Seminars in Fetal and Neonatal Medicine 24 (2019) 142–148

Contents lists available at ScienceDirect

Seminars in Fetal and Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Effects of unconventional recreational drug use in pregnancy

Summon Chomchai[a], Jariya Phuditshinnapatra[a], Pattaraporn Mekavuthikul[a], Chulathida Chomchai[b,*]

[a] Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[b] Mahidol University International College, Mahidol University, Nakhon Pathom, Thailand

ARTICLE INFO

Keywords:
New psychoactive drugs
Synthetic cathinone
Synthetic cannabinoid
Kratom
Tramadol

ABSTRACT

Recreational drug toxicity is a rapidly evolving aspect in clinical practice. The prevalence of recreational drug abuse in the past decade has achieved an epidemic scale due to invention of new agents and ease of accessibility to the abused drugs. "Unconventional recreational drugs" is the term that includes new psychoactive drugs and medications diverted for recreational goals. Misuse of unconventional recreational drugs during pregnancy can affect both the pregnant woman and the fetus. However, the problems are usually unrecognized and overlooked by healthcare professionals. In this articles, obstetric complications, teratogenicity and neonatal abstinence syndrome from exposure during pregnancy to synthetic cannabinoids, synthetic cathinones, tramadol, kratom, olanzapine, quetiapine, ketamine and ketamine are reviewed. The main purpose is to create awareness about maternal, fetal and neonatal effects of these unconventional recreational drugs, so healthcare professionals will have improved vigilance for these under-recognized issues.

1. Introduction

Misusing drugs and chemicals for recreational purposes is a common and growing problem in adolescents and young adults worldwide. The types and patterns of abuse include the typical illicit substances such as methamphetamine, cocaine and heroin, as well as, 'emerging' substances which are referred to as new psychoactive substances (NPS) [1,2]. In addition, during recent years there are also increasing numbers of pharmaceuticals that are being used for recreational purposes. A new psychoactive substance is defined by the United Nations Office on Drugs and Crime as substances of abuse which are not scheduled under the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances. The essence of NPS are their psychoactive effects which closely mimic those of conventional recreational drugs such as the amphetamines. Substances in the NPS group consist of synthetic chemicals such as synthetic cannabinoids, synthetic cathinones and piperazines, as well as plant-based substances such as kratom or mitragynine and khat whose active substance is cathinone [1–3]. The use of NPS has increased globally, reaching an epidemic scale in the past decade. More than 900 NPSs have been reported thus far and one or more NPSs are found in over 110 countries around the world [2,3]. The primary reasons behind this unprecedented popularity are the perceptions that they are unscheduled and thus represent 'legal high' options, as well as the misconception that some agents such as kratom are benign due to their plant-based nature. Moreover, many substances such as synthetic cannabinoids have nicknames which are misleading as 'spice' or 'herbal high' implying that they are somehow plant-derived [2,3] (see Table 1).

To add fuel to this epidemic, the number of synthesized substances for recreational use has increased phenomenally in the past ten years, making detection of NPS in biological samples collected from abusers extremely difficult. Consequently, development of detection techniques can hardly keep up with the rate of new agents being created [4,5]. Moreover, diversion of prescription and over the counter medications for non-medical use has recently become another major source of recreational drugs. In addition to opioids and ketamine which have long been diverted for misuse, other common drugs with seemingly no abuse potential such as promethazine, dextromethorphan, gabapentin, baclofen, venlafaxine, olanzapine and quetiapine all have been associated with recreational abuse [6,7]. According to the National Institute on Drug Abuse, the number of new and current 'legal' recreational drug users is second only to cannabis. In USA in 2012, at least 48 million people have used medications for non-medical purposes at least once in a life time and 7 million people actively use psychotherapeutic agents for non-medical reasons [8].

The use of psychoactive substances has been associated with lowered inhibition, and higher risks of unplanned sexual intercourse and pregnancy. And users of recreational drugs are often young, and of

* Corresponding author.Mahidol University International College, 999 Phutthamonthon 4 Road, Salaya, Nakhon Pathom, 73170, Thailand.
E-mail address: chulathida.cho@mahidol.ac.th (C. Chomchai).

https://doi.org/10.1016/j.siny.2019.01.010

Table 1
Summary of pregnancy, fetal and neonatal effects of unconventional recreational drugs.

Substance	Effects on pregnancy	Effects on fetus	Effects on the neonates	Treatment of neonatal effects	References
Cathinone and synthetic cathinone	Higher concentration partitioned into placenta and fetal brain than in maternal blood and brain (A)	Exposure in early pregnancy results in decreased survival Exposure in late pregnancy results in apoptosis of brain cells (A)	Neonatal abstinence syndrome (NAS) (H)	Phenobarbital for NAS	[25, 26, 27, 28, 29, 30]
Synthetic cannabinoids	Eclampsia-like syndrome (H)	Craniofacial abnormalities (A) Ocular changes (A)	Withdrawal syndrome in newborn	–	[17, 18]
Tramadol	No effects reported	Oxidative damage to perkinje cells of the cerebellum (A)	Severe congenital defects (H) Atrial and ventricular septal defects (H) NAS similar to opioid (H) Minimal partition into breast milk (H)	Diazepam, phenobarbital, tincture opium and clonidine for NAS	[34, 35, 36, 37, 38, 39, 40]
Kratom	No effects reported	Spina bifida-like neural tube defect (A)	Withdrawal syndrome in newborn (H)	Benzodiazepine and morphine for NAS	[45, 46, 47, 48]
Olanzapine and quetiapine	Extrapyramidal syndrome (H) May increase the risk of gestational diabetes (H)	Congenital malformations and neural tube defects (H)	NAS (H) Extrapyramidal syndrome (H)	Phenobarbital, clonazepam and diphenhydramine for extrapyramidal syndrome	[53, 54, 55, 56, 57, 58, 59, 60]
Ketamine	No effects reported	Enlarged heart and ventricular dysfunction (A) Apoptosis of areas in the brain and delayed synaptogenesis (A)	Generalized hypotonia (H)	–	[64, 65, 66]
Promethazine	No data	No effects reported	Increased risk of cleft lip, cleft palate, syndactyly and polydactyly (H)	–	[71]

A-animal data, H-human data, NAS-Neonatal abstinence syndrome.

child-bearing age. Treatment Episode Data Set (TEDS) issued by the Substance Abuse and Mental Health Services Administration (SAMHSA) shows that as many as 4 in 100 women seeking treatment for substance abuse are pregnant [9]. Due to the existing perception of minimal harm, women may continue to use recreational drugs either sporadically or regularly throughout their pregnancy. This, coupled with the variety of drugs mentioned earlier, makes abuse of emerging or unconventional recreational drugs a serious and vastly under-recognized issue in perinatal and neonatal medicine. Consequently, this article reviews the effects of commonly abused unconventional recreational drugs, including tramadol, kratom, promethazine, synthetic cathinones, synthetic cannabinoids, ketamine and antipsychotics on the health of the pregnant woman, and her fetus.

2. Synthetic cannabinoids

Synthetic cannabinoids (SCBs) are a group of synthetic compounds that have actions that are similar to Δ9-tetrahydrocannabinol (Δ9-THC), the active substance in cannabis. SCBs were first synthesized in the 1960s as research agents to study the pharmacology of Δ9-THC. Since their first synthesis and subsequent marketing in 2004, the number of SCBs have exceeded 500 compounds [10]. SCBs and their metabolites exert effects on the cannabinoid receptors type 1 (CB1) and type 2 (CB2). SCBs are generally more potent than Δ9-THC because SCBs actions are purely agonistic on the CB1 and CB2 receptors, while tetrahydrocannabinol from natural cannabis exerts partial agonist actions on the CB1 receptor. Moreover, SCBs have higher affinity to CB1 and CB2 receptors than Δ9-THC [10]. CB1 receptors are found in the brain and is responsible for psychoactive, visual and auditory effects of cannabis. And while CB2 are found in lymphoid and immune cells, its stimulation can increase serotonergic activity in the brain [11]. Samples of commonly found SCBs compounds are JWH-018, JWH-073, JWH-250, UR-144, JWH-398, JWH-412, HU-210, AB-CHMINACA and MAB-CHMINACA, while the street names for the SCBs include Spice, K2, herbal incense and Bonsai [12,13]. SCBs are usually produced as plants-based materials, which are applied with the synthetic SCB in solvent solution. Abuse of SCBs may be done via ingestion, inhalation, vaping, smoking and snorting. Reported physiological and psychiatric effects of SCBs include tachycardia, hypertension, bradycardia and hypotension, drowsiness, lethargy, agitation, hallucination, nausea, vomiting, hyperemesis and panic attack [11,13–16]. Reported complications of SCBs abuse include acute kidney injury, myocardial infarction, psychosis, seizure, hepatotoxicity, rhabdomyolysis, hyperthermia, excited delirium and serotonin syndrome [10,16]. Regular exposure to SCB can cause drug tolerance and physical dependence while withdrawal symptoms include tachycardia, hypertension, irritability, anxiety, craving, agitation, mood swing and nightmares [10,11,13].

2.1. Effects on pregnancy and the neonates

2.1.1. Animal data

The data on the perinatal and neonatal effects of SCBs is extremely sparse. The most pronounced effects on the fetus is seen in mice who were administered intraperitoneal synthetic cannabinoid CP-55,940 on gestational day 8. The fetuses were found to have significant craniofacial abnormalities, including facial cleft and cleft palate on day 17. Moreover, a clear dose-response relationship was demonstrated for ocular changes, ranging from microphthalmia to anophthalmia [17].

2.1.2. Human data

In humans, a few sporadic case reports document the effects of in-utero exposure to synthetic cannabinoids in pregnancy and in the newborn. In one case, a 19-year-old women with regular use of SCB presented at gestational age of 34 weeks with eclampsia-like syndrome consisting of hypertension, agitation, seizure and proteinuria [18]. Cesarean section was performed due to fetal distress. She developed

paranoid psychosis and hypokalemia on day 1 after the delivery. In another case, a pregnant woman smoked an SCB product labelled as "Bonsai" regularly throughout pregnancy and had smoked the last dose just before delivery, the patient developed irritability, tremor and jitteriness, which were aggravated by light, sound and touch stimuli at 4 h post-delivery. The baby had an uneventful perinatal course and blood chemistry, serological results, electrocardiography, echocardiography and transfontanelle and abdominal ultrasonography were unremarkable. The symptoms gradually subsided and disappeared entirely on day 10 [18]. A 22-year old, regular abuser of SCB, synthetic cocaine, marijuana and ecstasy presented at gestational age of 31-week with self-harming behaviors. The infant had a birth weight of 3,260 g with Apgars of 8 and 9 and no physical abnormality [19].

3. Synthetic cathinones

Khat is a shrub that is native in the Southwestern Arabian Peninsula and Eastern Africa. Khat chewing for stimulant and euphoric effects have been a cultural practice in the region for centuries. The principle active component of Khat is cathinone (β-ketoamphetamine), which has similar structure and clinical effects to amphetamines [20]. Synthetic cathinones are a group of synthetic chemical analogs of cathinone. In 2007, a new trend emerged with recreational use of synthetic analogs of cathinones, with mephedrone (4-methylcathinone), methylone, and 3,4-methylenedioxypyrovalerone (MDPV) as the most commonly found agents [21,22]. Synthetic cathinones are usually sold as a bath salt or plant food and labelled as 'not for human consumption'. Common street names include Blizzard, Cloud 9, Ivory Wave and Meow or Meow Meow and can appear as white or beige powders, as crystals or as liquids dissolved in alcohol [21,22]. Synthetic cathinones can be abused via ingestion, snorting, ingestion, intravenous injection or even by intraocular, rectal or sublingual application [23]. Cathinone exerts its effects by enhancing the actions of norepinephrine, dopamine and serotonin through increasing the release and blocking the reuptake of these transmitters [24]. Synthetic cathinones are usually more potent than cathinones and cause more pronounced sympathomimetic manifestations that include tachycardia, hypertension, confusion, agitation, hallucination, mydriasis and hyperthermia. Medical and psychiatric complications that are reported include myocardial infarction, rhabdomyolysis, paranoid, psychosis, excited delirium, violent behaviors, seizure, serotonin syndrome and hyponatremia [14,22–24]. Chronic use of synthetic cathinones may result in tolerance and withdrawal symptoms can occur which include craving, depression and anxiety [16,24].

3.1. Effects on pregnancy and the neonate

3.1.1. Animal studies

A pharmacokinetic study done by injecting saline-dissolved cocktail of the three commonly found synthetic cathinones, mephedrone, methylone and MDPV intraperitoneally into pregnant mice demonstrated significant amount of all three substances in the placenta and fetal brain. Moreover, total exposure, as represented by area under the curve (AUC) of all 3 substances were significantly higher in the placenta and fetal brain than in the maternal plasma and brain [25]. In particular, fetus exposed to MDPV at 7 days, which corresponded to human fetus in the 3rd trimester, exhibited significant apoptosis of brain cells in the piriform cortex, retrosplenial cortex, hippocampus and nucleus accumbens, as compared to control litters injected with saline. This suggests that exposure to MDPV, even in late pregnancy, may cause significant harms to the developing brain of the fetus. Exposure to MDPV in early pregnancy, on the other hand, is associated with decreased survival and abnormal behavior in newborns [26]. When pregnant C57Bl/6J mice were exposed to MDPV subcutaneously at gestational days 8–14, corresponding to the latter half of first trimester, the MDPV group had significantly lowered survival rate of the offspring, lower maternal care behavior and higher spontaneous locomotion among pups at post-natal dates 7 and 21. The increased locomotion was interpreted as agitation. The changes in maternal and pup behaviors were postulated to be dopaminergic effects of MDPV in the brains [27].

3.1.2. Human case reports

A 21-year-old women at 36 weeks gestational age presented with confusion and agitation. The sudden change in mental status, coupled with high blood pressure, 160/90 mmHg, and pulse of 130/minute made intoxication with psychoactive substance a likely differential diagnosis. She delivered a stillborn 2,380-g baby via cesarean section. Maternal and fetal blood and urine showed the presence of synthetic cathinones 3,4-methylenedioxy-a-pyrrolidinohexanophenone (3,4-MDPHP) and α-pyrrolidinohexanophenone (α-PHP). There were no gross fetal abnormalities [28].

Withdrawal syndromes from cathinones have been reported in newborn infants. A 37-week infant developed irritability, jitteriness, high pitch cry and hyperreflexia at 20 h post-delivery. Prenatal history revealed that his mother was a heroin-user on methadone maintenance therapy but who also smoked 4-methylethcathinone (4-MEC), a synthetic cathinone. Her urine toxicology screen was negative except for methadone but 4-MEC was detected in the meconium using high performance liquid chromatography–tandem mass spectrometry. Neonatal abstinence syndrome (NAS) from methadone was ruled out by the medical team and the infant was diagnosed with NAS due to 4-MEC. The infant was treated with phenobarbital and the symptoms improved 12 days later [29]. Because cathinone in the form of Khat has extensive cultural use in many parts of the world, its exposure during pregnancy has become a significant phenomenon as well. Effects of exposure to khat during pregnancy included higher chance of elevated blood pressure, pre-eclampsia, loss of appetite, gastric reflux, constipation, breech presentation, preterm labor, fetal distress, perinatal mortality and neonatal admission to the ICU [30]. Because cathinone and synthetic cathinone have similar chemical structures and clinical effects, it should be anticipated that fetuses exposed to synthetic cathinones may have clinical findings which approximate that of khat exposure during pregnancy.

4. Tramadol

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. It exerts its analgesic effects by blocking serotonin reuptake and norepinephrine reuptake in descending neuronal inhibitory pathways, leading to decreased pain perception. In addition, it is metabolized by cytochrome P450 2D6 to the M1 metabolite, O-desmethyltramadol, which shows moderate mu-opioid receptor agonism [31]. In an extensive post-marketing survey study of Ultram®, tramadol is initially believed to have very low abuse potential despite its opioid nature. However, following its extensive use as a prescription pain-killer of choice, abuse of tramadol has reached epidemic proportions [31,32]. In certain parts of the world such as in Thailand and Iran, it has become the 'legal' drug of choice among teenagers and young adults and is the leading cause of overdose-related deaths. In Thailand, tramadol is often mixed with promethazine cough syrup and ingested as part of a concoction known as 'pro', from Procodyl®, the trade name of the cough syrup containing promethazine. Tramadol is given the nick name 'taxi' owing to the color of its yellow/green capsules which mimic the colors of taxis in Thailand.

Because of the mu-agonist activity of its M1 metabolite, toxic manifestations and withdrawal of tramadol follow that of opioid, with lesser degree of severity being observed. Different ethnic populations may have different susceptibilities to the effects of the M1 metabolite. Cytochrome P450 2D6 exhibits polymorphism, and ultra-rapid metabolizers can have as much as 40% higher serum level of M1 metabolite, leading to opioid-like toxicity such as depressed mental status, coma and respiratory depression. Overdose data suggests that these

symptoms are more likely to occur when tramadol is combined with other CNS depressants such as benzodiazepines or alcohol. On the other hand, tramadol's mechanism as a reuptake inhibitor of monoamines may explain other symptoms of toxicity which include hypertension, tachycardia, recurrent seizures and features of serotonin syndrome [31,33].

4.1. Effects of tramadol abuse in pregnancy and neonatal outcomes

4.1.1. Animal data

Pregnant Spraque-Dawlay rats exposed orally to tramadol at 50 mg/kg/day in on gestation days 10–21 showed significantly more degenerated purkinje cells and oxidative damage in the cerebellum on postnatal days 7, 14 and 21 than control animals fed with normal saline. The timing and dose of tramadol administration in this study was representative of the timing of neuronal differentiation and synaptic development in the brain and the dose approximates that of the dose use for recreational purposes [34].

4.1.2. Human data

A well designed population-based study performed on the Swedish birth registry to assess the teratogenicity of tramadol interviewed women using structured questionnaires for history of drug use during pregnancy and found that of the 1,682,846 women who gave birth to 1,797,678 infants during 1997–2003, there were 1775 infants who were exposed to tramadol during pregnancy. Of these, 96 had congenital malformation, 70 of which were severe. The adjusted odds ratios with confidence intervals for congenital malformation, severe congenital malformation, cardiovascular defect, isolated cardiac septal defects and pes equinovarus associated with tramadol exposure were 1.30 (1.06–1.69), 1.33 (1.05–1.70), 1.56 (1.04–2.29), 1.78 (1.02–2.90) and 3.63 (1.66–6.89), respectively. The most common types of cardiovascular defect found were ventricular septal defects and atrial septal defects [35]. However, it should be kept in mind that this study only included livebirths. Stillbirths which may have experienced more severe effects of intrauterine exposure to tramadol were not included.

As mentioned earlier, the pharmacologic effects of tramadol closely approximated that of opioids. This includes the occurrence of withdrawal symptoms in adults and NAS in children. A report documents the symptoms experienced by a male infant known to have been exposed to tramadol. Symptoms included tachypnea, tachycardia, hypertonia, signs of tetany upon touching and a light single convulsion. The infant received diazepam for 7 days and phenobarbital for 13 days, after which the symptoms subsided. His mother had been using 300 mg/day of tramadol for 4 years. She also tested positive for tramadol and its metabolites, O-monodesmethyltramadol, N-monodesmethyltramadol and N,O-didesmethyltramadol in her urine on day 2. The infant also had tramadol in his serum on day-of-life 2 and 9 [36].

The second case was a mother who used tramadol 400 mg/day to treat low back pain and had reduced the dose to 200 mg/day during the last week before delivery. On day-of-life 2, the infant developed high pitch cry, trembling and shorten sleep periods [37]. The third case was an infant whose mother had used 300 mg/day of tramadol for chronic low back pain and the infant presents with irritability, tachycardia and vomiting. The fourth case report was of a mother who used 600–800 mg of tramadol for her shoulder pain and the infant was noted to have jitteriness and myoclonus on day-of-life 2 [38]. The infants in all of the above cases required pharmacologic treatments of NAS that ranged from phenobarbital to tincture of opium to clonidine for a period ranging from 10 to 14 days. The infant in the last case experienced recurrence of NAS, namely jitteriness, decreased oral feed intakes and increased stool frequency, after the clonidine was discontinued on day 12. The infant continued on clonidine until the 18th day of life [39]. Exposure to tramadol in breast milk also is of concern for women who take tramadol for pain control. Breast milk samples of 75 women who were receiving tramadol 100 mg every 6 h on days 2–4 post caesarean section had an estimated exposure dose of 112 μg/kg/day (95% confidence interval 102–122) tramadol and 30 μg/kg/day (95% confidence interval 28–32) active metabolites. This is approximately 2.88% of the total dose of maternal exposure [40]. Due to the high likelihood of withdrawal symptoms in regular users, coupled with its ability to partition into breast milk, pregnant women should refrain from using tramadol on a continued basis to prevent the occurrence of NAS. However, because the relative infant dose of tramadol is estimated to be well below the acceptable limit of 10% and there has been no observed adverse effects in infants who were exposed to tramadol from the breast milk, there is no evidence that short-term exposure to tramadol in breast milk causes significant harm to the infant [40].

5. Kratom

Kratom is a plant native to Southeast Asia. It is widely known to be a stimulant and used as a reliever of everyday aches and pains and fatigue for field laborers [41]. Active ingredients in Kratom include mitragynine (60%), 7-hydroxymitragynine (2%), paynantheine, speciogynine, and speciophylline. While mitragynine is found in the highest proportion, 7-hydroxymitragynine is much a more potent compound [42]. Kratom leaves can be chewed, smoked or brewed as tea [41]. Use of kratom has gained popularity in North and South America and Europe. In Thailand, Malaysia, Australia and New Zealand, Kratom is scheduled as a narcotic agent. In USA, the Drug Enforcement Agency (DEA), classifies kratom as “drug of concern” [42]. Nevertheless, it can be bought online or in “head shops” (shops specializing in drug paraphernalia and recreational drugs) [41]. At low doses, kratom is reported to have stimulant effects, including increasing the state of alertness, talkativeness and tachycardia. However, at higher doses, analgesic and sedative effects dominate via mitragynine and 7-mitragynine effects on mu- and delta-opioid agonist receptors. Sedative effects are the result of sympatholytic activity through alpha-2 adrenergic receptor stimulation [42,43]. Adverse effects from kratom include nausea, loss of appetite, weight loss, constipation, abdominal pain, insomnia, frequent urination, hyperpigmentation of cheek, loss of consciousness, seizure and cholestatic hepatitis [43]. Chronic use leads to tolerance, leading to constant increases the daily dose and occurrence of withdrawal after cessation of use. Withdrawal symptoms include myalgia, insomnia, fatigue, chest discomfort, abdominal cramp, diarrhea, labile mood, aggression, irritability and agitation [43,44].

5.1. Animal data and human data on congenital malformation and NAS

Exposure of Spraque-Dawlay rats to Mythragyna speciosa extracts in low, moderate and high doses during gestational days 8–13 showed significantly higher incidence of spina bifida–like neural tube defects, including widening of vertebral arch of cervical, thoracic and lumbar spinal cord and an increase in the transverse diameter of the brain [45]. However, in humans, neither obstetric complications nor congenital anomalies have been reported.

There are three published case reports of withdrawal symptoms in neonates whose mothers used kratom during pregnancy. In a case report from Thailand, a baby whose mother was a chronic kratom abuser developed hypertonicity and diaphoresis on day-of-life 2. The symptoms subsided with supportive care [46]. A 29-year-old woman who used 18–20 g of kratom powder three times a day to relieve her back pain symptoms throughout the entire pregnancy had an uneventful pregnancy and delivery. On day-of-life 5, the infant developed feeding intolerance, jitteriness, irritability and emesis and was admitted to the NICU and treated with intravenous morphine with maximal does of 10 mg/kg/hour until abstinenceabated. The patient was then switched to oral morphine [47]. In another case in the USA, a 1-day old infant whose mother admitted to using kratom during pregnancy developed diarrhea and tachypnea and the infant was diagnosed as neonatal opioid abstinence syndrome by a neonatologist and treated with

morphine and benzodiazepine [48]. This suggests that based on limited available case reports, NAS from kratom can be treated with morphine and benzodiazepine but the long term outcomes of these infants are uncertain [47,48].

6. Olanzapine and quetiapine

Antipsychotic drugs can be classified into first generation (typical) antipsychotics and second generation (atypical) antipsychotics. First generation antipsychotics, such as haloperidol and chlorpromazine, exert their effects through dopamine D2 receptor inhibition. Second generation antipsychotics, such as olanzapine, are less potent D2 antagonists and exert their effects through serotonin receptors. The abuse of second generation antipsychotics, especially quetiapine and olanzapine, have gained popularity since the year 2000 [49,50]. The main subjective effects are sedation and euphoria. Specifically, olanzapine is also known as “trip terminator”, a medication to treat the “bad trip” or dysphoria which can occur with the abuse of novel psychoactive substances [51]. The medication is usually ingested or crushed and snorted or dissolved and injected intravenously. Street names for quetiapine include Susie Q, Q ball, Quell or Baby heroine and the street name for olanzapine is Lillys [49,50]. Adverse effects found after misuse of these antipsychotics include confusion, agitation, drowsiness, hypotension, seizure, respiratory depression, cardiac arrhythmias and extrapyramidal syndrome [50].

6.1. Effects on pregnancy and newborn

Olanzapine and quetiapine significantly traverse the placenta into the fetus with passage ratios of 72.1% and 23.8%, respectively [52]. All data on the effects of exposure to quetiapine during pregnancy are derived from patients being treated for psychiatric disorders and not from drug misuse. In 2011, the US FDA issued a warning for extrapyramidal or withdrawal symptoms in infants whose mother had used antipsychotic drug in the third trimester. This was based on 69 cases reported on the FDA's Adverse Event Warning System since October 2008. Symptoms included agitation, hypertonia, hypotonia, somnolence, respiratory distress and feeding disorder [53]. There have been a few publications reporting treatment of antipsychotic-induced extrapyramidal syndrome or withdrawal syndrome in neonates. Non-pharmacological treatments include adequate rest and sleep with reduced environmental stimuli. With no improvement, treatment with phenobarbital, clonazepam and diphenhydramine could control the symptoms successfully [54–56]. Uses of second-generation antipsychotics during pregnancy have been found to increase the risk of gestational diabetes mellitus [57,58]. From a systematic review of women who used olanzapine during pregnancy, 26 congenital malformations were found with 4 neural tube defects among them. Due to possible confounding effects from patients' psychiatric conditions and exposure to other psychiatric drugs, it remained inconclusive whether the anomalies had resulted from olanzapine [59]. Other prospective studies were conducted and found no increase in teratogenic risks [53,60].

7. Ketamine

Ketamine is a general anesthetic agent that is a derivative of phencyclidine. Since the 1990s’, ketamine has become a popular recreational drug among partygoers and in nightclubs. The effects desired by misusers are euphoria and hallucinations. Ketamine is available as clear, colorless liquids or as a white power. The modes of administration are mainly by snorting or intravenous injection. Street names for ketamine include K, K-Hole, Super K and Special K [61,62]. Adverse effects associated with ketamine abuse are delirium, tachycardia, hypertension, hallucination, respiratory depression, abdominal pain, frequent urination, aseptic cystitis and inflammation in the urinary tract [62,63]. Chronic use of ketamine causes physical dependence and withdrawal symptoms in chronic abusers include irritability, depressed mood, fatigue and aggressive behavior [61,62].

7.1. Adverse effects in pregnancy in the neonates

Although ketamine has been used widely for induction of anesthesia in pregnant women, adverse outcomes from in utero ketamine exposure have mainly been reported in animal studies. The main difference between ketamine exposure in pregnant women who are administered ketamine for general anesthesia and those who misuse ketamine is that latter will have early and multiple exposures to the drug throughout pregnancy. When Xenopus embryos were treated with ketamine at stages of 8–21 days (before the gastrula stage to complete neural tube closure), problems such as enlarged heart and decreased ventricular shortening fraction, reflecting ventricular dysfunction were noted [64]. In pregnant rats at gestational age 14 days that were administered ketamine at a sedative dose for 2 h, pups ages 0 and 30 days were noted to have increased cellular apoptosis and neuronal death in many parts of the brain. Moreover, there was impaired pre- and post-synaptic protein expression and delayed synaptogenesis of the prefrontal cortex. These findings suggest that prenatal exposure to ketamine can result in impaired fetal neuronal development [65]. There has only been one confirmed human case report of recreational ketamine exposure exists, where an infant girl was born at 38 weeks gestation via caesarean section to a 30-year-old woman who admitted to using ketamine recreationally, with last use during the first trimester. The newborn was born with generalized hypotonia. Neurologic workup including cranial ultrasound and TORCHES titers were all negative. However, hair analysis found high levels of ketamine and norketamine, signifying the exposure happened during last 2–3 months of pregnancy. Hypotonia ultimately resolved within 21 days of life [66].

8. Promethazine

Promethazine is a phenothiazine compound that has antihistamine, antiemetic and sedative properties [67,68] and in many circumstances, is given to pregnant women therapeutically. On the other hand, promethazine is also widely popular as a recreational drug of abuse among teenagers who either drink the readily available antitussive formula such as promethazine with codeine or Phenergan® with codeine, as it is called in the US. In other countries where ready-mixed formulas are not available, teenagers often mix promethazine cough syrup into a concoction comprising of other drugs such as tramadol (see section 4-tramadol) [67,69,70]. Intended effects of abuse is euphoria. However, abusers usually present at the emergency department because of seizures or anticholinergic syndrome, which includes drowsiness, confusion, agitation, hallucination and hypertension [68,70].

8.1. Effects on pregnancy and the neonate

As is the case with ketamine, exposure to promethazine during pregnancy can be therapeutic. In such instances, exposure is isolated and often occurs late in the pregnancy. Recreational use and abuse will lead to early and repeated exposure throughout pregnancy. There are currently two studies evaluating promethazine for its teratogenic effects. A population based case-control study from the Hungarian Case–Control Surveillance of Congenital Abnormalities found that, among cases with congenital abnormalities, 16% had recreational exposure to promethazine during pregnancy. The control group consisted of 38,151 overall controls and 834 Down syndrome controls had 15.8% and 17.0% of mothers who were treated with promethazine during pregnancy. Adjusted odds ratios with 95% confidence intervals for cleft lips or cleft palate, and polydactyly or syndactyly were 1.5 (1.1–2.0) and 1.3 (1.0–1.8) respectively [71]. In another study from Hungary, outcomes of pregnancy in women who overdosed with promethazine were evaluated but no increased risk of congenital anomalies were

found [72].

9. Conclusion

The category of unconventional recreational drug will be a dynamic and ever-evolving entity. New types of substances will be emerging through new discoveries and diversion of existing ones. Healthcare practitioners need to have a high index of suspicion and be acquainted with epidemiology of recreational drug in their locality and stay abreast with the times. Recognition of the substance misuse is the crucial element in managing cases of pregnant women with substance misuse. History taking is still the mainstay. Recognition of the toxic syndromes in the pregnant women and her newborn such as agitated delirium, intense sympathomimetic and serotonin syndrome or the presence of neonatal abstinence syndrome are keys to detecting drug use during pregnancy. In many circumstances, laboratory analysis of the biological sample is another aid to confirm the diagnosis. Unfortunately, the laboratory tests are usually not available and turn-around time is too long to support clinical judgment. Therefore, clinical decisions need to rely mainly on clinical clues form history and physical examination.

10. Practical points

- Misusers of new psychoactive drugs usually present with syndrome similar to classical toxic syndromes, such as sympathomimetic, excite delirium and serotonin syndrome. However, the manifestations tend to be much more intense than those from conventional recreational drugs.
- Neonatal abstinence syndrome may have specific manifestation such as jitteriness, irritability and high-pitched crying; or be non-specific, such as tachycardia, tachypnea and poor feeding. Therefore, high index of suspicion is always warranted.
- Benzodiazepine and phenobarbital are usually safe and effective in treating neonatal abstinence syndrome from unconventional recreational drugs except for kratom, where morphine could be an option.

10.1. Research directions

- Trends of unconventional recreational drug abuse should be closely monitored.
- Physicians should be encouraged to report maternal, fetal and neonatal outcomes in women who abuse unconventional drug during pregnancy.
- A registry for pregnancy outcomes of women who abuse unconventional recreational drugs should be developed as a platform to exchange and harmonize the information on this evolving entity. In addition, the registry can yield the prevalence of problems and cohorts to study long-term effects of unconventional recreational drugs.

Conflicts of interest

None of the authors has any conflict of interest to declare.

References

[1] Graddy R, Buresh ME, Rastegar DA. New and emerging illicit psychoactive substances. Med Clin 2018;102:697–714.
[2] Helander A, Backberg M. New Psychoactive Substances (NPS) - the Hydra monster of recreational drugs. Clin Toxicol 2017;55:1–3.
[3] Pirona A, Bo A, Hedrich D, Ferri M, van Gelder N, Giraudon I, et al. New psychoactive substances: current health-related practices and challenges in responding to use and harms in Europe. Int J Drug Pol 2017;40:84–92.
[4] Adamowicz P, Tokarczyk B. Screening analysis for designer stimulants by LC-MS/MS. Methods Mol Biol 2019;1872:165–80.
[5] Zawilska JB. "Legal highs" - new players in the old drama. Curr Drug Abuse Rev 2011;4:122–30.
[6] James J. Dealing with drug-seeking behaviour. Aust Prescr 2016;39:96–100.
[7] 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;27:1286–92.
[8] Wendell AD. Overview and epidemiology of substance abuse in pregnancy. Clin Obstet Gynecol 2013;56:91–6.
[9] Martin CE, Longinaker N, Terplan M. Recent trends in treatment admissions for prescription opioid abuse during pregnancy. J Subst Abuse Treat 2015;48:37–42.
[10] White CM. The pharmacologic and clinical effects of illicit synthetic cannabinoids. J Clin Pharmacol 2017;57:297–304.
[11] Papaseit E, Perez-Mana C, Perez-Acevedo AP, Hladun O, Torres-Moreno MC, Muga R, et al. Cannabinoids: from pot to lab. Int J Med Sci 2018;15:1286–95.
[12] Madras BK. The growing problem of new psychoactive substances (NPS). Current topics in behavioral neurosciences 2017;32:1–18.
[13] Paul ABM, Simms L, Amini S, Paul AE. Teens and spice: a review of adolescent fatalities associated with synthetic cannabinoid use. J Forensic Sci 2018;63:1321–4.
[14] Bae K, Kwon NJ, Han E. A review on the abuse of three NPS (synthetic cannabinoids, kratom, poppers) among youths in Asia. Forensic Sci Int 2018;292:45–9.
[15] Rivera JV, Vance EG, Rushton WF, Arnold JK. Novel psychoactive substances and trends of abuse. Crit Care Nurs Q 2017;40:374–82.
[16] Schifano F, Orsolini L, Papanti D, Corkery J. NPS: medical consequences associated with their intake. Current topics in behavioral neurosciences 2017;32:351–80.
[17] Gilbert MT, Sulik KK, Fish EW, Baker LK, Dehart DB, Parnell SE. Dose-dependent teratogenicity of the synthetic cannabinoid CP-55,940 in mice. Neurotoxicol Teratol 2016;58:15–22.
[18] Orsolini L, Papanti D, Corkery J, De Luca MA, Cadoni C, Di Chiara G, et al. Is there a teratogenicity risk associated with cannabis and synthetic cannabimimetics' ('Spice') intake? CNS Neurol Disord - Drug Targets 2017;16:585–91.
[19] Cabán B, Slack LA, Huffman CA, Whitecar PW, Haley C. Synthetic cannabinoid and synthetic cocaine use during pregnancy in a soldier. J Subst Abuse Alcohol 2013;1:1002–3.
[20] Patel NB. Khat (Catha edulis Forsk) - and now there are three. Brain Res Bull 2018https://doi.org/10.1016/j.brainresbull.2018.07.014.
[21] El-Menyar A, Mekkodathil A, Al-Thani H, Al-Motarreb A. Khat use: history and heart failure. Oman Med J 2015;30:77–82.
[22] Katz DP, Bhattacharya D, Bhattacharya S, Deruiter J, Clark CR, Suppiramaniam V, et al. Synthetic cathinones: "a khat and mouse game". Toxicol Lett 2014;229:349–56.
[23] Weinstein AM, Rosca P, Fattore L, London ED. Synthetic cathinone and cannabinoid designer drugs pose a major risk for public health. Front Psychiatry 2017;8:156.
[24] Banks ML, Worst TJ, Rusyniak DE, Sprague JE. Synthetic cathinones ("bath salts"). JEM (J Emerg Med) 2014;46:632–42.
[25] Strange LG, Kochelek K, Keasling R, Brown SD, Pond BB. The pharmacokinetic profile of synthetic cathinones in a pregnancy model. Neurotoxicol Teratol 2017;63:9–13.
[26] Adam A, Gerecsei LI, Lepesi N, Csillag A. Apoptotic effects of the 'designer drug' methylenedioxypyrovalerone (MDPV) on the neonatal mouse brain. Neurotoxicology 2014;44:231–6.
[27] Gerecsei LI, Csillag A, Zachar G, Gevai L, Simon L, Dobolyi A, et al. Gestational exposure to the synthetic cathinone methylenedioxypyrovalerone results in reduced maternal care and behavioral alterations in mouse pups. Front Neurosci 2018;12:27.
[28] Adamowicz P, Hydzik P. Fetal death associated with the use of 3,4-MDPHP and alpha-PHP. Philadelphia, Pa: Clinical toxicology; 2018. p. 1–5.
[29] Pichini S, Rotolo MC, Garcia J, Girona N, Leal L, Garcia-Algar O, et al. Neonatal withdrawal syndrome after chronic maternal consumption of 4-methylethcathinone. Forensic Sci Int 2014;245:e33–5.
[30] Abdel-Aleem AM, Abdulkader Al-Aghbari AA, Mohamed Mustafa SA, Ali Ahmed Nasr AM, Abdulbari Assad MM. Khat chewing during pregnancy: an insight on an ancient problem. Impact of chewing khat on maternal and fetal outcome among Yemeni pregnant women. J Gynecol Neonatal Biol 2015;1:28–31.
[31] Miotto K, Cho AK, Khalil MA, Blanco K, Sasaki JD, Rawson R. Trends in tramadol: pharmacology, metabolism, and misuse. Anesth Analg 2017;124:44–51.
[32] Bassiony MM, Salah El-Deen GM, Yousef U, Raya Y, Abdel-Ghani MM, El-Gohari H, et al. Adolescent tramadol use and abuse in Egypt. Am J Drug Alcohol Abuse 2015;41:206–11.
[33] Beakley BD, Kaye AM, Kaye AD. Tramadol, pharmacology, side effects, and serotonin syndrome: a review. Pain Physician 2015;18:395–400.
[34] Aboulhoda BE, Hassan SS. Effect of prenatal tramadol on postnatal cerebellar development: role of oxidative stress. J Chem Neuroanat 2018;94:102–18.
[35] Kallen B, Reis M. Use of tramadol in early pregnancy and congenital malformation risk. Reprod Toxicol 2015;58:246–51.
[36] Meyer FP, Rimasch H, Blaha B, Banditt P. Tramadol withdrawal in a neonate. Eur J Clin Pharmacol 1997;53:159–60.
[37] Willaschek C, Wolter E, Buchhorn R. Tramadol withdrawal in a neonate after long-term analgesic treatment of the mother. Eur J Clin Pharmacol 2009;65:429–30.
[38] Hartenstein S, Proquitte H, Bauer S, Bamberg C, Roehr CC. Neonatal abstinence syndrome (NAS) after intrauterine exposure to tramadol. J Perinat Med 2010;38:695–6.
[39] O'Mara K, Gal P, Davanzo C. Treatment of neonatal withdrawal with clonidine after long-term, high-dose maternal use of tramadol. Ann Pharmacother 2010;44:1342–4.
[40] Ilett KF, Paech MJ, Page-Sharp M, Sy SK, Kristensen JH, Goy R, et al. Use of a sparse sampling study design to assess transfer of tramadol and its O-desmethyl metabolite into transitional breast milk. Br J Clin Pharmacol 2008;65:661–6.
[41] Singh D, Narayanan S, Vicknasingam B. Traditional and non-traditional uses of

Mitragynine (Kratom): a survey of the literature. Brain Res Bull 2016;126:41–6.
[42] White CM. Pharmacologic and clinical assessment of kratom. Am J Health Syst Pharm AJHP Official J Am Soc Health-Syst Pharm 2018;75:261–7.
[43] Warner ML, Kaufman NC, Grundmann O. The pharmacology and toxicology of kratom: from traditional herb to drug of abuse. Int J Leg Med 2016;130:127–38.
[44] Singh D, Muller CP, Vicknasingam BK. Kratom (Mitragyna speciosa) dependence, withdrawal symptoms and craving in regular users. Drug Alcohol Depend 2014;139:132–7.
[45] Bala YM, Abubakar DA, Siti NSAK, Tariq BAR, Qamar UA. In-utero effects of the crude ethanolic extract of the leaves of mitragyna speciosa on neural tube formation in rats. Asian J Exp Biol Sci 2010;1:404–8.
[46] Trakulsrichai S, Tongpo A, Sriapha C, Wongvisawakorn S, Rittilert P, Kaojarern S, et al. Kratom abuse in ramathibodi poison center, Thailand: a five-year experience. J Psychoact Drugs 2013;45:404–8.
[47] Mackay L, Abrahams R. Novel case of maternal and neonatal kratom dependence and withdrawal. Canadian family physician Medecin de famille canadien 2018;64:121–2.
[48] Cumpston KL, Carter M, Wills BK. Clinical outcomes after Kratom exposures: a poison center case series. Am J Emerg Med 2018;36:166–8.
[49] 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;38:72–9.
[50] Klein L, Bangh S, Cole JB. Intentional recreational abuse of quetiapine compared to other second-generation antipsychotics. West J Emerg Med 2017;18:243–50.
[51] Valeriani G, Corazza O, Bersani FS, Melcore C, Metastasio A, Bersani G, et al. Olanzapine as the ideal "trip terminator"? Analysis of online reports relating to antipsychotics' use and misuse following occurrence of novel psychoactive substance-related psychotic symptoms. Hum Psychopharmacol 2015;30:249–54.
[52] Newport DJ, Calamaras MR, DeVane CL, Donovan J, Beach AJ, Winn S, et al. Atypical antipsychotic administration during late pregnancy: placental passage and obstetrical outcomes. Am J Psychiatry 2007;164:1214–20.
[53] Kulkarni J, Storch A, Baraniuk A, Gilbert H, Gavrilidis E, Worsley R. Antipsychotic use in pregnancy. Expert Opin Pharmacother 2015;16:1335–45.
[54] Cleary MF. Fluphenazine decanoate during pregnancy. Am J Psychiatry 1977;134:815–6.
[55] Collins KO, Comer JB. Maternal haloperidol therapy associated with dyskinesia in a newborn. Am J Health Syst Pharm AJHP Official J Am Soc Health-Syst Pharm 2003;60:2253–5.
[56] Erol S, Ozcan B, Celik IH, Bas AY, Demirel N. Neonatal abstinence syndrome due to prenatally citalopram exposure: a case report. Arch Argent Pediatr 2017;115:e424–7.
[57] Gentile S. Pregnancy exposure to second-generation antipsychotics and the risk of gestational diabetes. Expert Opin Drug Saf 2014;13:1583–90.
[58] Park Y, Hernandez-Diaz S, Bateman BT, Cohen JM, Desai RJ, Patorno E, et al. Continuation of atypical antipsychotic medication during early pregnancy and the risk of gestational diabetes. Am J Psychiatry 2018;175:564–74.
[59] Nielsen RE. Treatment of psychosis during pregnancy - a case report and a mini-review. Acta Neuropsychiatr 2011;23:210–4.
[60] McKenna K, Koren G, Tetelbaum M, Wilton L, Shakir S, Diav-Citrin O, et al. Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study. J Clin Psychiatr 2005;66:444–9. quiz 546.
[61] Bokor G, Anderson PD. Ketamine: an update on its abuse. J Pharm Pract 2014;27:582–6.
[62] Sassano-Higgins S, Baron D, Juarez G, Esmaili N, Gold M. A review of ketamine abuse and diversion. Depress Anxiety 2016;33:718–27.
[63] Myers Jr. FA, Bluth MH, Cheung WW. Ketamine: a cause of urinary tract dysfunction. Clin Lab Med 2016;36:721–44.
[64] Guo R, Liu G, Du M, Shi Y, Jiang P, Liu X, et al. Early ketamine exposure results in cardiac enlargement and heart dysfunction in Xenopus embryos. BMC Anesthesiol 2016;16:23.
[65] Zhao T, Li C, Wei W, Zhang H, Ma D, Song X, et al. Prenatal ketamine exposure causes abnormal development of prefrontal cortex in rat. Sci Rep 2016;6:26865.
[66] Su PH, Chang YZ, Chen JY. Infant with in utero ketamine exposure: quantitative measurement of residual dosage in hair. Pediatr neonatol 2010;51:279–84.
[67] Burns JM, Boyer EW. Antitussives and substance abuse. Subst Abuse Rehabil 2013;4:75–82.
[68] Tsay ME, Procopio G, Anderson BD, Klein-Schwartz W. Abuse and intentional misuse of promethazine reported to US poison centers: 2002 to 2012. J Addiction Med 2015;9:233–7.
[69] Agnich LE, Stogner JM, Miller BL, Marcum CD. Purple drank prevalence and characteristics of misusers of codeine cough syrup mixtures. Addict Behav 2013;38:2445–9.
[70] Tang AK, Tang WK, Liang HJ, Chan F, Mak SC, Ungvari GS. Clinical characteristics of cough mixture abusers referred to three substance abuse clinics in Hong Kong: a retrospective study. East Asian archives of psychiatry Official J. Hong Kong 2012;22:154–9. College of Psychiatrists = Dong Ya jing shen ke xue zhi: Xianggang jing shen ke yi xue yuan qi kan.
[71] Bartfai Z, Kocsis J, Puho EH, Czeizel AE. A population-based case-control teratologic study of promethazine use during pregnancy. Reprod Toxicol 2008;25:276–85.
[72] Petik D, Acs N, Banhidy F, Czeizel AE. A study of the potential teratogenic effect of large doses of promethazine used for a suicide attempt by 32 pregnant women. Toxicol Ind Health 2008;24:87–96.