

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

Originally submitted: 30 March 2020;

Revised submitted: 17 August 2020;

Accepted for publication: 20 August 2020;

Published online:

DOI:

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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Financial disclosure/conflict of interest statement

F.S. was a member of the UK Advisory Council on the Misuse 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.

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