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RESEARCH ARTICLE

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Changing trends in novel benzodiazepine use within Scottish prisons: detection, quantitation, prevalence, and modes of use

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Abstract

Drug use within prisons is increasingly complex and unpredictable. Benzodiazepines are currently one of the most common drugs detected in individuals leaving Scottish prisons; however, understanding illicit benzodiazepine use within prisons and assessing the potential harm to individuals is challenging due to the lack of available analytical data on the substances circulating. Increasingly, materials, such as paper and clothing, infused with novel benzodiazepines have been identified as a smuggling route into Scottish prisons. Methods were developed for the qualitative and quantitative analysis of benzodiazepines using gas chromatography–mass spectrometry (GC–MS) and applied to 495 seized samples from 11 Scottish prisons, including papers, cards, blotters, powders, tablets, and clothing. Evolution in the benzodiazepines being detected was demonstrated, with etizolam being the most prevalent throughout 2020/2021 following which flubromazepam and bromazolam detections increased. Additionally, significant changes in the smuggling methods and drug formats detected occurred over time following policy changes within prisons. These data represent the first reported widescale etizolam quantitation data and demonstrate high levels of variability across all sample types, most notably within tablets (0.34–2.33 mg per tablet). Additionally, concentration mapping of a whole seized card sample revealed the total concentration of drug present (312.5 mg) and demonstrated variability across the surface of the card (1.16–1.87 mg/cm^2). These data highlight the challenges of consistent dosing for individuals and the high risks of unintentional overdose. Increased understanding of the challenge of such drug smuggling and benzodiazepine use will aid in the development of strategies to reduce supply and mitigate harm.

KEYWORDS
bromazolam, drug market evolution, new psychoactive substances, novel benzodiazepines, prison

1 | INTRODUCTION

Benzodiazepines are positive allosteric modulators of the γ-aminobutyric acid type A ($GABA_A$) receptor known for their anxiolytic and sedative effects[1] and are the most widely prescribed psychotropic drugs globally.[2] Structurally, benzodiazepines consist of a benzene ring fused to a heterocyclic diazepine ring; however, chemically similar classes of compounds have been developed, such as the thienotriazolodiazepines. Some of these compounds (e.g., etizolam) are approved for medical use and are available on prescription in countries such as India, Italy, and Japan.[2–4] Some, most notably etizolam in recent years, have since emerged on the illicit drugs market. While structurally distinct from benzodiazepines, such compounds exhibit similar clinical and pharmacological properties and are often referred to as "benzodiazepine-type drugs," "designer benzodiazepines," or "novel benzodiazepines."[3] We will use the term "novel benzodiazepines" in this paper.

Since 2007, a variety of novel benzodiazepines have entered the international illicit drugs market. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is currently monitoring the prevalence and related harms of 33 novel benzodiazepines across Europe.[5] Previously, the diversion of prescription benzodiazepines, particularly diazepam (Valium) and alprazolam (Xanax), accounted for the majority of the illicit benzodiazepine tablets circulating in the European market; however, more recently, there has been an increase in the availability of illicitly produced tablets and blotters.[2,3] Intelligence data suggest that these are commonly imported as finished products from India or as bulk powders from China.[3] In the latter case, they may be prepared into tablets, blotters, or capsules in the country of intended use.[3,6,7] Often, for consumers on the illicit drug market, these products are indistinguishable from their pharmaceutical counterparts, and in recent years, the prevalence of novel benzodiazepines in seizures of such products has increased.[2,3] In Scotland, such preparations, in particular tablets, are colloquially referred to as "street benzos" or "street Valium"[2] with people often unaware of the specific drug or the dose of the drug they are consuming.[7,8]

Since 2008, there has been a dramatic rise in the number of deaths involving novel benzodiazepines in Scotland. In 2021, novel benzodiazepines, predominantly etizolam, were implicated in 842 of 1330 Scottish drug-related deaths.[9] In North America, novel benzodiazepines are increasingly being detected in mixtures with opioids such as heroin and fentanyl, a mixture often referred to as "benzo-dope" or "down."[10]

Novel benzodiazepines are used illicitly for a variety of reasons including self-medication for anxiety or sleeping disorders.[11] It is common for individuals to partake in polydrug use with novel benzodiazepines often consumed alongside opiates, alcohol, or other psychoactive substances either to enhance their effects; alleviate withdrawal symptoms;[3,6,12] or reduce insomnia due to the use of stimulants.[6,12,13] Unintentional polydrug use can also occur due to the long half-lives and slow metabolic clearance of some benzodiazepine-type drugs, and the use of multiple central nervous system (CNS) depressants can greatly increase the risk of overdose leading to respiratory depression and death.[13] It is noteworthy that very few of the novel benzodiazepines detected on the illicit market have been subject to clinical trials or pharmacological studies, so data on their relative effects and harms remain limited within the scientific literature. It is assumed that their effects closely resemble those of prescription benzodiazepines, including sedation, amnesia, muscle relaxation, and anticonvulsive activity.[11] Novel benzodiazepines are reported anecdotally to vary greatly in their potency, onset times, and pharmacological half-lives making consistent dosing challenging for individuals and their effects unpredictable, especially when the individual drug present, the mass present per dosage unit, and the number of dosage units consumed may be inconsistent.[2,3]

Problematic benzodiazepine use in prisons has been reported globally.[14–19] Prisoners often favor depressants such as benzodiazepines as a means of passing the time and coping with the unique stressors of prison life.[20–24] Within the Scottish Prison Service (SPS), current estimates of benzodiazepine trends rely on the annual SPS prisoner survey and mandatory drug testing programs, such as Addiction Prevalence Testing (APT) and Drug Trend Testing (DTT). Within the latest SPS Prison Survey carried out in 2019, 28% of respondents stated they had used drugs within prison in the month prior to the survey, of which 46% stated they had used benzodiazepines.[25] Across 2021/2022, 769 tests were carried out on individuals entering Scottish prisons as part of DTT, with 28% of these tests positive for benzodiazepine-type drugs. Within the same year, benzodiazepines were found to be one of the most common drugs detected in individuals when leaving prison. However, information on the specific benzodiazepine-type drugs detected at both stages is not available.[26] This challenge is further exacerbated by declining response rates to the SPS prison survey since 2017, with only 30% of prisoners responding to the 2019 survey.[25] The lack of analytical data and a possible non-response bias from the surveys create significant barriers when estimating the extent and nature of unprescribed benzodiazepine use within the Scottish prisons.

Previously, most benzodiazepines used in prisons were obtained through the misuse of medications prescribed within the prisons (prescription diversion)[20]; however, they may also be smuggled into the prisons via visitors and throwing over the perimeter (known as throw-overs).[24] Since 2017, infused papers have been increasingly identified as a drug smuggling route into prisons around the world. This smuggling method has mainly been associated with new psychoactive substances (NPS), particularly synthetic cannabinoid receptor agonists (SCRAs), due to their low cost and high potency, requiring smaller amounts of the drugs to elicit the desired effect and facilitating their invisible infusion onto paper. The infused papers are then transported into the prisons via mail systems.[24]

This study reports the qualitative detection of novel benzodiazepines within the Scottish prisons. We report their detection in a wide variety of sample matrices, including tablets, powders, blotters, papers, cards, and textiles, and their likely modes of use. Additionally, we consider the effects of local drug screening and drug search policies in Scottish prisons and developments in national and international drugs legislation on the prevalence of individual benzodiazepine-type drugs in Scottish prisons. A method for the quantitation of etizolam, the most prevalent benzodiazepine-type drug detected over the study

period, within powders, tablets, paper/card, and blotters was developed and applied to seized prison samples. To the best of the authors' knowledge, this is the first report in the scientific literature of the detection of benzodiazepines in infused paper, card, and textiles. The study also provides detailed quantitative data for etizolam in a variety of drug formats using an analytical method validated to internationally recognized standards.

2 | MATERIALS AND METHODS

2.1 | Materials

Methanol (HPLC grade ≥ 99.9%) was supplied by Fisher Chemicals (Loughborough, UK). Bupivacaine hydrochloride monohydrate was supplied by Sigma Aldrich (Poole, UK).

2.1.1 | Reference standards

Neat reference standards of clonazolam (98.5% purity), desalkylgidazepam (bromonordiazepam; 98.8% purity), etizolam (99.4% purity), flualprazolam (99.4% purity), flubromazepam (99.6% purity), and flubromazolam (99.1% purity), and a solution (1 mg/ml in methanol) of bromazolam (99.6% purity) were purchased from Chiron AS (Trondheim, Norway). Diazepam (≥98% purity) was purchased from Sigma Aldrich (Poole, UK). Phenazepam (99.3% purity) was purchased from LGC Standards (Middlesex, UK).

2.1.2 | Seized samples

Non-attributable samples seized by the SPS between December 2019 and August 2022 were analyzed. The items were recovered during personal or cell searches or following detection of a benzodiazepine during the screening of incoming items (mostly mail) by prison staff using Ion Mobility Spectrometry (IMS) instruments. After seizure, samples were individually sealed into labeled tamperproof evidence bags and stored securely by the SPS. Samples were reviewed for their involvement in any judicial proceedings, and if deemed, exempt were set aside for laboratory analysis as part of the Scottish Prisons Non-Judicial Drug Seizure Monitoring Project. All samples considered suitable for analysis were anonymized by SPS staff, transferred to Police Scotland and delivered to the Home Office licensed drug testing laboratory at LRCFS at the University of Dundee.

2.2 | Methods

2.2.1 | Qualitative analysis

The method for the extraction of benzodiazepines from blotters, papers, and cards and subsequent analysis by gas chromatography–mass spectrometry (GC–MS) are similar to that described previously for SCRA-infused materials.[27] This method was adapted for the extraction of powders, tablets, and textiles within this study.

For blotter samples, half of a blotter was sampled and extracted in 0.5 mL of 0.25 mg/mL bupivacaine in methanol by ultrasonication (5 min). For paper/card samples, 2×1 cm^2 samples were taken from opposite corners and extracted in 0.5 mL of 0.25 mg/mL bupivacaine in methanol by ultrasonication (5 min). For powder samples, 10 mg of the material was dissolved in 1 mL of 0.25 mg/mL bupivacaine in methanol and vortexed (1 min). For tablet samples, one tablet from seizures where multiple tablets with similar visual characteristics were present was randomly selected, crushed using a mortar and pestle, and the resulting powder processed as previously described for powder samples. For textiles, the item(s) were examined for any visual or tactile trace of concealed drugs (e.g., items in waistbands) or infused drugs (e.g., staining, discoloration, fabric stiffness, etc.). If no concealed drugs were found, 2×2 cm^2 pieces were cut from opposite corners (e.g., for trousers, a 1×2 cm^2 piece from left cuff and 1×2 cm^2 piece from waistband on right-hand side were taken). If there was visible staining, one piece was cut from the stained portion. The 2×2 cm^2 pieces were extracted in 1 mL of 0.25 mg/mL bupivacaine in methanol by ultrasonication (5 min).

2.2.2 | Preparation of etizolam calibration and check standards

A stock solution of 1 mg/mL etizolam was prepared by dissolving 5 mg of etizolam reference standard into 5 mL of 62.5 µg/mL bupivacaine in methanol. A 7-point calibration range of 25, 50, 75, 100, 150, 200, and 250 µg/mL etizolam was prepared using the 1 mg/mL etizolam stock solution and 62.5 µg/mL bupivacaine in methanol. Three check standards were prepared by an independent analyst at 40, 125, and 225 µg/mL using a separate etizolam stock solution to that used in the calibration range and 62.5 µg/mL bupivacaine in methanol. The etizolam stock solution, calibration standards, and check standards were stored in a freezer (−20°C) until use.

2.2.3 | Quantitative analysis

For powder and tablet samples, 10 mg of the homogenized sample was weighed into a 1.5 mL Eppendorf tube. The sample was sequentially extracted by sonication five times for 5 min in 200 µL of 62.5 µg/mL bupivacaine in methanol and centrifuged for 3 min. Each of the five extracts was combined to give a total volume of approximately 1 mL. For blotter samples, one whole blotter was sampled and sequentially extracted five times in 500 µL of 62.5 µg/mL bupivacaine in methanol and sonicated for 5 min. Each of the five extracts were combined to give a total volume of approximately 2.5 mL. For paper and card samples, 1×1 cm^2 sample was sequentially extracted five times in 500 µL of 62.5 µg/mL bupivacaine in methanol and sonicated for 5 min. Each of the five extracts was combined to give a total

volume of approximately 2.5 mL. All samples, except for blotter samples, were analyzed without further dilution. Following this, if the etizolam detector response for any of the sample extracts analyzed fell outside the calibration range, they were diluted appropriately using 62.5 μg/mL bupivacaine in methanol and re-injected. As single blotter samples typically contained a higher mass of etizolam than observed in the other seized material extracts, a 10× dilution of the original sample extract was prepared for analysis. During each extraction, a small volume of solvent was unrecoverable. Experimental work demonstrated that on average, 91% (powders/tablets) to 95% (card/paper) of the supernatant was recovered during the sequential extraction of samples. This volume loss falls within the reported error of the method (±10%), and as such all quantitation results have been calculated as μg/mL despite the minor loss in extraction volume. Full data relating to the recovery volumes can be found in the supporting information.

Full validation data, including that related to extraction efficiency for the different sample formats, can be found in the supporting information. In brief, to ensure near-exhaustive extraction of etizolam from test samples, sequential extractions in methanol were carried out using representative samples which were known to contain etizolam. This study found that five extractions were sufficient for the total extraction of etizolam from all sample types.

2.3 | Instrumental analysis

Analysis was performed using a 7820A gas chromatograph coupled to a 5977E mass spectrometer (Agilent technologies, Santa Clara, CA, USA). Injection mode: 1 μL sample injection was used, with a 15:1 split for qualitative analysis and 10:1 split for quantitative analysis, into a 4 mm internal diameter deactivated glass liner prepacked with quartz wool, injection port temperature: 250°C, carrier gas: He, flow: 1 mL/min. Column: HP-5MS UI, 30 m × 0.25 mm × 0.25 μm (Agilent Technologies). GC oven: 110°C held for 1 min; 30°C/min to 280°C, held for 11 min; total run time: 17.67 min (qualitative) and held for 8 min; total run time: 14.67 min (quantitative); transfer line: 290°C. The mass spectrometer was operated in electron (EI) ionization mode. Ionization conditions are as follows: 70 eV in full scan mode (45–450 amu), ion source: 230°C, quadrupole: 150°C.

2.3.1 | Qualitative analysis

Compound identification by GC–MS was carried out by comparison of the compound retention times and mass spectra in seized samples to a reference standard of known origin. For a positive identification, GC–MS retention times from seized sample extracts had to fall within 0.05 min of the retention time of reference standards of known origin or 0.1 min in cases of high benzodiazepine concentration which had distorted peak shape and shifted chromatographic peak apex. Seized samples and reference standards were analyzed within 24 h of each other under the same instrumental conditions. In addition, if the compound identified was included in the SWGDRUG mass spectral library (version 3.12, released 16 January 2023), a reverse match (RMatch) factor, which measures the difference between the mass spectrum of the unknown chromatographic peak to spectra held in the spectra library, was required to be greater than 850/1000 for positive identification.

Prior to April 2021, full analytical confirmation of novel benzodiazepines was not the principal focus of the Scottish Prisons Non-Judicial Drug Seizure Monitoring Project. Compound identifications made before that date were solely based on the SWGDRUG mass spectral library results and were therefore considered to be preliminary identifications.

2.3.2 | Quantitative analysis

For each analysis batch, the instrument was calibrated using a 7-point calibration curve (25–250 μg/mL). Two independently prepared check standards (40 and 125 μg/mL) were injected at the beginning and end of each sequence. The maximum allowable bias for these check standards was ±15% based on recommendations by the American National Standards Institute (ANSI) and the United Nations Office on Drugs and Crime (UNODC).[28,29] In four of the analyzed batches, one out of the four check standards fell out with the allowable bias range. However, as the remaining three check standards were within the allowable bias range, these batches were still deemed acceptable.

All resulting quantitative data were processed using an R-Script. In brief, raw data files produced by the Agilent software were converted using ProteoWizard into ms1 files. The R-Script then extracted metadata such as peak area and retention time from each *.ms1 file. Using these data, alongside a Microsoft Excel dataframe which contained details of the instrument sequence such as sample and file name, the R-Script processed all relevant data to produce a quadratic calibration curve and solved for x. This allowed the script to produce an output which included the calculated peak area ratio, calculated concentration for each sample. This output dataset is produced as a *.csv file. The R-Script is available online (https://doi.org/10.5281/zenodo.8046760).[30]

2.3.3 | Method validation

Method validation of the quantitation of etizolam in seized samples was performed according to the American National Standards Institute (ANSI) and American Academy of Forensic Science Standards Board (ASB), Standard 036 Standard Practices for Method Validation in Forensic Toxicology.[29] The following validation parameters were evaluated: limit of detection, limit of quantitation, precision, and bias. Bias for this method was calculated as ± 10%, and full validation data can be found within the supporting information.

2.4 | Mapping of Etizolam concentration across a seized card

Previous studies have demonstrated high variability in SCRA concentrations across the surface of infused paper and card samples.[27] To

understand the extent to which this may also affect card infused with benzodiazepines and to determine the total mass of etizolam present in a typical infused greeting card, a greeting card seized in August 2021, found during qualitative analysis to contain etizolam, was selected for detailed quantitative analysis using a method adapted from Norman et al (2020).[27] A clean sheet of tracing paper, printed with a 1 cm^2 grid, was secured to the card and used as a guide to sample the whole card into 2 cm^2 samples which were labeled to retain information on their relative spatial position. Each 2 cm^2 sample was extracted and analyzed using the quantitative procedure described previously.

3 | RESULTS AND DISCUSSION

3.1 | Qualitative results for seized prison samples

3.1.1 | Novel benzodiazepine detections

Since 2018, the Scottish Prisons Non-Judicial Drug Seizure Monitoring Project, a collaboration between SPS and the Leverhulme Research Centre for Forensic Science (LRCFS) at the University of Dundee, has analyzed over 3700 samples from nonattributable suspected drug samples, seized as a result of personal or cell searches or the screening of incoming mail using IMS.[31] Novel benzodiazepines were detected in 495 out of the 3700 samples seized from Scottish prisons and submitted for testing between February 2019 and January 2023. Throughout the duration of this project, the number of detections of novel benzodiazepines entering prisons through the mail system infused in papers, cards, blotters, and clothing has increased accounting for approximately 20% of the positive illicit drug detections in the samples tested. A summary of the types of novel benzodiazepines detected, alongside the sample types in which they were detected, is provided in Table 1. Full analytical data (GC–MS) are provided in the supporting information.

Typically, seized tablets and powders were white, blue, or yellow in color (Figure 1 and Figure 2). Full data regarding tablet markings detected within this study can be found within the supporting information with examples of some of the most prevalent markings shown in Figure 1. The most commonly observed markings for seized tablets found to contain etizolam in the Scottish prisons were "ROCHE 10" ($n = 6$ seizures), "DC10" ($n = 6$ seizures), and "10" ($n = 6$ seizures). In March 2022, bromazolam was detected for the first time in Scottish prisons in a green colored "Xanax" bar-type tablet. From August 2022, bromazolam was detected within seized blue tablets imprinted with "MSJ" on one side, a mark typically associated with diazepam tablets marketed by MSJ Industries, a Sri Lankan manufacturer.[32,33] This is now the most prevalent tablet type for bromazolam seized in the Scottish prisons.

As shown in Figure 1, tablets found to contain etizolam and bromazolam bear the same markings as those used by legitimate pharmaceutical companies for diazepam tablets. For example, "ROCHE"

TABLE 1 Benzodiazepines detected in tablets ($n = 95$), powders ($n = 73$), blotters ($n = 47$), paper ($n = 98$), card ($n = 158$), and textiles ($n = 24$) seized from Scottish prisons between January 2019 and January 2023.

Benzodiazepine(s)	Tablets	Powders	Blotters	Paper	Card	Textiles	Total
Bromazolam	11	17	5	4	1	-	38
Desalkylgidazepam	1	1	-	-	-	-	2
Clonazolam	-	1	-	-	-	-	1
Diazepam	21 (6[a])	(2[a])	-	-	2	3	34
Etizolam	25 (18[a])	25 (16[a])	16 (21[a])	36 (13[a])	69 (45[a])	9 (8[a])	301
Flualprazolam	3 (2[a])	(2[a])	-	7	1	-	15
Flubromazepam	4	1	1	14	13	1	34
Flubromazolam	-	(1[a])	-	-	-	-	1
Nitrazepam	1	-	-	-	-	-	1
Phenazepam	1	-	-	-	-	-	1
Temazepam	(1[a])	-	-	-	-	-	1
Bromazolam and Alprazolam	-	1	-	-	-	-	1
Bromazolam and Flubromazepam	-	-	2	1	-	-	3
Etizolam and Clonazolam	-	-	-	-	(2[a])	-	2
Etizolam and Flubromazepam	1	6	1	21	25	3	57
Etizolam, Bromazolam, and Flubromazepam	-	-	1	-	-	-	1
Flubromazepam and Flualprazolam	-	-	-	1 (1[a])	-	-	2
Total	95	73	47	98	158	24	495

[a]Prior to April 2021, compound identifications were solely based on the SWGDRUG mass spectral library results; additionally, no temazepam reference standard was available at the time this sample was analyzed in October 2021. These samples were therefore considered to be preliminary identifications and are reported within brackets.

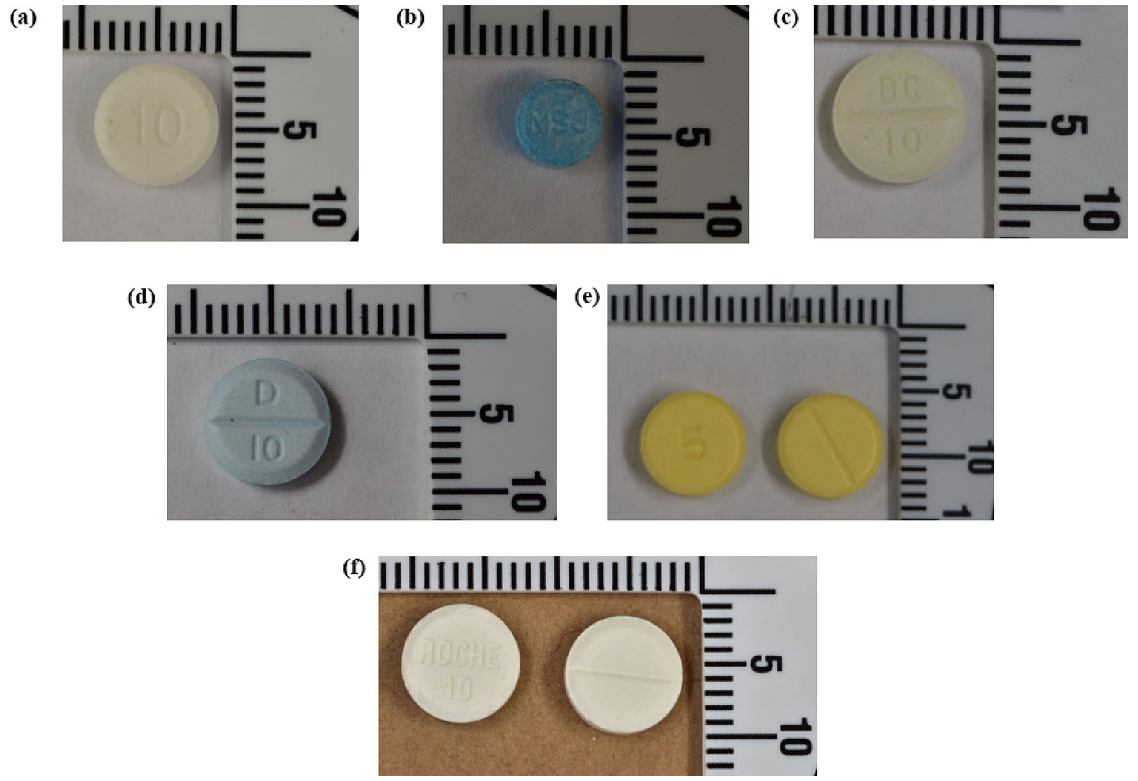

FIGURE 1 Examples of seized tablets: (a) FL22/0702, seized in July 2022, found to contain etizolam; (b) FL23/001, seized in January 2023, found to contain bromazolam; (c) FL21/0449, seized in July 2021, found to contain etizolam; (d) FL21/0478-3, seized in June 2021, found to contain etizolam; (e) FL21/0315-1, seized in April 2021, found to contain diazepam; and (f) FL22/0626, seized in March 2022, found to contain etizolam.

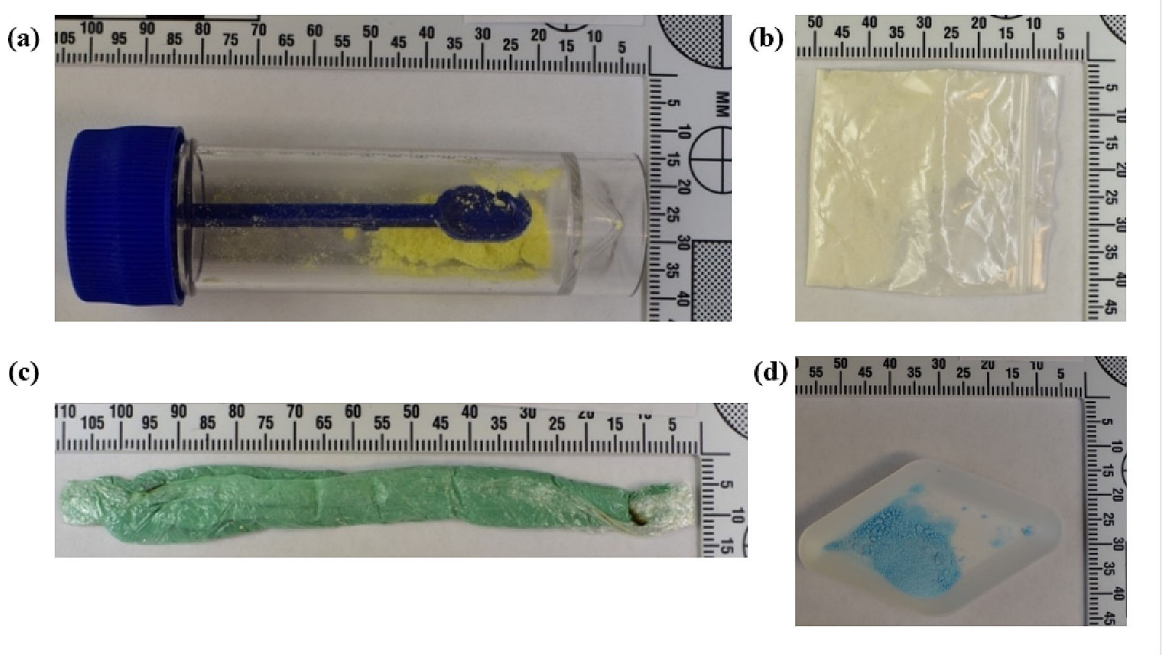

FIGURE 2 Examples of seized powders: (a) FL22/0201: 0.30 g yellow powder seized in December 2021 found to contain etizolam; (b) FL22/0680-1: 1.16 g white powder seized in June 2022 found to contain etizolam; (c) FL22/0705-1: 1.33 g green powder seized in July 2022 found to contain bromazolam; and (d) FL22/0978: 0.23 g blue powder seized in October 2022 found to contain bromazolam.

markings emulate the markings on tablets licitly produced by the UK pharmaceutical company Roche Products Ltd, "D10" markings emulate the 10 mg diazepam tablets produced by the pharmaceutical company Actavis,[34] and the crescent marking ")" emulates the company logo for UK pharmaceutical company Crescent Pharma Ltd where "A272" is the marking on their 2 mg diazepam tablets and "A278" is the marking on their 10 mg diazepam tablets.[35] The similarity in the markings makes it challenging for individuals to distinguish these illicitly produced tablets from licitly produced diazepam tablets. It is unlikely that individuals would be aware of the identity of the drug present or the amount of drug present per tablet and the consistency of dose between tablets. This situation has previously been described as a "perpetual cycle of consumption roulette".[2]

Previously, diverted prescriptions accounted for the bulk of tablets circulating within the Scottish market[2]; however, increasingly, these tablets are being illicitly produced.[3] The low cost and ease of accessing materials such as pill-presses and bulk powders, including etizolam and flualprazolam, have made the production of illicit tablets a popular alternative to the diversion of licitly produced and prescribed benzodiazepines.[6,36,37] Within the 2021/2022 WEDINOS annual report, 1045 samples were submitted from across the UK with diazepam stated as the purchase intent; however, only 42.7% contained diazepam.[38] The results of this study have shown that similarly, despite the likeness of the tablets to commercially produced diazepam tablets, only 27.4% (26 out of 95) of the tablets seized and tested contained diazepam, while 45.3% (43 out of 95) were found to contain etizolam as the only drug present.

Blotters marked with "ETI 2.0" and "INTAS" (see Figure 3a) containing etizolam were first seized in Scottish prisons in September 2020. Following these initial seizures, some variation in blotter color (off-white or light pink) and size was noted and blotters marked with "ETI 3.0 INTAS" (Figure 3b) and "ETZ 5 mg" (Figure 3d) have since been detected. In October 2022, a total of 1632 blotters, with "Actavis 5" markings (Figure 3c), were seized in 4 of the 15 Scottish prisons, all of which contained bromazolam. Due to their size (approximately 5–10 mm^2) and thickness (approximately 1 mm), such blotters are often concealed in incoming mail and have been found by SPS within greetings cards, gift tags, footwear, and seams of clothing sent into prisons (Figure 3e). From anecdotal evidence provided by SPS, blotters appear to be used sublingually. INTAS is a pharmaceutical company based in Gujarat, India, and Actavis, now known as Accord Healthcare, is a pharmaceutical company based in Ireland which is also owned by INTAS and produces benzodiazepine products such as diazepam tablets.[39] In India, INTAS produces etizolam tablets under the brand name "Etilaam"; however, the company does not manufacture etizolam blotters[4] confirming that these blotters are illicitly produced counterfeits.

Unmarked blotters (Figure 3b) were first seized in February 2021 and their prevalence has increased over time. Such blotters have most commonly been found to contain either etizolam or bromazolam. However, unmarked blotters seized in the Scottish prisons have also been found to contain the SCRA ADB-HEXINACA[40] (1 seizure, $n = 779$ blotters) and the novel synthetic opioid metonitazene

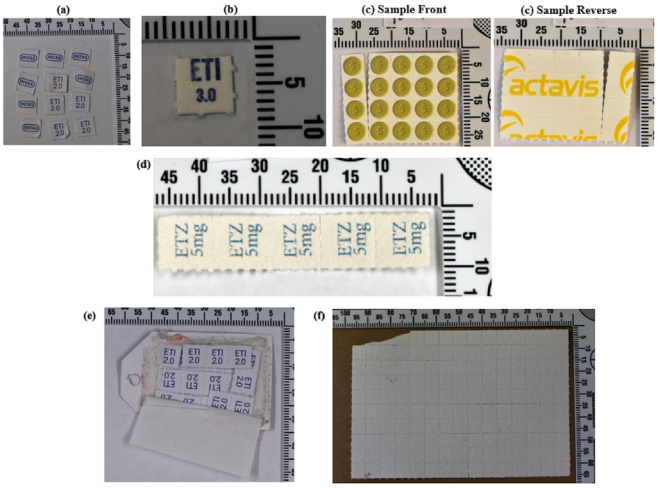

FIGURE 3 Examples of seized blotters: (a) FL21/0241-3, ETI 2.0/INTAS blotters seized in July 2022, found to contain etizolam; (b) FL21/0182, ETI 3.0 blotters seized in March 2021, found to contain etizolam; (c) FL22/0904, seized in October 2022, found to contain bromazolam; (d) FL21/0134, ETZ 5 mg blotters seized in march 2021, found to contain etizolam; (e) FL21/0021, ETI2.0/INTAS blotters concealed within a gift tag, seized in January 2021, found to contain etizolam; (f) FL21/0282, unmarked blotters seized in March 2021, found to contain etizolam.

(1 seizure, $n = 360$ blotters). These seizures were detected and seized during the screening of incoming mail by prison staff using IMS before they could enter the illicit drug market within the prison. However, samples such as these, particularly the sample containing metonitazene, are indistinguishable from samples generally understood by individuals to contain benzodiazepines and therefore pose a serious threat to life if consumed. Images of these seizures and data regarding blotter markings detected within this study can be found within the supporting information.

Etizolam was first detected in paper samples seized in Scottish prisons in yellow/green powder coated paper in September 2019. The paper appeared to be designed to look like a child's painting/handprint using poster paint and had visible powder coating the surface of the paper (images of this seizure can be found in the supporting information). By August 2020, the first etizolam infused paper samples were seized, although it is unclear if these papers were deliberately infused with etizolam or if they were contaminated with traces of etizolam powder prior to their seizure. Etizolam was first detected infused into greetings/Christmas cards in December 2020 with no visible powder contamination. Between January 2021 and December 2021, this was the most commonly seized sample type found to contain benzodiazepine-type drugs submitted for laboratory testing. To the best of the author's knowledge, only one study to date has reported the detection of etizolam within an impregnated letter seized from a prison mail system.[41] Initially, papers and cards were found to contain only etizolam; however, following its international control, from November 3, 2020,[42,43] an increase in the prevalence of card and paper samples infused with flubromazepam, present both with and without etizolam,

was observed. Of all the samples submitted for testing where a mixture of etizolam and flubromazepam was detected, over 86% (46 of 53) of these detections occurred in paper/card samples.

Prisoners have been observed by SPS staff to use novel benzodiazepine-infused cards and papers either sublingually or by boiling them in a kettle and then drinking the resulting liquid. Pieces of card and paper confirmed to contain novel benzodiazepines have been found within seized mugs and kettles submitted for laboratory testing. However, benzodiazepine-type drugs, including all of the benzodiazepines detected within this study, are reported to be practically insoluble in water.[44–49] It is therefore suspected that fruit juice or other items may be added to increase solubility or that the liquid containing undissolved powder extracted from the paper and/or card is consumed by the individual. The novel benzodiazepine desalkylgidazepam (bromonordiazepam) has been detected on three e-cigarette burner components seized in November 2022 analyzed as part of this study (images of this seizure are available in the supporting information). This provides some anecdotal evidence that novel benzodiazepine-infused papers are being vaped, a common mode of use of SCRA-infused papers. The recently emerged SCRA; ADB-5′Br-BUTINACA was detected in the same sample extracts.[50,51] Since there is no indication of the drug present in drug-infused paper and cards, it is not known if prisoners are intentionally vaping novel benzodiazepines or if the paper is being vaped in the belief that it is infused with a SCRA. As far as the authors are aware, there are no published studies on the thermal stability of novel benzodiazepines or their effects if vaped compared with being ingested or used sublingually.

Prisoners within residential areas in Scottish prisons may wear their own clothing,[52] with restrictions of the type of clothing allowed, rather than receiving prison-issued clothing as is the case in jurisdictions such as the United States.[53] The delivery of clothing items to prisoners provides an additional smuggling route for drugs, although it has typically been utilized by sewing drugs into the waistbands of clothing or linings of jackets and coats.[24,54–56] Novel benzodiazepines were first detected in textile/clothing samples seized in Scottish prisons in October 2020. Most contained etizolam (71%; $n = 17$), although similar to paper and card samples; flubromazepam was first detected in February 2022, and its prevalence, particularly in a mixture with etizolam, increased between February and October 2022. Examples of different seized textile samples are shown in Figure 4. Of the samples submitted for analysis, 37.5% ($n = 9$) were small items, mostly socks (Figure 4g; $n = 7$), although boxer shorts (Figure 4a) and fabric face masks (Figure 4f) have also been infused with benzodiazepine-type drugs; 45.8% of samples ($n = 10$) were larger items, mainly shirts (Figure 4e; $n = 5$), although benzodiazepines have also been detected on towels (Figure 4b), shoes (Figure 4c), and jogging bottoms (sweatpants, Figure 4d). The remaining 16.7% of samples ($n = 4$) were pieces of textile cut from larger unknown items. It is important to note that seized infused textiles analyzed in this study appeared both unworn/new and worn/used.

As noted with infused paper and cards, benzodiazepine-infused textiles have been observed by SPS staff to be boiled in kettles as a method of recovering the benzodiazepine-type drug and drinking the resulting liquid or liquid suspension. This has been confirmed through the detection of benzodiazepines on damp textile samples ($n = 1$) and textile fragments found in kettles ($n = 2$) or mugs ($n = 1$).

3.1.2 | Evolution of the benzodiazepine-type drug market within Scottish prisons

Changes in international legislation can greatly impact the prevalence of compounds available on the NPS market, both locally and globally.[57–59] The evolution of the benzodiazepine-type drugs detected in seizures from Scottish prisons submitted for testing between 2019 and January 2023 is shown in Figure 5a. While diazepam, available on prescription in the UK, was consistently present throughout the study, novel benzodiazepines dominated the benzodiazepine-type drug market within the Scottish prisons during the study period. Between 2020 and the end of 2022, etizolam was the most prevalent benzodiazepine-type compound detected within seized samples from Scottish prisons in this study. However, following its international control by the United Nations (UN) in November 2020 and a subsequent ban on exportation by India in March 2021,[60] the novel benzodiazepines detected in samples seized in Scottish prisons became increasingly variable. It is notable that this legislation coincided with multiple large seizures of benzodiazepine-type drugs in the UK, including the seizure of over 28 million etizolam tablets by the National Crime Agency (NCA) in July 2020 from one illicit laboratory,[61] and the significant disruption of organized crime gangs involved in the drug supply chain across the UK. The short-term impact of this disruption may have been further exacerbated by the legislation introduced by the UN and India, potentially creating a substantial long-term effect on the availability of etizolam within the UK. In the 6 months following the legislative changes, the proportion of diazepam detections in seized samples, in tablet and powder form, increased, possibly indicating an initial reversion to prescription diversion. From July 2021, flubromazepam and bromazolam were detected for the first time in seized items, neither of which are currently under international control. Furthermore, in July 2022, the first detections of desalkylgidazepam occurred in white tablets imprinted with a "10" and again in January 2023 in a white powder. While the proportion of flubromazepam and desalkylgidazepam detections in seized samples submitted for analysis have remained stable, the proportion of bromazolam detections have rapidly increased throughout 2022 and into the beginning of 2023. At the time of writing, bromazolam is the most prevalent novel benzodiazepine-type drug detected in seized samples from the Scottish prisons submitted for testing as part of this study; however, it should also be noted that the number of samples submitted for testing has greatly decreased over the study period.

As the market has appeared to adapt to the international control of etizolam or changes in supply, an increase in the prevalence of mixtures of benzodiazepines, particularly etizolam and flubromazepam, in seizures from Scottish prisons was observed. Flubromazepam and etizolam were most commonly present in similar abundance, indicating purposeful mixing.

FIGURE 4 Examples of benzodiazepine-infused textiles: (a) FL21/0036-2: pair of boxer shorts seized in December 2020 and found to contain etizolam; (b) FL21/0874: large grey towel seized in October 2021 and found to contain etizolam; (c) FL22/0501: 1 of 19 pieces of a shoe found in a kettle seized in April 2022 and found to contain etizolam and flubromazepam; (d) FL21/0320: piece cut from bottom of an elasticated leg of fleece-lined jogging bottoms (sweatpants) seized in April 2021 found to contain etizolam; (e) FL22/0360: blue t-shirt seized in February 2022 found to contain etizolam and flubromazepam; (f) FL22/0272–2: fabric face mask seized in December 2021 found to contain diazepam; and (g) FL22/0895–3: pair of socks seized in May 2022 found to contain diazepam.

No studies are available on the relative potency of bromazolam, flubromazepam, and desalkylgidazepam; however, taking the information with the appropriate caution, anecdotal information from user forums suggests that approximately 1–3 mg of bromazolam and 6 mg of flubromazepam are equivalent to 1 mg of etizolam.[62,63] Data regarding the potency of desalkylgidazepam are further limited; however, recent studies have reported dosages of 6–9 mg, described in "trip reports" and on research chemical websites.[64]

Alongside changing trends in drug prevalence, significant variation over time was observed in the types of samples seized from within Scottish prisons and submitted for analysis (Figure 5b). In 2019, samples submitted to the study containing benzodiazepine-type drugs consisted entirely of powders and tablets. From August 2020, the use of mail systems to smuggle novel benzodiazepine-type drugs within infused letters and greetings cards rapidly became the most common smuggling method. By the end of 2021, infused paper and cards were the most commonly seized novel benzodiazepine format, accounting for more than 80% (90 out of 108) of seized samples from Scottish prisons submitted for testing. It is possible that this change in drug format may have been driven in part by the COVID-19 pandemic induced lockdowns, which resulted in a ban on prison visitations, thus restricting one of the main smuggling routes for powders and tablets containing benzodiazepine-type drugs into prisons. The pandemic also forced restrictions within the Scottish Courts, leading to significantly fewer jury trials and hearings.[65,66] As a result, the number of individuals entering or leaving the Scottish prison system significantly decreased, further impacting the ability of suppliers to physically transport controlled substances into the institutions. By this time, the importation of SCRAs through the mail system was well-established in UK prisons, and so these factors may have resulted in a shift in the benzodiazepine-type drug supply in Scottish prisons from powders and tablets to infused papers and cards.

In response to the increasing volume of NPS entering prisons through the mail systems, in December 2021, Scottish prisons began photocopying incoming letters and cards and issuing these copies in place of the original mail item.[67] The effects of this change in policy are reflected within this study with a notable decrease in the submission of seized cards and papers in the first quarter of 2022, a trend which continued throughout the year. These data demonstrate the impact of closely monitoring NPS markets using projects such as the Scottish Prisons Non-Judicial Seized Drug Monitoring Project and its use in shaping drug screening and harm reduction policies in prisons. However, it is important to note that the closing of established smuggling routes may simply lead to a reversion to more traditional smuggling routes for benzodiazepine-type drugs, such as perimeter throwovers of tablets and powders and smuggling by visitors (and staff), or the development of alternative smuggling routes and methods.

Clothing infused with etizolam was detected for the first time in October 2020 and information from prison staff and testing of further samples indicate that this smuggling method is still in use. Studies exist surrounding the removal of drugs, such as methamphetamine, from clothing contaminated by exposure to clandestine laboratories,[68] through washing with consumer-grade detergent. However, the relative insolubility of benzodiazepines in water may result in challenges when applying these methods to clothing infused with benzodiazepine-type drugs. Further research is required to assess optimal washing conditions, that would ensure the effective removal of benzodiazepine-type compounds through prewashing clothing and textiles, before they enter general circulation within the prisons.

3.1.3 | Benzodiazepine mixtures

When detected in mixtures, novel benzodiazepines were most commonly detected with other novel benzodiazepines, but they have also

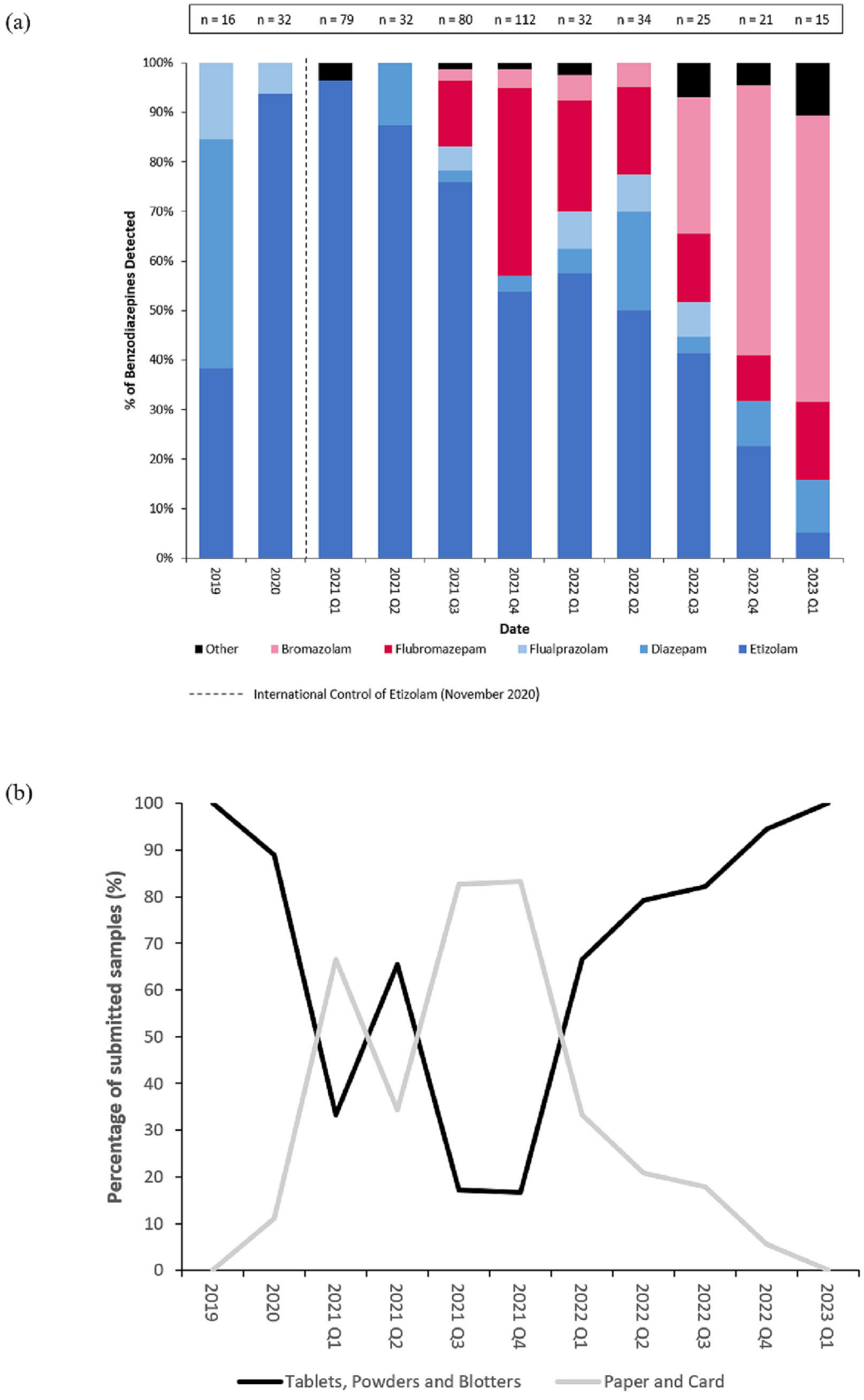

FIGURE 5 (a) Benzodiazepine detections between February 2019 and January 2023. Sample total differs from Table 1 as 17 samples analyzed in 2021 had an unknown seizure date. (b) Evolution of benzodiazepine sample formats detected with Scottish prisons between tablets, powders, and blotters and infused papers and cards from 2019 to January 2023.

been detected with non-benzodiazepine-type drugs ($n = 67$), including SCRAs ($n = 35$), stimulants ($n = 15$), opioids ($n = 6$), androgenic anabolic steroids (AAS) ($n = 5$), anticonvulsants ($n = 3$), antipsychotics ($n = 2$), and z-drugs (zopiclone, $n = 1$). It is important to note that some of these mixtures may have occurred through cross-contamination of items, for example, when they are being handled and concealed together by prisoners. The presence of novel benzodiazepines and SCRAs together may simply arise due to their high prevalence in Scottish prisons. A summary of the novel benzodiazepine and SCRA mixtures observed within seized samples is provided in Table 2.

While it is possible that these mixtures may have occurred intentionally, the proportions of benzodiazepines to SCRAs infused on the paper and card seem to vary widely, with SCRAs being the dominant compound in some samples and benzodiazepines being dominant in others. This would seem to indicate a less purposeful motivation behind the mixture and potential cross-contamination prior to seizure. Additionally, five infused paper samples were found to contain flualprazolam with a mixture of the SCRA ADB-4en-PINACA and the synthetic opioid metonitazene. As discussed previously, there is no visual indication regarding the drug content of these samples and so individuals will be unaware of which compound type is present, leading to increased incidences of unintentional polydrug use. If the papers or cards with a mixture of novel benzodiazepines and SCRAs are ingested or used sublingually, the SCRA could have a significantly reduced or delayed effect on the user as SCRAs may be metabolized prior to entering the circulatory system.[69,70] On the other hand, if the papers or cards are vaped or smoked, the effect of smoking or vaping a benzodiazepine is unknown. Although the prevalence of benzodiazepine-type drugs in paper and card and subsequent smuggling into prisons appears to be decreasing in Scottish prisons, research to investigate the pyrolysis of benzodiazepines and the effects of vaping benzodiazepines in isolation and combination with SCRAs and other drugs would be beneficial. This would improve risk assessment for people who use drugs of this new, potentially unintentional, mode of drug use and further inform harm reduction services within prisons.

AAS (oxymetholone and mestanolone) were detected in three tablet samples and one paper sample and oxandrolone in one powder sample. Whether these mixtures were intentional, or a result of contaminated production equipment, is unknown. However, it is notable that the tablets included markings typically associated with benzodiazepine tablets, "ROCHE 10" and "D10" (images of these seizures are available in the supporting information). It is unlikely that individuals would be aware of the presence of AAS within these tablets, resulting in further incidences of unintended polydrug use.

3.2 | Quantitation of etizolam in seized samples

The mass of benzodiazepine-type drugs present in seized samples is rarely reported by forensic service providers in the UK, and as a result, the amount of drug consumed by individuals of illicitly produced benzodiazepine-type drugs by dosage unit remains largely unknown. Etizolam is a prescribable medicine in Japan, India, and Italy and is typically produced by pharmaceutical manufacturers in tablet form containing 0.25 to 1 mg active ingredient.[71–73] Approximately 1 mg of etizolam is equivalent to the standard dose of 10 mg of diazepam.[71–74] Due to the large-scale illicit production of tablets and powders containing etizolam within the UK,[2,3,75] the true mass of etizolam present and the variability within and across batches circulating within Scotland is unknown, may be unpredictable, and makes assessment of harm to individuals within the unregulated illicit market highly challenging. To provide reliable analytical data on the etizolam content of seized samples, a GC–MS quantitation method was developed,

TABLE 2 Mixtures of novel benzodiazepines and synthetic cannabinoids detected in seized samples ($n = 35$) from the Scottish prisons between January 2021 and January 2023.

	Novel benzodiazepine(s)						
Synthetic cannabinoids	Etizolam	Flubromazepam	Bromazolam	Etizolam + Flubromazepam	Flubromazepam + Flualprazolam	Etizolam + Flubromazepam + Bromazolam	Total
ADB-BUTINACA	4	1	-	16	1	1	23
ADB-4en-PINACA	4	-	-	-	-	-	4
ADB-HEXINACA	-	1	1	1	-	-	3
BZO-HEXOXIZID	1	-	-	-	-	-	1
MDMB-4en-PINACA	-	-	1	-	-	-	1
ADB-BUTINACA + MDMB-4en-PINACA	1	-	-	-	-	-	1
ADB-5′Br-INACA + MDMB-5′Br-INACA	-	-	-	1	-	-	1
ADB-4en-PINACA +ADB-BUTINACA +ADB-HEXINACA	1	-	-	-	-	-	1
Total	11	2	2	18	1	1	35

validated, and applied to seized etizolam samples recovered from Scottish prisons. As far as the authors are aware, these data represent the first published large-scale study of etizolam concentrations in illicitly produced powders, tablets and blotters, and infused papers and greetings cards.

3.2.1 | Etizolam concentrations in different sample matrices

A total of 193 seized samples (26 tablets, 28 powders, 30 blotters, 46 papers, and 63 cards) containing etizolam were quantified using the validated GC–MS quantitative method. A data summary is provided in Table 3, and full analytical data are provided in the supporting information.

The tablets analyzed in this study contained an average of 1.02 mg etizolam; however, high variability was observed with etizolam mass ranging from 0.34–2.33 mg per tablet. Such variability will lead to inconsistent dosing and effects. Two of the seized powders analyzed in this study contained a much higher proportion of etizolam (78.1% and 88.0% [w/w]) than the other samples analyzed ($n = 26$). These two high purity samples may represent undiluted etizolam powders without the addition of excipients and additives. The low purity samples may represent crushed tablets, or the powder prepared with diluents and additives prior to the tableting process, as adulterants similar to those detected in tablets were observed (e.g., phenacetin), and they had a comparable purity on a % w/w basis. Prisoners consuming such high purity powders, visually indistinguishable from low purity powders, would be at a considerably higher risk of harm, especially if they are combining the use of these drugs with other CNS depressants.

The mean etizolam concentration in the blotters analyzed in this study ($n = 30$) was 1.06 mg/blotter, with a range of 0.22–1.93 mg/blotter. Across the different blotter types, unmarked blotters had a mean of 0.57 mg/blotter (range = 0.22–0.87 mg/blotter) and blotters with "ETI" markings contained an average of 1.27 mg etizolam per blotter (range = 0.71–1.93 mg per blotter). On average, no significant difference was observed between the different "ETI/INTAS" markings (e.g., ETI 2.0 and ETI 3.0); however, sample numbers for ETI 3.0 ($n = 1$, 0.71 mg per blotter) and ETZ 5 mg (n = 1, 0.34 mg per blotter) were limited, and so further analysis of these sample types would be beneficial to increase understanding of the differences between blotter markings.

Concentrations of etizolam detected in paper and card samples analyzed were highly variable (0.05–1.39 mg/cm^2 for paper; 0.03–1.16 mg/cm^2 for card). Such high variability and variability in extraction efficiency are likely to make consistent dosing impossible. There is currently no reliable information on the methods used by prisoners to extract benzodiazepines from cards and papers, and it is not possible to determine how much etizolam might be consumed using this method; however, the dosing is likely to be highly variable. In some cases, paper samples containing benzodiazepines may be vaped in the belief that they contain SCRAs.

3.2.2 | Concentration mapping of etizolam across a single card sample

To determine the total mass of etizolam present in a single card, determine card etizolam mass equivalence to etizolam tablets, and to determine concentration variability across a single card, a seized card sample was selected at random for detailed quantitative etizolam analysis. The card showed no visible signs of staining and was divided into a total of 63 2 cm^2 squares for analysis. Due to the size of the card, 10 mm from the right-hand side (adjacent to column L) was not analyzed. The quantitative data are summarized in Figure 6. Full analytical data can be found in the supporting information.

TABLE 3 Quantitation of etizolam content in samples seized in Scottish prisons (February 2019 and January 2023).

		Concentration of etizolam			
Sample type		**Minimum**	**Maximum**	**Average**	**Standard deviation**
Tablets ($n = 26$)		0.34 mg per tablet (0.25% [w/w])	2.33 mg per tablet (1.39% [w/w])	1.02 mg per tablet (0.69% [w/w])	0.46 mg per tablet (0.29% [w/w])
Powders	High purity ($n = 2$)	78.1% (w/w)	88.0% (w/w)	83.5% (w/w)	7.68% (w/w)
	Low purity ($n = 26$)	0.19% (w/w)	0.97% (w/w)	0.46% (w/w)	0.18% (w/w)
Blotters (mg per blotter)	All blotters ($n = 30$)	0.22	1.93	1.06	0.48
	"ETI/INTAS" markings ($n = 22$)	0.34	1.93	1.27	0.37
	Unmarked ($n = 8$)	0.22	0.87	0.57	0.24
Paper (mg per cm^2) ($n = 46$)		0.05	1.39	0.25	0.28
Card (mg per cm^2) ($n = 63$)		0.03	1.16	0.43	0.28

Note: The bias of the quantitative method determined during validation was 10% for all calculated values.

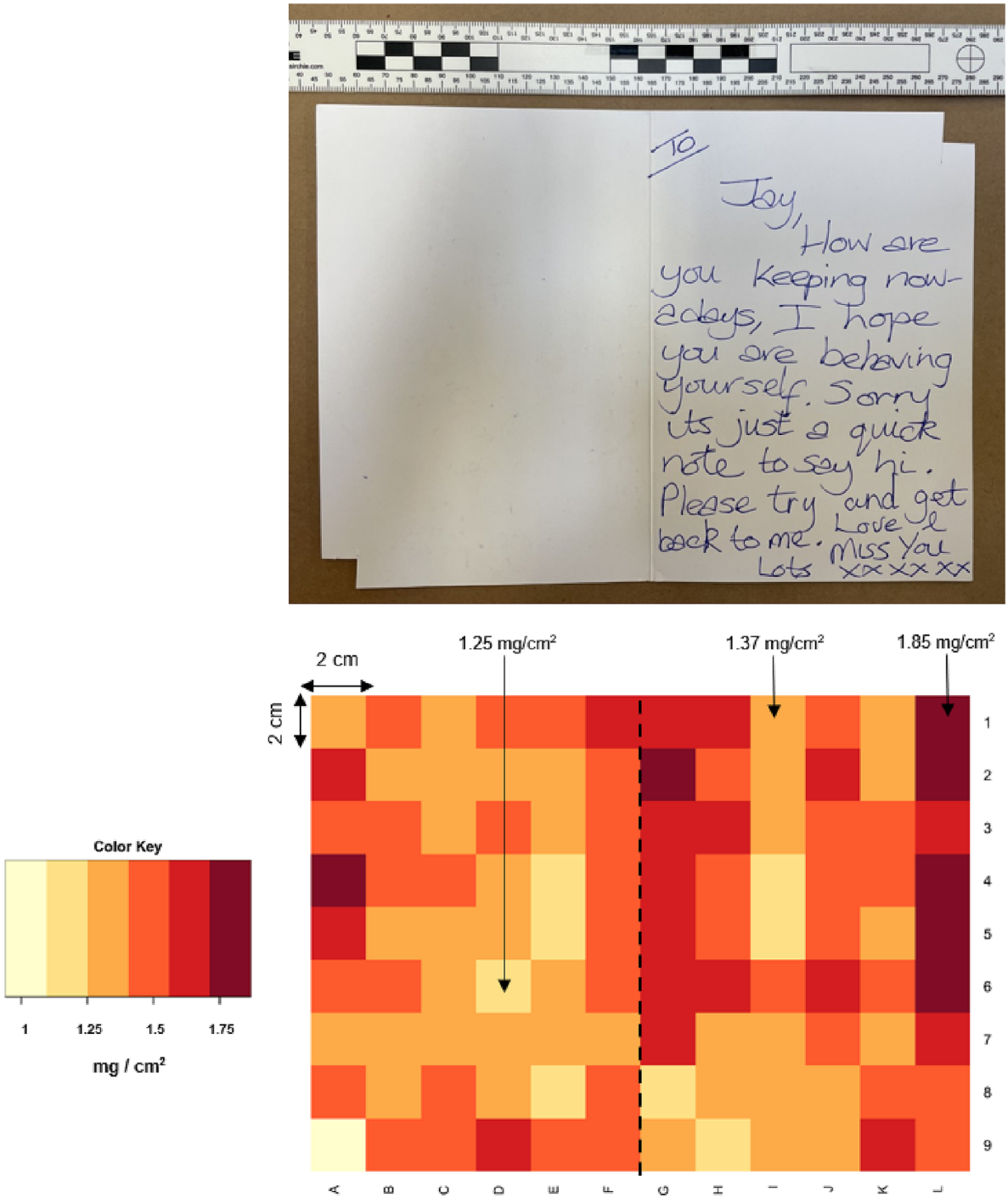

FIGURE 6 Concentration mapping of etizolam across a whole greeting card. The bias of the quantitative method determined during validation was 10% for all calculated values.

Etizolam concentrations across the card ranged from 1.16 to 1.87 mg/cm^2, and the entire card contained a total of 312.5 mg of etizolam. The etizolam content for this single card was therefore equivalent to the mass of etizolam in 306 tablets, based on the average etizolam content of seized tablets within this study (1.02 mg per tablet), and so each card represents a significant etizolam seizure. Compared with previous studies on the variability of SCRAs across a sheet of paper, etizolam dosing appears to be more consistent across this sample. Norman et al. (2020)[27] demonstrated that drug distribution across a paper sample can be affected by the way in which it is laid to dry after infusion. Although dosing appears to be more consistent across this particular card, higher levels of variability may be present within other cards and paper samples.

4 | CONCLUSION

In this study, we report the detections of benzodiazepine-type drugs in a variety of sample types encountered in Scottish prisons, with some drug formats being reported for the first time. Quantitative analysis of etizolam, the most commonly detected benzodiazepine-type drug detected in seized samples submitted for analysis during the study period, indicated significant variability in the concentration of etizolam present, both between and within drug formats. Near-real-time laboratory monitoring of the prison drugs market through programs such as the Scottish Prisons Non-Judicial Seized Drug Monitoring Project provides vital intelligence on drug type and drug format and trends informing health and safety procedures, security screening and harm reduction measures within the prisons.

The study directly supported the introduction of photocopying of incoming mail (paper and cards) in Scottish prisons and to explore changes to the supply of clothing to prisoners from uncontrolled external suppliers or to develop methods of pre-washing clothing to remove infused psychoactive substances. Such an approach can be used to identify and counteract emerging risks, to monitor the effect of drug screening policy changes, and to identify any unintended consequences of such policy changes.

AUTHOR CONTRIBUTIONS

Conceptualization: V. M., C. M., C. N., and N. N. D.; methodology: V. M., A. B., C. M., C. N., and H. M.; validation: V. M.; data analysis: V. M., R. R., A. B., and C. N.; R-Script writing: V. M. and H. M.; writing—original draft: V. M.; writing—review and editing: All; supervision: C. M., C. N., N. N. D., and H. M.

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CONFLICT OF INTEREST STATEMENT

CM is employed by Chiron AS, a supplier of reference materials, some of which were purchased for use in this study. The other authors do not report any potential conflicts of interest.

DATA AVAILABILITY STATEMENT

All data relating to quantitation of samples using the software code R-Script, created during this research, are openly available from the University of Dundee Institutional Repository, Discovery (https://doi.org/10.15132/10000235). The software code R-Script developed for this research is available online (https://doi.org/10.5281/zenodo.8046760). The raw data for qualitative analysis relating to the Scottish Prisons Non-Judicial Drug Seizure Monitoring Project, created during this research, are confidential; however, all results from the qualitative analysis of these data are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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