Synthetic cannabinoid-related deaths in England, 2012-2019

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SYNTHETIC CANNABINOID-RELATED DEATHS IN ENGLAND, 2012-2019

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CSC's PhD (2009-2013) was supported by a BBSRC CASE studentship and during that time she received research materials and financial support from Merck & Co. In 2018 she received support from MicroControl Instruments to conduct *in vivo* electrophysiology and imaging experiments. CSC sits on the Novel Psychoactive Substances sub-group of the Home Office's independent Advisory Council on the Misuse of Drugs (ACMD) as the NPSAD representative.

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

The analysis undertaken in this project was not pre-registered. The results should therefore be considered exploratory.

ABSTRACT

Aim: To identify drug-related death trends in England associated with synthetic cannabinoid receptor agonists (SCRAs) reported to the National Programme on Substance Abuse Deaths (NPSAD).

Design: Case reports from NPSAD (England) where a SCRA was detected in post-mortem tissue(s) and/or implicated in the death were extracted. Cases were analysed and compared against non-SCRA related deaths reported to NPSAD (England) that occurred over the same time period (2012-2019).

Findings: 165 death reports were extracted, with 18 different SCRAs detected. Following the first death in 2012, a subsequent sharp increase is evident. Acute drug use was the underlying cause of death in the majority of cases (87.9%). Decedents were predominantly found dead (68.6%), with a large proportion of those witnessed becoming unresponsive described as "suddenly collapsing" (81.6%). Psychoactive polydrug use of both prescription medications and illicit substances was detected in 90.3% of cases, with alcohol the most commonly co-detected (50.3%), followed by opioids (42.2%), benzodiazepines/Z-drugs (32.1%), stimulants (32.1%, [28.5% cocaine]), and cannabis (24.8%).

Compared to all NPSAD deaths (England) that occurred over the same time period, SCRA-related decedents were more predominantly male (90.3% vs 72.0%; $p<0.01$), and lived in more deprived areas ($p<0.01$). Whilst a comparatively significant proportion of decedents were homeless (19.4% vs 4.1%), living in a hostel (13.3% vs. 2.3%) or in prison (4.9% vs 0.2%) at time of death (all $p<0.01$), the greatest majority of SCRA-related decedents were living in private residential accommodations (57.6%).

Conclusions: The dataset presented here is the largest regarding SCRA-related mortalities reported to date. Incidences of SCRA-related deaths in England have dramatically increased. Lack of effective deterrents to SCRA use under current UK legislation, compounded by limited knowledge as to the physiological impacts of SCRA consumption and their interaction with other co-administered substances, can be identified as contributory factors to this increasing mortality trend.

Key words: synthetic cannabinoid receptor agonist, spice, cannabinoid, drug-related death, substance abuse, novel psychoactive substance, drug toxicity, England

INTRODUCTION

Synthetic cannabinoid receptor agonists (SCRAs) interact with endogenous cannabinoid receptors, the receptors that mediate the effects of the major active ingredient in cannabis, delta-9-tetrahydrocannabinol (THC) (1). Acting as full agonists at the CB_1 receptor, SCRAs possess greater potency in comparison to THC, which acts as a partial agonist at CB_1 and CB_2 receptors (1-3).

SCRAs were first created in the 1980s to explore the therapeutic potential of cannabinoid pathways (4). At the time of writing, one SCRA is licensed for medicinal use in the UK: Nabilone (a THC derivative), for emesis secondary to cytotoxic chemotherapy (5). Several clinical trials are also currently underway testing the efficacy of SCRAs as treatments for a wide range of conditions (www.clinicaltrials.gov). Academic research and patents describing SCRA synthesis have therefore been published and are readily available (6). Easy access to these SCRA synthesis protocols, compounded with the flexibility of the basic SCRA molecular structure (7), has enabled the manufacture of a number of novel SCRA compounds in recent years (8).

Commercial production of SCRAs targeting recreational users commenced in the UK in the mid-2000s (9, 10). Marketed openly as 'legal highs', they were aimed at a niche middle class demographic of experimental users ('psychonauts') interested in exploring recreational drug diversity (11). SCRAs were sold in shops specialising in tobacco and cannabis paraphernalia ('head shops') under a variety of brand names including K2, Kronic and Mamba (6, 12). Now collectively known as 'Spice', SCRA products were typically available infused into inert herbal material for smoking (9, 13) or as e-cigarette liquid for vaping (6, 11). These preparations were perceived as more appealing to the target customer demographic than direct inhalation of powder formulations (14). Motivations for use of these SCRA 'legal highs' appears not to have conferred from the enjoyment of their effects; paradoxically, SCRA users have indicated a preference for cannabis due to the negative effects of SCRAs (15, 16). Rather, attractions for 'legal high' SCRA use included that they were legal, did not appear on standard drug tests and were readily available (17-22). Indeed, following the control of many SCRA compounds as Class B substances under the Misuse of Drugs Act (MDA) 1971 or their banning by the Psychoactive Substances Act (PSA) 2016, there was a subsequent decline in recreational use of SCRAs in the general population (23, 24). However, there is still significant prevalence in some vulnerable sub-groups, particularly homeless and prison populations (6, 11, 20-22, 24, 25), who continue to seek SCRAs due to their widespread availability and difficulty in detecting analytically. SCRAs also appeal to these users for their profound effects: their strongly intoxicating effects are cited to provide release from unbearable situations by enabling detachment from reality (24, 26-28).

The SCRA dose-effect is unpredictable: the same dose can induce profound intoxication in some subjects, whilst remaining imperceivable in others (29, 30). Inhalation technique appears key, as higher serum drug concentrations are detected in those reporting profound intoxication (30). Repeated administrations may therefore induce sudden and unexpected intoxication, increasing risk of accidental overdose. Common clinical features of illicit SCRA use include tachycardia, agitation, vomiting, confusion, dizziness, hallucinations, and reduced level of consciousness (12). In recent years, increasing numbers of SCRA-related deaths have been reported globally (11, 31). In this article, we provide evidence that SCRA-related deaths in England have increased at an astonishing rate in recent years. We have extracted case reports from the National Programme of Substance Abuse Deaths (NPSAD) where a SCRA was found at post-mortem and/or implicated in the death and provide analysis on the type(s) of SCRA(s) involved, and the circumstances surrounding these fatalities.

METHODS

National Programme on Substance Abuse Deaths (NPSAD)

NPSAD regularly receives information from Coroners on deaths related to drugs occurring in both substance users and non-users in England, Wales, and Northern Ireland as described previously (32). A death is referred to a Coroner if it has an unknown cause, is violent or unnatural, sudden and unexplained, occurred during an operation or before the person came out of an anaesthetic, or may have been caused by an industrial disease or poisoning (33). Toxicology tests are requested dependent upon individual case circumstances and at the discretion of the Coroner. Coroners voluntarily report a death to NPSAD if a psychoactive drug is detected at post-mortem, implicated in the death, or if the decedent had a history of substance misuse.

The Central Office for Research Ethics Committees of the National Patient Safety Agency confirmed (February 2006) that NPSAD does not require NHS Research Ethics Committee review as the subjects of the research are deceased.

Case Identification

A range of documents are contained in Coronial inquest files, although this varies from case to case. Typically, a Coroner has access to: witness statements; General Practitioner records; hospital reports; psychiatric and substance abuse team reports; post-mortem and toxicology reports. SCRAs are tested for using a variety of mass spectrometry and high-pressure liquid chromatography methods, where they are identified by comparison against a routinely-updated library of known SCRA analogues, or deduced using advanced detection methods (34). However, as insufficient information exists to correlate blood SCRA concentrations to effect, Coroners use the additional information sources to determine whether and how SCRA use contributes to causing death (35).

A retrospective study design was employed to identify all SCRA-related cases reported from England by searching the NPSAD database using the 'synthetic cannabinoid' term.

Data Analysis

Data entry, analysis and statistical tests were performed using IBM® SPSS™ Statistics for Windows version 25. The English Indices of Deprivation 2019 was used to obtain deprivation data (36).

RESULTS

165 people died in England and were reported to NPSAD where a SCRA was detected in post-mortem tissue(s) and/or implicated in the death by 1st April 2020. Presence at post-mortem indicates a decedent died with the SCRA(s) in their system, with an implicated listing indicating the SCRA(s) directly contributed to causing the death. Following the first report in 2012, it is clear that SCRA-related fatalities have drastically risen in recent years (**Figure 1**).

Types of SCRA detected

18 different SCRAs were detected in toxicology reports submitted to NPSAD (**Table 1**). Multiple new SCRAs were detected almost every year since the first in 2012, and there is a shifting pattern over time as to the most dominantly detected SCRAs (**Figure 2**). Indeed, six SCRAs were first detected within only a seven-month period (November 2018 - May 2019; **Table 1**).

Cause of Death

Circumstances that lead to death are categorised according to their contribution, as follows:

Cause 1a: The immediate cause of death (and underlying if no 1b or 1c cited)
Cause 1b: Any disease/circumstances underlying Cause 1a
Cause 1c: Any disease/circumstance underlying Cause 1b
Cause 2: Any disease/circumstance that did not cause the death but contributed in some way

It is not a requirement, or appropriate, for a Cause 1b, 1c or 2 to be cited for all deaths.

Acute drug use was the most common immediate and underlying cause of death, with SCRA use cited in the majority of cases (**Table 2**). Whilst physiological system failures were cited as an immediate cause of death in 32.7% of cases (n=54/165; 23.6% of which were cardiorespiratory, a rate similar to that reported (23%) in a recent global systematic review (31)) acute drug use was often the underlying cause (**Table 2**). Qualitative analysis of cases with narratives provided (n=121/165) revealed that decedents were found dead in 68.6% of cases (n=83/121), concording with the rate reported (63%) in a recent global systematic review (31). Where the decedent was witnessed becoming unresponsive (31.4% of cases; n=38/121), the majority were described as having suddenly collapsed (81.6%; n=31/38). Naloxone administration was evident in 9 cases.

A single SCRA was detected in 126 cases, with co-administration of multiple SCRAs evident in 39 cases; the most common combination was that of 5F-ADB and AB-FUBINACA (n=24/165). Alcohol was the most commonly co-detected substance (50.3% of cases; n=83/165; cases where alcohol was attributed to post-mortem production [≤10mg/dl] (37) were excluded). In 80.1% of these cases (n=67/83) the blood alcohol of decedents was associated with intoxication (>50mg/dl), with 48.2% at a blood alcohol level associated with drunkenness (50-199mg/dl; n=40/83)), and 31.3% (n=27/83) at a level where coma may occur (>200mg/dl) (38). Polydrug use was common with two or more substances from legal prescription and/or illicit sources detected in 90.3% of cases (n=149/165). An increasing trend in polydrug administration is evident, with the average number of co-administered substances in 2012-2016 (mean 3.6; mode 1) significantly lower than that of 2018 (mean 5.6; mode 6; $p<0.01$) and 2019 (mean 5.7; mode 5; $p<0.01$). In 42.2% of cases (n=70/165) SCRA(s) were detected with at least one opioid, and in 32.1% of cases (n=53/165) with at least one benzodiazepine/Z-drug, with an overlap of 42 cases where both opioid(s) and benzodiazepine/Z-drug(s) were co-detected in combination (25.5% of cases). Excluding SCRAs themselves, there were 124 detections of other illicit substances from 84 decedents (49.7% of cases); most notably 53 decedents (32.1% of cases) had co-administered stimulants (47 of which included cocaine [28.5% of cases]) and 41 cannabis (24.8% of cases). Indeed, a high proportion of decedents had been known to use drugs (57.0%; n=94/165). Medications available on prescription in the UK were detected in 64.8% of cases (n=107/165). Prescribing history was provided for 91 decedents, of which 50 decedents (54.9% of cases) were prescribed drugs that are directly

psychoactive. Antidepressants were the most commonly prescribed (41.8%; n=38/91) followed by opioids (18.7%; n=17/91), antipsychotics (15.4%; n=14/91), gabapentinoids (12.1%; n=11/91) and benzodiazepines/Z-drugs (9.9%; n=9/91).

Demographics

The proportion of male SCRA-realted decedents is significantly higher than that observed for all deaths reported to NPSAD from England over the same time period (p<0.01; **Table 4**), concording with the proportion reported (88%) in a recent global systematic review (31). Whilst the age of decedents for SCRA-related deaths is not significantly different to all death reported to NPSAD from England over the same time period, decedents who died in 2012-2015 (mean age 34.5±10.3) when compared to those who died in 2018-2019 (mean age 40.0±8.9) were significantly younger (p<0.05; **Figure 3A**).

The proportion of SCRA-related decedents living in private housing accommodation is significantly lower than that for all deaths reported to NPSAD from England over the same time period (p<0.01), whilst the proportions of those living in a hostel, prison, or homeless are significantly higher (all p<0.01; **Table 4**). The usual address of SCRA-related decedents was on average located in one of the most deprived areas of England (decile score 1-3; **Figure 3B**). Furthermore, when compared to the usual addresses of decedents for all deaths reported to NPSAD from England over the same time period, SCRA-related decedents were significantly more likely to have been living in the more deprived areas (p<0.01; **Figure 3B**). Just 18.5% of SCRA-related decedents who died in 2012-2015 were living in the least deprived areas of England (deciles 6-10; n=5/27), despite the decedents who died in this time period accounting for only 10.9% of total SCRA-related deaths (n=18/165).

DISCUSSION

With over 180 different SCRA variants analytically confirmed in Europe as of January 2019 (7), SCRAs have consistently ranked as one of the largest groups of novel psychoactive substances on the European drug market (10). Whilst prevalence of SCRA use among the general population has declined in recent years (39), the number of SCRA-related deaths in England has concomitantly risen. The dataset presented here is the largest reported to date, exceeding the total number of cases included in a recent global systematic review (31).

Heterogeneous in harm

Notably, no deaths involving nabilone, the clinically approved SCRA in the UK, nor marinol, a SCRA used clinically in the US for HIV/AIDS-induced anorexia and chemotherapy-induced nausea and vomiting (40), were reported to NPSAD by time of publication, supporting their documented safety profiles (41).

The Welsh Emerging Drug and Identification of Novel Substances (WEDINOS) laboratory, the UK's only year-round drug submission and testing facility, detected illicit SCRAs in 6.25% of submissions received January 2017 - December 2019 (42); 43.2% of these SCRA detections were 5F-ADB, 22.8% 4F-MDMB-BINACA and 18.9% AB-FUBINACA. Whilst the proportions of deaths where 5F-ADB and AB-FUBINACA were detected in cases reported to NPSAD are reflected by their frequency of WEDINOS detections, the proportion of deaths in which 4F-MDMB-BINACA was detected is markedly lower (4.1% of SCRA-related death reports). It has been suggested that some SCRAs possess comparatively lower toxicities, potentially accounting for discrepancies between their prevalence of use estimations and incidences of mortality (43). Indeed, whilst 30% of test purchases were positive for the SCRA cumyl-PEGACLONE in a recent German study, only one case was reported where cumyl-PEGACLONE was directly implicated in causing death, and even then this was in combination with other SCRAs (5F-ADB and 5F-MDMB-P7AICA) and underlying health conditions (44). Cumyl-PEGACLONE was first detected in the UK in 2016 (45), but no deaths involving this SCRA were reported to NPSAD at time of writing. Some SCRA users possess 'inverted expertise' having demonstrated awareness of such trends, often earlier and to a greater extent than the support services trying to help them (46). Engaging SCRA users to combine their knowledge with available data is required to provide an up-to-date evidence base for healthcare professionals to provide effective treatments and interventions.

Isolated use is a SCRA-specific risk

Underlying cause of death was overwhelmingly attributed to acute drug abuse, with SCRAs implicated in the majority. Treating SCRA toxicity with naloxone may be effective due to inter-connectedness between the opioid and cannabinoid systems (but could be due to antagonising effects of co-administered opioids) (47); furthermore, naloxone blocks alcohol-mediated effects and there is a high concurrence of alcohol co-consumption (48). Effective naloxone administration requires the presence of educated and equipped witnesses, but a majority of SCRA users become unresponsive in isolation (24), contrary to other recreational drug taking behaviours (49). Unwitnessed overdose therefore represents a significant SCRA-specific risk of which greater awareness is needed amongst both SCRA users and their associates.

Intervention opportunities by healthcare professionals to treat SCRA toxicity is consequentially limited. This is further exacerbated by misidentification of SCRA users presenting with drug toxicity: a recent study found only 55.5% of patients presenting with SCRA intoxication had detectable SCRAs on analytical testing, suggesting that clinicians often mis-attribute effects of other drugs or medical conditions to SCRA use (50). Tools to identify individuals presenting with SCRA toxicity are needed in order to best provide treatment. It is reported that 'a user's breath has a pungent and unpleasant acrid burnt smell, and there may be changes in [their] voice, with a slightly higher pitch – like when helium has been inhaled, but not as squeaky' (51).

Lack of effective UK legislation

The shifting pattern in detected SCRAs cannot be attributed to prohibitive UK legislations acting as deterrents: neither MDA amendments introduced in 2009, 2013 and 2016 controlling some SCRAs, nor their generic ban under PSA (2016), appear to have influenced the mortality rate. Rather, it is likely due to legislative changes in China, where a large proportion of SCRAs are thought to be manufactured (6). The control of eight SCRAs, including 5F-ADB and AB-FUBINACA, by the State Council of China in August 2018 correlates with the shift away from these SCRAs being the most dominantly detected by both NPSAD and WEDINOS (42), and towards newer generation SCRAs such as 4F-MDMB-BINACA and 5F-MDMB-PICA. SCRA-related deaths in England are not projected to drammatically decrease, indicating need for alternate interventions. A ban citing commonly used names for SCRA preparations (e.g. 'Spice', 'K2', 'Kronic', and 'Mamba') as opposed to specific SCRA molecular structural variants may prove more effective, as was observed in Australia (52).

From 'herbal highs' to the 'heroin of cannabis'

The reputation of SCRAs has drastically evolved, with online 'psychonaut' discussion forums which originally encouraged SCRA use now acting as deterrents (53). This is reflected by the evolving demographic with decedents dying in 2012-2015 younger and, on average, living in less deprived areas than those who died from 2016 onwards. This decedent demographic shift may indicate effectiveness of the 2016 Psychoactive Substances Act in deterring SCRA use in younger individuals living in less deprived areas (23, 24).

It is well documented that SCRAs are increasingly problematic in homeless and prison populations (9, 22, 28, 54). However, these data indicate that a greater proportion of decedents were living in private residential accommodation at time of death, albeit in socioeconomically deprived areas. This needs serious consideration in the design of targeted strategies addressing SCRA use, which currently focus on homeless and prison populations (55, 56). Furthermore, as almost half of the decedents were known to misuse drugs, healthcare and other supporting professionals should be routinely inquiring about SCRAs in polysubstance users and informing them about SCRA-specific risks.

Knowledge of SCRA-disease/drug interactions is scarce

Cardiorespiratory complications were citated as immediate causes of death in a marked proportion of cases, correlating with circumstance of sudden collapse. Whilst SCRA cardiotoxicity is an established concern (12, 57), the mechanisms of SCRA-mediated cardiac and respiratory failure are poorly understood (58, 59). Furthermore, the cardiac and respiratory effects of SCRAs in combination with other cardiotoxic (e.g. stimulant) and/or respiratory depressant (e.g. opiate) substances are poorly characterised and represent an urgent area of enquiry. Such research is required to recommend effective interventions, for example as to whether cardiac QT interval monitoring in SCRA users attending drug services should be undertaken, as is suggested for those prescribed methadone who also use crack cocaine (60).

Whilst the number of substances detected by toxicology in SCRA-related decedents dramatically increased from 2012 to 2019, evidence for SCRA drug-drug interactions remains scarce. Studies indicate that some SCRA types interact with cytochrome P450 pathways, which may negatively impact the pharmacodynamics of other co-administered substances leading to adverse events (61-70). However, these studies used older SCRA types, which differ substantially in terms of molecular structure to those which are currently prevalently used (42). Indeed, only four SCRAs for which this metabolism data is available were detected in cases reported to NPSAD (AB-CHIMINACA, AKB-48, AM2201, STS-135), and account for just 9 of the 217 SCRA detections. This noticeable absence of *in vivo* human investigations of SCRA pharmacodynamics is likely due in part to insufficient toxicity data making human administration studies unfeasible, and the absence of on-site toxicology in clinical settings in the UK limiting observational data linking patient presentations to specific SCRAs. This is in contrast to other cannabinoid-based drugs, including illicit cannabis, for which drug interaction data is easily accessible (71). Further research into potential drug-drug interactions with new and

emerging substances is needed in order to better understand potential adverse events, and advise people determined to use SCRAs of harmful interactions that may occur with co-administered illicit or prescription medications.

SCRA users display high rates of other substance use (18), concording with patterns observed in other illicit drug users (49). However, the proportion of SCRA-related decedents who were known to use drugs reported to NPSAD is near two-fold of that reported in a recent global systematic review (31). Furthermore, the proportions of decedents reported to NPSAD co-administering opioids, benzodiazepines/Z-drugs, stimulants and alcohol consistently outstrips those observed in the review (31). Of particular concern is the mortality rate associated with opioid-SCRA co-administration, as this is 10-fold higher than the rate reported in living users (72). Whether this represents an increased mortality risk associated with opioid-SCRA co-intoxication is unclear. A need for understanding risks conferred by patterns of substance misuse including SCRAs appears to be critically important in the UK context.

Limitations

As detection methods for SCRAs have advanced (34, 73) and requests for SCRA toxicology tests to be performed have become more frequent (25), part of the increase in recent NPSAD reporting is potentially an artefact of improved SCRA detection. However, as standard toxicology screens to do not include SCRAs (35), and even when requested there are detection limitations (34, 74), the occurrence of SCRA-related deaths is likely under-reported. Furthermore, as NPSAD is reported to voluntarily and Coronial investigations are not carried out for all deaths, the figures presented here likely under-represent the true number of SCRA-related deaths occurring in England.

It is also unclear as to how SCRAs directly cause death, especially given their high rate of co-administration with other substances (18). Coroners have limited information on SCRA toxicity upon which to base their conclusions (35), and may be influenced to implicate SCRAs due to their notoriety (9, 16, 22).

Conclusions

SCRAs are considered one of the most fataly toxic novel psychoactive substances (75). Despite a reduction in their overall use prevalence (23, 24), deaths attributable to their consumption have risen. Lack of effective deterrents to SCRA use under current UK legislation, compounded by limited knowledge as to the physiological impacts of SCRA consumption and their interaction with other co-administered substances, can be identified as contributory factors to the increased mortality trend. New legislative, healthcare and substance use service approaches are urgently required to reduce SCRA-related harms in the broader deprived demographic identified in this study. Increasing pre-clinical research and effective clinical assessment and engagement of SCRA users will substantiate the knowledge base required to achieve these aims.

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FIGURES & TABLES

Figure 1: Deaths reported to NPSAD from England by April 1st 2020 where a SCRA was detected at post-mortem and/or implicated in causing the death. The average time between death and conclusion of Coronial inquest for deaths where a SCRA was present was approximately 7 months. It is therefore anticipated that further deaths will be reported to NPSAD that occurred in 2019. Based on jurisdiction reporting trends a projected number of SCRA-related deaths expected to be received by NPSAD has been extrapolated.

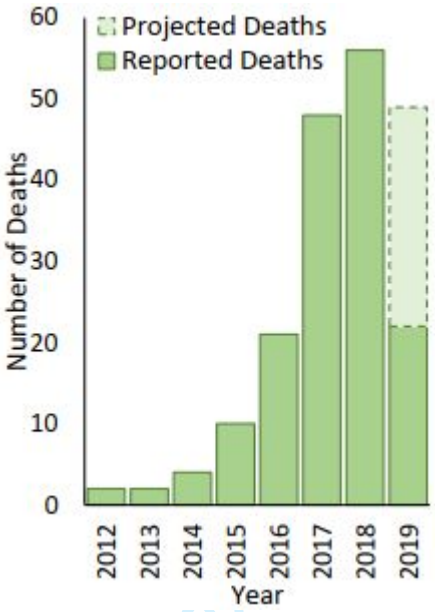

Figure 2: SCRA types detected at post-mortem and/or implicated in causing death in cases reported to NPSAD from England. 5F-ADB and AB-FUBINACA detections have dominated in recent years, representing 40.6% and 18.9% of total detections, respectively. 2019 data are for reported only (i.e. not projected) detections. Note that total detections sum to greater than the total number of SCRA-related cases as in some cases multiple SCRA variants were detected: a total of 217 SCRA detections were made across the 165 reported cases. ^AB-FUBINACA also includes figures for AMB- and EMB-FUBINACA and their metabolites as detectors have limited capability in differentiating between these compounds (34).

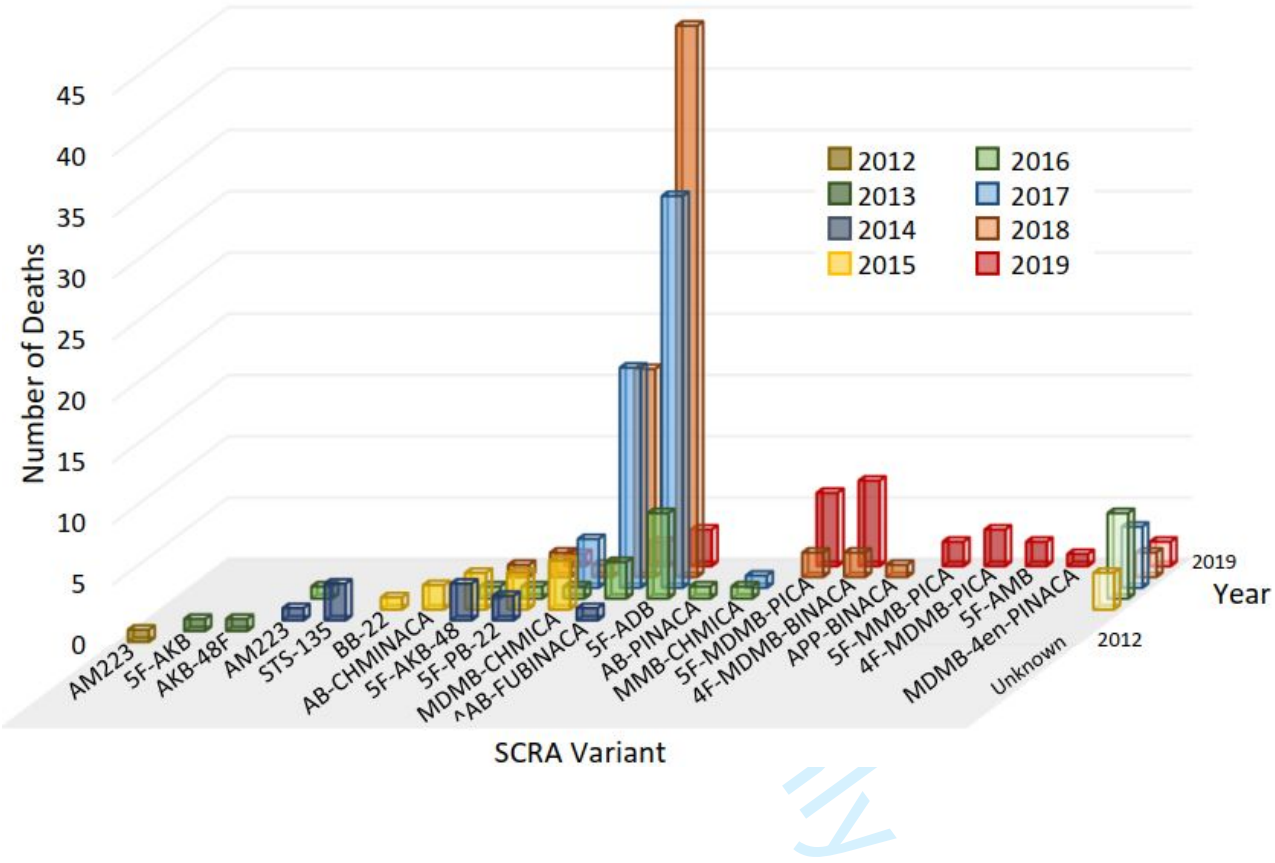

Figure 3: A. Percentage of cases by age range per year of SCRA-related decedents reported to NPSAD from England. Decedent numbers for 2012-2015 have been summed due to low figures for these years. **B. Deprivation decile by postcode of usual address of SCRA-related decedents and all decedents reported to NPSAD from England 2012-2019.** A ranking within the first decile represents the most deprived areas in England, whilst a ranking within the tenth decile represents the least deprived areas. These rankings are based upon assessment of income, employment, education, health and disability, crime, barriers to housing and services, and living environment statistics (36). Homeless decedents were excluded from this analysis by default due to lack of a usual address (n=32), as were those whose usual address was outside England (n=2).

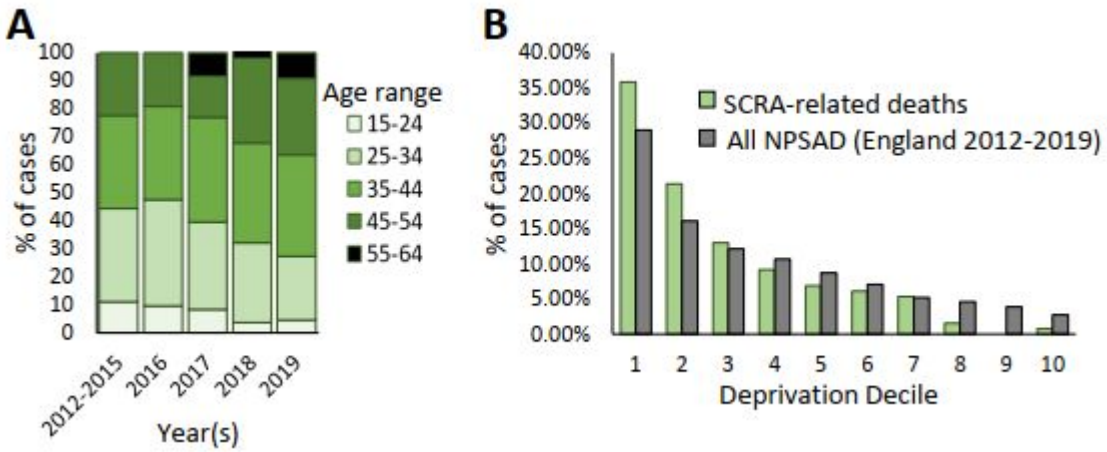

Table 1: Year during which each SCRA type was first detected in cases reported to NPSAD from England. ^AMB- and EMB-FUBINACA have not been separately classified from AB-FUBINACA as detectors have limited capability in differentiating between these compounds (34). *Indicates the six SCRAs detected within the seven-month period (November 2018 - May 2019).

2012	2013	2014	2015	2016	2017	2018	2019
AM2201	5F-AKB	5F-PB-22	BB-22	5F-ADB		5F-MDMB-PICA*	5F-MMB-PICA*
AM223	AKB-48F	5F-AKB-48	AB-CHMINACA	AB-PINACA		4F-MDMB-BINACA*	4F-MDMB-PICA*
		AKB-48	MDMB-CHMICA	MMB-CHMICA		APP-BINACA*	5F-AMB*
		STS-135					MDMB-4en-PINACA
		AB-FUBINACA^					

Table 2: Immediate and underlying causes of death listed on death certificates of SCRA-related decedents in cases reported to NPSAD from England. As more than one immediate and/or underlying cause of death was cited in some cases, these will add to greater than the total number of deaths.

Cause	Immediate Cause % of Decedents (n)	Underlying Cause % of Decedents (n)
Acute drug use	67.3% (n=111)	87.9% (n=145)
Implicating SCRA(s)	57.6% (n=95)	75.8% (n=125)
Not implicating SCRA(s)	9.7% (n=16)	12.1% (n=20)
Physiological system	32.7% (n=54)	12.1% (n=20)
Cardiac	10.3% (n=17)	7.3% (n=12)
Respiratory	13.3% (n=22)	6.1% (n=10)
Neurological	9.1% (n=15)	3.6% (n=6)
Hepatic	1.2% (n=2)	1.8% (n=3)
Mental health	0.6% (n=1)	0.6% (n=1)
Gastrointestinal	0.6% (n=1)	-
Trauma	-	-
Other	3.0% (n=5)	3.0% (n=5)

Table 3: Age, gender and usual living circumstances of SCRA-related decedents in cases reported to NPSAD from England. Complementary data for all cases submitted to NPSAD from England within the same time period have been provided for comparison.

Age & Gender	% SCRA-related deaths (n)	% All NPSAD Cases (England 2012-2019)
Men	90.3% (n=149)	72.0%
Women	9.7% (n=16)	28.0%
Mean Age (± SD)	38.41 ± 9.40	40.11 ± 13.73
Usual Living Circumstances		
Private residential	57.6% (n=95)	80.9%
Hostel	13.3% (n=22)	2.3%
Homeless	19.4% (n=32)	4.1%
Prison	4.9% (n=8)	0.2%
Unknown	-	11.3%
Other^	4.9% (n=8)	1.3%

^Rehab, hospital, hotel, nursing home, boat, caravan, shed, workplace