REVIEW

RECREATIONAL USE OF POPULAR OTC DRUGS – PHARMACOLOGICAL REVIEW

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Abstract

Over-the-counter medicines use disorder is a serious and growing health problem affecting mainly adolescents. Drugs from many therapeutic classes, including antitussive agents such as dextromethorphan and codeine, antihistamine drugs diphenhydramine and dimenhydrinate, nasal decongestant pseudoephedrine and anti-inflammatory drug benzydamine are used for this purpose. Habitual users of most of these drugs can develop symptoms of substance dependence. When used in large quantities, these drugs can cause numerous toxic effects, including death. Recently many countries introduced legal restrictions in codeine, dextromethorphan and pseudoephedrine sales.

Rezumat

Abuzul de medicamente eliberate fără rețetă reprezintă o problemă gravă a sănătății care afectează în principal adolescenții. În acest scop, sunt utilizate medicamente din mai multe clase terapeutice, incluzând agenți antitusivi precum dextrometorfan și codeină, medicamente antihistaminice difenhidramină și dimenhidrinat, pseudoefedrină decongestionant nazal și benzidamină medicament antiinflamator. Utilizatorii obișnuiți ai majorității acestor medicamente pot dezvolta simptome de dependență la aceste substanțe. Atunci când sunt utilizate în cantități mari, aceste medicamente pot provoca numeroase efecte toxice, putând cauza inclusiv moartea. Recent, multe țări au introdus restricții în vânzările de codeină, dextrometorfan și pseudoefedrină, în farmacii.

Keywords: OTC medication use disorder, dextromethorphan, codeine, pseudoephedrine

Introduction

Substance use disorder is a widespread problem in society. Medications that should be used to treat diseases only, are also used for reasons other than indicated [23]. Prescription medications have been used for this purpose for many decades (e.g., painkillers or sedatives) but nowadays also over the counter (OTC) medications are frequently abused. Diagnosis of substance use disorder is based on The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition DSM-5 [3]. Patients must display 2 of the following 11 symptoms within 12-months to be diagnosed with substance use disorder: consuming more alcohol or other substance than originally planned; worrying about stopping or consistently failed efforts to control one's use; spending a large amount of time using drugs/alcohol, or doing whatever is needed to obtain them; use of the substance results in failure to "fulfil major role obligations" such as at home, work, or school; "craving" the substance (alcohol or drug); continuing the use of a substance despite mental or physical health problems caused or worsened by it; continuing the use of a substance despite its having negative effects in relationship with others; repeated use of the substance in a dangerous situation; giving up or reducing activities in a person's life because of the drug/alcohol use; developing a tolerance to the alcohol or drug; experiencing withdrawal symptoms after stopping use.

OTC drugs use disorder often arises as a sequel of previous genuine medical problems [10], but some of these drugs are abusively used, especially by adolescents from the beginning to get desired mood [5, 9, 36]. The wide variety and accessibility of OTC drugs and lack of surveillance mechanisms make it difficult to gather accurate data regarding this problem [36]. Nevertheless, available data show that OTC drug use disorder is very popular. A survey of community pharmacies in Jordan revealed that 94% of respondent pharmacists suspected that some level of non-prescription drug use disorder occurred regularly among their patients [9] and a study in Tulare County, California, regarding Drug Court clients, found that 16.2% admitted to abusing OTC medications, mostly ephedrine and other stimulants [23]. About 3.1 million people in the USA between 12 and 25 years of age (5.3 %) reported using OTC cough and cold medications to up lift their state of mind in

2006, according to the Substance Abuse and Mental Health Services Administration [36].

A systematic review of literature in English was conducted in search electronic databases. PubMed and MEDLINE were browsed by using search terms such as "OTC abuse", "non-prescription drug abuse", "codeine", "dextromethorphan", "pseudoephedrine", "benzydamine", "antihistamines" combined with words such as "abuse/disorder/misuse". We have selected only full-text, English-language papers published after 1990.

Frequently abused OTC drugs

Dextromethorphan

Dextromethorphan (DMX) is the d-isomer of levorphanol, an opioid related to codeine. Its antitussive activity is based on its action on σ– receptors without significant affinity for μ-opioid receptors and the δ-opioid receptor, which are responsible for analgesic and central nervous system (CNS) depressant effects [8].

DMX is also used as a popular substance of abuse [26]. The popularity of DMX use disorder is growing: from 1999 through 2004, the frequency of all DMX abuse cases reported to the California Poison Control System (CPCS) increased 10-fold, which can be only partially elucidated by a general increase in the frequency of reported cases [5].

After oral administration, DMX is quickly absorbed in the gastrointestinal tract with peak serum levels reached within 2 - 2.5 h. DMX crosses the blood-brain into the cerebral spinal fluid by approximately 33 - 80% [18]. The antitussive activity of dextromethorphan lasts for approximately 5 - 6 hours with a plasma half-life of 2 - 4 hours [32]. Whereas maximal daily dose of this drug is 120 mg, some of the users intentionally overdose it (in the form of tablets or as a syrup) reaching doses exceeding sometimes 1000 mg in one dose [36].

When taken in large quantities (usually over 100 mL of cough syrup), DMX is rapidly metabolized by the liver (mainly by CYP2D6) and is O-demethylated to produce its active metabolite dextrorphan (DOR). DMX is then further N-demethylated and partially conjugated with glucuronic acid and sulphate ions. DMX is eliminated renally unchanged or as a demethylated metabolite [7]. In a study conducted in Poland around 10% of the population exhibited poor metabolism phenotype. In this group of patients, high doses of DMX may lead to acute poisoning [38].

DMX and DOR possess pharmacodynamic and psychoactive properties consistent with those of other NMDA receptor antagonists such as phencyclidine (PCP) and ketamine, both classified as dissociatives. Intoxication effects are different, but are generally consistent with NMDA receptor antagonism, sigma opioidergic agonism and serotonin enhancement. Rarely reported psychosis may require doses greater than 600 mg DMX [26].

In the study conducted in CPCS the most common adverse effects related to DMX use disorder were tachycardia, lethargy, hypertension, confusion, altered mental status, mydriasis, agitation, gastrointestinal effects, dizziness, ataxia, hallucinations, slurred speech, nystagmus and fever. Deaths are rare (no fatalities in CPCS study) but sometimes reported especially among teens [5].

Additional compounds in the drug can also cause toxicity in the setting of DMX use disorder. OTC cough formulations often contain not only DMX but also other active agents such as chlorpheniramine, acetaminophen or pseudoephedrine (PSE). A person who abuses DMX preparation containing chlorpheniramine may also display such anticholinergic symptoms as increased heart rate; warm, dry and flushed skin; dry mucosa; pupil dilation; excited delirium; urinary retention and diminished bowel movement. Severe chlorpheniramine poisoning has also been associated with seizures, rhabdomyolysis and hyperthermia. PSE intoxication is similar to that of chlorpheniramine, except that a patient may exhibit diaphoresis. In contrast, an overdose of acetaminophen produces delayed hepatic injury, which is potentially fatal. A rare consequence of DMX use disorder is bromism, caused by a neurotoxic effect of bromine (DMX is produced as the crystalline hydrobromide salt) on the brain, which results in drowsiness, psychosis, seizures and delirium [7].

DMX users abuse often multiple drugs. In a study conducted in Hong Kong, 6% of the urine samples of patients hospitalized, because of cough mixture abuse, contained DMX. The most frequently detected substances were promethazine (75%), pseudoephedrine (67%), codeine (60%), ephedrine (57%), zopiclone (17%), and hydrocodone (16%) [39].

Habitual users of DMX can develop symptoms that meet DSM-5 criteria for substance dependence. In a one case report, a 44 year old man was taking up to 1800 mg DMX daily for over 5 years. The patient exhibited physical withdrawal symptoms when he tried to stop consumption, about 1 year before admission. The patient completed behavioural therapy – based detoxification program and left the hospital after 3 weeks of treatment, in good general conditions [27].

Pseudoephedrine

Pseudoephedrine (PSE) is a sympathomimetic vasoconstrictor that is closely related to adrenaline in structure. It is a popular nasal decongestant used either alone (in preparations like Sudafed®, which contains 60 mg of PSE) [12] or in combination with other drugs such as ibuprofen or loratadine [21]. PSE has mainly indirect effects on adrenergic

receptors, particularly on cardiac beta-receptors and peripheral alpha 1 receptors, through displacement of noradrenaline from the cytoplasmic pool [12]. PSE is rapidly absorbed, with a median T_{max} of 120 min when administered orally [21]. PSE is a drug abused sometimes itself, but more notably, it may serve as a substrate for synthesis of much more dangerous compounds mainly methcathinone (MCAT) and methamphetamine (MA) [20, 31].

In the study conducted in community pharmacies in France [30] it was found that around 15% of patients used PSE longer than indicated (5 days), but only one man, who used it to treat nasal congestion declared that PSE had deleterious consequence on his health, social or professional life. One of the reasons for PSE use disorder could be for its stimulant effects in sport, although recent results indicate that it is not significantly effective [33]. There are also reports suggesting abusing of PSE in order to improve mood in depressed patients [42].

As mentioned above, PSE is a substrate for MA synthesis, which is a strong central nervous system stimulant which causes alertness, increased energy and euphoria. MA is particularly popular among adolescents because it is easily available, relatively inexpensive, and produces long lasting psycho-active effects. Unfortunately, prolonged use of MA is associated with many health problems that are not limited to the CNS and are responsible for increased morbidity and mortality among drug users [31]. Recently, immediate release PSE hydrochloride tablets (Nexafed®, Acura Pharmaceuticals Inc, Palatine, IL) presenting barriers to converting PSE to MA have been introduced. These tablets are characterized by a substantial reduction in the extraction and conversion of PSE to MA from the product, while maintaining the efficacy to treat nasal congestion [6].

The growing problem is also the production of MCAT from PSE tablets. MCAT is a psycho-stimulant drug that increases the release of catechol-amines in the brain and has similar behavioural effects to MA such as euphoria, agitation, anxiety and hallucinations.

MCAT mixture for injection is synthesized at home by the drug addicts from OTC cold remedies containing ephedrine or PSE in reaction involving the use of potassium permanganate and acetic acid. The significant concentration of manganese in the final mixture is responsible for the occurrence of Parkinsonian syndrome known as manganism which is characterized by multiple neurological problems. Unfortunately, the syndrome is unresponsive to available antiparkinsonian medications and even when mild improvement is observed, it is only on a short-term, and the condition may worsen progressively despite discontinuation of injecting the drug [37].

Codeine

Codeine is a naturally occurring morphine derivative, which is widely used as an antitussive agent. It is a weak opioid with bioavailability of approximately 30 - 40% after oral administration. It is metabolized in part into morphine and its metabolites morphine-3-glucuronide, morphine-6-glucuronide, norcodeine (NORC) and codeine-6-glucuronide (C-6-G). This process depends on the activity of cytochromes CYP2D6 and CYP3A4. Codeine activity seems to be related not only to its main metabolite morphine but it is also active by itself and through its metabolites NORC and C-6-G [24].

The genetic variability in the expression of cytochromes CYP2D6 and CYP3A4 means that patients can be slow, medium, normal or ultra-rapid metabolizers, with a significant variation in terms of analgesia and side effects. About 10% of the Caucasian population belongs to the slow metabolizer category and therefore, in these patients, codeine has a reduced analgesic efficacy. On the contrary, rapid metabolizers convert codeine at a high rate into morphine and other metabolites, and therefore they are more exposed to the risk of side effects [24]. In 2013 the European Medicines Agency issued a document in which codeine use was contraindicated in patients of any age who are known to be CYP2D6 ultra-rapid metabolizers due to an increased risk of developing serious and life-threatening adverse reactions [13]. Codeine is present in many OTC preparations, typically in combination with other analgesic drugs such as acetaminophen or ibuprofen. These combinations provide greater pain relief than any of the agents alone [24, 25].

Codeine/acetaminophen combination use disorder was studied in 118 patients [34]. Among the 21 cases of dependence on codeine analgesics, adverse effects were described by 9 patients. Four patients declared physical symptoms such as constipation, nausea, vertigo and stomach ache and six patients exhibited the following psychological symptoms: depressive mood, anxiety, tiredness, inattention, irritability and sleepiness [34].

Morbidity associated with misuse of codeine–ibuprofen analgesics was studied. Substance dependent individuals who escalate their dose of medication above the recommended amounts were found to be at risk of harm from the accompanying simple analgesic, including toxicity from non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen. The toxic effects included gastrointestinal disease, renal failure, anaemia and severe hypokalaemia [16].

In a report from India, dependence of codeine syrup was studied. Almost all the patients reported feeling alert and more active and most were over-talkative

after taking those cough syrups. These effects are not caused by sole codeine but rather by the combination of this drug with the sympathomimetic agent ephedrine which is also present in the syrup. The effect produced by the combination of ephedrine (a stimulant) and codeine (a depressant) along with chlorpheniramine/promethazine (anti-histamines with sedative properties) is distinct from that of any of these agents used separately, and is reported to be pleasurable in a special way [25]. Recently it has been found that patients dependent on codeine present striatum dopamine impairment which is similar to the more addictive opioids (including heroin or morphine) abusers. These neuropathological damages to the brain may account for the codeine dependence [19].

Diphenhydramine and dimenhydrinate

Antihistamines are used mainly to treat symptoms of allergy. However, older members of the group like diphenhydramine (DPH) or its derivative dimenhydrinate (DMH) are often subject to substance use disorder. DPH is a first generation antihistamine drug with additional anticholinergic and sedative effects. Both absorption and tissue distribution of DPH are rapid and the drug undergoes extensive liver metabolism [17]. Because of these sedative properties, DPH is widely used as an OTC sleep remedy often in combination with other drugs (acetaminophen).

DPH use disorder appears to be associated with the ability of this compound to elevate mood, increase energy levels and produce hallucinogenic effects. Increases in dopaminergic neurotransmission in mesolimbic brain pathways following anti-muscarinic administration may produce rewarding properties and drug-seeking behaviour. The documented reasons for DPH use disorder included insomnia, calming effects and mild euphoria. The daily doses of DPH ranged from 480 - 3000 mg, compared with the usual therapeutic dose for insomnia of 50 mg. In the reported cases of DPH use disorder most of the patients were schizophrenic and used DPH in order to minimize extra-pyramidal side effects which are a common adverse effect of antipsychotic medications [41].

In overdose, anticholinergic and sedative effects of DPH often prevail. Central Nervous System (CNS) symptoms depend on age. Children and adolescents intoxicated with DPH are especially sensitive to the anticholinergic effect, often present with CNS stimulation manifested by excitement, tremors, hyperactivity, hallucinations, hyperpyrexia, and tonic-clonic seizures. Adults, who are usually more susceptible to the sedative effect, often present with CNS depression leading to coma and only seldom have seizures. In few reported cases of lethal DPH poisoning in adults, pulmonary oedema was a characteristic feature [22].

DMH, an antiemetic used to prevent motion sickness, is composed of the anti-histaminergic agent DPH and 8-chlorotheophylline, but DPH is an active ingredient of this drug. First reports of abuse of DMH were published in the 1968 and it is still popular among youngsters as a cheap hallucinogen. The concerns with DMH abuse involve two possible clinical scenarios: acute and chronic abuse. The acute poisoning (after ingestion of doses over 750 mg DMH) consists of anticholinergic and CNS symptomatology. In 55% of the cases of antihistamine overdoses CNS depression is registered. Seizures, catatonic stupor, hallucinations, toxic psychosis, and extrapyramidal movements can also occur. Cardiac dysrhythmias, potentially resulting in death, have been also reported in DMH overdose. Chronic abuse of DMH may cause daytime drowsiness, psychomotor and learning impairment and lead to dependence and tolerance [35].

Benzydamine

Benzydamine hydrochloride (BH) is a locally acting nonsteroidal anti-inflammatory drug (NSAID) with local anaesthetic and analgesic properties [1]. BH is mostly used as a mouthwash, oral spray or powder for vaginal irrigation [29]. Absorption through the skin and mucosa is usually low (less than 10% of the total dose). After oral administration, BH preparations are rapidly absorbed. Approximately the 64% of the dose is absorbed by one hour and complete absorption occurs in 4 - 6 hours. Hallucinations, stimulation of CNS, excitation, hyperactivity, paranoia, dry mouth, and convulsions may occur in oral dosages of 500 - 3000 mg [1]. Although the mechanism of action for the hallucinogenic effects of BH is not fully understood, it is assumed that structural similarity between BH and serotonin may cause activation of the serotonergic 5-HT_{2A} receptors. A similar phenomenon is responsible for hallucinations caused by LSD ingestion [29].

In one of few reported cases, a 22 year old male experienced hallucinations and delusions after ingestion of 750 mg BH from 15 coated tablets. The symptoms improved spontaneously and the patient was transferred to the relevant service for addiction treatment [4]. In recent years, BH use disorder has become popular among teenagers in Brazil. Among those recently taking BH, 36.7% associated this drug with another substance (alcohol, flunitrazepam, marijuana and coffee). In most cases, BH was purchased from a pharmacy without a prescription. The most frequently (50%) reported effects were visual hallucination or nonspecific sensory changes. 70% respondents reported unwanted effects (mainly nausea and vomiting) [29].

OTC medications are widely abused because they are inexpensive, legal, extensively accessible and because there are low age requirements or limits on the amount purchased. Many patients think that OTC medications are less toxic than prescription or illicit drugs. Abusers of prescription drugs or illicit substances may also abuse OTC medications or substitute an OTC drug when other substances are unavailable [36].

Harmful effects of the OTC drug use disorder may be either directly related to their pharmacological or psychological effects or related to the adverse effects of another active ingredient in a compound formulation e.g. acetaminophen or ibuprofen. There are also harms related to other consequences, such as progression to abuse of other substances, economic costs and effects on personal and social life [11]. In many of these cases, treatment for acute and potentially lethal overdoses requires admission to a health care facility for treatment and observation, since non-prescription drug use disorder is known to cause significant morbidity and mortality [36].

OTC drugs use disorder is a growing problem for all healthcare specialists, especially pharmacists and medical doctors. Strategies for doctors to solve this issue include inquiring about prescription, OTC, herbal and illegal drugs consumed by their patients; treating pain aggressively and appropriately; referring addicted patients to 12-step programs such as Alcoholic Anonymous, Narcotics Anonymous, and Pills Anonymous; and finally considering detoxification, either inpatient or outpatient [23].

It is a challenge for pharmacists to be vigilant and try to prevent drug use disorder. Individualized drug counselling focuses directly on reducing or stopping the addict's illicit drug use and is one of the most effective methods in combating substance use disorder [11]. Unfortunately, the level of counselling is still inadequate. The study conducted in 70 chain pharmacies located in Bucharest and other main cities of Romania found that patients received counselling about cough and cold medication (which are often abused) precautions and contraindications in 37.3% cases whereas secondary effects or adverse reactions of these drugs were discussed only in 14.1 % cases [28].

Fortunately, some legal restrictions in PSE, DMX and codeine sales in many countries have been recently introduced. PSE sale is restricted in many places in the world: in USA this drug is sold only by prescription in the amounts smaller than 9 grams *per* month. Besides, many states have implemented more stringent laws which even decrease the allowed PSE value sale (many states introduced electronic tracking based on driver license or other allowed identification which are scanned at the point of sale of PSE-containing products). Two states (Oregon and Mississippi) have adopted the strictest PSE laws to date, making PSE a Schedule III controlled substance available by prescription only [15]. In 2008, legal measures were introduced in UK to manage the misuse of medicines containing PSE or ephedrine. A review of evidence conducted in 2012 shows that the measures are continuing to effectively manage the risk of substance use disorder of these medicines. It is nowadays illegal to sell without a prescription any product that contains more than 720 mg PSE or 180 mg ephedrine, a combination of products that contain totally more than 720 mg PSE or 180 mg ephedrine or a product that contains PSE and a product that contains ephedrine in one transaction [40].

Codeine is an OTC drug only in 15 European Union states and in the countries that allow OTC sale of codeine many restrictions are present [14].

Recent legislation changes in Poland stipulate that pharmacies are not allowed to sell more than one package of a medicine containing pseudoephedrine, dextromethorphan or codeine in a single transaction [2].

Romania has quite strict regulations regarding availability of potential drugs of abuse. Although benzydamine and antihistamine drugs have OTC status, the sale of most of the above discussed drugs is regulated. All dextromethorphan preparations are prescription only available, codeine is available as OTC drug in only few combination drugs containing paracetamol or ibuprofen. Pseudoephedrine is not available without prescription as a single drug but only in combination with ibuprofen. Nevertheless, it is important to remember that thanks to open borders of European Union, the high risk of abuse of these products always exists. Awareness and vigilance of pharmacists is an important element of preventing of OTC drugs substance use disorder.

Conclusions

OTC drugs substance use disorder is a significant and growing challenge for a healthcare system. Drugs which are most frequently used abusively are dextromethorphan, codeine and pseudoephedrine but also benzydamine or antihistamines may be used for this purpose. Prolonged overdose use of these drug may lead to development of full substance dependence. Individuals who abuse these drugs may also suffer from poisoning with other active ingredients from a compound formulation e.g. acetaminophen or ibuprofen. Recently, many countries have introduced legal restrictions in sales of dextromethorphan, codeine and pseudoephedrine which are supposed to limit the accessibility and

abuse of OTC drugs. Pharmacists and physicians should educate their patients about risks connected with inadequate usage of non-prescription drugs.

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