

Understanding the use of prescription and OTC drugs in obtaining illicit highs and the pharmacist role in preventing abuse

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Abstract

There have been increasing reports of misuse of a range of prescription and over-the-counter (OTC) drugs for recreational purposes. The use of psychoactive pharmaceuticals and 'pharming' are new, widespread phenomena involving the non-medical use of prescription and OTC drugs, which are recreationally used to achieve psychoactive effects either on their own or in combination with other substances.

This article provides an overview of the topic, focusing on a range of medicines (e.g. prescription medicines such as quetiapine, gabapentinoids, Z-drugs, bupropion, venlafaxine, and over-the-counter medicines such as loperamide, dextromethorphan, benzydamine, promethazine, chlorphenamine, diphenhydramine and hyoscine butylbromide) that have emerged as misused and diverted, or already described through the literature, as well as recorded by drug users' online websites reporting new trends and experimentations of drug abuse.

This rapidly changing drug scenario represents a challenge for pharmacy, psychiatry, public health and drug control policies. Moreover, possibly resulting from the COVID-19 pandemic, drug use-habits and availability have changed, causing a shift in behaviours relating to both prescription and OTC medicines. Healthcare professionals should be aware of potential prescription drugs diversion, recognise misuse cases, consider the possibility of polydrug misuse, and prevent it where possible. Pharmacists can play a key role in preventing and

reducing drug abuse and should be involved in evidence-based actions to detect, understand and prevent drug diversion activities and the adverse effects of drug-misuse.

Key words: drug abuse; prescription drug misuse; over-the-counter drug abuse; novel psychoactive substances (NPS); pharmacovigilance

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Key points

- The use of 'psychoactive pharmaceuticals' and 'pharming' are increasingly reported phenomena involving the non-medical use of prescription (e.g. pain relievers, tranquilizers, stimulants, sedatives) and OTC drugs (e.g. loperamide, promethazine, antitussive cough syrups), either on their own or in combination with other licit or illicit substances, for recreational purposes.
- A range of medications have emerged as misused and diverted, known anecdotally to be used, or already described through the literature or pharmacovigilance datasets, as well as recorded by drug users' online websites reporting new trends and experimentations of drug abuse.
- Drug use-habits and availability may have changed as result of the COVID-19 pandemic, causing a shift in behaviours relating to both prescription and OTC medicines.
- Pharmacists should play a key role in preventing and reducing drug abuse and be involved in evidence-based actions in order to detect, understand and prevent drug diversion activities and drug-misuse adverse effects.

Introduction

In recent years, drug abuse scenarios have evolved due to the appearance of novel psychoactive substances (NPSs) and the recreational use of pharmaceuticals [1-4]. Misuse of prescription drugs is a growing health problem, involving not only specific drug-related risks, but also the context in which they are consumed, e.g. the concomitant abuse of other substances with synergistic effects, psychiatric diagnoses and social circumstances [4-8]. Therefore, side-effects, drug interactions and individual variation in responses (including both possible comorbidities, such as a mental disorder, renal or hepatic dysfunction, systemic diseases; and a previous substance abuse or dependence) [2, 9] might be associated with a range of severe adverse drug reactions (ADRs), including seizures, arrhythmias and respiratory arrest, and fatalities [10-11]. In this context, 'pharming' is a new, worldwide phenomenon involving the non-medical use of prescription (e.g. pain relievers, tranquilisers, stimulants, sedatives) and over-the-counter (OTC) drugs (e.g. those containing dextromethorphan and promethazine) [2,7, 12-15]. According to data from the United Nations Office on Drugs and Crime (UNODC), the prevalence of prescription drug misuse and related fatalities are increasing worldwide [16-18]. Vulnerable groups at higher risk of misusing medications are adolescents and young adults; women; older adults; and healthcare professionals [19]. Other at-risk groups include people with mental illnesses, inmates, and individuals suffering from acute or chronic pain who might abuse of opiate medications [17]. A range of factors are thought to contribute to the non-medical use of prescription/OTC drugs, such as:

- The perception of prescription drugs' as more socially acceptable;
- Less stigmatising;
- Safer than the intake of illicit substances, as well as their likely lack of detection in standard drug screens [13].

This article aims to undertake a comprehensive review of the relevant literature describing the drugs primarily associated with potential diversion, typical patterns of their misuse, and harms associated with medicine abuse; report factors which might influence and exacerbate diversion in the current COVID-19 crisis; and consider how pharmacists can play a crucial role in the reduction and prevention of substance abuse.

Material and Methods

A literature search was performed on PubMed, Medline, and Web-of-Science in May 2020 and covered the last 20 years. We used combinations of the following search terms [Title/Abstract]: 'prescription drug', 'non-prescription drug', 'over-the-counter drug', 'misuse', 'abuse', 'non-medical use', 'addiction', and 'dependence'. Additional searches were then undertaken based on identified medicines, and these included 'gabapentinoid', 'antidepressants', 'antipsychotics', 'Z-drugs', 'dextromethorphan', 'antihistamine', 'loperamide', 'benzylamine', 'pseudoephedrine', 'scopolamine'. Finally, authors performed further secondary searches by using the reference listing of all eligible papers. All titles/abstracts were examined, and full texts of potentially relevant papers obtained. Relevant works were selected in order to obtain a full representation of the available literature on the selected topic. Experimental and observational studies; post-marketing surveillance reports; case reports; case series; and fatalities' reports were included. The exclusion criteria included: non-original researches (e.g. review, commentary, editorial, book chapter, letter to the editor); non full-text articles (e.g. meeting abstract); works in a language other than English; animal/in vitro studies; and articles that did not cover the abuse/misuse/dependence of the selected drugs.

Opioids and benzodiazepines are traditionally misused, and, even though mostly controlled, these agents are still diverted, associated with risky behaviours and higher overdose risk [18].

The emergence of potent new, 'designer' benzodiazepines or new, synthetic opioids on the drug market is a reason for continued concern [20-21]. These medicines were excluded from this review as these categories require additional insight that is beyond the scope of this work. Image and performance enhancing drugs were excluded from consideration in this review because their typical pattern of use is quite different from a typical recreational value (e.g. aesthetic use, competitive bodybuilding, etc.) [22-23]. Similarly, cognitive enhancers were not considered in this review as their primary use is to maintain wakefulness, improve recall, and enhance executive functions [22, 24].

'Abuse' was specifically defined as the intentional, non-therapeutic use by a patient or consumer of a product, OTC or prescription, for a perceived reward or desired non-therapeutic effect including, but not limited to, getting high (euphoria) [25]. 'Misuse' was defined as the intentional use for a therapeutic purpose by a patient or consumer of a product, OTC or prescription, other than as prescribed or not in accordance with the authorised product information [25]. 'Drug misuse' is used to distinguish improper or unhealthy use from use of a medication as prescribed or alcohol in moderation [19]. These include the use of drugs to produce pleasure, alleviate stress, and/or alter or avoid reality [19]. 'Addiction' refers to a chronic, relapsing disorder characterized by compulsive drug seeking, continued use despite harmful consequences, and long-lasting changes in the brain [19]. 'Dependence' refers to a maladaptive pattern of substance use leading to clinically significant impairment or distress [26]. It is manifested by three or more of the following criteria, occurring at any time in the same 12-month period: i) Tolerance; ii) Withdrawal; iii) Taking the substance often in larger amounts or over a longer period than was intended; iv) Having a persistent desire or unsuccessful efforts to cut down or control substance use [26]. Physical dependence developed as a result of physiological adaptation in response to repeated drug use, manifested by

withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Psychological dependence refers to a state in which individuals have impaired control over drug use based on the rewarding properties of the drug (ability to produce positive sensations that increase the likelihood of drug use) or the psychological distress produced in the absence of the drug [26]. In 2013, the American Psychiatric Association (APA) updated the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), replacing the categories of substance abuse and substance dependence with the unique category of substance use disorder (SUD) [27].

A total of n= 314 publications were identified, after removing duplicates (n= 9), and applying the exclusion criteria a total of n= 74 papers were retrieved and analysed (see supplement 1). The findings are described in detail, organised in relation to the specific drug/group of drugs (see Table 1 [7, 9, 12, 28-48].

Prescription drugs misuse

Prescription drug abuse has become a concerning modern-day epidemic [49-51], especially in young adults and adolescents where their use has surpassed all illicit drugs with the exception of marijuana [52-53]. Traditionally concern has centred on opioids, benzodiazepines, and stimulants, but other widely prescribed drugs may be misused, abused or diverted for non-medical purposes [54]. Young people take prescription drugs for recreational purposes (e.g. to get 'high'); to relieve anxiety or relax; or to improve academic performance [5, 7-8, 55]. Drugs might be acquired from friends or relatives, directly prescribed by a doctor, from a drug dealer, or via the internet [2, 56-57]. Although there is little nationwide data on the prevalence of prescription drug abuse among young people in the UK, there are an increasing number of reports to suggest the problem is growing [16].

Quetiapine

According to the literature, quetiapine appears to be the most documented second-generation antipsychotic being abused due to its sedative, relaxant and anxiolytic characteristics [58-59]. High rates of quetiapine-related ambulance attendances/emergency department visits have been reported: data from the 2005 to 2011 Drug Abuse Warning Network (DAWN) for prevalence of emergency department (ED) visits among the U.S. general population involving quetiapine showed an increase between 2005 and 2011, from 35,581 ED visits to 67,497 [60]. Similar data regarding increasing quetiapine rates of ambulance attendances have been recorded in Australia, and associated with concurrent heroin and opioid replacement therapy toxicity, history of heroin and alcohol misuse, and mood disorders [61]. Moreover, drug-seeking behaviours, such as an illicit drug provision, and an increase in quetiapine availability on the black-market have been registered [62]. Prison inmates, psychiatric outpatients, users with a history of drug misuse and opioid addicts represent the most at-risk of misusing populations [30, 47]. Finally, intranasal and intravenous routes of consumption have been described [63] (see Table 1).

Gabapentinoids

Gabapentin and pregabalin are approved treatments for epilepsy and neuropathic pain disorders [44, 64-65]. Both have increasingly been reported for their misuse potential, however, pregabalin is considered to have a higher abuse potential due to its rapid absorption, faster onset of action and higher potency [29, 42; 66-67]. Death, physical dependence, and the propensity to cause depression of the central nervous system (CNS), especially when used in combination with opioids and sedatives are harms identified for both gabapentinoids [42]. The principal population at risk for addiction are those with other current or past SUD, mostly

opioid and polydrug users [29, 42, 66-67]. Opioid users often misuse pregabalin to self-treat physical pain, to achieve a desired psychoactive effect (e.g. potentiate the effects of heroin/cocaine), and combat opioid withdrawal symptoms [42, 66, 68-70]. Moreover, rates of pregabalin misuse-related ambulance attendances have increased markedly over the past 10 years, e.g. in Australia from 0.28 cases per 100 000 population in the first half of 2012 to 3.32 cases per 100 000 in the second half of 2017 [71]. Thus, pregabalin and gabapentin were found to have the potential for misuse, addiction and overdose [29, 42, 66-67]. In 2018, after safety warnings following an increase in deaths related to their use, the Advisory Council on the Misuse of Drugs (ACMD) recommended that both are controlled under the Misuse of Drugs Act 1971 as Class C substances, and scheduled under the Misuse of Drugs Regulations 2001 as Schedule 3, so as not to preclude legitimate use on prescription (Table 1) [72].

Z-drugs (zolpidem, zaleplon, zopiclone)

Z-drugs were introduced in the 1980s for the short-term treatment of insomnia [44]. It was believed that they possessed a favourable and safer profile compared with benzodiazepines, due to their receptor selectivity and improved pharmacokinetic properties [73]. Their significant hypnotic effects involve both a sleep latency reduction and a sleep quality improvement through an increased γ -aminobutyric acid (GABA) transmission at the same GABA-type A receptor as benzodiazepines. In recent years, concern has grown for their safety due to abuse and dependence issues [9, 36], drug-assisted sexual assaults and dangerous sleep behaviours (e.g. sleep eating, sleep driving and sleepwalking). Problematic use of hypnotic drugs has been described in male and young recreational users of high-dose drugs. They are often abused with other licit/illicit drugs via intranasal/intravenous administration [74]. A second abusing population was studied and comprised long-term users, including patients with comorbidities of mood/neurotic disorders and SUDs, and older people using Z-drug hypnotics

to treat insomnia and were then unable to cut down the dosages needed to manage withdrawal symptoms [75-76]. Zolpidem and zopiclone presented with the same dependence risk, but zopiclone was most indicated in overdose adverse drug reactions [9] and sold on the black market [77]. Similarly to benzodiazepines, since 2013 Z-drugs have been controlled as Class C and Schedule 4 substances under the Misuse of Drugs Act and Regulations respectively (Table 1) [78-79].

Bupropion

Among antidepressants, the dopaminergic, stimulant-like activities of bupropion may explain its possible recreational value [4]. It is a second-generation antidepressant acting as a selective inhibitor of catecholamine (i.e. noradrenaline and dopamine) reuptake [44]. In the UK it is licensed as smoking cessation treatment only [80]. A 14-year retrospective review showed that 975 single substance bupropion cases were reported to the National Poison Data System (NPDS) with "intentional abuse" as the coded reason for exposure in individuals aged 13 and older [46]. The prevalence of abuse increased by 75% from 2000 to 2012, and mostly involved adolescents and young adults, who reported clinical effects of tachycardia, seizures, and agitation/irritability [46]. Its recreational use by oral/nasal/intravenous routes has been reported, with people misusing the drug to get a 'high' similar to the one obtained through other stimulants, such as cocaine [31, 81-84] (Table 1).

Venlafaxine

Venlafaxine is an antidepressant in the serotonin-norepinephrine reuptake inhibitor class [44]. Its recreational use is related to its reuptake inhibition with dose-dependent effects on selective serotonin (5-HT) transmission at low doses (<150 mg/day); on both 5-HT and norepinephrine systems at moderate doses (>150 mg/day); and on dopamine at high doses (>300 mg/day)

[41]. Large venlafaxine dosages might be consumed to produce amphetamine/ecstasy-like effects [31-32], with euphoria and increased sociality, and dissociative effects including distorted sense of time and “numbness” described [31-32]. Patients with prior SUD, e.g. opioid abuse/dependence, appeared to be more vulnerable to venlafaxine misuse [41, 85]. Fatalities have been reported relating to numerous overdose cases with associated symptoms of tachycardia, seizures, coma, and serotonin syndrome; moreover, dependence issues after long-term use have been described [4, 41, 86]. A retrospective review of venlafaxine exposures reported to the NPDS from 2000 to 2016 described 752 intentional-abuse venlafaxine exposures on the total of 85,621, with prevalence decreasing from 107/10,000 venlafaxine exposures in 2000 to 59.3/10,000 in 2016 [87]. Median age was 23 years and 50% were female [87]. Primary route was ingestion (90.8%) with 4.7% using venlafaxine via inhalation/intranasal administration. The most frequent clinical effects reported were tachycardia (33.9%), drowsiness (20.7%), and agitation (11.5%) [87]. The decrease in intentional abuse exposures in the study was explained by authors through several reasons, including underreporting or a possible decrease in the prevalence of venlafaxine abuse as patients shift to other agent, but changes in prescribing patterns for venlafaxine were excluded [87].

Over-the-counter drugs misuse

The potential for misuse of OTC medications that have not previously been deemed to have a diversion potential has been reported worldwide [40, 88-89]. Their abuse appears facilitated by their accessibility, low cost, decreased perception of potential for harm, and growing social acceptability [2, 7, 12, 15, 90]. In contrast to prescribed and illicit drugs, medications available for individuals to purchase legally without prescription have been perceived to be relatively safe [2, 7, 12, 90]. They are typically purchased not only from pharmacies, but also from non-

medical outlets (e.g. online illicit websites, and the darknet). The internet can be used to obtain them without restrictions, e.g. prescription drugs might be obtained without prescription [90]. Apart from the previously described OTC products that can be misused, such as some codeine-containing cough syrups, and decongestants (e.g. pseudoephedrine) other medicines have been found to be misused [2, 7, 12, 90]. Alcohol and illicit drug use are highly associated with the abuse of OTC medications [2, 7].

Loperamide

Loperamide is a common anti-diarrhoeal drug, that binds to μ -opioid receptors in the gastrointestinal tract, decreasing peristalsis and increasing sphincter tone [41]. At therapeutic doses (2mg, with a maximum dosage of 16mg) loperamide does not exert cross central opioid effects; however, at high dosages (50-800mg), it might be recreationally abused to achieve a euphoric state, this is informally referred to as “lope high” [40]. It might be used to manage and cope with opioid withdrawal symptoms [7, 40, 91-92]. Loperamide toxicity involves gastrointestinal (e.g. nausea, vomiting, constipation), CNS (e.g. respiratory depression, altered mental status, miosis), and cardiovascular effects (e.g. ventricular dysrhythmias and electrocardiogram alterations, such as prolonged QT, QRS widening and torsades-de-pointes), which might be fatal [41, 93-101]. Consistently, loperamide exposures reported to the NPDS indicated intentional misuse and abuse, there was a 91% increase in reported exposures from 2010 to 2015 with a total of 201 and 383 exposures in 2010 and 2015, with a rate of approximately 38 cases per year) [102], most of them involving single-agent loperamide abuse and cardiotoxicity ([102-103]. Since September 2019 the Food and Drug Administration (FDA) have limited loperamide package sizes in an effort to reduce inappropriate use [104]. Few pharmacies currently regulate its sale [105], and no regulations exist to prevent purchasing at nonpharmacy online outlets. Interested pharmacies can implement policies to reduce excessive

access and prevent harm. However, collateral purchasing at other retail stores or pharmacies may still occur [105].

Dextromethorphan

As an analogue of codeine and a semisynthetic morphine derivative, dextromethorphan is a component of many cough and cold medicines. At therapeutic doses, dextromethorphan produces minimal analgesic and antitussive effects. At high doses, acting as a N-methyl-D-aspartate receptor antagonist, it produces the hallucinogenic and dissociative effects, which are recreationally searched. Neurobehavioural effects are dose-related, ranging from a mild to moderate stimulation with restlessness and euphoria (at 100-200 mg doses), to a dissociated state characterised by hallucinations, paranoia, perceptual distortions, delusional beliefs, ataxia, and out-of-body experiences at doses >1000 mg, these experiences are referred to as 'robo-ing', 'robo-copping', or 'robo-tripping' (Table 1) [7, 45, 48, 106-108].

Benzydamine (BZY)

BZY acts as an analgesic and antipyretic, and is used for the topical treatment of inflammations of the oral and vaginal mucosae. BZY has been reported to be misused in several countries, including Brazil, Italy, Romania, Poland and Turkey, at high doses (i.e. 500-3000 mg) to reach stimulant effects on the CNS (e.g. euphoria; hyperreactivity; insomnia; abnormal behaviour; and psychotic symptoms, including paranoia and visual hallucinations) [109-115]. BZY diversion issues might involve young people and the concomitant use of alcohol/cannabis [38-39, 43]. Even though the molecular mechanism underlying the psychoactive and reinforcing effects of BZY is still unknown, a central cannabinoidergic mechanism of action has been hypothesised [48, 116] (Table 1). Informal self-reports, hosted by internet drug fora and social networks have contributed to the diffusion of BZY abuse, providing information about routes

of administration, dosages and substance preparation from commercial products, as well as advice about other psychotropic substances to be used in combination with BZY to both enhance its pleasurable effects and dampen undesired ones [38-39, 43].

Antihistamine Drugs

Promethazine

As a histamine (H)₁ receptor antagonist, promethazine is commonly used for symptomatic relief from nausea and vomiting, for allergic conditions, motion sickness, and the common cold. Often available with codeine in common cough suppressants, its abuse potential appears related to its calming and sedating effect, and enhancement of other co-ingested substances, such as benzodiazepines and opioids [34, 48, 117]. The abuse of promethazine mixed with a soft drink and candy with some variants including purple coloured alcohol (“purple drank”) has become popular in young people for its euphoric effects and easy accessibility [12, 28, 37]. Despite being preferred to other substances, such as benzodiazepines, for the treatment of anxiety and sleep disorders in substance-dependent patients, promethazine has been reported to be misused among people with a SUD or an opioid dependence as a substitute for another drug (e.g. if the desired drug is unavailable or too costly) or to augment the effects of an inadequate opioid dosing (i.e. to delay the onset of opioid withdrawal) [118-121] (Table 1).

Chlorphenamine

As a first generation H₁-receptor antagonist, chlorphenamine is used as a cheap sleep aid or anxiolytic [13]. Chlorphenamine has potent antimuscarinic properties, and its abuse has been related to pleasurable feelings like euphoria, which reinforce the repetitive use of the drug and the possibility of developing drug dependence, but might also cause psychotic symptoms in predisposed individuals, e.g. people with mental illnesses or concomitantly abusing of other

drugs [122]. Together with dextromethorphan in cough and cold suppressants, or simultaneously consumed with serotonergic drugs, it might cause a significant serotonin toxicity [107, 122-125]. A fatality has been registered involving chlorphenamine used concomitantly with an opioid [126]. The abuse of chlorphenamine has been described by data collected from the Texas Poison Center Network Toxic Exposure Surveillance System, and its intentional use or abuse appears to be increasing, particularly in the youngsters [127].

Diphenhydramine

Diphenhydramine is an OTC drug acting on peripheral and central H₁ receptors, causing reduction of allergic symptoms and sedation, respectively [128]. The abuse of diphenhydramine appears related to multiple potential mechanisms of action, including a potent competitive antagonism on muscarinic receptors, causing sinus tachycardia, xerostomia, mydriasis, blurred vision, ileus, urinary retention, CNS depression, agitation, hyperactivity, or psychosis [107, 128]. At high dosage and concomitantly assumed together with other drugs, e.g. alcohol, cannabis, and stimulants, diphenhydramine can have a stimulatory effect in children and young adults, instead of the sedating properties seen in adults, such as elevated mood, increased energy levels, and mild euphoria [128]. Increased dopaminergic neurotransmission in the mesolimbic pathway is thought to cause rewarding properties and drug-seeking behaviour [107, 128].

Hyoscine butylbromide

Also known as scopolamine butylbromide, hyoscine butylbromide is a plant-derived anticholinergic agent, commonly used as an antispasmodic drug [35]. A dose of 10 mg or more is used to control intestinal and other smooth muscle spasms, for the symptomatic relief of irritable bowel syndrome and as a premedication in anaesthesia [35]. Its use and abuse as a

psychoactive substance has been popular among young people, who obtain it from proprietary products (e.g. Buscopan®) [35]. At supratherapeutic dosages (from 1.2 mg as a single dose, while the recommended dose for adults is one to two tablets of 0.3 mg as a single dose) it exerts potent CNS effects, including restlessness, excitement, euphoria, disorientation, irritability and characteristic delirium-like states with auditory/visual/and tactile hallucinations, altered mood, insomnia and cognitive dysfunctions [33, 35, 129]. An advisory warning was issued in 2016 by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) regarding 17 intoxications involving cocaine containing scopolamine, although it has not been formally notified as an NPS (Table 1) [130-131].

Discussion

The non-medical use of prescription drugs and OTC medications for recreational purposes is a global health concern due to the unpredictable effects of some drugs used in abnormal dosages and unlicensed administration, but also due to the possibility of their diversion in the context of polydrug misuse [13]. It is particularly concerning that drugs that have not been considered as being potentially abused, such as loperamide, might be diverted at high dosages, and possibly cause serious cardiotoxic effects and fatalities [102-103].

Abuse of drugs during the COVID-19 pandemic

The COVID-19 outbreak has challenged public health policies due to additional concerns relating to drug users and people with SUDs [132-133]. Individuals in this vulnerable category might be exposed to additional risks, such as: physical problems, e.g. hepatic/renal dysfunctions, neuropathies, obesity, cardiovascular diseases, etc.; and psychological comorbidities, e.g. mood and anxiety disorders, psychoses, etc.; homelessness, incarceration, economic difficulties, and other socioeconomic issues deriving from drug addiction [133-138].

Moreover, the COVID-19 pandemic is impacting drug markets, there have been reports of supply shortages of numerous drugs, e.g. opioids, at the street level, as well as price increases for consumers on the black market and reductions in purity [133-134, 139]. These issues, in combination with a general economic loss, can encourage shifts to more risky drug using behaviours (such as the use of domestically produced substances); use of prescription/OTC drugs; or mixing with cheaper drugs (such as 'street benzos') and synthetic cannabinoids [139]. As access to drug services is disrupted by quarantine, social distancing and other restrictive measures adopted to stop the spread of COVID-19 [133-135, 137, 140], and community pharmacies being challenged by staff shortages, service disorganisation, and self-isolation [133, 137, 141], the recent crisis creates an urgent requirement for expanded drug service provision, to protect vulnerable populations and to minimise additional burdens on the health system.

Pharmacist's role in drug abuse prevention, education, and assistance

As more users turn from street drugs to prescription/OTC products, pharmacists must increase their vigilance when supplying medicines, and be aware of medicines' potential to end up on the black market [57]. Pharmacists have long taken responsibility for assuming an important role in substance abuse prevention, education, and enhancing their services during and post-pandemics to support their patients [142]. As healthcare providers, they should participate in or contribute to the development of specific prevention and assistance programmes within healthcare organisations or public services [143-144]; avoid potentially risky prescribing practices (e.g. prescribing larger quantities of pain medication than is clinically needed); and collaborate with outpatient and ambulatory care providers to prevent substance abuse after discharge.

Pharmacists should engage in open communication to provide reassurance to patients and develop a trusting relationship, especially in vulnerable populations who might be less

confident in communicating diversion/misuse issues to healthcare professionals. Pharmacists might be able to help identify patients who may have problems related to substance abuse, and refer them to the appropriate service, e.g. mental or addiction services [145-148]. Additionally, pharmacists should be involved in ensuring safe and effective medication-use systems, including the development of the pharmacotherapeutic elements of drug detoxification protocols and organisational responsibilities for medication supply, distribution, and control [145].

Implication for practice

Pharmacists are well placed to play a crucial role in the prevention and control of drug diversion behaviours (Brushwood, 2017) and therefore reduce the negative impacts of their misuse. Pharmacists can help prevent medicines' misuse and diversion by:

- Giving clear information about the effects medications may have; providing advice about any possible drug interactions;
- Making drug records that might prevent consultations with multiple doctors and subsequent duplicate prescriptions ('doctor shopping') for a drug with misuse potential.

It is vital that pharmacists ensure the continuity of care for people who use drugs and people with drug use disorders by facilitating access to community maintenance programmes, (e.g. provision of methadone or buprenorphine to opioid users [149-150]. Harm-avoiding interventions could be adopted, including guidance for facilitating controlled substance prescribing [132, 137, 151]; and telehealth for monitoring drug-dependent patients, while providing access to virtual support groups through online meetings [132, 141, 152].

In the context of a trusted pharmacist-patient relationship, pharmacists should inform at-risk individuals of drug dosages and drug-interactions, counsel them on harmful combinations

among medications, as well as interactions between medications and alcohol or other illicit substances [153]. The use of drug combinations including several CNS-depressants (e.g. benzodiazepines, opioids, gabapentinoids) together with OTC products, alcohol or other illicit substances should be discouraged [18, 154-155]. Finally, clinicians and pharmacists, should be aware of potential pressures from patients to prescribe more drugs than needed; on excessive sales of prescription/OTC products which might be diverted and abused; and on eventual aggression towards pharmacy staff [156]. Developing multidisciplinary support platforms, including both health and social support, could help reduce mental distress due to misinformation among users, and teaching problem-solving strategies to cope with drug abuse, e.g. the management of stress in order to prevent relapses during the pandemic [157]. Telemental health might provide users prevention interventions, through telepsychiatry, digital platforms, dedicated hotlines, and mental health apps [158-160].

Conclusion

The abuse of prescription and OTC drugs has become of increasing public concern across the globe. The current drug scenarios are greatly challenging health care providers and pharmacists, particularly during the COVID-19 pandemic. These healthcare professionals are recommended to be vigilant and develop strategies to ensure continuity of care for people who use drugs and people with drug use disorders and prevent possible medicines' misuse and diversion.

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F.S. was a member of the UK Advisory Council on the Misuse of Drugs (ACMD) from 2011 to 2019; he is currently an EMA Advisory board (psychiatry) member. J.M.C. is a member of the ACMD's Novel Psychoactive Substances and Technical Committees. The authors have no other relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Author contributions

The article idea was conceived by AG. The review and study design were developed by AG and SC. SC drafted the first version of the manuscript with input from all authors. All authors contributed to the views expressed and approved the final version of the manuscript.

References

- [1] Graddy R, Buresh ME, Rastegar DA. New and Emerging Illicit Psychoactive Substances. *Med Clin North Am.* 2018 Jul;102(4):697-714. DOI: 10.1016/j.mcna.2018.02.010.
- [2] Hughes GF, McElnay JC, Hughes CM, McKenna P. Abuse/misuse of non-prescription drugs. *Pharm World Sci.* 1999;21(6):251-255. DOI:10.1023/a:1008788726842.

- [3] Schifano F. Recent Changes in Drug Abuse Scenarios: The New/Novel Psychoactive Substances (NPS) Phenomenon. *Brain Sci.* 2018 Dec 13;8(12). pii: E221. DOI: 10.3390/brainsci8120221.
- [4] Schifano F, Chiappini S, Corkery JM, Guirguis A. Abuse of Prescription Drugs in the Context of Novel Psychoactive Substances (NPS): A Systematic Review. *Brain Sci.* 2018 Apr 22;8(4). pii: E73. DOI: 10.3390/brainsci804007.
- [5] Chiappini S, Schifano F. What about "Pharming"? Issues Regarding the Misuse of Prescription and Over-the-Counter Drugs. *Brain Sci.* 2020, 10, 736; DOI:10.3390/brainsci10100736.
- [6] Lessenger JE, Feinberg SD. Abuse of Prescription and Over-the-Counter Medications. *J Am Board Fam Med* 2008;21:45–54.
- [7] Levine DA. "Pharming": the abuse of prescription and over-the-counter drugs in teens. *Curr Opin Pediatr.* 2007, 19(3): 270-274. DOI: 10.1097/MOP.0b013e32814b09cf.
- [8] Wood D. Drug diversion. *Aust Prescr* 2015;38:164–6.
- [9] Schifano F, Napoletano F, Chiappini S, Guirguis A, Corkery JM, Bonaccorso S, et al. New emerging psychoactive substances and associated psychopathological consequences. *Psychol Med.* 2019 Jul 22:1-13. DOI: 10.1017/S0033291719001727.
- [10] McCabe SE, Veliz PT, Dickinson K, Schepis TS, Schulenberg JE. Trajectories of prescription drug misuse during the transition from late adolescence into adulthood in the USA: a national longitudinal multicohort study. *Lancet Psychiatry.* 2019 Oct;6(10):840-850. DOI: 10.1016/S2215-0366(19)30299-8.

- [11] Scherbaum N, Schifano F, Bonnet U. New Psychoactive Substances (NPS) - a Challenge for the Addiction Treatment Services. *Pharmacopsychiatry*. 2017 May;50(3):116-122. DOI: 10.1055/s-0043-102059.
- [12] Burns JM, Boyer EW. Antitussives and substance abuse. *Subst Abuse Rehabil* 2013, 4: 75–82. DOI: 10.2147/SAR.S36761.
- [13] Cooper RJ. Over-the-counter medicine abuse – a review of the literature. *J Subst Use* 2013 Apr; 18(2): 82–107. DOI: 10.3109/14659891.2011.615002.
- [14] Jouanjus E, Falcou A, Deheul S, Roussin A, Lapeyre-Mestre M. Detecting the diverted use of psychoactive drugs by adolescents and young adults: A pilot study. *Pharmacoepidemiol Drug Saf*. 2018, 27: 1286–1292. DOI: 10.1002/pds.4624.
- [15] McCarthy M. Prescription drug abuse up sharply in the USA. *Lancet*. 2007, 369: 1505–1506. DOI:10.1016/S0140-6736(07)60690-4.
- [16] Advisory Council on the Misuse of Drugs (ACMD). Diversion and illicit supply of medicines; 2016. [Cited 2020 May 26]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/580296/Meds_report-final_report_15_December_LU__2_.pdf
- [17] United Nations Office on Drugs and Crime (UNODC). The non-medical use of prescription drugs. Policy direction issues; 2011. [Cited 2020 May 26]. Available from: http://www.unodc.org/docs/youthnet/Final_Prescription_Drugs_Paper.pdf
- [18] United Nations Office on Drugs and Crime (UNODC) World Drug Report 2019. [Cited 2020 May 26]. Available from: <https://www.unodc.org/wdr2019/>

- [19] National Institute on Drug Abuse (NIDA). Drug Misuse and Addiction. 2020 July 13. [Cited 2020 August 15]. Available from: <https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/drug-misuse-addiction>.
- [20] Arillotta D, Schifano F, Napoletano F, Zangani C, Gilgar L, Guirguis A, et al. Novel Opioids: Systematic Web Crawling Within the e-Psychonauts' Scenario. *Front Neurosci*. 2020 Mar 18;14:149. DOI: 10.3389/fnins.2020.00149.
- [21] Orsolini L, Corkery JM, Chiappini S, Guirguis A, Vento A, De Berardis D, et al. New/Designer Benzodiazepines': an analysis of the literature and psychonauts' trip reports. *Curr Neuropsychopharmacol*. 2020 Jan 10. DOI: 10.2174/1570159X18666200110121333.
- [22] Corazza, O. (ed.) & Roman-Urrestarazu, A. (ed.), 17 Oct 2018, 1 ed. New York: Routledge. 386 p. Handbook on Novel Psychoactive Substances. What clinicians should know about NPS.
- [23] Wilens TE, Kaminski TA. Prescription Stimulants: From Cognitive Enhancement to Misuse. *Pediatr Clin North Am*. 2019 Dec;66(6):1109-1120. DOI: 10.1016/j.pcl.2019.08.006.
- [24] Corazza O, Bersani FS, Brunoro R, Valeriani G, Martinotti G, Schifano F. The diffusion of Performance and Image-Enhancing Drugs (PIEDs) on the Internet: The Abuse of the Cognitive Enhancer Piracetam. *Subst Use Misuse* 2014 49 (14): 1849-1856.
- [25] Medical Dictionary for Regulatory Activities (MedDRA) Version 21; 2018. [Cited 2020 May 26]. Available from: https://www.meddra.org/sites/default/files/guidance/file/smq_intguide_21_0_english.pdf.
- [26] American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV). American Psychiatric Association, Washington D.C., 1994.
- [27] American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5). American Psychiatric Association, Washington D.C., 2013.

- [28] Agnich LE, Stogner JM, Miller BL, Marcum CD. Purple drank prevalence and characteristics of misusers of codeine cough syrup mixtures. *Addict Behav.* 2013;38(9):2445-2449. DOI:10.1016/j.addbeh.2013.03.020.
- [29] Bonnet U, Scherbaum N. How addictive are gabapentin and pregabalin? A systematic review. *Eur Neuropsychopharmacol.* 2017 Dec;27(12):1185-1215. DOI: 10.1016/j.euroneuro.2017.08.430.
- [30] Chiappini S, Schifano F. Is There a Potential of Misuse for Quetiapine? Literature Review and Analysis of the European Medicines Agency/European Medicines Agency Adverse Drug Reactions' Database. *J Clin Psychopharmacol.* 2018;38(1):72-79. DOI:10.1097/JCP.0000000000000814.
- [31] Evans EA, Sullivan MA. Abuse and misuse of antidepressants. *Subst Abuse Rehabil.* 2014; 5, 107–120. DOI: 10.2147/SAR.S37917.
- [32] Francesconi G, Orsolini L, Papanti D, Corkery JM, Schifano F. Venlafaxine as the 'baby ecstasy'? Literature overview and analysis of web-based misusers' experiences. *Hum Psychopharmacol* 2015; 30: 255–261. DOI: 10.1002/hup.2476.
- [33] Jalali F, Afshari R, Babaei A. Smoking crushed hyoscine/scopolamine tablets as drug abuse. *Subst Use Misuse.* 2014 Jun;49(7):793-7. DOI: 10.3109/10826084.2014.880178.
- [34] Jensen LL, Rømsing J, Dalhoff K. A Danish Survey of Antihistamine Use and Poisoning Patterns. *Basic Clin Pharmacol.* 2017, 120: 64–70. DOI: 10.1111/bcpt.12632.
- [35] Kummer S, Rickert A, Daldrup T, Mayatepek E. Abuse of the over-the-counter antispasmodic butylscopolamine for the home synthesis of psychoactive scopolamine. *Eur J Pediatr.* 2016;175(7):1019-1021. DOI:10.1007/s00431-015-2683-5.

- [36] Lähteenmäki R, Neuvonen PJ, Puustinen J, Vahlberg T, Partinen M, Räihä I, Kivelä SL. Withdrawal from long-term use of zopiclone, zolpidem and temazepam may improve perceived sleep and quality of life in older adults with primary insomnia. *Basic Clin Pharmacol Toxicol*. 2019 Mar;124(3):330-340. DOI: 10.1111/bcpt.13144.
- [37] Miuli A, Stigliano G, Lalli A, Coladonato M, D'Angelo L, Esposito F, et al. "Purple Drank" (Codeine and Promethazine Cough Syrup): A Systematic Review of a Social Phenomenon with Medical Implications. *J Psychoactive Drugs*. 2020 Aug 4:1-10. DOI: 10.1080/02791072.2020.1797250.
- [38] Opaleye ES, Noto AR, Sanchez Zv, Moura YG, Galduróz JC, Carlini EA. Recreational use of benzydamine as a hallucinogen among street youth in Brazil. *Braz J Psychiatry*. 2009;31(3):208-213. DOI:10.1590/s1516-44462009000300005.
- [39] Opaleye ES, Sanchez ZM, Moura YG, Locatelli DP, Noto AR. An anti-inflammatory as a recreational drug in Brazil. *Addiction*. 2011 Jan;106(1):225. DOI: 10.1111/j.1360-0443.2010.03196.x.
- [40] Reeves RR, Ladner ME, Perry CL, Burke RS, Laizer JT. Abuse of Medications That Theoretically Are Without Abuse Potential. *South Med Journal* 2015;108(3):151-157. DOI: 10.14423/SMJ.0000000000000256.
- [41] Schifano F, Chiappini S. Is there such a thing as a 'lope' dope? Analysis of loperamide-related European Medicines Agency (EMA) pharmacovigilance database reports. *PLoS One*. 2018;13(10):e0204443. Published 2018 Oct 4. DOI:10.1371/journal.pone.0204443.
- [42] Schifano F, Chiappini S. Pregabalin: A range of misuse-related unanswered questions. *CNS Neurosci Ther*. 2019;25:659–660. DOI:10.1111/cns.13115.

- [43] Schifano F, Corazza O, Marchi A, Di Melchiorre G, Sferrazza E, Enea A, Davey Z, Blaszkowski U, Deluca P; Psychonaut web mapping e rednet research projects. [Analysis of online reports on the potential misuse of benzidamine]. Riv Psichiatr. 2013 May-Jun;48(3):182-6. DOI: 10.1708/1292.14286. Italian.
- [44] Stahl SM, Grady MM. Stahl's essential psychopharmacology: prescriber's guide. Cambridge, United Kingdom ; New York, NY : Cambridge University Press, 2017.
- [45] Stanciu CN, Penders TM, Rouse EM. Recreational use of dextromethorphan, "Robotripping"-A brief review. Am J Addict. 2016 Aug;25(5):374-7. DOI: 10.1111/ajad.12389.
- [46] Stassinis GL, Klein-Schwartz W. Bupropion "Abuse" Reported to US Poison Centers. J Addict Med. 2016;10(5):357-362. DOI:10.1097/ADM.0000000000000249.
- [47] Vento AE, Kotzalidis GD, Cacciotti M, Papanti DG, Orsolini L, Rapinesi C et al. Quetiapine Abuse Fourteen Years Later: Where Are We Now? A Systematic Review. Subst Use Misuse. 2020;55(2):304-313. DOI:10.1080/10826084.2019.1668013.
- [48] Zaprutko T, Koligat D, Michalak M, Wieczorek M, Józiasz M, Ratajczak M, et al. Misuse of OTC drugs in Poland. Health Policy. 2016 Aug;120(8):875-81. DOI: 10.1016/j.healthpol.2016.06.008.
- [49] Hernandez SH, Nelson LS. Prescription drug abuse: insight into the epidemic. Clin Pharmacol Ther. 2010;88(3):307-317. DOI:10.1038/clpt.2010.154.
- [50] Lipari RN, Williams M, Van Horn SL. Why Do Adults Misuse Prescription Drugs? In: The CBHSQ Report. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); July 27, 2017.1-10.

- [51] McCabe SE, Cranford JA, West BT. Trends in prescription drug abuse and dependence, co-occurrence with other substance use disorders, and treatment utilization: results from two national surveys. *Addict Behav.* 2008;33(10):1297-1305. DOI:10.1016/j.addbeh.2008.06.005.
- [52] Fortuna RJ, Robbins BW, Caiola E, Joynt M, Halterman JS. Prescribing of controlled medications to adolescents and young adults in the United States. *Pediatrics.* 2010;126(6):1108-1116. DOI:10.1542/peds.2010-0791.
- [53] Kelly BC, Wells BE, Leclair A, Tracy D, Parsons JT, Golub SA. Prescription drug misuse among young adults: looking across youth cultures. *Drug Alcohol Rev.* 2013;32(3):288-294. DOI: 10.1111/dar.12016.
- [54] D'Souza RS, Eldrige JS. Prescription Drug Monitoring Program. In: StatPearls. Treasure Island (FL): StatPearls Publishing; February 19, 2020.
- [55] Jouanjus E, Guernec G, Lapeyre-Mestre M, the French Addictovigilance Network. Medical prescriptions falsified by the patients: a 12-year national monitoring to assess prescription drug diversion. *Fundam Clin Pharmacol.* 2018; 32(3): 306-322. DOI: 10.1111/fcp.12356.
- [56] Soussan C, Andersson M, Kjellgren A. The diverse reasons for using Novel Psychoactive Substances - A qualitative study of the users' own perspectives. *Int J Drug Policy.* 2018;52:71-78. DOI:10.1016/j.drugpo.2017.11.003.
- [57] Sukkar E, Osborne K. Pharmacists can help prevent misuse of prescription drugs by young people. *Pharm J* 2017; 298, 7902. DOI: 10.1211/PJ.2017.20202998.
- [58] Evoy KE, Teng C, Encarnacion VG, et al. Comparison of Quetiapine Abuse and Misuse Reports to the FDA Adverse Event Reporting System With Other Second-Generation Antipsychotics. *Subst Abuse.* 2019;13:1178221819844205. Published 2019 May 1. DOI:10.1177/1178221819844205.

- [59] Klein L, Bangh S, Cole JB. Intentional Recreational Abuse of Quetiapine Compared to Other Second-generation Antipsychotics. *West J Emerg Med.* 2017;18(2):243-250. DOI:10.5811/westjem.2016.10.32322.
- [60] Mattson ME, Albright VA, Yoon J, Council CL. Emergency Department Visits Involving Misuse and Abuse of the Antipsychotic Quetiapine: Results from the Drug Abuse Warning Network (DAWN). *Subst Abuse.* 2015;9:39-46. Published 2015 May 24. doi:10.4137/SART.S22233.
- [61] Heilbronn C, Lloyd B, McElwee P, Eade A, Lubman DI. Trends in quetiapine use and non-fatal quetiapine-related ambulance attendances. *Drug Alcohol Rev.* 2013 Jul;32(4):405-11. DOI: 10.1111/dar.12028.
- [62] Kim S, Lee G, Kim E, Jung H, Chang J. Quetiapine Misuse and Abuse: Is it an Atypical Paradigm of Drug Seeking Behavior?. *J Res Pharm Pract.* 2017;6(1):12-15. DOI:10.4103/2279-042X.200987.
- [63] Reeves RR, Brister JC. Additional evidence of the abuse potential of quetiapine. *South Med J.* 2007;100(8):834-836. DOI:10.1097/SMJ.0b013e3180f62d53.
- [64] EMC. 2020. Gabapentin. [Cited 2020 November 5]. Available from: <https://www.medicines.org.uk/emc/product/2362/smpc>
- [65] EMC. 2020. [Cited 2020 November 5]. Pregabalin. Available from: <https://www.medicines.org.uk/emc/product/1761/smpc>
- [66] Chiappini S, Schifano F. A Decade of Gabapentinoid Misuse: An Analysis of the European Medicines Agency's 'Suspected Adverse Drug Reactions' Database. *CNS Drugs.* 2016 Jul;30(7):647-54. DOI: 10.1007/s40263-016-0359-y.

- [67] Schifano F. Misuse and abuse of pregabalin and gabapentin: cause for concern? *CNS Drugs*. 2014;28(6):491-496. DOI:10.1007/s40263-014-0164-4.
- [68] Al-Husseini A, Wazaify M, Van Hout MC. Pregabalin Misuse and Abuse in Jordan: a Qualitative Study of User Experiences. *Int J Ment Health Addict*. 2018;16(3):642-654. DOI:10.1007/s11469-017-9813-4.
- [69] Baird CR, Fox P, Colvin LA. Gabapentinoid abuse in order to potentiate the effect of methadone: a survey among substance misusers. *Eur Addict Res*. 2014;20(3):115-118. DOI:10.1159/000355268.
- [70] Buttram ME, Kurtz SP. Preliminary Evidence of Pregabalin Misuse among Prescription and/or Illicit Opioid (Mis)users. *J Psychoactive Drugs*. 2020;52(2):172-175. DOI:10.1080/02791072.2020.1734695.
- [71] Crossin R, Scott D, Arunogiri S, Smith K, Dietze PM, Lubman DI. Pregabalin misuse-related ambulance attendances in Victoria, 2012-2017: characteristics of patients and attendances. *Med J Aust*. 2019;210(2):75-79. DOI:10.5694/mja2.12036.
- [72] Advisory Council on the Misuse of Drugs (ACMD). Addendum to advice on the anticonvulsant drugs Pregabalin and Gabapentin; 2018. [Cited 2020 November 5]. Available from: <https://www.gov.uk/government/publications/advice-on-the-anticonvulsant-drugs-pregabalin-and-gabapentin/addendum-to-advice-on-the-anticonvulsant-drugs-pregabalin-and-gabapentin-october-2018>
- [73] Gunja N. The clinical and forensic toxicology of Z-drugs. *J Med Toxicol*. 2013;9(2):155-162. DOI:10.1007/s13181-013-0292-0.
- [74] Hockenhull J, Black JC, Haynes CM, Rockhill K, Dargan PI, Dart RC, Wood DM. Nonmedical use of benzodiazepines and Z-drugs in the UK. *Br J Clin Pharmacol*. 2020 May 30. DOI: 10.1111/bcp.14397.

- [75] Griffiths RR, Johnson MW. Relative abuse liability of hypnotic drugs: a conceptual framework and algorithm for differentiating among compounds. *J Clin Psychiatry*. 2005;66 Suppl 9:31-41.
- [76] Rousselet M, Feuillet F, Gerardin M, Jolliet P, Hardouin JB, Victorri-Vigneau C. The French addictovigilance network clinical assessment: Z-drugs, true false twins. *Expert Opin Drug Saf*. 2017;16(9):1063-1069. DOI:10.1080/14740338.2017.1346084.
- [77] Jaffe JH, Bloor R, Crome I, Carr M, Alam F, Simmons A, Meyer RE (2004) A postmarketing study of relative abuse liability of hypnotic sedative drugs. *Addiction* 99:165–173.
- [78] Advisory Council on the Misuse of Drugs (ACMD). Advice on the control of Z-drugs (zaleplon, zolpidem and zopiclone); September 2013. [Cited 2020 May 26]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/237037/ACMD_advice_Z_drugs.pdf
- [79] Marsden J, White M, Annand F, Burkinshaw P, Carville S, Eastwood B, et al. Medicines associated with dependence or withdrawal: a mixed-methods public health review and national database study in England. *Lancet Psychiatry*. 2019; 6(11):935-950. DOI: 10.1016/S2215-0366(19)30331-1.
- [80] EMC. Zyban 150 mg prolonged release tablets; 2019. [Cited 2020 August 16]. Available from: <https://www.medicines.org.uk/emc/medicine/2948/>
- [81] Hu LY, Lu T, Chen YT. Have we underestimated the possibility of bupropion sustained-release addiction? *Aust. N. Z. J. Psychiatry* 2016; 50, 925–926. DOI: 10.1177/0004867416632928.
- [82] McCormick J. Recreational bupropion abuse in a teenager. *Br J Clin Pharmacol*. 2002;53(2):214. DOI:10.1046/j.0306-5251.2001.01538.x.

- [83] Reeves RR, Ladner ME. Additional evidence of the abuse potential of bupropion. *J. Clin. Psychopharmacol.* 2013; 33, 584–585. DOI: 10.1097/JCP.0b013e318295fe2f.
- [84] Stall N, Godwin J, Juurlink D. Bupropion abuse and overdose. *CMAJ.* 2014;186(13):1015. DOI:10.1503/cmaj.131534.
- [85] Namdari B. Venlafaxine abuse in a patient with schizophrenia and prior history of substance dependence: a case report. *J Addict Dis.* 2013;32(4):393-395. DOI:10.1080/10550887.2013.84997.
- [86] Bosse GM, Spiller HA, Collins AM. A fatal case of venlafaxine overdose. *J Med Toxicol.* 2008;4(1):18-20. DOI:10.1007/BF03160945.
- [87] Leonard JB, Klein-Schwartz W. Characterization of intentional-abuse venlafaxine exposures reported to poison control centers in the United States. *Am J Drug Alcohol Abuse.* 2019;45(4):421-426. DOI:10.1080/00952990.2019.1599382.
- [88] Benotsch EG, Koester S, Martin AM, Cejka A, Luckman D, Jeffers AJ. Intentional misuse of over-the-counter medications, mental health, and polysubstance use in young adults. *J Community Health.* 2014;39(4):688-695. DOI: 10.1007/s10900-013-9811-9.
- [89] Le VT, Norris Turner A, McDaniel A, Hale KM, Athas C, Kwiek NC. Nonmedical use of over-the-counter medications is significantly associated with nonmedical use of prescription drugs among university students. *J Am Coll Health.* 2018 Jan;66(1):1-8. DOI: 10.1080/07448481.2017.1356312.
- [90] Cooper RJ. 'I can't be an addict. I am.' Over-the-counter medicine abuse: a qualitative study. *BMJ Open.* 2013;3(6):e002913. DOI:10.1136/bmjopen-2013-002913.

- [91] MacDonald R, Heiner J, Villarreal J, Strote J. Loperamide dependence and abuse. *BMJ Case Rep.* 2015;2015:bcr2015209705. Published 2015 May 2. doi:10.1136/bcr-2015-209705.
- [92] Powell JW, Presnell SE. Loperamide as a Potential Drug of Abuse and Misuse: Fatal Overdoses at the Medical University of South Carolina. *J Forensic Sci.* 2019 Nov;64(6):1726-1730. DOI: 10.1111/1556-4029.14115.
- [93] Ali M, Mujahid A, Bulathsinghala CP, Surani S. Cardiac Arrhythmia Secondary to Loperamide Abuse and Toxicity. *Cureus.* 2020;12(2):e6936. Published 2020 Feb 10. DOI:10.7759/cureus.6936.
- [94] Antoniou T, Juurlink DN. Loperamide abuse. *CMAJ.* 2017;189(23):E803. DOI:10.1503/cmaj.161421.
- [95] Atoot A, Sholem S, Khaddash I, Zuberi J. Transient Brugada Pattern Induced by Loperamide Abuse. *Cureus.* 2020;12(5):e8037. DOI:10.7759/cureus.8037.
- [96] Katz KD, Cannon RD, Cook MD, Amaducci A, Day R, Enyart J, et al. Loperamide-Induced Torsades de Pointes: A Case Series. *J Emerg Med.* 2017 Sep;53(3):339-344. DOI: 10.1016/j.jemermed.2017.04.027.
- [97] Marraffa JM, Holland MG, Sullivan RW, Morgan BW, Oakes JA, Wiegand TJ, et al. Cardiac conduction disturbance after loperamide abuse. *Clin Toxicol (Phila).* 2014 Nov;52(9):952-7. DOI: 10.3109/15563650.2014.969371.
- [98] Nattel S. An Emerging Malignant Arrhythmia Epidemic Due to Loperamide Abuse: Underlying Mechanisms and Clinical Relevance. *JACC Clin Electrophysiol.* 2016;2(7):790-792. DOI:10.1016/j.jacep.2016.10.009.
- [99] Rasla S, Parikh P, Hoffmeister P, St Amand A, Garas MK, El Meligy A, Minami T, Shah NR. Unexpected Serious Cardiac Arrhythmias in the Setting of Loperamide Abuse. *R I Med J* (2013).

2017 Apr 3;100(4):33-36. Erratum in: R I Med J (2013). 2017 Aug 1;100(8):8. Parikh, Parag [added]; Hoffmeister, Peter [added]; Shah, Nishant R [added].

[100] Stefek B, Wolfe LT, Cohen M. Brugada Syndrome Associated With Adolescent Loperamide Abuse. *Pediatrics*. 2018;142(4):e20181423. DOI:10.1542/peds.2018-1423.

[101] Wightman RS, Hoffman RS, Howland MA, Rice B, Biary R, Lugassy D. Not your regular high: cardiac dysrhythmias caused by loperamide. *Clin Toxicol (Phila)*. 2016;54(5):454-458. DOI:10.3109/15563650.2016.1159310.

[102] Vakkalanka JP, Charlton NP, Holstege CP. Epidemiologic Trends in Loperamide Abuse and Misuse. *Ann Emerg Med*. 2017;69(1):73-78. DOI:10.1016/j.annemergmed.2016.08.444.

[103] Eggleston W, Marraffa JM, Stork CM, Mercurio-Zappala M, Su MK, Wightman RS, Cummings KR, Schier JG. Notes from the Field: Cardiac Dysrhythmias After Loperamide Abuse - New York, 2008-2016. *MMWR Morb Mortal Wkly Rep*. 2016 Nov 18;65(45):1276-1277. DOI: 10.15585/mmwr.mm6545a7.

[104] Food and Drug Administration (FDA). FDA limits packaging for anti-diarrhea medicine loperamide (Imodium) to encourage safe use; 2019. [Cited 2020 August 16]. Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-limits-packaging-anti-diarrhea-medicine-loperamide-imodium-encourage-safe-use>

[105] Feldman R, Everton E. National assessment of pharmacist awareness of loperamide abuse and ability to restrict sale if abuse is suspected [published online ahead of print, 2020 Jul 5]. *J Am Pharm Assoc* (2003). 2020;S1544-3191(20)30264-8. DOI:10.1016/j.japh.2020.05.021.

[106] Martinak B, Bolis RA, Black JR, Fargason RE, Birur B. Dextromethorphan in Cough Syrup: The Poor Man's Psychosis. *Psychopharmacol Bull*. 2017;47(4):59-63.

- [107] Sansgiry SS, Bhansali AH, Bapat SS, Xu Q. Abuse of over-the-counter medicines: a pharmacist's perspective. *Integr Pharm Res Pract*. 2017; 6: 1–6. DOI: 10.2147/IPRP.S103494.
- [108] Schwartz RH. Adolescent abuse of dextromethorphan. *Clin Pediatr (Phila)*. 2005;44(7):565-568. DOI:10.1177/000992280504400702.
- [109] Acar YA, Kalkan M, Cetin R, Cevik E, Cinar O. Acute Psychotic Symptoms due to Benzydamine Hydrochloride Abuse with Alcohol. *Case Rep Psychiatry*. 2014: 290365. DOI:10.1155/2014/290365.
- [110] Anand JS, Lukasik-Głębocka M, Korolkiewicz RP. Recreational abuse with benzydamine hydrochloride (tantum rosa). *Clin Toxicol*. 2007; 45(2): 198-199. DOI: 10.1080/15563650600981210.
- [111] Ballesteros S, Ramón MF, Martínez-Arrieta R. Ingestions of benzydamine-containing vaginal preparations. *Clin Toxicol (Phila)*. 2009;47(2):145-149. DOI:10.1080/15563650801938670.
- [112] Can B, Oz I, Ozer H, Simsek T. Hallucinations after Ingesting a High Dose of Benzydamine Hydrochloride. *Clin Psychopharmacol Neurosci*. 2016;14(4):407-408. DOI:10.9758/cpn.2016.14.4.407.
- [113] Doğan M, Yılmaz C, Çaksen H, Güven AS. A case of benzydamine HCL intoxication. *East J Med* 2006, 11(1): 26–28.
- [114] Gürü M, Şafak Y, Cengiz GF, Kuru E, Örsel S. Chronic psychosis related to benzydamine hydrochloride abuse. *Neurocase*. 2019 Jun - Aug;25(3-4):156-158. DOI: 10.1080/13554794.2019.1617318.
- [115] Rotolo MC, Pellegrini M, Solimini R, Pichini S, Pacifici R. 'Smart drugs', the new drugs on the web: two cases of acute intoxication. *Biochim Clin*. 2014; 38(3): 268-271.

- [116] Avvisati R, Meringolo M, Stendardo E, Malavasi E, Marinelli S, Badiani A. Intravenous self-administration of benzydamine, a non-steroidal anti-inflammatory drug with a central cannabinoidergic mechanism of action. *Addict Biol.* 2018;23(2):610-619. DOI:10.1111/adb.12516.
- [117] Tsay ME, Procopio G, Anderson BD, Klein-Schwartz W. Abuse and Intentional Misuse of Promethazine Reported to US Poison Centers: 2002 to 2012. *J Addict Med.* 2015;9(3):233-237. DOI:10.1097/ADM.0000000000000124.
- [118] Chiappini S, Corkery JM, Schifano F, Guirguis A. Beyond the purple drank. Study of promethazine abuse according to the European Medicines Agency (EMA) adverse drug reactions (ADR) reports *J Psychopharmacol* 2020, in press.
- [119] Clatts M, Giang le M, Goldsamt L, Colón-López V. Nonmedical use of promethazine hydrochloride among heroin injectors in Vietnam: unrecognized risks and unintended consequences. *Subst Use Misuse.* 2010;45(4):515-527. DOI:10.3109/10826080903452520.
- [120] Lynch KL, Shapiro BJ, Coffa D, Novak SP, Kral AH. Promethazine use among chronic pain patients. *Drug Alcohol Depend.* 2015;150:92-97. DOI:10.1016/j.drugalcdep.2015.02.023.
- [121] Shapiro BJ, Lynch KL, Toochinda T, Lutnick A, Cheng HY, Kral AH. Promethazine misuse among methadone maintenance patients and community-based injection drug users. *J Addict Med.* 2013;7(2):96-101. DOI:10.1097/ADM.0b013e31827f9b43.
- [122] Banerji S, Anderson IB. Abuse of Coricidin HBP cough & cold tablets: episodes recorded by a poison center. *Am J Health Syst Pharm.* 2001 Oct 1;58(19):1811-4. DOI: 10.1093/ajhp/58.19.1811.

- [123] Dickerson DL, Schaepper MA, Peterson MD, Ashworth MD. Coricidin HBP abuse: patient characteristics and psychiatric manifestations as recorded in an inpatient psychiatric unit. *J Addict Dis.* 2008;27(1):25-32. DOI:10.1300/J069v27n01_03.
- [124] Kirages TJ, Sulé HP, Mycyk MB. Severe manifestations of coricidin intoxication. *Am J Emerg Med.* 2003;21(6):473-475. DOI:10.1016/s0735-6757(03)00168-2.
- [125] Monte AA, Chuang R, Bodme M. Dextromethorphan, chlorphenamine and serotonin toxicity: case report and systematic literature review. *Br J Clin Pharmacol.* 2010; 70:6: 794–798. DOI: 10.1111/j.1365-2125.2010.03747.x.
- [126] Kinoshita H, Tanaka N, Jamal M, Kumihashi M, Okuzono R, Ameno K. A fatal case due to cough syrup abuse. *Soud Lek.* 2012;57(4):69-70.
- [127] Baker SD, Borys DJ. A possible trend suggesting increased abuse from Coricidin exposures reported to the Texas Poison Network: comparing 1998 to 1999. *Vet Hum Toxicol.* 2002;44(3):169-171.
- [128] Saran JS, Barbano RL, Schult R, Wiegand TJ, Selioutski O. Chronic diphenhydramine abuse and withdrawal. A diagnostic challenge. *Neurol Clin Pract.* 2017 Oct; 7(5): 439–441. DOI: 10.1212/CPJ.0000000000000304.
- [129] Cheng SW, Hu WH, Hung DZ, Yang DY. Anticholinergic poisoning from a large dose of Scopolia extract. *Vet Hum Toxicol.* 2002;44(4):222-223.
- [130] Ham S, Tae KK, Kim K, Sooyoung C, Heh-In I. Drug Abuse and Psychosis: New Insights into Drug-induced Psychosis. *Exp Neurobiol.* 2017 Feb;26(1):11-24. DOI: 10.5607/en.2017.26.1.1.
- [131] Lakstygal AM, Kolesnikova TO, Khatsko SL, Zabegalov KN, Volgin AD, Demin KA, et al. DARK Classics in Chemical Neuroscience: Atropine, Scopolamine, and Other Anticholinergic

Deliriant Hallucinogens. ACS Chem Neurosci. 2019 May 15;10(5):2144-2159. DOI: 10.1021/acschemneuro.8b00615.

[132] Enforcement Administration (DEA). COVID-19 information page; 2020. [Cited 2020 May 26]. Available from: www.deadiversion.usdoj.gov/coronavirus.html

[133] European Monitoring Centre for Drug and Drug Addiction (EMCDDA). The implications of COVID-19 for people who use drugs (PWUD) and drug service providers; March 2020. [Cited 2020 May 26]. Available from: http://www.emcdda.europa.eu/publications/topic-overviews/covid-19-and-people-who-use-drugs_en

[134] Chiappini S, Guirguis A, John A, Corkery JM, Schifano F. COVID-19: The Hidden Impact on Mental Health and Drug Addiction. Front Psychiatry 2020a; 11:767. DOI: 10.3389/fpsy.2020.00767.

[135] GOV.UK. COVID-19: guidance for commissioners and providers of services for people who use drugs or alcohol; 2020. [Cited 2020 May 26]. Available from: <https://www.gov.uk/government/publications/covid-19-guidance-for-commissioners-and-providers-of-services-for-people-who-use-drugs-or-alcohol/covid-19-guidance-for-commissioners-and-providers-of-services-for-people-who-use-drugs-or-alcohol>

[136] Pfefferbaum B, North CS. Mental Health and the Covid-19 Pandemic. NEJM 2020 Aug 6;383(6):510-512. DOI: 10.1056/NEJMp2008017.

[137] Volkow ND. Collision of the COVID-19 and Addiction Epidemics. Ann Intern Med. 2020. DOI: 10.7326/M20-1212.

[138] Zhu S, Wu Y, Zhu CY, Hong WC, Yu ZX, Chen ZK, et al. The immediate mental health impacts of the COVID-19 pandemic among people with or without quarantine managements. Brain Behav Immun. 2020 Apr 18. pii: S0889-1591(20)30601-2. DOI: 10.1016/j.bbi.2020.04.045.

[139] United Nations (UN). COVID-19 causes some illegal drug prices to surge, as supplies are disrupted worldwide; 2020. [Cited 2020 May 26]. Available from: <https://news.un.org/en/story/2020/05/1063512>

[140] Volkow ND. Coping with the Collision of Public Health Crises: COVID-19 and Substance Use Disorders. NIH Director's Blog with Dr. Volkow, April 21, 2020. [Cited 2020 May 26]. Available from: <https://directorsblog.nih.gov/2020/04/21/coping-with-the-collision-of-public-health-crises-covid-19-and-substance-use-disorders/>.

[141] Green TC, Bratberg J, Finnell DS. Opioid use disorder and the COVID 19 pandemic: A call to sustain regulatory easements and further expand access to treatment. *Subst Abus.* 2020;41(2):147-149. DOI: 10.1080/08897077.2020.1752351.

[142] Hogue MD, Hogue HB, Lander RD, Avent K, Fleenor M. The nontraditional role of pharmacists after Hurricane Katrina: process description and lessons learned. *Public health rep.* 2009; 124(2): 217-223. DOI: 10.1177/003335490912400209.

[143] Substance Abuse and Mental Health Services Administration (SAMHSA). COVID-19 and Opioid Treatment Programs; 2020. [Cited 2020 November 5]. <https://www.samhsa.gov/sites/default/files/sample-otp-covid-19-faqs.pdf>

[144] Wazaify M, Hughes CM, McElnay JC. The implementation of a harm minimisation model for the identification and treatment of over-the-counter drug misuse and abuse in community pharmacies in Northern Ireland. *Patient Educ Couns.* 2006 Dec;64(1-3):136-41. DOI: 10.1016/j.pec.2005.12.008.

[145] American Society of Health-System Pharmacists (ASHP) (2016). ASHP statement on the pharmacist's role in substance abuse prevention, education, and assistance. *Am J Health-Syst Pharm.* 2016; 73:e267-70. DOI: 10.2146/sp140002.

- [146] Cooper RJ. Surveillance and uncertainty: community pharmacy responses to over the counter medicine abuse. *Health Soc Care Community*. 2013;21(3):254-262. DOI:10.1111/hsc.12012.
- [147] Sheridan J, Manning V, Ridge G, Mayet S, Strang J. Community pharmacies and the provision of opioid substitution services for drug misusers: changes in activity and attitudes of community pharmacists across England 1995-2005. *Addiction*. 2007;102(11):1824-1830. DOI:10.1111/j.1360-0443.2007.02016.x.
- [148] Wagner AG, Guerra de Andrade A. Pharmacist professionals in the prevention of drug abuse: updating roles, and opportunities. *Brazil J Pharmac Sciences*. 2010; 46(1). DOI: 10.1590/S1984-82502010000100003.
- [149] Becker WC, Fiellin DA. When Epidemics Collide: Coronavirus Disease 2019 (COVID-19) and the Opioid Crisis. *Ann Intern Med* 2020. DOI:10.7326/M20-1210.
- [150] Simeone R. Doctor Shopping Behavior and the Diversion of Prescription Opioids. *Subst Abuse*. 2017; 11: 1178221817696077. DOI: 10.1177/1178221817696077.
- [151] Levander XA, Wakeman SE. Covid-19 will worsen the opioid overdose crisis if we don't prepare now. *STAT*, 2020. [Cited 2020 November 5]. Available from: <https://www.statnews.com/2020/03/17/covid-19-will-worsen-the-opioid-overdose-crisis-if-we-dont-prepare-now/>
- [152] World Health Organization (WHO), 2020. [Cited 2020 May 26]. Available from: http://www.euro.who.int/__data/assets/pdf_file/0010/437608/Alcohol-and-COVID-19-what-you-need-to-know.pdf

- [153] Spoth R, Trudeau L, Shin C, Redmond C. Long-term effects of universal preventive interventions on prescription drug misuse. *Addiction*. 2008;103(7):1160-1168. DOI:10.1111/j.1360-0443.2008.02160.x.
- [154] Chary M, Yi D, Manini AF. Candyflipping and Other Combinations: Identifying Drug-Drug Combinations from an Online Forum. *Front Psychiatry*. 2018;9:135. DOI:10.3389/fpsyt.2018.00135.
- [155] Clinical Guidelines on Drug Misuse and Dependence Update 2017. Independent Expert Working Group, 2017. Drug misuse and dependence: UK guidelines on clinical management. London: Department of Health.
- [156] Crowley DM, Jones DE, Coffman DL, Greenberg MT. Can we build an efficient response to the prescription drug abuse epidemic? Assessing the cost effectiveness of universal prevention in the PROSPER trial. *Prev Med*. 2014;62:71-77. DOI:10.1016/j.ypmed.2014.01.029.
- [157] Rajkumar RP. COVID-19 and mental health: A review of the existing literature. *Asian J Psychiatr*. 2020;52:102066. doi:10.1016/j.ajp.2020.102066.
- [158] Ransing R, Adiukwu F, Pereira-Sanchez V, Ramalho R, Orsolini L, Schuh Teixeira AL, et al. Mental Health Interventions during the COVID-19 Pandemic: A Conceptual Framework by Early Career Psychiatrists. *Asian J Psychiatry* 2020;51: 102085. DOI: 10.1016/j.ajp.2020.102085.
- [159] Reger MA, Stanley IH, Joiner TE. Suicide Mortality and Coronavirus Disease 2019—A Perfect Storm? *JAMA Psychiatry*. Published online April 10, 2020. DOI:10.1001/jamapsychiatry.2020.1060.
- [160] Smith K, Ostinelli E, Cipriani A. Evid Based Ment Health 2020;23:45–46. Evid Based Ment Health 2020;23:45–46. DOI:10.1136/ebmental-2020-300155.

