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MINIREVIEW

Non-fentanyl-derived synthetic opioids emerging during recent years

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Abstract

Purpose Since the appearance of fentanyl followed by its many kinds of analogues around 1988, North America has been exposed to fierce synthetic opioid pandemic resulting in more than 130,000 deaths due to their overdoses until May 2019, when China declared to prohibit the licit fentanyl analog production. However, the Chinese announcement did not go into force in USA due to the adroit strategies of tough traffickers. Thus, contrary to the expectation, the number of synthetic opioid products and their poisoning cases in USA has increased by about 30%; especially, various benzimidazole synthetic opioids have revived on the illicit drug market during a recent few years. In this article, the recent abrupt changes in the situations of illicit synthetic opioid market and their current abuses are described.

Methods Various databases, such as SciFinder, Google, and Google Scholar, were utilized to collect relevant reports referring old but newly appearing synthetic opioids.

Results At the present time, there are several families of new synthetic opioids, which are not fentanyl derivatives; MT-45 and its analogs, benzamide and 2-phenylacetamide opioids (U-series opioids), and benzimidazole opioids. Most of the above substances had been developed in 1950s to 1970s, but had never been used as analgesic medicines, because of their severe adverse effects, such as respiratory depression, physical dependence, and resulting deaths. However, there is possibility that these drugs will become main illicit synthetic opioids in place of the fentanyl analogs during coming several years from this time.

Conclusions All of the above non-fentanyl-derived families had been developed 50–70 years ago to establish them as analgesic medicines, but had been unsuccessful. These drugs largely appeared in the illicit drug markets in North America, Europe, and Australia, during recent years. Pharmacological, toxicological, and metabolic studies are insufficient for benzamide and 2-phenylacetamide opioids, and are very scant especially for benzimidazole opioids. This time we should start studying pharmacotoxicology of the newly emerging synthetic opioids to alert forensic toxicologists in the world and to suppress their rapid and wide spread in the world.

Keywords Non-fentanyl synthetic opioids · Benzimidazole opioids · Benzamide and acetamide opioids · U-series opioids · MT-45 and its analogs · Chinese generic legislation in 2019

Introduction

Fentanyl was first synthesized by Paul Janssen in 1959 [1] and approved for medical use in USA in 1968 for severe pain treatment. This drug partly extended to be used as a heroin-like recreational drug soon after 1968. The first medical examiner case of fentanyl poisoning appeared in a journal in 1980s [2]. Fentanyl analogs (FAs) also began to be synthesized in the early 1970s for the purposes of clinical analgesia and research, but fentanyl and FAs have been misused in place of heroin due to their cheaper costs [3]. Most of synthetic opioids began to be synthesized in China after 1980s, and more than 90% of them were shipped to the USA [4]. Fentanyl and FAs had been controlled under Schedule I of the 1961 UN Single Convention on Narcotic Drugs since 1964. Since 2013, a number of new FAs started emerging on the drug market to circumvent drug prohibition laws [1]. Nowadays, more than 1400 FAs have been described in scientific and patent literature [5].

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In May 2019, China has postulated generic legislation which includes about 1400 of fentanyl-related substances in the supplementary list of controlled narcotic drugs and psychotropic substances with non-medical use [6]. This means that China has prohibited a majority of the production of previously legal FAs, resulting in possible inability of shipping most of dangerous FAs to the USA. Also, in USA, fentanyl core-structure scheduling by the U.S. Drug Enforcement Administration (DEA) has been established in 2018 [7]. Both Chinese and USA Acts should have effectively controlled a majority of FAs. In spite of such scheduling situations in the USA, especially during the recent 5 years (2016–2020), fentanyl and its analogs have been said to be associated with more than 130,000 deaths in North America [8], far exceeding the number of the fallen of Americans (estimated as 58,000) in the Vietnam War. Therefore, a large void of FAs should have suddenly appeared on the North American illicit drug market. In response to such a situation, alternative opioid drugs belonging to different drug families has begun to appear, but many scientists may usually think that it will take a few years to fill such a large void; however, contrary to such anticipation, a number of such drugs are rapidly growing on the illicit drug market mainly in the North America very recently; they are not newly synthesized compounds, but the synthetic opioids developed as long as 60–70 years ago, which had failed to become licit medical analgesics, because of severe side effects, such as respiratory depression and physical dependence, have revived to appear the drug market.

According to the definition proposed by UNODC, such drugs, which was developed in 1960s–1970s, but have recently become available on the illicit market again can belong to the new psychoactive substances (NPS) [9].

In this article, we discuss non-fentanyl-derived synthetic opioids by dividing them into the below groups shown in two tables.

1. U-compounds (most of them developed by the Upjohn Company in 1970s; benzamides and 2-phenylacetamides) plus MT-45 and its related compounds (developed by Dainippon Pharmaceutical Co. Ltd. in 1970s) (Table 1)
2. Benzimidazole opioids (developed by CIBA Aktiengesellschaft in the late 1950s–1960s) plus brorphine (invented by Paul Janssen in 1967) (Table 4).

The chemical structures, molecular weight, and formal names are shown in the supplementary material section of this article.

U-compounds including AH-7921

Many of the drugs included in this group already started appearing in public for recreational purpose before May 2019 when China stopped production of fentanyl and FAs (see Table 1). The AH-7921, a benzamide compound belonging to the U-compounds, developed by Allen and Hanburys Ltd. in the mid-1970s, has been very active in this group. Before the postulation of generic legislation by China for fentanyl-related substances in 2019 [6], the synthetic opioids sometimes appeared as the combination of FA and U-compounds [10]. Although the U-compounds and AH-7921 were developed in 1970s by Upjohn Company and Allen and Hanburys Ltd., respectively, the earliest appearance of AH-7921 was 2012 in the UK [11], and the most recent one found in public was U-51754 displayed online in 2021 (Table 1). No generic scheduling has been conducted legally for the family of the U-compounds at this time (Table 2) [12–16], but U-47700 and AH-7921 are controlled in many countries [12–14].

Analgesic potencies of the U-compounds are generally not high (0.9–7.5) [11–13, 15, 16]. The characteristics of these compounds are that some of them are acting to different type(s) of opioid receptor(s). The analgesic receptors are mu (μ), kappa (κ), and delta (δ) opioids receptors [17]. The receptors do not exist as a complex, but are located separately in the brain, spinal cord, and peripheral sensory neurons; for μ opioid receptor, it is located even in the intestinal tract. The most typical opioid receptor is the μ type one. The μ type receptor functions to provoke analgesia, physical dependence, respiratory depression, miosis, and euphoria; the κ type receptor functions to provoke analgesia, anticonvulsant effects, depression, dissociative/hallucinogenic effects, diuresis, miosis, and dysphoria; the δ type receptor functions to provoke analgesia, antidepressant effects, convulsant effects, physical dependence, and respiratory depression [18, 19]. The most typical U-compound U-47700 largely acts on the μ opioids' receptor [20]; its euphoric action and psychological and physical dependence are the causes for its repeated abuse, which lead many of its users to respiratory depression and deaths. U-48800, U-50488, and U-51754 have similar 2-phenylacetamide structures (see supplementary material Fig. S1), and are active ligands of κ opioid receptor [11]; but the users of 2-phenylacetamides suffer from the symptoms such as dysphoria and auditory hallucination [16, 17, 20]. These three 2-phenylacetamides are uncontrolled at this time. U-49900 [9] is a structural benzamide analog of U-47700, and appeared online in 2016; thus, it may have an activity as a μ opioid receptor agonist, but no deaths have been reported being involved in the intake of U-49900.

Table 1 Analgesic potencies, binding affinities, first appearance, human deaths, and analyses for U-compounds and MT-45 with its related compounds

Compound	Analgesic potencies in animal behavioral studies[a] (morphine = 1)	In vitro-binding affinities (EC_{50}) to human MOR (nM)[b]	First appearance in public	Human deaths (conc. in peripheral blood)	Analysis[c]
1. AH-7921	1.7 [11], 0.9 [13]	26.9 [21]	July 2012 in Norway and Sweden [11]	At least 18 [14]	LC–MS/MS [26] GC–MS [26]
2. U-47700	7.5 [11, 12]	8.8 [21]	Appearance on the recreational drug market in 2014, USA [20]	At least 32 [20] (7.8–3040 ng/mL [20])	LC–MS/MS [26, 28] LC–QTOF-MS [26] GC–MS [26]
3. U-49900	na [15]	na	Appearance in 2016 on a popular online forum [11]	na (1.0–3.5 ng/mL [22])	UHPLC–HRMS/MS [23, 24] GC–MS [24]
4. 3,4- Methylenedioxy-U-47700	na	na	Detected in a single sample in 2018, Poland [16]	na	LC–QTOF–MS/MS [29]
5. U-47931E (bromadoline)	na	na	Started to be sold on web sites in 2017 in Europe [16]	na	UPLC–MS/MS [22]
6. U-48800	7.5 [11] (acts on KOR [11])	na	Included in seized material in 2018, USA [20]	At least 8 [22] (0.27–6.2 ng/mL [22])	UPLC–MS/MS [22]
7. U-50488	na (acts on KOR [11])	na	na	na	UPLC–MS/MS [25]
8. U-51754	0.75 [16] (acts on KOR [16])	na	Appearance in online illicit vendor sites in 2018 [16]	na	UHPLC–MS/MS [27]
9. MT-45 (racemic)	0.8 [39]	525 [40]	First detected in a seizure in 2013 in Japan [38]	At least 30 in Sweden and USA [37]	UPLC–QTOF-MS [37] GC–MS [26]
10. AD-1211 ((*S*)-enantiomer)	15 [44]	na	na	na	na
11. Diphenpipenol ((*S*)-enantiomer)	105 [46]	na	na	na	NMR [46] LC–QTOF-MS [46]
12. 2F-MT-45	na	200 [48]	Detected in a tablet in 2016, UK [37]	na	NMR [37] UPLC–QTOF-MS [37] GC–MS [37]

The reference numbers are shown in brackets

EC_{50} half maximal (50%) effective concentration, *KOR* κ opioid receptor, *MOR* μ opioid receptor, *na* data not available

[a]Analgesic potencies were estimated using rodents by hot plate test or tail-flick method (morphine or fentanyl was tested simultaneously as control)

[b]Although the parameters were all for human MOR, but the each experimental condition was not the same; the values cannot be exactly compared with each other. The data give only broad approximation

[c]The abbreviations for instrumental methods are used very commonly; thus, the explanation of the abbreviations has been skipped

There was a report [21] describing the in vitro-binding ability expressed as EC_{50} of target U-47700 and AH-7921 using human μ opioid receptor which was produced by recombinant techniques using morphine as the standard agonists. The U-47700 and AH-7921 gave EC_{50} values of 8.8 and 26.9 nM, respectively (Table 1).

The appearance of U- and AH- compounds in public started from 2012; therefore, these new compounds have been occasionally coexisting from 2012 up to the present time mainly in the North America, Europe, Australia, and other countries, although the amounts of FAs directly shipped from China have been decreased dramatically since 2019 [6].

Among U- and AH- compounds, only U-47700, U-48800, and AH-7921 were reported to cause human deaths (Table 1) [14, 20, 22].

As shown in Table 2, some U- and AH- compounds are controlled legally. U-47700 is being controlled in nine countries; AH-7921 in eight countries; U-47931E (bromadolin) in two countries; U-51754 in one country.

Table 2 Legal status of the U-compounds and MT-45

Compound	Country	Legal status	References
U-47700	USA	Schedule I	[12]
	Canada	Schedule I	
	UK	Class A	
	Australia	S9 (Prohibited Substance)	
	Germany	Anlage II	
	Sweden	Illegal	
	Finland	Illegal	
	China	Controlled	
	Japan	Narcotic	
AH-7921	USA	Schedule I	[13, 14]
	Canada	Regulations amending the food and drug regulations	
	UK	Class A	
	Australia	S9 (Prohibited Substance)	
	Germany	Anlage II	
	Sweden	Illegal	
	Norway	Illegal	
	Japan	Narcotic	
U-49900 and U-77891	State of North Carolina (USA)	Schedule I (no federal law)	[15]
U-47931E (bromadoline)	Canada	Schedule I	[16]
	Sweden	Illegal	
U-51754	Latvia	Controlled	[16]
MT-45	USA	Schedule I	[37, 39, 42, 43]
	Canada	Regulations amending the food and drug regulations	
	UK	Class A	
	Germany	Anlage II	
	Sweden	Illegal	
	China	Controlled	
	Japan	Narcotic	

Analytical methods for the U-compounds have been well studied [22–29] including pretreatments and instrumental analyses by liquid chromatography (LC)–tandem mass spectrometry (MS/MS), ultra-high-performance liquid chromatography (UHPLC)−MS/MS, UHPLC−high-resolution mass spectrometry (MS), LC−quadrupole time-of-flight-MS, and gas chromatography−MS. The pretreatments are mainly conventional liquid-liquid (L-L) extraction and solid-phase extraction (SPE). For details for the pretreatment procedures for seized materials and biological samples, please refer to each reference of the "analysis" column shown in Table 1.

AH-7921, U-47700, U-49900, U-50488, and MT-45 were generally stable over a 36-week period when blood samples were stored in the refrigerator or freezer. Most analytes were stable for at least 2 weeks at room temperature [30].

Except for U- and AH- compounds listed in Table 1, there were some additional U-compounds and the related compounds identified in seized materials and a biological fluid, which were not circulated widely [31–36] (Table 3). Since all of them are not controlled, some of them will be detected in place of the controlled U-compound opioids.

Table 3 List of novel U-compounds found in seized drug materials or biological fluid reported recently (modified from Ref. [20])

U-compound	Sample type	Date of report	References
Isopropyl-U-47700	Biological fluid	May 2018	[31]
Furanyl UF-17[a]	Seized material	Jun 2019	[32]
UF-17[a]	Seized material	Jun 2019	[33]
N-Methyl U-47931E	Seized material	Nov 2019	[34]
3, 4-Difluoro-U-47700	Seized material	Mar 2020	[35]
N-Ethyl-U-47700	Seized material	Mar 2020	[36]

[a]Contains a U-compound-like core structure, but not pharmacologically active

MT-45 and its related compounds

As stated before, MT-45 was developed in 1970s by Dainippon Pharmaceutical Co., Ltd. in Japan. The chemical structure of MT-45 is quite different from U- and AH-compounds except for the presence of a cyclohexyl ring

moiety in common. The whole feature of MT-45 is somewhat similar to fentanyl, but a piperazine ring is present at the central part of this compound (see Fig. S1), while in fentanyl, a piperidine ring exists at the central part of the compound. The structure of MT-45 is said to be relatively similar to diphenidine, an *N*-methyl-D-aspartic acid (NMDA) receptor agonist [37]. The compound was first detected in seized samples in Japan [38]. Racemic MT-45 has about 0.8 of the in vivo analgesic potency of morphine [39] and in vitro affinity to human μ opioid receptor at EC_{50} of 525 nM [40]. In spite of both in vivo and in vitro relatively low potencies, MT-45 caused as many as 30 deaths [40]; we could find two and one monographs on MT-45 published by European Monitoring Centre for Drug and Drug Addiction and World Health Organization, respectively [41–43].

Dainippon Pharmaceutical Co., Ltd. also created MT-45 analogs AD-1211 [44, 45] and diphenpipenol [46, 47] in 1970s. The (*S*)-enantiomers of both compounds showed 15 and 105 of the in vivo analgesic potencies, respectively, which were much more potent than that of MT-45 (Table 1). Moreover, McKenzie et al. [37] detected a tablet in Manchester, UK, in October 2016, in which 2F-MT-45 was identified. Whether or not 2F-MT-45 was synthesized together with MT-45 by Dainippon Pharmaceutical Co., Ltd. in 1970s is unknown. 2F-MT-45 showed a higher in vivo analgesic potency and a smaller in vitro EC_{50} value; it was a μ opioid receptor agonist [48]. Among MT-45 and its related compounds, only MT-45 is being controlled in several countries (Table 2).

Benzimidazole opioids

Benzimidazole opioids are not newly developed compounds; they were developed in the late 1950s–1970s by CIBA Aktiengesellschaft in Switzerland, just a little bit earlier the time of development of U- and AH- compounds and MT-45. Wikipedia have mentioned as many as 39 kinds of benzimidazole opioids together with their in vivo analgesic potencies [49]. The top 14 substances with highest in vivo potencies are listed in Table 4. Their in vivo analgesic potencies [49] are obviously higher than those of the U- and AH-compounds and MT-45 (Table 1), but generally comparable to those of fentanyl analogs such as sufentanyl, remifentanil, α-methylfentanyl, trans-3-methylfentanyl, cyclopropylfentanyl, furanylfentanyl, and ocfentanil; only carfentanil was exceptional because its in vivo potency is about 10,000 times higher than that of morphine potency [50]. The rest 25 benzimidazole opioids with lower analgesic potencies (in vivo) are shown in Table S3.

The experiment measuring in vitro affinity /binding (EC_{50}) to human μ opioid receptor shown in Table 4 has been conducted by a single research group [51]. Therefore, their values can be compared with each other; they are consistent with the reciprocal values of in vivo analgesic potencies (Table 4).

Although the development of the benzimidazole opioids was performed in the oldest period (late 1950s–1970s), their appearance in public is very recent (2019–2021) [52–57]; exceptionally, etonitazene was found at illegal drug market in 1998, Moscow [58].

The fatalities involved in the benzimidazole opioids were reported mainly for in etonitazene [59], isotonitazene [60, 61], and metonitazene [55]; top fatalities are found for isotonitazene (Table 4). On the "Human deaths" column of Table 4, there are many compounds without fatality data available ("na"), implying that deaths involved in other compounds of benzimidazole opioids will appear in the near future.

In Table 5, the legal status of this type of compounds is shown [53, 58, 62–64]. Isotonitazene, etonitazene, metonitazene, and etodesnitazene are controlled currently. Isotonitazene is controlled by several countries in USA, European countries, and Japan.

The analytical procedures are also described in each reference of Table 4 [51, 53–55, 57, 65, 66]. The pretreatments of compound products or biological samples such as L–L extraction and SPE methods are usually described in the references. The most reliable tools for instrumental quantification are MS techniques. These analytical methods are essentially the same as described for U- and AH- compounds and MT-45 shown in Table 1.

Brorphine

Brorphine was synthesized back in 1967 by Paul Janssen. It appeared online that this compound was circulating in 2019, USA [67]. It had the in vitro affinity (EC_{50}) of 30.9 nM, which was a μ opioid receptor agonist more potent than morphine [67]. However, the in vivo analgesic potency had not been investigated at this time. Brorphine is one of the most recent synthetic opioids, resulting in more than 100 deaths in a few months in USA [68]. Because of many deaths associated with brorphine, it has been designated as Schedule 1 in the USA, and also controlled in the UK [69] (Table 5).

Discussion

It is surprising that most synthetic opioids were developed many years ago (1950s–1970s) by several companies. At beginning, the pharmaceutical companies aimed to apply the developed drugs to effective analgesics, but most of them had been unsuccessful for medical contribution, mainly

Table 4 Analgesic potencies, binding affinities, first appearance, human deaths, and analyses for benzimidazole compounds and brorphine aligned according to analgesic potency

Compound	Analgesic potencies in animal behavioral studies [49] (morphine = 1)	In vitro-binding affinities (EC_{50}) to human MOR (nM) [51][a]	First appearance in public	Human deaths (conc. in peripheral blood)	Analysis
1. Etonitazene	1000	0.661	Found at illegal drug material in 1998, Moscow [58]	na	LC–QTOF-MS [51] GC–MS [51]
2. *N*-Desethylisotonitazene (metabolite of isotonitazene)	~1000	0.614	Identified as a metabolite of isotonitazene in 2019, USA [52]	na	LC–QTOF-MS [51] GC–MS [51]
3. Isotonitazene	500	1.63	Found at Europe drug market in 2019 [53]	At least several hundred fatalities in Europe and North America [61] (0.59–2.28 ng/mL [61])	LC–QTOF-MS [65] GC–MS [65]
4. Protonitazene	200	3.95	Identified in blood sample in 2021, USA [54]	na	GC–MS [53] LC–QTOF-MS [54]
5. Metonitazene (main metabolite of 5-aminometonitazene)	100	8.14	Identified in a white powder seized in 2020, USA [55]	At least 20 deaths (0.52–33 ng/mL [55])	LC–TOF–MS [55] LC–MS/MS
6. Etonitazepipne	100	na	na	na	na
7. Etonitazepyne	Around 100	na	Identified in a toxicology case in May 2021, USA [56]	na	LC–HRMS/MS [66] GC–MS [66] NMR [66]
8. Isotodesnitazene	~75	34.8	na	na	LC–QTOF-MS [51] GC–MS [51]
9. Etodesnitazene (etazene)	70	54.9	Identified from gray powder in 2020, Poland [57]	na	LC–MS/MS [57] GC–MS/MS [57]
10. Propylnitazene	50	na	na	na	na
11. Etoetonitazene	50	na	na	na	na
12. α-Methylmetonitazene	50	na	na	na	na
13. Metonitazene phenethyl homolog	50	na	na	na	na
14. Methylthionitazene	50	na	na	na	na
15. Brorphine	na	30.9 [67]	Mentioned on drug fora that brorphine was circulated in 2019, USA [67]	At least 100 [68] deaths in USA (0.1–10 ng/mL [68])	LC–MS/MS [68] LC–HRMS [67]

For abbreviations, see the footnote of Table 1

[a]The EC_{50} values were obtained from a single study [51]; the values can be compared with each other

because of severe side effects potentially resulting in deaths as described before. Among the synthetic opioids developed, fentanyl was modified to more than 1400 FAs, which were manufactured at clandestine laboratories in China to ship the products to North America. Many kinds of FAs began to appear on the USA illicit drug market since around 2013. This resulted in more than 130,000 deaths of people in North America [8].

At almost the same time, the U-compounds including AH-7921 were manufactured in China and began to appear on drug markets largely in the USA together with in European countries, but their pharmacotoxic effects were generally much lower than those of FAs, resulting only 100 deaths (Table 1).

As described before, China pledged to the USA to place all forms of fentanyl and FAs on the regulatory schedule in May 2019 [6]; this means stopping of the production of FAs

Table 5 Legal status of some benzimidazole opioids and brorphine

Compound	Country	Legal status	References
Etonitazene	USA	Schedule I	[58]
	Canada	Schedule I	
	UK	Class A	
	Germany	Anlage I	
	Japan	Designated Substance	
Isotonitazene	USA	Schedule I	[53, 62]
	UK	Under Psychoactive Substances Act	
	Australia	Regulations amending the food and drug regulations	
	Germany	Anlage II	
	Sweden	Illegal	
	Belgium	Illegal	
	Poland	Illegal	
	Estonia	Illegal	
	Latvia	Illegal	
	Lithuania	Legislation on Medicine	
	Norway	Legislation on Medicine	
	Japan	Designated Substance	
Metonitazene	USA	Schedule I	[63]
	UK	Under Psychoactive Substances Act	
	Sweden	Illegal	
Etodesnitazene (etazene)	UK	Under Psychoactive Substances Act	[64]
Brorphine	USA	Schedule I	[69]
	UK	Under Psychoactive Substances Act	

in China. However, illicit FAs from China remain widely available, especially in the USA. Chinese traffickers are too tough using various strategies to circumvent the new regulation, focusing on developing new chemical precursors, relocating some manufacturing places to India, rerouting precursor shipments through the third countries, and changing the market schemes not to be detected by judicial authorities. Insufficient supervision of Chinese Government and sometimes mild regulations of the chemicals and pharmaceutical industries also might enable such evasion and circumvention. Due to the operations of the Chinese traffickers, there is more than 30% increase in opioid-overdose cases in 2020 as compared to those in 2019 in USA [70]. In addition to such circumventing operations of traffickers, especially under a couple of recent years during the global pandemic of coronavirus (SARS-CoV-2), it is also suggested that various stressors such as stay-home orders, disruption of social activities, and economic hardships due to the pandemic contributed to increasing the number of abuse cases of illicit opioids in USA [70]. After massive scheduling of FAs proposed by Chinese Government was enacted, the increase of recreational abuse and deaths due to FAs could be observed at almost the same time; it should also be pointed out that the same phenomenon was also observed as for benzimidazole synthetic opioids; after enacting of massive scheduling made by Chinese Government [5], there was a possibility that it contributed an opportunity of the revival of old but much more potent benzimidazole synthetic opioids. The Wikipedia has mentioned 39 kinds of benzimidazole opioids [45]. Only about ten of them have appeared on the illicit drug market (Table 4) especially in USA just after the enforcement of the Chinese massive generic scheduling of fentanyl and FAs; many of the rest potent benzimidazole opioids are probably ready to appear on the markets of North America and Europe, together with other countries.

According to the lists shown in Tables 1 and 4, the human death rates caused by U- and AH- compounds, MT-45, benzimidazole compounds, and brorphine were not in good parallel with their in vivo analgesic potencies or in vitro bindings to human μ opioid receptors; there may be various factors to cause deaths due to the synthetic opioids regarding the toxicities (potencies), the uses such as overdoses, mental and physical conditions, and individual constitution [71]. Table 1 shows that U-47700, AH-7921, and MT-45 caused relatively many deaths, although all toxicities/potencies were not so high. It should be mentioned that U-48800 caused at least 8 deaths despite the action as a κ opioid receptor agonist [22]. MT-45 is less potent than morphine (Table 1), but it caused at least 30 deaths; although MT-45 is less potent than morphine as a μ opioid receptor agonist, its metabolic product M1 was reported to antagonize *N*-methyl-D-aspartate receptor with the risk of fatality [48]. The numbers of deaths caused by compounds seem to strongly affect the

legislative status; U-47700, AH-7921, MT-45, etonitazene, and isotonitazene are controlled in many countries (Tables 2, 5).

In Japan, the suppression of NPS abuse has been successfully conducted by shortening the interval between the first drafting of the NPS-controlling bill and time when the law came in force down to only about 1 month since 2015. Before 2015, it took about 1 year to the enforcement of a new NPS law. Therefore, the NPS retailors had a sufficient time of 1 year to sell new NPS legally; they used to do good business during the 1 year. The shortening of business time from 12 months to only 1 month gave a fatal blow to each retailor; almost all head shops selling NPS disappeared from that time in Japan. However, the online deals of the illicit NPS are still surviving. The scale of dealing NPS via the darknet was estimated to be relatively smaller than the licit head shop NPS deals before enacting regulations to such head shop deals. On the other hand, it was reported that only 2.1% of distributed NPS is being purchased from head shops, while 50.7% from the Internet nowadays, according to the whitepaper published by National Police Agency (NPA) in Japan [72]. As a result, about a half of NPS deals seems suppressed in Japan; this kind of strategy was very effective currently, except that the abuses of classical methamphetamine and cocaine are still being serious problems to our society. This kind of suppression strategy enacted by the governmental level should be used for synthetic opioids also in the USA and other countries.

Conclusions

In this review, we have discussed non-fentanyl derived synthetic opioids, which would consist of U-compounds (benzamides and 2-phenylacetamides), MT-45 together with its related compounds, benzimidazole opioids, and brorphine, also showing their pharmacological and toxicological information. Although above non-fentanyl derived families had been developed 50–70 years ago as analgesic medicines, these drugs largely appeared in the illicit drug markets in North America, Europe, and Australia increasing the number of fatalities, during recent years; social disruptions due to global pandemic of coronavirus could also contribute to abuse of the drugs especially during a couple of recent years.

This time, it should be necessary to study pharmacotoxicology of the newly emerging synthetic opioids to alert forensic toxicologists in the world and to observe carefully their trend of abuse, and to suppress their rapid and wide spread in the world.

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Declarations

Conflict of interest There are no financial or other relations that could lead to a conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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