling (Ferrence 2001). Similarly, receiving substance-related messages from the media can influence the perceptions, attitudes, beliefs and behaviors associated with those substances. From a socio-ecological perspective, it becomes necessary to consider how, nowadays, the entire population lives in a world where the main opportunities for social interaction, and the main stimuli concerning a wide range of behaviors (Huang et al. 2014), are conveyed

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through the mass media, and through social networks.

The *Theory of Triadic Influence*, which takes into account different types of models to explain the development of addiction, divides these ecological influences according to the type and level of influence (Connell et al. 2010). In this respect, since exposure can increase young people's use of substances and normalize the perception of their acceptability (Thompson 2005), it is today associated with the use of illicit drugs among teenagers and young adults (Holody et al. 2016). Also the "normalization theory" fits into the context of those theoretical models that explain the function of desensitization to stimuli that social networks offer in impersonal ways (McEvoy et al. 2014). Nowadays, in fact, the sharing of messages comes not only from traditional sources, but especially from the Internet (Montagne 2011). This phenomenon, and its correlation to substance consumption, has already been reported (Schifano et al. 2003) as potentially stimulating the use of substances in adolescents and young adults (Martinotti et al. 2014, 2015). For example, music videos are now accessed mainly via on-line channels such as YouTube, which dominates the music videos' sharing market in the United Kingdom and is particularly popular among adolescents. In 2014 the site attracted more than 1 billion viewers, about five times more than 2006 (Ofcom 2011).

When categorized by genre, the highest proportion of videos showing dangerous behaviors related to the use of substances regarded pop, hip hop and rap music. The high levels of use of this online video platform reveal how the exposure to these images can have an important effect on young people (Cranwell et al. 2015). Music represented the highest increase in media consumption from 1999 to 2009 and this led to a growing concern for exposure to harmful messages, often acknowledged and perceived as normal by adolescents (aged 13–17) and young adults (aged 18–24). Therefore, listening to a certain type of music can be associated with an increase in risky behaviors for adolescents and young adults, who are the main consumers of musical products (Holody et al. 2016).

The chemistry of Purple Drank

Purple Drank is a recreational drug consisting of cough syrup (based on codeine, promethazine hydrochloride) mixed with a soft drink, usually Sprite or alcohol. The chemical composition (codeine, or 3-methylmorphine) is a phenanthrene alkaloid with three fused benzene rings at its backbone, found in *Papaver somniferum*, with concentrations up to 10% (Frick et al. 2005). While extracted from poppy plants in the past, it is today derived from a semi-synthetic process via methylation of morphine. Since codeine is a pro-drug, with only one-tenth of morphine's strength, it requires metabolic activation by O-demethylation of morphine through cytochrome P450 2D6 (CYP2D6). Codeine-6-glucuronide, deriving from glucuronidation of codeine, represents the main metabolite (80% of the metabolism) (Dinis-Oliveira 2019). Morphine's analgesic activity is mainly associated with this latter metabolite, a strong μ-receptor agonist with a higher affinity than morphine itself (Paul et al. 1989). Considering the activity of the cytochrome P450 2D6, the entire world population could be divided into three groups: poor metabolizers (PM), extensive metabolizers (EM) and ultra-rapid metabolizers (UM) (Cowan, Landman, and Saini 2017). These differ in the ratio of codeine metabolized into morphine: Persons with the PM phenotype convert about 10% of codeine to morphine, while those with EM about 40% of codeine, and those with UM convert about 51%. Furthermore, in PM subjects only about 4% of the morphine derived from codeine is converted into morphine-6-glucuronide, versus 39% in EM subjects and 58% in UM subjects (Kelly et al. 2013). The proportion of UM and PM varies throughout the population, particularly among different ethnic groups (Verhamme et al. 2008). Thereby, clinical response to the same codeine dose differs dramatically, varying from an absence of response in PM persons to an exaggerated response in the UM persons, which could be fatal if untreated, particularly among children. The link between the use of codeine and life-threatening or fatal respiratory depression has been documented extensively in a series of case reports, which, by 2004, have begun to appear regularly in literature (Koren et al. 2006; Lynn et al. 1993; Nishtala, Salahudeen, and Sarah 2016; Yanai 2012). For many of these young persons, the cytochrome *P*-450 2D6 (CYP2D6) genotyping revealed functional duplication of the CYP2D6 allele, resulting in the UM phenotype (Reilly et al. 2015). Along with the risk of death from acute poisoning due to respiratory depression, other common health risks related to a prolonged use of codeine are physical complications (perforated peptic ulcers, hepatotoxicity and gastrointestinal bleeding) and psychiatric sequelae (impulsivity, depression, compulsive behaviors and anxiety) (Wang, He, and Chen 2011; Yanai 2012).

Another key component of Purple Drank is promethazine (PM) ((*RS*)-*N, N*-dimethyl-1-(10 *H*-phenothiazine-10-yl) propan-2-amine hydrochloride), a phenothiazine's derivative. It is a first-generation H1 receptor antagonist, an antihistamine and antiemetic medication that can also have strong sedative effects (Balthazar et al. 2010). Moreover, promethazine has strong anticholinergic properties, since it blocks responses to acetylcholine through the mediation of muscarinic receptors. This explains why an overdose of promethazine could lead to anticholinergic

toxidrome, caused by the competitive antagonism of acetylcholine at the peripheral and central muscarinic receptors, accompanied by a wide range of signs and symptoms (Naicker et al. 2017). At a peripheral level symptoms include: dry mouth, difficulty swallowing, mydriasis with blurred vision and photophobia. Pupils are dilated and not responsive to light, the skin becomes dry and red due to cutaneous vasodilation, and gastrointestinal effects and urinary retention are common. At a cardiovascular level sinus tachycardia is also frequent. Extrasystole and blood pressure could be either low, due to peripheral vasodilation, or elevated because of agitation. Agitation causes heat production that may lead to fever; anhidrosis causes minor heat loss and a dysregulation of the hypothalamic site in controlling the body temperature, a dopamine mediated process (Rinder et al. 1988; Schwartz and Erk 2004). The central anticholinergic syndrome is characterized by agitation, hyperactive delirium, slurred speech, psychosis, visual and/or auditory hallucinations and seizures (Erickson et al. 2005; Martinotti et al. 2018; Verheijden et al. 2016). This clinical situation can be described with a doggerel: "*Blind as a bat, mad as a hatter, red as a beet, hot as Hades, dry as a bone, the bowel and bladder lose their tone, and the heart runs alone*" (Stead et al. 2006).

Treatment for antihistamine overdose is mainly a supportive/symptomatic therapy, consisting of the maintenance of adequate ventilation and cardiovascular function, intravenous fluid infusions and urinary catheterization (Linares et al. 2015). Gastric emptying may be recommended within one hour of ingestion, together with administration of activated charcoal (Krenzelok and Leikin 1996; Walker et al. 2014). Severe agitation or seizure may be controlled through the use of intravenous diazepam or phenytoin and severe hypertension through parenteral sodium nitroprusside (Fluke 1982). In case of severe central anticholinergic effects the treatment of choice is represented by a slow intravenous injection of physostigmine (Naicker et al. 2017), a short-acting anticholinesterase, with the need to make sure not to exceed cholinesterase inhibition because it would lead to cholinergic toxicity (Verheijden et al. 2016). A useful adjunctive treatment option, especially in patients at risk of respiratory depression or cardiac toxicity, is represented by Dexmedetomidine, a selective alpha-2 agonist with sedative, analgesic and anxiolytic properties (Burns et al. 2000; Cantisani et al. 2013; Gee, Lin, and Tobias 2015). Both these social and medical aspects were taken into consideration to evaluate the "Purple Drank" phenomenon, in relation to the growing media coverage and the increased misuse among the younger generation.

This review examines the "purple drank" phenomenon, taking into consideration its clinical and social implications. All data collected have been examined in order to have a broad and updated picture of the phenomenon, acknowledging the profiles of abusers and the perception of the phenomenon on both a health and media level.

Methods

The literature search conducted on April 11, 2019 through PubMed, Scopus and Web of Science, using the string "*Purple AND drank*", produced 138 records. Original articles, open label or double-blind trials, prospective or retrospective observational studies, case series and case reports were included. We decided to include articles written in English and French, in order to expand the range of data extraction. The exclusion criteria were animal studies/in vitro experiments, reviews, meta-analysis and commentaries, articles regarding other substances not explicitly called "Purple drank" (e.g., "codeine syrup", "promethazine", "cough syrup"), or articles that appeared multiple times across the three search engines.

The articles' search was conducted individually by four members of the research team, Andrea Miuli (AM), GS, AL and MC, under the supervision of Professor GM and Professor MdG. The articles written in French were evaluated by AL and LD. The analysis of the eligibility of the articles was then carried out independently by four members and the flow charts, once completed, were finally compared. Any doubts arising about the papers were eventually submitted to the authors. Of the resulting 138 records (Scopus = 10; PubMed = 8; Web of Science = 120), 122 articles were analyzed, after the removal of the duplicates. The non-original articles were 3, and those not written in English/French were 2. From the 117 articles assessed for eligibility, 111 were removed because they were not relevant to the aim of our research. Finally, 6 articles were selected for our qualitative synthesis. One article was then added manually for its relevance to the topic (Figure 1). The Cochrane Risk of Bias tool was used by AM and GS, and reviewed by GM and MdG to assess the risk of bias.

This methodological process was submitted and approved by PROSPERO and identified by the code CRD42019134968 which was assigned by the team that coordinates this international review register.

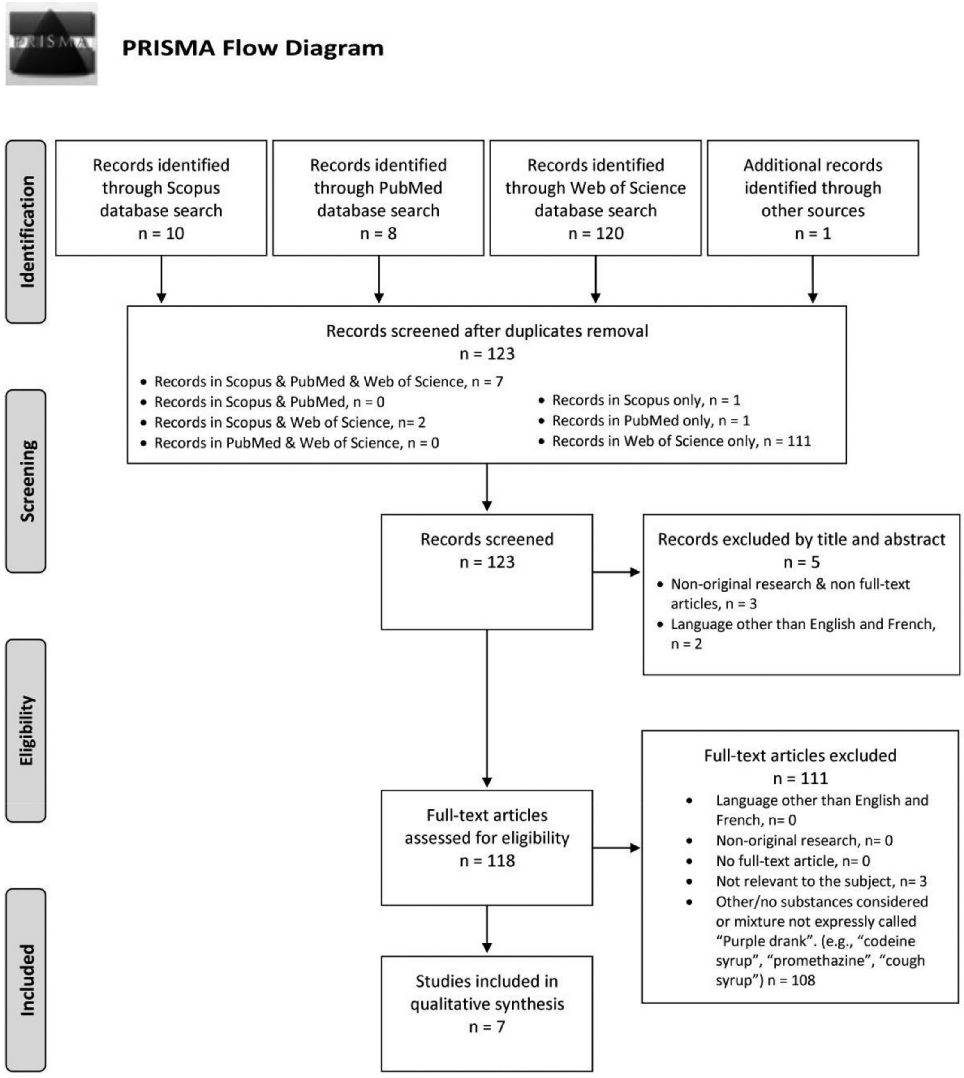

Figure 1. Operative Methods, PRISMA Flow Diagram.

Results

Of the six eligible articles found, five examined the abuse and effects of Purple Drank and other drugs on young adults (Table 1).

Garcin et al. (2016) reported the effects of Purple Drank on three adolescents analyzed in two different cases. In the first, a couple of youngsters were found in an initial state of drowsiness, followed by hallucinations and anticholinergic toxidrome. In the latter is described how the chronic use of this substance leads to addiction due to increasing dosage, up to 1 liter of daily intake of Purple Drank by one adolescent. The woman described in the first case, after consumption of Purple Drank (300 ml of antitussive containing codeine and 30 tablets of promethazine 25 mg) and some cannabis, was brought to the hospital in a state of altered consciousness (Glasgow score 12) and oscillating aggressive episodes, reactive pupils and dry mucous for 6 hours. This state was followed by constant aggressive agitation, acute delusion and visual hallucinations for 36 hours, determining an increase in Creatine Phosphokinase. The other subject (male), after the assumption of the same codeine/promethazine cocktail and massive doses of alcohol and cannabis, presented drowsiness, confusion and visual hallucinations, all of which normalized after a few hours (Garcin et al. 2016).

In addition to Garcin et al. (2016), four articles investigated the Purple Drank phenomenon from epidemiological points of view. Jouanjus and Falcou (2018) administered questionnaires to 19 pharmacists in France in order to detect unusual requests of nonprescription drugs of customers, focusing on the population under 26 years of age. These questionnaires revealed 29 requests for drugs containing codeine, 17 requests for drugs containing promethazine (both components of Purple Drank) while only 3 reports concerned the prescription for dextromethorphan and one the prescription for ketamine. Those requesting these drugs

Table 1. Main findings of included studies.

First author; year of publication	Name of article; original	Mean age (years)	N participants	Substances considered	Aim	Outcome
Agnich L.E. 2013	Purple drank prevalence and characteristics of misurers of codeine cough syrup mixtures.	20.06	2349	Alcohol, tobacco, marijuana, ecstasy or MDMA, novel drugs as purple drank, salvia, synthetic cannabinoids, bath salts, pharmaceutical misuse, heroin, cocaine, inhalants, methamphetamine, hallucinogens.	To determine the prevalence and characteristics of purple drank users among a sample of college students in the southeastern United States.	152 (6,5%) students of the sample reported use of Purple Drank and male (9.3%) were twice than female (3,9%). African-Americans(5,4%), Asian-Americans(5,1%) and White (6,1%) self-reported the lowest use while it was significantly more common among Hispanics (15,6%) and Native Americans (16,7%).
Garcin L. 2016	Purple drank: A dangerous cocktail. [Purple drank: un dangereux cocktail à connaître]	15	2	Purple Drank (codeine, promethazine); alcohol; cannabis.	Describe a double case of intoxication of young users.	Assess acute symptoms and treatment in the emergency department.
Hart M. 2014	"Me and my drank": exploring the relationship between musical preferences and purple drank experimentation.	20.06	2349	Alcohol, tobacco, marijuana, ecstasy or MDMA, novel drugs as purple drank, salvia, synthetic cannabinoids, bath salts, pharmaceutical misuse, heroin, cocaine, inhalants, methamphetamine, hallucinogens.	To examine the relationship between musical preferences and use of purple drank.	Use of purple drank is rare among those that prefer country/western music (2.6%) and jazz/other (2.7%). It was more common among those that listen to rock/alternative (7.2%), and even more prevalent among those who primarily prefer rap/hip-hop (10.2%).
Jouanjus E. 2018	Detecting the diverted use of psychoactive drugs by adolescents and young adults: A pilot study	18–20 years old	41	Codeine-containing drugs; promethazine; ketamine.	Addictovigilance using questionnaires filled out by pharmacists.	Identification of a specific population at risk for addiction; prevention of complications.
Miller B.L. 2015	Marketing a Panic: Media Coverage of Novel Psychoactive Drugs (NPDs) and its Relationship with Legal Changes	NA	25 newspapers published in 13 states with 11 million daily subscribers	Salvia divinorum; synthetic cannabinoids; synthetic cathinones (Bath salts); codeine promethazine hydrochloride cough syrup concoctions (Purple drank)	To explore the representation of Novel Psychoactive Drugs in print media in the USA.	Purple drank use has been more frequently linked to athletes, musicians, and black males; media focused on the most hyperbolic cases of drug use rather than on scientific and empirical evaluations; the stigmatization of already marginalized groups is exacerbated by media sensationalism.
Jagtap P.K. 2018	Development of Novel Dynamic Drop-to-Drop Microextraction Coupled with GC-MS for the Trace Level Screening of Phenothiazine Drug in Human Biological Samples	NA	blood samples of several patients	Promethazine	Determination of Promethazine in biological fluids using a new solvent free microextraction technique	Satisfactory selectivity and sensitivity of the method; applicability to real blood samples of patients using cough syrup or esthetic drinks (purple drank)
Cherian R. 2018	Representations of Codeine Misuse on Instagram: Content Analysis	NA	1156 posts	Purple Drank (Lean, Sizzurp, Texas Tea)	Characterize representations of codeine misuse through analysis of public posts on Instagram	Most related hashtags: promethazine, lean, codeinecrazy, purpledrank, coughsyrup, doublecup; other associated hashtags: weed, cannabis, kush.

were mainly males (85%) aged between 15 to 25, most of which between 18 and 20 years old (Statista 2019). Codeine, dextromethorphan, ethylmorphine and noscapine were listed as prescription drugs in July 2017. By contrast, in Australia, drugs containing codeine and promethazine are still bought without prescription, since pharmacists strongly state that listing these substances as prescription drugs would negatively impact people's management of pain.

A review of U.S. newspaper articles from 2005 to 2013 (Miller et al. 2014) described how the media paid attention to Novel Psychoactive Substances (NPS). They found 715 articles regarding NPS, 7% of which related to Salvia divinorum, 46% to synthetic cannabinoids, 33% to bath salts and 13% to Purple Drank. The attention given by the media to Purple Drank during this period of time was constant, while the articles on other NPS, with the exception of Salvia divinorum, rapidly increased in 2010. Almost all newspapers reported predominantly about synthetic cannabinoids, while the San Jose Mercury News dealt with Purple Drank in 47.5% of its articles. This work also provides a demographic profile of Purple Drank users, often identified in news reports with young black males, athletes or musicians. This "average user" description was not provided for other drugs. Moreover, the attention given to Purple Drank may have reflected current events, as matching peaks in the number of published articles on Purple Drank were registered in early 2013 and in mid 2012, when the American football player JaMarcus Russell was arrested for the possession of codeine syrup and the American rapper Lil' Wayne had seizures, presumably due to Purple Drank abuse. Agnich et al. (2013) and Hart et al. (2014) analyzed variables like race, gender, sexual orientation and musical preferences in a large sample of American university students (N = 2349). Of this sample, one hundred and fifty-two (6.5%) students reported using Purple Drank, with the percentage of males (9.3%) twice that of the females (3.9%). Contrary to Miller et al. (2014), these two papers show that African-Americans (5.4%), Asian-Americans (5.1%) and White-Americans (6.1%) self-reported lower use of Purple Drank, while Hispanics (15.6%) and Native Americans (16.7%) reported higher levels of use. An association between Purple Drank and people living in major urban environments (12.2%) was also found, as well as an association with music preferences, in the specific with hip hop and rap music (10.2%), rock and metal music (7.2%) even if in lower percentages, and LGBT persons. The drug is mentioned in the lyrics of several songs belonging to these music genres, although the articles state that references to the drug are also found in other genres, such as country music. Nevertheless, country music listeners report the lowest use of Purple Drank (2.6%).

The most recent article identified in this review (Cherian et al. 2018) analyzes data about prescription opioid misuse detected through Instagram, using search tags related to Purple Drank (such as *#codeine; #SipLean; #Sizzurp*). The research group downloaded screenshots resulting in 1156 posts (weekends had more posts with the hashtag *#codeine*) with an average of 150–200 posts uploaded each day of the week. Codeine related hashtags (i.e. *#CodeineCrazy*) and the non-related ones (i.e. *#trap*) were also listed. In the first group, the most relevant hashtags were *promethazine, lean, codeinecrazy, purpledrank, coughsyrup, doublecup*. In the second group, the most relevant hashtags were related to cannabis use (i.e. *weed, cannabis* and *kush)* and less commonly associated with hip hop culture (i.e. *hip hop* and *rap*). Cherian et al. (2018) highlight how social media platforms provide a fertile ground to share information and pictures related to Purple Drank, not just in relation to a specific subculture.

In the last article in this review (Jagtap and Tapadia 2018) reported a novel phenothiazine detection technique – drop-to-drop solvent microextraction – that could have forensic and toxicologic implications in the future.

Risk of bias

The Cochrane Risk of Bias tool was used to examine the risk of bias (Higgins and Altman 2008). In spite of the heterogeneity of the articles analyzed, we found a relatively low risk of bias regarding parameters such as "adequate sequence generation" and "incomplete outcome data" (50% low risk of bias), "free of other bias" (nearly 75% low risk of bias) and "free of selective reporting" (over 90% low risk of bias). However, two parameters were not applicable to the articles included in the review ("allocation concealment" and "blinding of participants") (Figure 2).

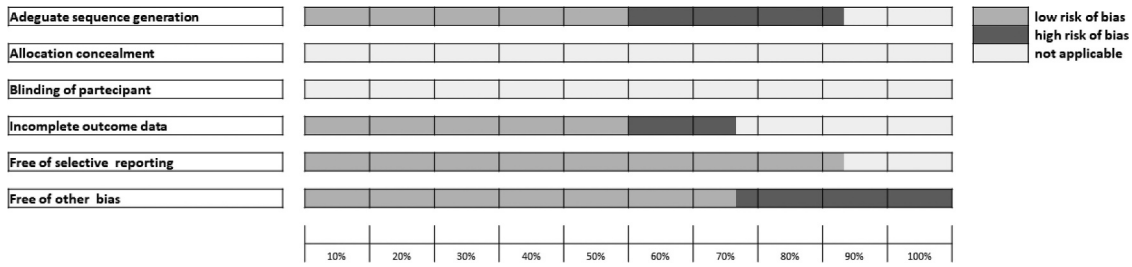

Figure 2. Risk of bias assessment (Cochrane risk of bias tool).

Discussion

Although these studies appear heterogeneous in their methods, they are useful to describe the phenomenon of PD, and to understand the impact it has on society. Garcin et al. (2016), focusing on the medical aspects, reports a kind of intoxication in which no other drug or substance seems to be involved (the assumption of marijuana was very low in dosage). The abuse of PD may be a potentially lethal condition, characterized by alteration of consciousness, aggressive agitation, acute delusions, visual hallucinations and anticholinergic toxidrome. Because of the close link between PD abuse and medical consequences, the results of this review may be useful not only in the treatment of intoxication, but also in helping the detection of the substances, allowing to investigate the consumed drug, thus suggesting an early -and more specific- treatment. This is linked to the awareness of the diffusion of the phenomenon among clinicians and the diffusion of its perception, especially by the media.

In this regard, Miller et al. (2014). underline how PD seems to be linked to a specific profile of users. If we consider codeine and promethazine abuse by black males in the U.S. as a part of the PD culture, the limitation of the phenomenon to subgroups, as declared by U.S. newspapers (Miller et al. 2014), would be accurate. However, our review underlines how PD misuse is more heterogeneous and not strictly related to ethnic backgrounds or music and sport preferences. Several studies show different profiles of codeine abusers, describing how the behavior is widespread among other countries as well (Lam et al. 1996; Mattoo et al. 1997).

Although some studies in the past have investigated the use of codeine in specific population subgroups (Peters et al. 2007a) we were able to exclude the relationship between ethnic/social subgroups and an increased risk of addiction to PD among university students (Agnich et al. 2013; Hart et al. 2014). The relationship between PD and hip hop and rap music cannot be excluded. Nonetheless, we should underline that the link between PD and music could affect other music genres, such as rock and metal, which are related to the use of drugs in general. Therefore, the phenomenon cannot be confined to DJ Screw and rap music. This is well demonstrated also in the work by Cherian et al. (2018) which shows how the greatest number of non-codeine-related hashtags displaying pictures of PD on Instagram regards the use of other substances, such as cannabis, and is not simply limited to rap, hip hop and trap music. Several studies also highlight how the number of PD abusers is increasing: this could be related to an underestimation of abuse/risk, because the components of PD are mainly drugs that can be found in pharmacies, thus considered "safer" for possible abusers (Elwood 2001). This occurs because doctors and pharmacists, in a setting where young students think that the use of codeine syrup is "cool", may facilitate the acquisition of such drugs (Peters et al. 2007b). This aspect could be observed also from the data collected through a validation study by the Beliefs about Cough Medicine Abuse Scale in China (Shek and Lam 2008). In this work about half of the respondents declared they did not feel worried about dating people who use cough syrup in a recreational way, just as they did not think it could be addictive. These data suggest that the education of young people and a better understanding of the risk factors (psychological, social and economic) associated with drug use could be crucial aspects for a better understanding of the PD phenomenon. The latter is increasing in Europe as well. In fact, as it was explained above, there is a large diffusion of PD in France, which leads to the enforcement of specific laws, as shown in our findings. One of the many interpretations of the numerous French articles concerning PD could be that the greatest increase in the number of European prescriptions for opioids takes place precisely in France and in the United Kingdom (Trouvin, Berenbaum, and Perrot 2019). Furthermore, according to the latest data from the report of the European Monitoring Center for Drugs and Drug Addiction (EMCDDA 2019), France appears to be the first European country by number of patients in replacement therapy for opioid addiction (178,665 patients).

The possible role of social media on PD phenomenon

As shown in the work by Cherian et al. (2018), there is a strong influence on the PD phenomenon by social networks, in particular Instagram. Substance use is influenced by environmental factors (Xian et al. 2008) and social networks are now an integral part of the environmental context in which the population lives. The influence of social networks on the use of abuse-substances and their negative role on possible relapses has been studied for a long time and it finds extensive support in the international scientific literature. Considering that the copious presence of content concerning alcohol on Twitter during the weekend could mutate such behavior into something more "accepted" by society, (Moreno and Whitehill 2014), also PD, whose presence on social networks is rapidly increasing, could follow the same principles as the other abuse-substances previously investigated.

Some limitations need to be considered when evaluating these review findings. We decided not to investigate the

misuse of codeine and promethazine hydrochloride cough syrup in general, but to examine specifically the phenomenon of PD: this exclusion criterion led us to find only seven results. Another possible limitation could be given by the decision to include only papers that were written in English and French, thus determining the exclusion of data reported in other languages. Therefore, the sample of studies included is limited and heterogeneous and a quantitative analysis of the phenomenon was not possible.

The confinement of PD abuse among southern U.S. inhabitants and the relationship between race and abuse seem to be obsolete. The abuse prevalence in Europe, and the differences between European and American users, may be interesting topics for future research; moreover, further investigations about the diffusion of trap music in Europe and possible links to PD abuse should be taken into consideration. In addition, new platforms of media sharing should be contemplated according to the current use of social networks. Nowadays, for example, it may be useful to investigate not only the influence of lyrics, but also the effects of online music videos and the influence of new social networks, such as Instagram, on the young generation. This aspect is congruous with the evidence from research and dissemination of NPS via the Internet (Orsolini et al. 2017). All these results can be useful to prevent the damaging effects of PD in an extremely fragile young population.

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