REVIEW

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A Comprehensive Review of Pethidine, One of the Most Abused Drugs in the Health Sector

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Abstract

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Pethidine (PET), used to treat pain in humans, is a controlled drug that has drawn attention for abuse. It is also challenging to figure out whether a person taking this drug for pain relief intends to abuse it or use it for treatment. PET abuse is still on the rise as of right now, despite efforts to limit PET use and explore substitute options. As of today, chambers of pharmacists in various provinces of Türkiye have issued hundreds of statements on PET abuse. PET addiction is a public health problem that affects not only the individual but also the community and the environment in which they live. The abuse of this drug is most common in the health sector, which further increases the seriousness of the situation. This is thought to be due to long and stressful working lives and easy access to these drugs. PET has both clinical and forensic importance due to the effects it causes or produces. This review aims to review the general characteristics, pharmacology, side effects, forensic significance, analytical detection techniques, and addiction prevention efforts of PET. In this context, it is believed that this review will draw attention to the dangers of PET abuse, shed light on the individual and social problems caused by PET addiction, and help to solve these problems to some extent.
Keywords: Aldolan, meperidine, drug abuse, addiction, public health

Öz

Sağlık Sektöründe En Çok Kötüye Kullanılan İlaçlardan Biri Olan Petidin Üzerine Kapsamlı Bir İnceleme

İnsanlarda ağrı tedavisinde kullanılan petidin (PET), kötüye kullanımıyla da dikkat çeken kontrole tabi bir ilaçtır. Bu ilacı ağrı kesici olarak kullandığını bildiren bir kişinin ilacı kötüye kullanma niyetinde mi yoksa tedavi amaçlı mı kullandığını anlamak da oldukça güçtür. PET kullanımını sınırlama ve ikame seçenekleri keşfetme çabaları olmasına rağmen PET'in kötüye kullanımı halen artmaktadır. Günümüz itibari ile Türkiye'nin çeşitli illerindeki eczacı odaları PET suistimali konusunda yüzlerce bildiri yayınlamıştır. PET bağımlılığı, kişinin yanı sıra toplumu ve içinde yaşadıkları çevreyi de etkileyen bir halk sağlığı sorunudur. Bu ilacın kötüye kullanımı en çok sağlık sektöründe görülmektedir, bu da durumun ciddiyetinin daha da arttırmaktadır. Bunun sebebinin ise uzun ve stresli çalışma hayatı ve bu ilaçlara kolay erişimin olmasından kaynaklandığı düşünülmektedir. PET, neden olduğu veya ürettiği etkiler nedeniyle hem klinik hem de adli öneme sahiptir. Bu derlemenin amacı, PET'in genel özelliklerini, farmakokinetiğini, farmakolojisini, yan etkilerini, adli önemini, analitik tespit tekniklerini ve bağımlılığını önleme çalışmalarını gözden geçirmektir. Bu bağlamda, bu derlemenin PET'in kötüye kullanımının tehlikelerine dikkat çekeceğine, PET bağımlılığının yol açtığı bireysel ve toplumsal sorunlara ışık tutacağına ve bu sorunların çözümüne bir nebze de olsa yardımcı olacağı düşünülmektedir.
Anahtar Kelimeler: Aldolan, meperidin, ilaç suistimali, bağımlılık, sağlık sektörü

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INTRODUCTION

Opioids, which play a unique role in society, are one of the most effective and fundamental drugs widely used for pain relief (1,2). Discussions about the advantages and disadvantages of these drugs which have strong analgesic, sedative, and various pharmacokinetic properties are still ongoing (3,4). Especially in recent years, opioid abuse and addiction have become an important public health problem and this situation has become a serious concern both worldwide and, in Türkiye (2,5,6). The rapid development of addiction leads to an increase in social, economic, psychiatric, and medical problems (5,6). The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) reports that in 2021 there will be one million high-risk opioid users worldwide, opioids will be found in 76% of recent overdose deaths, and 510.000 opioid users will receive substitution treatment in 2019 (7). Other health problems among opioid users who refuse treatment include overdose, liver and/or kidney failure, psychiatric symptoms, and risk of hepatitis C and HIV infection (5,7,8).

Pethidine (PET), also known as meperidine, was first synthesized in Germany in 1939 by Eisleb and Schaumann during their research into compounds with atropine-like anticholinergic activity (4). It is known that PET, sold commercially under the trade names Dolantin, Dolantal, Aldolan, and Demerol, is the first synthetic opioid that can be injected into the muscle for pain relief in humans (4,9). Following animal studies, Cousins et al. first reported using PET for treating cancer-related pain in humans (4,10). Following this report, many articles were published confirming the efficacy of PET for pain relief and studies were conducted for its use in clinical applications (4). In 1950, although its reliability was not yet clear, it was approved for use in delivery rooms for pain relief (11). Later, many studies were reported on the possible side effects of PET use on both the newborn and mother (4,12,13).

PET is used in many areas including internal medicine, general surgery, neurology, and plastic surgery clinics, and is commonly used for amputation and pre- or post-operative treatment in childbirth (14-16). It can be seen that the commercial presentation forms of PET are oral (tablet) and injection (intramuscular, intravenous, and subcutaneous) (17). Although its use has decreased over time due to its potential side effects in the clinic (Figure 1), it is still considered one of the most commonly used and abused drugs (18-21).

The abuse of PET is most common in the healthcare sector, which significantly exacerbates the seriousness of the situation. This is largely attributed to the combination of long, stressful working hours and the easy access healthcare professionals have to these drugs (20,21). The dual importance of PET in both clinical and forensic contexts stems from the profound effects it can have, including addiction, overdose, and death. In this context, this review aims to comprehensively examine PET's general characteristics, pharmacology, side effects, forensic significance, analytical detection methods, and addiction prevention efforts. This contributes to a better understanding of the effects of PET and the challenges associated with its abuse, emphasizing the need for more effective regulations and preventive measures in the health sector.

METHOD

This research was conducted in PubMed, Google Scholar, and Web of Science databases. The literature review focused on studies on PET in general, and in particular, research on PET's analysis techniques, forensic and clinical science aspects, its abuse in the health sector, and case reports were examined in detail. The easy accessibility of PET in the healthcare sector and its high potential for abuse were frequently emphasized in case reports. The following criteria were considered when selecting articles and case reports: 1) available in English and electronically, 2) no significant conflict of interest in the studies, 3) Including various findings such as PET's properties, side effects, analysis methods, abuse, and potential dangers. Data extraction was performed by a single reviewer, who thoroughly assessed the accuracy, reliability, and application potential of each study and case presentation.

RESULTS

Physical and chemical properties

PET is a synthetic opioid in the phenylpiperidine class with the IUPAC name ethyl 1-methyl-4-phenylpiperidine-4-carboxylate (9,19,22). The molecular structures of PET and its metabolites, norpethidine (NPET), pethidinic acid (PETA), and norpethidinic acid (NPETA), are shown in Figure 2. PET and its metabolites are compounds that are related to each other in terms of molecular weight and pKa and also have similar physicochemical properties. The molecular formula, molecular weight, and CAS number of PET, NPET, PETA, and NPETA are given in Table 1. The protein binding rate of PET in blood is 65-75% (23). PET is an inexpensive, readily available, fast-acting, and easy-to-use drug (4,24,25). It may also be more advantageous than other opioids used as analgesics due to its moderate lipid solubility (4). Although PET, which has similar pharmacological effects to morphine, is considered to be a safer alternative to morphine, there is no definite consensus on its safety (19,26,27). In addition, fentanyl, which was synthesized in the late 1950s and has a similar chemical structure to PET but is 500 times more potent and effective as a painkiller than PET, has begun to be used as an alternative to PET due to its short-term effects and fewer side effects (28-30). The current global quantities of PET and fentanyl consumed for medical purposes between 1998 and 2017, in kilograms (Figure 1). These substances are controlled under the 1961 Convention (18).

Table 1. Molecular formula, molecular weight, and CAS number

	Pethidine	Norpethidine	Pethidinic Acid	Norpethidinic Acid
Molecular Formula	$C_{15}H_{21}NO_2$	$C_{14}H_{19}NO_2$	$C_{13}H_{17}NO_2$	$C_{12}H_{15}NO_2$
Molecular Weight	247.33	233.31	219.28	205.25
CAS Number	57-42-1	77-17-8	3627-48-3	3627-45-0

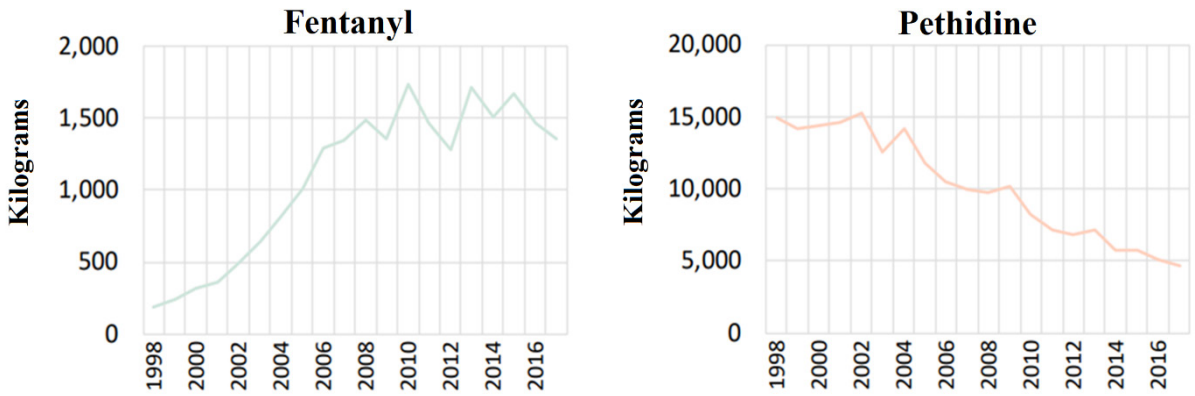

Figure 1. Consumption of PET and fentanyl between 1998 and 2017 (18)

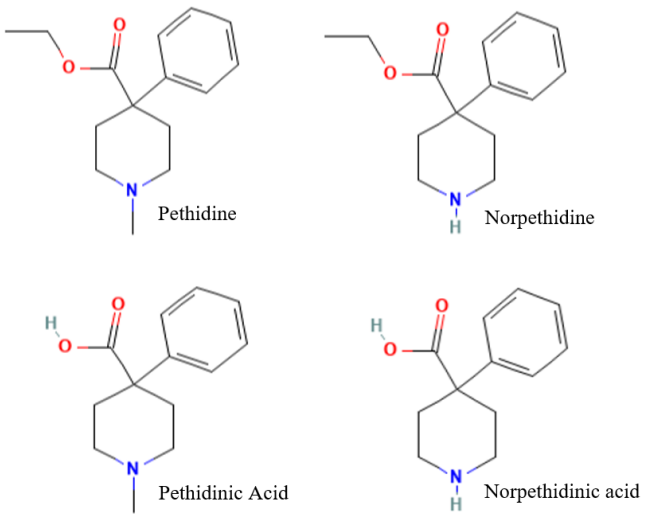

Figure 2. The molecular structures

Pharmacology

After oral administration, PET is readily absorbed and rapidly distributed in tissues (31). After oral administration, the analgesic effect lasts for a maximum of 20 to 60 minutes, but it is reported that with intramuscular injection, the maximum dose is reached within 40 minutes and provides an effect for 2-3 hours, and with intravenous injection, the time to reach the maximum dose is even shorter and the duration of effect is longer (10,32). Therefore, intramuscular, intravenous, or both injections are more commonly used (9). It has been observed that with epidural injection, the maximum dose in the cerebrospinal fluid is reached within 15 to 43 minutes (4). PET and NPET are known to pass from the placenta to the baby (10,33). As the blood-brain barrier is not fully functional in neonates and infants, it is thought that the drug may penetrate deeper and cause adverse reactions (34). In addition, although no clinical case of toxicity due to transmission from breast milk to the baby has been reported, the potential risks are not fully understood (4).

PET is extensively metabolized in the liver, mainly by cytochrome P450 (CYP2B6, CYP3A4 and CYP2C19). The majority of PET (90%) is converted into NPET through demethylation and into PETA through hydrolysis (4,35-40). Other metabolites include NPETA and conjugates of these acids (35). The only known active metabolite of PET is NPET (33,40). NPET has both analgesic and toxic effects. NPET has been shown to have approximately half the analgesic effect and twice the toxicity of PET (21,33,41). As PET is metabolized in the liver, long-term or systemic use may lead to the accumulation of NPET, especially in patients with liver and kidney dysfunction (30,42). This metabolite has been reported to cause central nervous system overstimulation, resulting in hyperreflexia, myoclonus, delirium, and, rarely, seizures (30,43).

PET has a half-life of 3 to 6 hours, while NPET has a half-life of 8 to 12 hours. However, this half-life may be increased in patients with renal failure (4). It is known that a large proportion of PET is metabolized and only a small proportion is excreted unchanged in the urine. However, most studies have ignored the effect of pH changes on PET excretion (44).

The excretion of PET and its metabolites may be affected by changes in urinary pH (44,45). PETA, NPETA, and their conjugates are not affected by changes in urinary pH because they have both acidic and basic residues (44).

In normal subjects, approximately 70% of the ingested dose is excreted in the urine within 24 hours. Of this, 10% is excreted as unchanged PET, 10% as NPET, 20% as PETA, 16% as conjugated PETA, 8% as NPETA, and 10% as conjugated NPETA. If the urine is acidic, approximately 30% more of an ingested dose is excreted as PET and NPET, and if the urine is alkaline, less than 5% is excreted as PET and NPET (46). In short, acidic urine increases PET excretion, whereas alkaline urine decreases PET excretion. In addition, experiments have shown that PET excretion is slower in the elderly than in the young (45). PET excretion reaches its peak in the first 2 hours after injection and then starts to decrease logarithmically. Although PET excretion decreases to almost zero within 2 days, it is still possible to detect it on the 3rd or 4th day. The mean excretion rates of PET and NPET in highly acidic urine over a 48-hour period following a single subcutaneous injection of 100 mg PET (44). Several comparative studies have examined the pharmacokinetics of PET and its trends in different ethnic groups and have found that there are no ethnic differences in the percentage recovery of PET and its major metabolites in urine (47). However, the presence of high concentrations of female sex hormones is likely to alter the metabolism and excretion mechanisms of PET (48).

PET exerts its analgesic effect by stimulating mu (μ) opioid receptors and its anti-tremor effect by stimulating kappa (κ) opioid receptors (4,22,31). The effects of PET on the nervous system have been confirmed by both in vivo and in vitro studies (4). PET has the same analgesic mechanism of action as morphine but is not as effective as morphine. 80-100 mg of PET administered intramuscularly has the same effect as 10 mg of morphine administered by the same route (4,31). The receptors that cause pain in the body as a result of damage to body tissue are called nociceptors. The μ-opioid receptor, which belongs to the group of G-protein coupled receptors (GPCRs) or seven-transmembrane (7TM) receptors, exerts its cellular effect by binding to the G-protein complex (49-51). PET's interaction with the μ-receptor causes the G-protein complex to bifurcate into Gα and Gβγ. The activated Gα subunit binds to adenylate cyclase and prevents the formation of cyclic adenosine monophosphate (cAMP). This leads to a decrease in cAMP levels in the environment (52-54), and the decrease in cAMP levels can affect the calcium (Ca^{2+}) and potassium (K^+) pumps in two ways:

The decrease in cAMP in presynaptic neurons causes changes in gene expression. This situation inhibits Ca^{2+} pumps, reducing Ca^{2+} entry into the cell, and the decrease in Ca^{2+} entry prevents neurotransmitter release. This reduces the excitation of postsynaptic neurons, thereby reducing pain (52,55). Figure 3 shows the presynaptic and postsynaptic mechanism of action of PET in reducing pain stimuli.

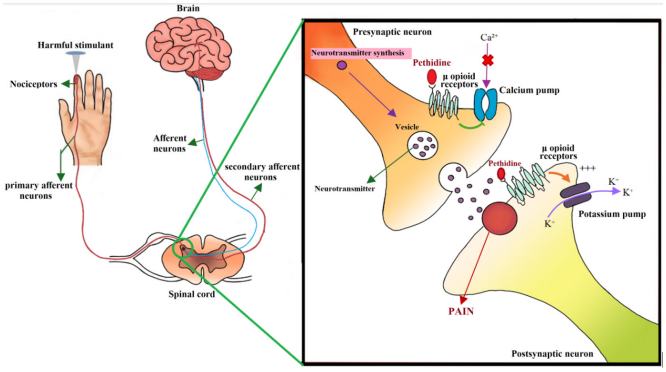

Figure 3. The pre and postsynaptic mechanisms involved in reducing pain

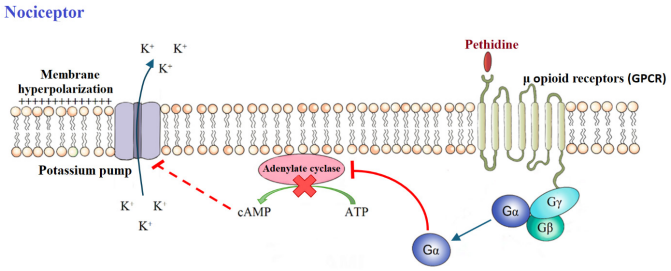

Figure 4. Illustration of the mechanism by which pain stimuli are reduced

The decrease in cAMP in postsynaptic neurons activates K^+ pumps, causing K^+ to leak out of the cell and hyperpolarize the neuronal membrane (22,52). This causes the neuron to become inactive and the pain signals coming from the neurons to decrease (52). Figure 4 shows the mechanism of pain signal reduction by K^+ pumps in the postsynaptic neuron.

Side effects

In a review of seventeen studies, including Türkiye, to measure the reliability of PET, it was found that the risk of using PET also depends on the route of administration and the dose used (25). The risk of observed reactions generally increases in direct proportion to the dose (4). Common reactions include palpitations, headache, rash, itching, visual disturbances, involuntary movements, nausea, vomiting, constipation, sweating, restlessness, and weakness, while serious reactions include shock, coma, seizures, tremors, hallucinations, bradycardia, cardiac arrest, severe hypotension, potential opioid dependence, withdrawal symptoms that may occur due to sudden discontinuation of the drug, and respiratory depression (22,39). In cases of excessive use of PET or use with monoamine oxidase inhibitors (MAOIs), serious reactions and fatal cases may be observed (22,26).

It has been reported that the accumulation of NPET in the body increases its neurological adverse potential. This neurological effect usually causes overstimulation of the central nervous system (e.g. serotonin increase). NPET neurotoxicity can result in a range of symptoms including nervousness, restlessness, tremors, confusion, and seizures (26). In addition, the anticholinergic activity of PET has been mentioned as a potential cause of delirium due to PET toxicity in previously published reports (56). While many studies in the literature report the safety of PET in use (25), PET was removed from the World Health Organization (WHO)'s list of safe drugs in 2003 due to its rapidly increasing misuse in recent years, its addictive properties, and the toxicity of its active metabolite NPET (19-21,22-27,31-33).

Importance in forensic sciences and legal medicine

Many drugs are promoted as harmless on the market but are later found to have the potential for abuse and addiction. The most well-known examples are morphine and PET (57). PET is reported to be widely used therapeutically and, due to its easy accessibility, is often abused by people who are prone to substance abuse or who have been treated with this drug at some point in their lives. People under the influence of this substance have been known to try to obtain the drug from different pharmacies with fabricated stories and complaints, traveling from city to city if necessary. Such situations make it difficult to understand whether the person is using the substance for treatment or abuse (58,59).

Most of the cases of PET abuse reported in the literature are thought to involve people working in the health sector (14,20,31,60). While PET abuse is very common among healthcare professionals, its use is almost non-existent in other sectors (20,31,61,62). This is thought to be due to long, stressful working hours and easy access to drugs (4,24,25). It should be kept in mind that suicide attempts may increase with the increase in diseases such as anxiety, burnout, and depression, especially considering the risk for health personnel due to their easy access to addictive substances (63,64). According to reports on drug-abusing doctors, 25% of all cases of drug abuse involve PET, and in Türkiye, PET is the second most common drug of abuse among doctors (26,60). It was found that sixty-six out of seventy-nine doctors whose prescribing rights were withdrawn for non-medical reasons between 1985 and 1994 were using PET. In thirty-four of the cases, others only became aware of their use after they had been using the substance for more than 2 years. The mortality rate among these doctors was also found to be high (65). Similar cases of abuse have been, and continue to be, reported in many countries (14,31).

It should never be forgotten that the performance of healthcare workers who abuse PETs may be negatively affected, and they may also endanger the patients under their care and the quality of service will significantly decrease (26,59,62). Another reason why addiction in healthcare is important is that it poses a threat not only to the individual but also to the work environment and patient safety (59). Furthermore, friends and/or family members of medical professionals struggling with PET addiction may unintentionally contribute to the problem. Even, the circumstance can turn into a collective offense with a tendency to hide a colleague's issue. Therefore, keeping silent, assisting the individual in obtaining the drug, and occasionally providing assistance in administering it all serve to exacerbate the gravity of the issue (59). It has been observed that addicts who have difficulty obtaining PET try to obtain it by illegal means (black market, theft, etc.), by forging prescriptions or having them forged, or by simulating illness or injury (66-69). However, people who abuse prescription drugs are at higher risk of moving on to illicit substance use (58). It is also worrying that people who inject PET drugs are vulnerable to infections such as hepatitis and HIV through the sharing of syringes (70).

Many case reports of PET abuse have been published in the literature. As of today, chambers of pharmacy in various cities of Türkiye continue to issue hundreds of declarations on PET abuse. The first fatal case of PET poisoning was reported in 1947 (71). Following this case, the importance of PET in forensic science was recognized and studies focused on PET. Table 2 shows some case examples of PET use and the age, sex, route of exposure, and medical history of the people in these cases. PET is reported to be used more frequently by women, middle-aged people, married people, people with children, and people with a certain level of education compared with other illicit substances (72). There are also cases where PET, which has strong withdrawal symptoms, is associated with crimes that are commonly encountered in forensic science. In these cases, people who have difficulty accessing PET are known to be involved in common crimes such as theft, fraud, black-marketing and even resorting to various illegal drugs (66-69, 73,74). Furthermore, it has been discovered that abusing PET drugs is linked to negative experiences during childhood. On the other hand, it has been noted that exposure to physical and/or sexual abuse, neglect, and domestic violence increases the likelihood of substance abuse and addiction. Because of all of these factors, it is seen that those who suffer from addiction experience emotional development impairment, lose their sense of self, become alienated from their families, and lose their sense of self (59).

Considering that most PET abuse cases examined were in the health sector and had similar motives, one of them was presented as an example. A 37-year-old nurse was introduced to PET at the age of 31 to relieve pain following surgery, and over time developed an addiction. Initially, she had no problems obtaining the drug due to her profession, but

when she was unable to obtain the drug, she experienced a withdrawal crisis and stole PET from the clinic. It is stated that she lost her job and subsequently had to divorce her husband. It is seen that, after being dismissed, the person continued to buy PET from places where she visited friends, under the pretext of stealing red prescriptions or lying about being ill. Finally, it was reported that, due to the side effects of the withdrawal syndrome, she was physiologically exhausted, uninterested in herself, and had ecchymosis marks on her body from the injections and soon died of an overdose of PET (61).

in the person's blood and body tissues. Based on the clinical history, the autopsy, and the results of the toxicological analysis, they reported that the cause of death was chronic mercury poisoning complicated by acute PET and sodium cyanide, and the manner of death was murder (75). The second case involved the murder of an 88-year-old, very wealthy and ill woman. Results were obtained from three different institutions that independently performed toxicological analyses to determine the cause of death. The high levels of PET found in the femur and brain tissue confirm that the victim had been exposed to high doses of PET shortly before

Table 2. People using PET: age, sex, route of exposure, and medical history

Case No	Age	Gender	Route of exposure	Medical history	Ref
1	37	Woman	Intravenous injection	Abuse	61
2	43	Woman	Intravenous injection	Abuse	68
3	23	Woman	Multi-drug use	Abuse	76
4	61	Man	Intravenous injection	Abuse	77
5	41	Man	Injection	Suicide attempt	69
6	43	Woman	Oral Tablets	Suicide	78
7	53	Man	Oral Tablets	Overdose Intake	79
8	24	Man	Intramuscular injection and multi-drug use	Serotonin Syndrome	80
9	44	Man	Tablets	Intoxication	71
10	34	Man	Injection	Abuse	36
11	58	Man	Intravenous injection	Abuse	81
12	30	Man	Intradermal injection	Abuse	82
13	32	Man	Multi-drug use	Multi-drug Intoxication	83
14	17	Woman	Oral	Overdose Intake	84
15	36	Man	Injection	Abuse	5
16	40	Man	Intramuscular and intravenous injection	Abuse	85
17	34	Man	Injection	Withdrawal syndrome	73
18	35	Woman	Intravenous injection of multiple drugs	Homicide	75
19	88	Woman	Intravenous injection	Homicide	74
20	36	Woman	İntravenous injection	Abuse	59
21	34	Man	Intramuscular and intravenous injection	Abuse	86
22	26	Woman	Intramuscular and intravenous injection	Abuse	86
23	38	Woman	injection	Abuse	87
24	54	Male	İntramuscularly injection	Abuse	88
25	Not stated	Woman	Intravenous injection	Abuse	89

As can be seen in Table 2, although most of these cases are cases of abuse, it is also possible to find cases of homicide. As a result of the literature review, two cases of homicide committed with PET were found. The first case involved a 35-year-old ill woman who was found dead by her husband. The toxicological analysis performed after the autopsy revealed high concentrations of mercury, cyanide, and PET

her death. In addition to PET, the substances pentazocine, promethazine, and metoclopramide were also found in the victim's blood (74). This is an important homicide case in which PET was detected in post-mortem tissue samples. In a suspected poisoning case, the occurrence of death due to a drug that the person had already used chronically

always poses difficulties for forensic toxicologists for all active substances. When analyzing post-mortem cases, drug concentrations determined from all blood and tissue samples should be evaluated together. In this way, it is possible to determine whether the patient was exposed to a drug above the therapeutic dose at one time.

Analyses performed for detection and determination

In forensic toxicology, the determination of drug use from biological samples is very important. Plasma, urine, and oral fluid are commonly used for the analysis of drugs of abuse (58,90,91). The availability of more than one biological material for sampling allows the selection of the most appropriate sample for the analyte to be examined (92).

PET and its metabolites have been analytically detected by liquid chromatography-mass spectrometry (LC-MS), gas chromatography-tandem mass spectrometry (GC-MS), and various detectors such as electron capture detector (ECD), nitrogen phosphorus detector (NPD), and surface ionization detector (SID) (31,33,35,40,58,90,91,93-96). The first report describing the determination of PET in human body fluids belongs to Ishii et al. (31). Acids such as PETA and NPETA may not be analyzed or detected by GC without derivatization (97). Since PETA is excreted in higher concentrations than PET and NPET, its absence in urine would be strong evidence that the person is not using PET, according to the literature (20). In addition, NPET is more abundant in urine than PET, so it is thought that detecting NPET may be more advantageous than PET in determining its abuse (20,31).

In the studies mentioned above, the active substance PET and its metabolites were analyzed in different matrices using different analytical techniques. Each analytical technique has performance parameters and limits of analysis that may vary according to the different matrices to be studied (urine, blood, hair, etc.). Considering the widespread abuse of PET, there is a need for a more sensitive, and rapid analytical method to determine the levels of PET, especially their metabolites (21,40,58,98). This way, addiction can be detected quickly, early measures can be taken, and the quality of life and services can be significantly improved.

Prevention and treatment

It's critical to diagnose and treat addicted workers as soon as possible. In this regard, since health professionals are known to be among the high-risk groups, comprehensive and successful programs should be implemented to prevent addiction among them. Two essential tactics in the fight against drug addiction are prevention and treatment. Early detection of substance-using staff and adherence to required protocols can stop the progression of addiction. Every healthcare facility should have policies in place for preventing substance use, quickly identifying abuse, and providing appropriate assistance when abuse occurs. When abuse is suspected, it is critical to locate the addict and carry out the required intervention as soon as possible. Preventive measures in particular must be developed and successfully integrated into routine activities (62).

The prevention, screening, and treatment of substance abuse, mental health issues, burnout, and age-related physical problems are the primary objectives of wellness programs for health professionals around the world. Health screenings linked to occupational health and safety in Türkiye are likewise arranged based on the units where employees are employed. Psychological issues, burnout, and substance use could be added to these screening programs for employees working in areas where there is a possibility of substance use, like operating rooms (62,99). An additional choice is that the phenylpiperidine group contains several opioid substitutes. Hydromorphone, oxycodone, and fentanyl are available in parenteral formulations and are suitable substitutes for morphine or PET (99). On the other hand, addiction to these drugs appears to be increasing as well. Strategies that will guarantee success in the fight against substance abuse involve expanding the list of addictive drugs, enforcing stringent periodic inspections, strengthening the follow-up mechanism with urgent non-routine inspections, and establishing protocols including techniques like toxicological screening and analysis (62).

CONCLUSION

Although the use of PET is being restricted in the health sector and alternative medicines are being introduced, the number of cases does not seem to be decreasing both in the world and in Türkiye. Even as of 2024, chambers of pharmacy in various provinces of Türkiye have issued hundreds of declarations on PET abuse (especially ampoule aldolan). In order to prevent this situation, it is seen that they try to inform each other and even expose individuals if necessary. PET addiction is an important problem that not only affects the individual, but also threatens his/her family, work environment, and, if the individual works in the health sector, the safety of patients.

PET has a very important place in both clinical and forensic sciences due to its many side effects such as causing intentional or unintentional poisoning and decreasing quality of life. Although hundreds of studies on PET have been published, no study includes all the information about its general properties, pharmacology, side effects, forensic importance, analytical techniques, and prevention, especially explaining its pharmacokinetic/genetic mechanisms. Within the scope of this review, an attempt has been made to address all the issues that are thought to be necessary to know about PET. Thus, it is believed that this review will contribute to the elucidation of cases related to PET and will help to some

extent to solve the individual and social problems caused by PET addiction both in Türkiye and in the world.

ACKNOWLEDGEMENT

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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This study is based on the revision of the Master's Thesis entitled "Simultaneous Determination of Pethidine and its Metabolite Norpetidine in Urine Sample by Gas Chromatography Mass Spectrometry (GC-MS)" by Zeynep Arslan, dated 2022.

Ethical Declaration

Since this study is a review article, there is no need for ethics committee approval and the Helsinki Declaration criteria were taken into consideration.

Authorship Contribution

Idea: ZA, ZT, Design: ZA, ZT, Oversight: ZT, Funding: ZT, Equipment: ZA, ZT, Data collection and processing: ZA, Analysis and interpretation: ZA, Literature review: ZA, ZT, Writing: ZA, Critical review: ZA, ZT

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