Misuse of Prescription and Over the Counter Drugs to Obtain Illicit Highs: How Pharmacists Can Prevent 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.*

I. INTRODUCTION

A variety of terms are used to describe when over the counter (OTC) and prescription only medication (POM) are used in a way other than as the manufacturers intended or as di- rected by a healthcare professional. In this research 'misuse' is used to describe the in- tentional inappropriate use of products. (where the administration route or dose may be altered), for non-medical purposes. This term is also used to describe specialist treat- ment providers, since across the UK, they continue to be commissioned as "substance misuse services (SMSs). Although misuse' is contested by some who may view it as stigmatising and inaccurate, 'an exception may be claimed if people are using pharma- ceuticals in ways that goes against advice from the supplier'.

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

This review is reported in line with PRISMA. The protocol has been registered on PROSPERO (CRD42020135216) and separately published. A search of Cochrane, OVID Medline, Pubmed, Scopus and Web of Science databases and grey literature was un- dertaken. Only English language publica- tions outlining OTC/POM misuse by adults in receipt of psychological/pharmacological interventions for substance misuse were in- cluded. Two reviewers conducted the title. abstract and full-text reviews using predeter- mined selection criteria and a piloted data extraction form to ensure a consistent ap- proach. A third reviewer resolved disagree- ments and the Mixed Methods Appraisal Tool assessed for bias. Ethical approval was not required.

Eligibility criteria

This review will consist of published studies which must meet all the following criteria:

- Adult participants (18 years or over)
- People who are misusing OTC/POM for non-medical purposes.

Prescription drug misuse

- Quetiapine
- Gabapentinoids
- Z-drugs(zolpidem, zaleplon,zopiclon)
- Bupropion
- Venlafaxine

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.

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)

Over-the-counter drugs misuse

Drug/drug classification	Administration path	Mechanism of action	Effects	Does it cause dependence?	Street names and brand names
Chlorpheniramine (antihistamine)	Oral	• Chlorpheniramine acts primarily as a potent H1 antihistamine drug • Moderate anticholinergic activity • Chlorpheniramine has been found to act as a serotonin reuptake inhibitor	• ACUTE EFFECTS: *psychiatric effects*: (i) sedating and anxiolytic properties; (ii) its abuse has been related to pleasurable feelings such as euphoria and stimulating effects; (iii) it may be associated with psychotic symptoms in predisposed individuals (e.g., people with mental illnesses or individuals concomitantly abusing other drugs) • CHRONIC EFFECTS: dependence	• Drug dependence is recorded after long-term use • Withdrawal symptoms, including excessive irritability, anger outbursts, insomnia, sweating, and craving	"Triple c" refers to Coricidin®, cough and cold tablets; the combination of codeine, methyl ephedrine chlorpheniramine, and caffeine is marketed as Bron®; Panadol® is a combination of chlorpheniramine, paracetamol and pseudoephedrine; Advil® includes ibuprofen, chlorpheniramine and phenylephrine; other brand names: Polaramine®, Chlortrimeton®
Codeine (opioid)	Oral, IV	• It is a selective agonist of the mu-opioid receptor; it is a natural isomer of methylated morphine, requiring metabolic activation by O-demethylation to morphine by CYP2D6	• ACUTE EFFECTS: *psychiatric effects*: euphoria, elation, analgesia, calmness; *physical effects*: respiratory depression, extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. The triad of coma, pinpoint pupils, and respiratory depression is strongly suggestive of opiate poisoning. In severe overdosage, death may occur • CHRONIC EFFECTS: dependence	• Codeine has an identified abuse liability potential, given its effect and development of tolerance within a short timeframe on regular or excessive use • Codeine-dependence was here recorded, and associated with daily use of codeine	Street names: "Captain Cody," "Cody," "Little C," "Schoolboy," "Doors & Fours." Common brand names for codeine and codeine containing combinations: Aspalgin® for aspirin and codeine; Nurofen Plus® for ibuprofen and codeine; Panadeine Forte® for paracetamol and codeine
Dextromethorphan (DXM) (non-competitive NMDA receptor antagonist and sigma 1 agonist antitussive)	Oral; IV and IN use also recorded in misuse cases	• At high doses, acting as a NMDA receptor antagonist, DXM and its potent metabolite dextrorphan inhibit the excitatory amino acid and neurotransmitter glutamate, causing hallucinogenic and dissociative states • DXM also exhibits binding activity at serotonergic receptors	• Neurobehavioural effects begin within 30–60 min of ingestion and persist for approximately 6 h • They are dose-related, starting from a mild to moderate stimulation with restlessness and euphoria (100–200 mg), to a state characterized by hallucinations, paranoia, perceptual distortions, delusional beliefs, ataxia, and out-of-body experiences (>1,000 mg) • ACUTE EFFECTS: (i) *psychiatric effects*: euphoria, altered mental status, mania, mood lability, irritability, dysphoria, insomnia; (ii) *physical effects*: tachycardia, hypertension, vomiting, mydriasis, diaphoresis, nystagmus, dystonia, loss of motor coordination; • CHRONIC EFFECTS: (i) toxic psychosis and cognitive deterioration; (ii) folate deficiency and neuropathy; (iii) since DXM is produced as the crystalline hydrobromide salt, bromism is a rare consequence that has been identified in heavy chronic abusers of DXM (neurotoxic effects, resulting in somnolence, psychosis, seizures, and delirium	• Although DXM is not thought to have addictive properties, its chronic use might determine addiction due to GABAergic/antiglutamatergic mechanisms, including substance-taking compulsive behaviors, tolerance, and autonomic withdrawal symptoms • EMCDDA: regarded as NPS	Street names: "Bromage," "Brome," "Candy," "Dex," "Dextro," "DM," "Drex," "DXM," "Red Devils," "Robo," "Rojo," "Skittles," "Triple C," "Tussin," "Velvet," and "Vitamin D." "Poor Man's Ecstasy"; the practice of using large amounts of DXM to achieve psychoactive effects is known as "robotrippin." Common brand names are: Balminil DM®, Benylin DM®, Bronchophan®, Buckleys CR, Calylin #1, Delsym®, Koffex DM®, Novahistex DM®, Robitussin®
Diphenhydramine (DPH) (antihistamine moiety of dimenhydrinate/DH)	Oral; IV and IN use also recorded in misuse cases	• It is a first generation H1-antihistamine • Diphenhydramine also acts as a potent anticholinergic agent • It can acutely block the cell membrane pump mechanism of central 5-hydroxytryptophane and peripheral noradrenaline neurons	• ACUTE EFFECTS: (i) *psychiatric effects*: euphoria, altered mental status, hallucinations, and/or psychosis; (ii) *physical effects*: tachycardia, xerostomia, mydriasis, blurred vision, ileus, urinary retention, CNS depression, agitation, and hyperactivity • CHRONIC EFFECTS: dependence	• Reported cases of DPH dependence have resulted from usage of large doses (often over 1,000 mg per day) over periods of months or years. Withdrawal symptoms include craving, worsening of insomnia, rhinorrhoea, nausea, irritability, restlessness, abdominal cramps, sweating, and diarrhea. Gradual tapering has been the only described detoxification treatment plan	Different brand names, including Benadryl®, Dimedrol®, Daedalon®, Sominex®, Unisom® and Nytol®
Promethazine (antihistamine)	Oral	• It is a phenothiazine derivative and a H1 receptor antagonist; It also acts as a direct antagonist at muscarinic (M1) and dopamine (D2) receptors. It is classified as a first-generation antihistamine molecule which easily penetrates the blood-brain barrier and is associated with adverse effects such as sedation	• ACUTE EFFECTS: from mild sedation and CNS depression to profound hypotension, respiratory depression, unconsciousness, and sudden death; overdosage might determine an antimuscarinic delirium, agitation and neuroleptic malignant syndrome • It can be used to enhance effects of other co-ingested substances, e.g., opioids • CHRONIC EFFECTS: NR	• EMCDDA: regarded as NPS • Dependence might develop after long-term use of promethazine cough mixtures (containing opioids)	Promethazine mixed with a soft drink and/or alcohol is known as "purple drank," "lean," "syzzurp," "Texas tea"; Phenergan® and Phenadoz® are common brand names
Pseudoephedrine (decongestant)	Oral; IV use also recorded in misuse cases	• Sympathomimetic properties, exerting a stimulating action on alpha, beta1-, and beta2-adrenergic receptors	• ACUTE EFFECTS: stimulant effects, e.g., euphoria, insomnia, diminished sense of fatigue, anorexia, and accelerated thinking; psychotic symptoms with auditory and visual hallucinations, persecutory delusions, fear, disorganized behavior might develop after high-dose consumption • CHRONIC EFFECTS: dependence	• Dependence might be developed after long-term use • Withdrawal symptoms include: dysphoria, restlessness, abnormal perceptions • Due to the possibility to be used to manufacture the class A controlled drug methylamphetamine, restrictions have been in place in the UK to manage the risk of products containing pseudoephedrine and ephedrine; in the US, a prescription is not needed in most States, and in remaining States there are limits on how much an adult subject can buy each month	"Chalk," "Crank," "Meth," "Speed"; "Russian Cocktail" includes pseudoephedrine consumed together with potassium permanganate and acetylsalicylic acid diluted in water; common brand names: Sudafed®, Nexalex®, Zephrex-D®; Clarifin® includes pseudoephedrine and loratadine

CNS, central nervous system; DH, Dimenhydrinate; DPH, Diphenhydramine; EMCDDA, European Monitoring Centre for Drugs and Drug Addiction; GABA, Gamma-Amino-Butyric Acid; H, Histamine; IN, Intranasal; IV, Intravenous; NMDA, N-Methyl-D-Aspartate; NPS, New Psychoactive Substance; OTC, Over-The-Counter; 5-HT, Serotonin.

Diphenhydramine

It can treat pain and itching caused by insect bites, minor cuts, burns, poison ivy, poison oak, and poison sumac when applied topically. In its oral form, it can treat hay fever, allergies, cold symptoms, and insomnia. In its injected form, it can treat severe allergic reactions, motion sickness, and symptoms of Parkinson's disease.

Promethazine

Promethazine is an antihistamine sometimes used as a sleeping pill. It is also known by the trade names Phenergan and Sominex.

It's available to buy without a prescription from a doctor. It is an ingredient in some over-the- counter cold and flu medicines, such as Night Nurse.

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

Abuse of drug during the Covid-19 pandemic

The impact of COVID-19 on self-medication practice can be explained in several ways. 14 First, lack of access to healthcare, especially in the first wave of the pandemic, in which hospital consultations were restricted. Second, fear of contracting the virus could reflect a lack of confidence in preventative measures. Third, unavailability of physicians either due to crowding or being infected. Fourth, COVID-19-related misinformation on social media, and fifth, accessibility of medicines after the large-scale implementa- tion of online drug ordering and home deliv- ery of medication worldwide.

Early warning tools that enable pharmacists and other professionals to monitor patients' OTC medicine dispensing history could assist in identifying potential abuse. However, the Real Time Prescription Monitoring (RTPM) systems that have been adopted in Canada, Australia, and the United States only monitor controlled medicines, and mixed data are available regarding the effectiveness of these systems in reducing the abuse of drugs.Therefore, the extension of RTPM systems to include OTC medicines could help identify those patients at risk of OTC medicine abuse.

Strategies to Reduce the Abuse and Misuse of OTC Medicines During Pandemics.

Strategies	Reducing the abuse of OTC medicines	Reducing the misuse of OTC medicines
Activating and updating pharmacovigilance systems	√	√
Appropriate relocation of resources and personnel	√	√
Open and maintain communication channels between healthcare providers and patients	√	√
Using social media on a large scale to fight misinformation and rumors	√	√
Integrate mental health services into health preparedness plans	√	√
Education of patients on the appropriate use of OTC medicines	√	√
Ensuring the mental health facilities remain open during pandemics	√	√
Implementation of early warning systems in community and hospital pharmacies	√	×
Reasonable restrictions on the online dispensing of OTC medicines	√	×
Training healthcare professionals on identifying the abuse of OTC medicine	√	×
Legislation permitting a pharmacist to examine the history of mental problems of individuals with suspicious behaviors before dispensing OTC medicines	√	×
Awareness-raising campaigns on the consequences of OTC medicine abuse	√	×

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 . 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 . As healthcare providers, they should participate in or contribute to the development of specific prevention and assistance programmes within healthcare organisations or public services avoid potentially risky prescribing practices (eg. prescribing larger quantities of pain medication than is clinically needed); and collaborate with outpatient and ambulatory care providers to prevent substance abuse after discharge.

Implications for practice

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.

II. CONCLUSIONS

With the substantial increase in the preva- lence of self-medication of OTC medicines during the pandemic, the patterns of abuse and misuse of these medicines could be in- creased. Maintaining people's mental health, patient education about medication use and adverse events, minimising misinformation and rumours, and improving access to health- care in a pandemic are recommended to be implemented in a multifactorial strategy for the prevention of abuse and misuse of OTC medicines in a pandemic.

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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