Table. US National Doxepin Spending and Use, 2023

Formulation	Total No. of annual 30-day supplies	Percentage of 30-day supplies	Annual retail spending, $ (millions)[a]	Percentage of spending	Price (retail spending per 30-day supply), $[a]
Low-dose tablets, brand name	3019	0.1	1.6	1.6	526
Low-dose tablets, generic	292 925	11.2	73.8	74.5	252
Liquid[b]	317 585	12.1	2.1	2.1	7
10-mg capsules	2 003 240	76.6	21.6	21.8	11

[a] Retail spending is the sum of consumer out-of-pocket and insurer spending prior to drug rebates.

[b] To calculate 30-day use and retail spending for liquid doxepin, a mean daily use of 6 mg (the highest dose for insomnia) was assumed. This dose was chosen because liquid doxepin is commonly substituted for Silenor for the treatment of insomnia.

available at the same per-milligram price as liquid doxepin, spending would have been reduced by $73.9 million (98%).

Discussion | Despite generic competition, low-dose doxepin tablets approved for insomnia have substantially higher prices and fewer 30-day prescriptions than similar doses of capsules or liquid doxepin, which can be used off-label to treat insomnia. This repurposed drug market failure may explain why low-dose doxepin is used less frequently than many other insomnia medications. Liquid doxepin may be a viable, less-expensive alternative, assuming patients are able to manage syringes to achieve the same low doses; alternatively, researchers could study whether the 10-mg capsules are effective for insomnia without anticholinergic adverse events. Study limitations include an inability to measure patient out-of-pocket costs or manufacturer rebates or to identify what percentage of doxepin liquid or 10-mg capsules were used for insomnia or depression. Additionally, fills rather than actual use were measured.

Well-intentioned repurposing of generic medications like doxepin can be hindered if the repurposing requires doses that are not interchangeable with original versions, allowing manufacturers to set high prices for the new version, which can limit patient access.

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Drafting of the manuscript: Cai.
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1. Krystal AD, Lankford A, Durrence HH, et al. Efficacy and safety of doxepin 3 and 6 mg in a 35-day sleep laboratory trial in adults with chronic primary insomnia. *Sleep*. 2011;34(10):1433-1442. doi:10.5665/SLEEP.1294

2. Krystal AD, Durrence HH, Scharf M, et al. Efficacy and safety of doxepin 1 mg and 3 mg in a 12-week sleep laboratory and outpatient trial of elderly subjects with chronic primary insomnia. *Sleep*. 2010;33(11):1553-1561. doi:10.1093/sleep/33.11.1553

3. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2017;13(2):307-349. doi:10.5664/jcsm.6470

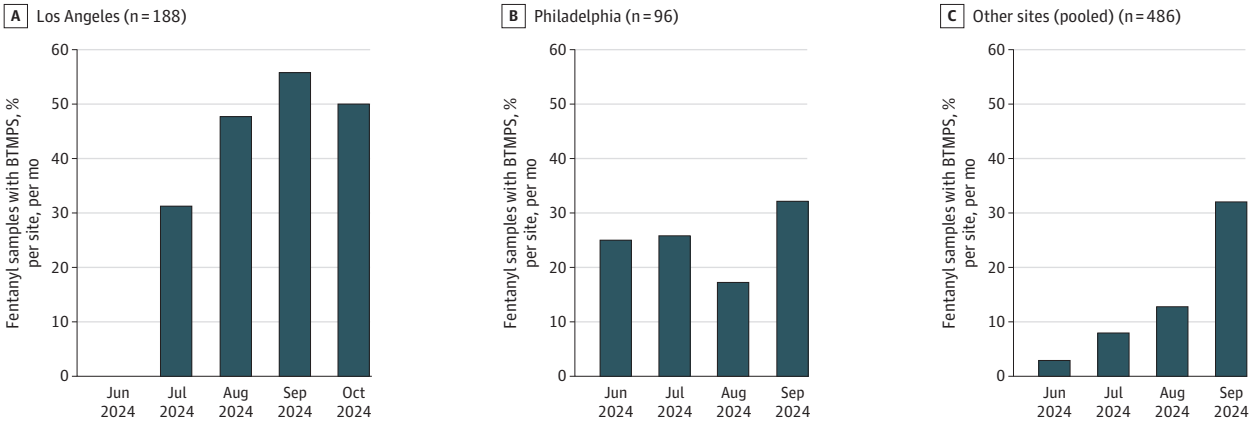
4. Geer J, Bogunovic-Sotelo O, Avorn J, et al. Managing insomnia in older adults: evidence-based strategies to improve treatment and reduce benzodiazepine use. Alosa Health. 2024. Accessed December 2, 2024. https://alosahealth.org/wp-content/uploads/2024/07/Insomnia-Benzo-EvDoc-7.30.24-Web.pdf

UV Stabilizer BTMPS in the Illicit Fentanyl Supply in 9 US Locations

Bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate (BTMPS) belongs to a class of molecules called hindered amine light stabilizers that are used in plastics manufacturing and as adhesives or sealants.[1] BTMPS has not been studied in humans or approved for human consumption, but animal studies have revealed cardiotoxicity, ocular damage, sudden death, other adverse health effects, and nicotinic antagonist effects.[2,3] In this study, we

Supplemental content

Figure. Percentages of Samples Sold as Fentanyl That Contained BTMPS



Drug product samples from community sites in Los Angeles, California (n = 188), and Philadelphia, Pennsylvania (n = 96), were quantitatively tested. Drug paraphernalia and residue samples (n = 486) from all other sites (Delaware, Maryland, Nevada, Puerto Rico, Washington, and additional cities in California) were qualitatively tested. Data in Los Angeles were collected from June 1, 2024, to October 17, 2024. Data from all other sites were collected from June 1, 2024, to September 30, 2024. Bar graphs show percentage of samples identified with bis(2,2,6,6-tetramethyl-4-piperidyl) (BTMPS), by month and site, of either all drug product samples sold as fentanyl or all paraphernalia/residue samples with fentanyl detected, labeled with counts of samples containing BTMPS by month and site.

characterize BTMPS's introduction to the illicit fentanyl supply in 9 US locations.

Methods | Samples were obtained from 9 community-based drug-checking programs within a national network of 12 programs (2 had <5 samples during study window and 1 declined to participate). Small amounts of actual drug product were obtained from participants voluntarily bringing in products expected to contain "fentanyl," "dope," or "tranq-dope" to drug-checking programs in Los Angeles, California, and Philadelphia, Pennsylvania. Trace residues from a wipe of used paraphernalia were obtained from sites in 2 California counties (Alameda and San Luis Obispo), Delaware, Maryland, Nevada, Washington, and Puerto Rico. Data were collected from June 1, 2024, to September 30, 2024, except for Los Angeles, where collection continued until October 15, 2024. Research activities in Philadelphia and Puerto Rico were approved by the WIRB-Copernicus Group; verbal informed consent was obtained. Los Angeles activities were determined by UCLA's institutional review board (IRB) to be public health surveillance and not subject to IRB oversight. Testing paraphernalia did not meet the definition of human subjects research.

Samples were sent to the National Institute of Standards and Technology and tested with direct analysis in real-time mass spectrometry (DART-MS) and quantitative liquid chromatography tandem mass spectrometry (LC/MS).[4] Samples qualitatively tested with DART-MS were compared against a library of more than 1300 compounds including drugs, cutting agents, and adulterants. Quantitative analysis using LC-MS/MS were reported as percentage by mass. The LC/MS quantitation panel included compounds across several classes: fentanyl and fluorofentanyl, fentanyl precursors, α_2 agonists, other common illicit drugs, and adulterants. Samples below the limit of quantitation were approximated and imputed to be 0.1%. Full sample collection and measurement information is available in the eAppendix in Supplement 1. We calculated descriptive statistics and conducted 2-tailed *t* tests (α = .05) to compare sample characteristics by BTMPS status using R version 4.4.1.

Results | There were 284 drug product samples tested in Los Angeles and Philadelphia. Of these, 98 (35%) contained BTMPS. In Los Angeles, the proportion of detected BTMPS per month increased from 0% in June to 56% in September and 50% in October. In Philadelphia, it was more stable, with 25% in June and 32% in September (**Figure**). BTMPS was identified in 13% of 486 trace residue samples from all additional locations combined, increasing from 3% in June to 32% in September.

Of 98 samples containing BTMPS, the mean percentage by mass was 8.6%, ranging from less than 0.1% to 56%. Mean percentage of fentanyl by mass was significantly lower in samples that contained BTMPS (3.1% vs 8.7% in samples without BTMPS; $P < .001$), as was percentage of fluorofentanyl, xylazine, 4-anilino-*N*-phenethylpiperidine (4-ANPP), and lidocaine (**Table**). The mean ratio of BTMPS to fentanyl was 7.4 (range, 0.02-197). Most samples (n = 62 [63%]) had more BTMPS than fentanyl by mass, with 8 having no detectable fentanyl and 14 having more BTMPS by a factor of 10 or greater.

Discussion | In 9 geographically diverse US locations, BTMPS was detected in drug product and residue samples over 4 months. The amount of BTMPS in available samples typically exceeded the amount of fentanyl, sometimes by orders of magnitude. This is concerning given lethality and health risks in animal studies.[2,5]

The high ratios of BTMPS to fentanyl may indicate a change in synthesis methods, possibly to stabilize a precursor such as 4-ANPP, which is susceptible to thermal and oxidative degradation.[6] BTMPS also might have been added for dilution.

Table. Mean Quantitative Results of Liquid Chromatography Mass Spectrometry on Samples of Drug Products Sold as Fentanyl, Stratified by Presence of BTMPS, June-October 2024

Substance	Mean % (range) [No.] [N = 284]		*P* value[a]
	Samples with BTMPS	Samples without BTMPS	
BTMPS	8.6 (0.1-55.7) [n = 98]		
Fentanyl	3.1 (0.1-16.5) [n = 92]	8.7 (0.1-48) [n = 180]	<.001
Fluorofentanyl	0.7 (0.1-5.9) [n = 25]	4.3 (0.1-25.6) [n = 38]	.001
4-ANPP	0.8 (0.1-5.8) [n = 65]	2.7 (0.1-28.6) [n = 129]	<.001
Phenethyl 4-ANPP	0.1 (0.1-0.2) [n = 14]	0.3 (0.1-5.4) [n = 40]	.28
Heroin		4.1 (0.4-6.8) [n = 3]	
Xylazine	1.1 (0.1-16) [n = 34]	6.2 (0.1-41.6) [n = 52]	.002
Medetomidine	3.1 (0.3-6.1) [n = 19]	2.8 (0.6-7.3) [n = 43]	.55
Methamphetamine	2.1 (0.1-5.8) [n = 8]	30.8 (0.1-81.9) [n = 3]	.55
Cocaine	5.6 (0.1-23) [n = 7]	2 (0.1-9.3) [n = 5]	.37
Lidocaine	3.7 (0.1-35.9) [n = 83]	12.2 (0.1-47.8) [n = 85]	<.001
Tetracaine	10.7 (0.1-21.1) [n = 17]	13.9 (0.1-65.4) [n = 37]	.25

Abbreviations: 4-ANPP, 4-anilino-*N*-phenethylpiperidine; BTMPS, bis(2,2,6,6-tetramethyl-4-piperidyl).

[a] By 2-tailed *t* test.

Ultimately, the reason for the introduction of BTMPS in fentanyl is unknown.

Study limitations include convenience sampling, a short study window, ability to quantify limited compounds, and possibility that paraphernalia used repeatedly could contain residue from multiple products. As drug-checking programs are not widely available and other surveillance methods do not screen for BTMPS, monitoring this compound may prove challenging. Research should explore the role of BTMPS in the illicit fentanyl supply, the extent of adulteration regionally, whether its inclusion is sustained, and health effects in humans.

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Data Sharing Statement: See Supplement 2.

1. Deng Q, He B, Shen M, Ge J, Du B, Zeng L. First evidence of hindered amine light stabilizers as abundant, ubiquitous, emerging pollutants in dust and air particles: a new concern for human health. *Environ Sci Technol*. 2024;58(2):1349-1358. doi:10.1021/acs.est.3c08884

2. IndustrialChemicals.gov.au. Decanedioic acid, bis(2,2,6,6-tetramethyl-4-piperidinyl) ester: human health tier II assessment. Published 2020. Accessed September 6, 2024. https://www.industrialchemicals.gov.au/sites/default/files/Decanedioic%20acid,%20bis(2,2,6,6-tetramethyl-4-piperidinyl)%20ester_Human%20health%20tier%20II%20assessment.pdf

3. Graham JH, Papke RL, Buccafusco JJ. Functional central nicotinic acetylcholine receptor antagonism by systemic administration of tinuvin 770 (BTMPS). *Curr Alzheimer Res*. 2005;2(2):141-147. doi:10.2174/1567205053585747

4. Appley MG, Robinson EL, Thomson A, Russell E, Sisco E. An analytical platform for near real-time drug landscape monitoring using paraphernalia residues. *Forensic Chem*. 2023;34:100489. doi:10.1016/j.forc.2023.100489

5. Krepuska M, Hubay M, Zima E, et al. Hemodynamic effects of the light stabilizer tinuvin 770 in dogs in vivo. *Open Med Chem J*. 2018;12:88-97. doi:10.2174/1874104501812010088

6. Venkatapathy R, Kauchak R, Botkins J, Magnuson ML. Degradation of immediate precursors of fentanyl and fentalogs. *Forensic Chem*. 2024;39:100573. doi:10.1016/j.forc.2024.100573

COMMENT & RESPONSE

AI IN MEDICINE

Regulation of Artificial Intelligence in Health Care and Biomedicine

To the Editor A recent Special Communication provided a detailed, succinct discussion on the regulatory challenges presented by the increasing use of artificial intelligence (AI) in health care.[1] However, we are compelled to point out the critical need for patient and caregiver involvement in creating safeguards for technologies that will ultimately affect the quality of care they receive.

Increased inclusion of patients and caregivers in conversations regarding oversight of these technologies is necessary to help regulators navigate the complex ethical and sociotechnical challenges that may arise throughout the AI life cycle, such as effects on data privacy, interpersonal relationships, and patient autonomy. However, meaningful patient engagement in the age of AI requires us to look beyond conventional structures. Processes for including these voices should ultimately reflect the diversity of the patients and caregivers who will be affected by their outputs, with purposeful consideration of making participation accessible to all. Current patient engagement practices often involve individuals who do not represent those who have substantial comorbidities or are most affected by health disparities. Inclusion of these perspectives will allow decision-makers to better understand how to navigate challenges related to fairness, as these technologies progress from development into real-world use.[2] The risk of inadvertently exacerbating health disparities with AI is a concern, with past examples including perpetuation of harmful narratives in large language models[3] and misallocation of health resources arising from the use of racially biased clinical decision support tools.[4]

In brief, AI ushers in a fundamental shift in health care that necessitates new frameworks for patient engagement. Consequently, solutions to the challenges posed by AI cannot come solely from developers, clinicians, or regulators; they must involve patients and caregivers as equal partners. We are encouraged by the increased focus on health disparities and patient values in the research community, which has increased awareness of how medical products, including software, may inadvertently contribute to inequitable health outcomes.[5] At this important stage in the development of regulatory approaches for these AI technologies, diverse perspectives and genuine opportunities for engagement will be key in reducing the risk of harm and improving health outcomes.

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1. Warraich HJ, Tazbaz T, Califf RM. FDA perspective on the regulation of artificial intelligence in health care and biomedicine. *JAMA*. 2025;333(3):241-247. doi:10.1001/jama.2024.21451

2. Rajkomar A, Hardt M, Howell MD, Corrado G, Chin MH. Ensuring fairness in machine learning to advance health equity. *Ann Intern Med*. 2018;169(12):866-872. doi:10.7326/M18-1990

3. Omiye JA, Lester JC, Spichak S, Rotemberg V, Daneshjou R. Large language models propagate race-based medicine. *NPJ Digit Med*. 2023;6(1):195. doi:10.1038/s41746-023-00939-z

4. Obermeyer Z, Powers B, Vogeli C, Mullainathan S. Dissecting racial bias in an algorithm used to manage the health of populations. *Science*. 2019;366(6464):447-453. doi:10.1126/science.aax2342

5. Charpignon ML, Byers J, Cabral S, et al. Critical bias in critical care devices. *Crit Care Clin*. 2023;39(4):795-813. doi:10.1016/j.ccc.2023.02.005

In Reply The US Food and Drug Administration (FDA) is committed to including patient perspectives in the development and evaluation of all medical products, and AI- and machine learning–enabled products are no different. We thank Mr Jaiswal and colleagues for highlighting the importance of