Brett Jonathan (Orcid ID: 0000-0003-3065-7495)

Wylie Claire (Orcid ID: 0000-0001-8076-4235)

Isbister Geoff (Orcid ID: 0000-0003-1519-7419)

The relative lethal toxicity of pharmaceutical and illicit substances; A 16-year study of the Greater Newcastle Hunter Area, Australia.

The relative lethal toxicity of pharmaceutical and illicit substances

Dr Jonathan Brett (Corresponding author and principle investigator)

Clinical Pharmacologist and Addiction Specialist

St. Vincent's Hospital, Sydney & New South Wales Poison Information Centre, Sydney

Australia

Research Fellow, Translational Australian Clinical Toxicology Program, School of

Medical Sciences, Faculty of Medicine and Health, The University of Sydney.

E: Jonathan.Brett@health.nsw.gov.au

T: +61 (02) 8382 1111

M: +61 487468199

Dr Claire E Wylie

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Research Fellow, Translational Australian Clinical Toxicology Program, School of Medical Sciences, Faculty of Medicine and Health, The University of Sydney.

E: claire.wylie@sydney.edu.au

Dr Jacques Raubenheimer

Biostatistician, Translational Australian Clinical Toxicology Program, School of Medical Sciences, Faculty of Medicine and Health, The University of Sydney.

E: jacques.raubenheimer@sydney.edu.au

Professor Geoff K Isbister

Senior NHRMC Research Fellow, School of Medicine and Public Health, University of Newcastle.

Clinical Toxicologist and Emergency Medicine Specialist, New South Wales Poison Information Centre & Hunter New England Toxicology Service

E: Geoff.Isbister@newcastle.edu.au

Professor Nick A Buckley

Director, Translational Australian Clinical Toxicology Program, School of Medical Sciences, Faculty of Medicine and Health, The University of Sydney.

Clinical Toxicologist, New South Wales Poison Information Centre and Royal Prince Alfred Hospital, Sydney.

nicholas.buckley@sydney.edu.au

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The relative lethal toxicity of drugs can be estimated according to the fatal toxicity index (FTI); the number of deaths per year of a daily dose, and case fatality; the number of deaths per overdose.
- Challenges in access to population level prescribing, poisoning and death data have hindered past attempts to estimate the relative lethal toxicity of drugs.
- This study estimates the relative lethal toxicity of drugs taken in overdose, which is of direct relevance to prescribers and policy makers.

WHAT THIS STUDY ADDS

- Population level death, prescribing and overdose data in Australia can be used to calculate FTI and CF for poisoning with pharmaceutical and illicit agents.
- FTI and CF calculated within this study are relatively well correlated.
- As a class, opioids had the highest FTI and CF, tricyclic agents were the most toxic antidepressants and benzodiazepines were significantly more toxic in combination overdoses compared to when taken alone.

ABSTRACT

Aims: We aim to calculate two metrics of relative lethal toxicity; the fatal toxicity index (FTI) (number of deaths per year of a daily dose) and the case fatality (CF) (number of deaths per overdose) with a focus on opioids, antidepressants, antipsychotics, benzodiazepines and illicit drugs.

Methods: This descriptive cohort study used the Australian National Coronial Information System (NCIS) to identify a population of individuals with drug-associated deaths in the Greater Newcastle Hunter Region between January 2002 and December 2016. This was combined with Australian medicine dispensing data and corresponding data from the Hunter Area Toxicology Service to calculate FTI and CF.

Results: There were 444 drug related deaths and 21,296 overdoses during the study period. FTI and CF were well correlated (Spearman's rho 0.64, P<0.001). Of the classes of interest, opioids had the highest FTI (40.3 95%CI 35.2-45.4 deaths per 100 years of use at the defined daily dose or deaths/DDD/100y) and CF (12.4% 95%CI 11.0-13.9). Fentanyl, methadone and morphine had the highest relative fatal toxicity within this class. Tricyclic antidepressants had the highest relative fatal toxicity of all antidepressants (FTI 14.5 95%CI 9.7-19.3 deaths/DDD/100y and CF 7.1% (95%CI 4.8-9.3)) and benzodiazepines appeared to be more associated with multiple agent deaths than single. Of the illicit drugs, heroin had the highest CF (26.4%, 95%CI 19.1-33.7).

Conclusion: Knowledge of relative lethal toxicity is useful to prescribers and medicines and public health policy makers in restricting access to more toxic drugs and may also assist coroners in determining cause of death.

context of deliberate overdose. Toxicovigilance is a term recently used to describe the practice of monitoring for the emergence of poisons causing significant morbidity and mortality in overdose [1]. For pharmaceutical agents, this field of research faces similar

difficulties to pharmacovigilance in that it occurs exclusively in a post-marketing environment that lacks the structure, regulation and economic incentives of the pre-marketing setting [2]. For patients at risk of overdose, knowledge of the relative lethal toxicity (e.g. the risk of death following a prescription or overdose relative to other medicines) is important as it may influence the decision to prescribe and choice of medicine prescribed. At a regulatory and public health level, this information can generate safety signals and inform policy decisions [3-5].

Estimating the relative lethal toxicity of poisons poses several challenges. Animal toxicity studies (e.g. LD50 data) cannot be reliably extrapolated to humans [6, 7] and so information regarding human toxicity is frequently derived from case reports and case series of single drug overdoses. However, these sources are subject to significant publication bias and only occasionally include patients who die as a result of their poisoning.

Case fatality (CF) is a metric of relative toxicity that estimates of the risk of death following overdose with a given agent. It is calculated by expressing the number of deaths associated with a given poisoning as a percentage of the number of people presenting to hospital with that poisoning. There have been large poisoning cohort studies estimating in-hospital case fatality [6]. However, this approach misses deaths from poisonings in which individuals die before reaching hospital, which represents the majority of people who die from many highly toxic agents, and so in most cases grossly underestimates true case fatality.

Another approach is to calculate the Fatality Toxicity Index (FTI); an estimation of the risk of death after a given agent is prescribed. This metric has typically been expressed as the number of deaths per million prescriptions or per million patient years and has been applied to antidepressants [8], benzodiazepines [9, 10] and antipsychotics [11]. However, no studies to date have systematically evaluated the fatal toxicity of the full range of agents involved in poisoning deaths. As a measure of lethality, the FTI has limitations including those introduced by the use of dispensing claims data and bias related to prescribing based on risk of overdose [11, 12]. Furthermore FTI cannot be used to quantify the relative lethality of non-prescription pharmaceuticals and non-pharmaceutical agents such as illicit substances.

Within this study we aimed to determine relative lethal toxicities of poisons causing deaths reported to the coroner within the Greater Newcastle Hunter Area over a 16-year period. Specifically we calculated the CF and FTI for individual agents and classes of agents to identify those with relatively higher lethal toxicity. We also evaluated the correlation between CF and FTI.

METHODS

Study populations

Drug-poisoning related deaths: We identified drug-poisoning related deaths (pharmaceutical and illicit) in the Hunter Valley Region, New South Wales, Australia between January 2001 and December 2016 using the National Coronial Information System (NCIS) database. The NCIS was established in July 2000 and is a national repository of coded information on all deaths referred to the Australian coroner, including all poisoning deaths. It contains a unique person identifier, date and

geographic location of death, case status and information on mechanism and cause of death. Each death record may also contain autopsy, police and forensic reports.

We extracted all closed coronial deaths occurring within Statistical Areas four (SA4) 106 (Hunter Valley excluding Newcastle) and 111 (Newcastle and Lake Macquarie) within the NCIS database between January 1, 2001 and December 31, 2016 inclusive, and then limited our search to those where the primary mechanism of death was coded as 'exposure to chemical or other substance'. We searched the four primary 'cause of death' fields (Cause of Death 1a to d) to identify all deaths where pharmaceutical or illicit drugs were listed. We then attempted to identify all drugs involved with that death by manually reviewing all other fields within the NCIS dataset.

We manually identified misspellings of drugs and converted brand to generic drug names to ensure complete data capture (Supplementary S1). In anticipation of causation being attributed to metabolites, we recoded drugs that were likely to be metabolites as the parent compound (as identified by clinical pharmacologist authors JB and MB). For example, if amitriptyline and nortriptyline were both listed as associated with a death, nortriptyline was assumed to be a metabolite and the death was attributed to an amitriptyline overdose only (Supplementary S2). For death records in which only a drug class was listed or non-specific terminology was use (such as 'drug'), we evaluated autopsy, forensic and police reports to identify the drug(s) most likely to be associated with death. A drug poisoning related death was included if at least one drug could be identified down to at least the drug class level.

For our primary analysis of deaths involving multiple drugs, we anticipated that some drugs would contribute more to the death than others, therefore we weighted the drug-poisoning related deaths according to the number of drugs implicated in each death. For each death, each attributed drug was therefore assigned a value equivalent to the reciprocal of the total number of agents associated with that death. For instance, if six drugs were involved in a death, each drug was considered to be contributing to one sixth of a death. All of these weighted deaths were summed for each drug to calculate the overall weighted number of deaths per drug.

Hospital presentations with drug overdose: We identified all drug overdose related presentations recorded within the Hunter Area Toxicology Service (HATS) database for the study period. The HATS database was established in 1987, and represents one of the largest poisoning cohorts in the world [13]. It provides information on all poisonings presenting to hospitals within a well-defined geographic region and contains a unique person identifier, date of presentation, reason for admission, poison(s) involved and whether the overdose resulted in death. We included admissions that were due to a drug overdose, excluding those with concurrent other reasons that may have superseded the drug as a reason for presentation. Such examples included exposure to pesticides and other toxic chemicals, carbon monoxide and other medical diagnoses or physical self-harm attempts, with the exception of alcohol intoxication and wrist/arm lacerations. We performed sensitivity analyses including all of these excluded presentations to evaluate the impact on our estimates of relative lethal toxicity.

As for the drug-poisoning related deaths, we weighted the hospital presentations with drug overdose according to the number of implicated agents in each overdose.

We correlated HATS deaths to deaths recorded in the NCIS database and reviewed cases in which a death was recorded within our HATS study population but not within our NCIS study population to determine why this may have occurred.

Pharmaceutical drug prescriptions: The Australian Statistics on Medicines (ASM) dataset is an annual publication produced by the Drug Utilisation Sub-Committee (DUSC) of the Pharmaceutical Benefits Advisory Committee (PBAC) and provides medicine utilisation data in the form of defined daily doses per 1000 population per day (DDD/1000/day) for all medicines funded by the Australian government's universal health care program; the Pharmaceutical Benefits Scheme (PBS). The DDD is a World Health Organization approved measure of drug utilization and represents the assumed daily dose of the drug when used for its main indication [14].

Population estimates: We used Australian Bureau of Statistics (ABS) mid-year population estimates for statistical areas four (SA4) 106 (Hunter Valley excluding Newcastle) and 111 (Newcastle and Lake Macquarie) as population level denominators, taking the average population size over the 16 year study period as the population at risk.

Data analysis

Our primary analysis included all drug related deaths, and our secondary analyses considered deaths only involving a single drug. Data coding and manipulation and

statistical analysis was performed in Microsoft Excel 2016, SAS/STAT version SAS/STAT version 13.2 of the SAS system (version 9.4) for Windows and Stata v15.1 (StataCorp, Texas, USA).

Case Fatality (CF)

We calculated the number of overdoses with each drug by adding the number of overdoses from the HATS study population to the number of drug-poisoning related deaths from the NCIS study population (to account for overdoses leading to out of hospital deaths). We then subtracted the number of deaths from the HATS study population to avoid double counting.

Case fatality was calculated by dividing the number of drug-poisoning related deaths by the number of hospital presentations with overdose for a given drug, expressed as a percentage with 95% confidence intervals (CIs). CIs for each drug were calculated using a binomial distribution in which the number of deaths associated with each drug represented the number of events and the number of overdoses represented the number of trials. For primary analyses, weights were applied to deaths and overdoses as above.

Fatal Toxicity Index (FTI)

We calculated FTI as the number of deaths per 100 years exposed to the DDD of that drug. For each medicine we used the number of deaths associated with that medicine as the numerator. For the denominator of each drug, we summed the DDD/1000pop/year over the entire 16-year study period and multiplied by the population size in in Greater Newcastle Hunter area; the average ABS mid-year population for SA 106 and 111

combined over the study period. We then divided this by 10 to give a metric of deaths per 100 years of use at the daily-defined dose (deaths/DDD/100y). The value of DDD/100y value has little meaning in isolation but is used to determine the FTI of substances relative to each other. A binomial distribution was used to calculate 95% CIs around FTI, assuming the number of deaths was the number of events and DDD/year is the number of trials. Deaths were weighted in the primary analysis as above.

Drug class analysis

We focused our analyses on specific drug classes frequently taken in overdose and anticipated to be frequently associated with drug related deaths; these included opioid, antidepressant, antipsychotic and benzodiazepine drug classes as defined by the Australian Medicines Handbook [15].

In our primary analysis we calculated CF and FTI for these classes for all deaths and then separately for deaths only involving single agents. For the situation in which a death or overdose included more than one drug of the same class, we considered these to be unique drugs when calculating weighted deaths and overdoses.

We calculated CF and FTI for all medicines taken in overdose and within the HATS study population, regardless of whether they resulted in a death and used these values to calculate median values of CF and FTI for all drugs and classes considered in our primary analysis, and only drugs involved in single drug deaths in our secondary analysis to facilitate observations of relative lethal toxicity. We retained methadone, buprenorphine, codeine and pholcodeine within these analyses, despite significant limitations related to capture of dispensings (see limitations).

Data visualisation and correlation analyses

Only drugs that were associated with a death were presented in this analysis. To summarise both the FTI and CF for each drug class of interest as well as the correlation between FTI and CF measures, we plotted the weighted FTI against the weighted CF with confidence intervals for each drug within each class of interest. We also presented an extrapolated line representing the median weighted FTI and CF for that drug class to illustrate the point of correlation between the two measures. For illicit drugs, only weighted CF was plotted.

Where values for both FTI and CF existed for drug deaths, we used Spearman rank correlation techniques to quantify their correlation, where $P < 0.05$ was considered significant.

To compare our primary (all drug deaths) and secondary (single drug deaths) analyses we plotted weighted FTI and CF against FTI and CI calculated for single drug deaths for each drug class of interest respectively. We used this to identify agents that had a substantially different lethal toxicity in single versus multiple agent overdoses.

Hunter New England Human Research Ethics Committee approved the use of HATS data (15/02/18/5.04) and Victorian Department of Justice Research Ethics Committee (CF/15/18367) approved the use of NCIS data. ABS and ASM data are publically available.

RESULTS

Drug-poisoning related deaths

We identified 444 drug-poisoning related deaths within the Hunter Valley Region between January 2001 and December 2016 using the NCIS dataset (Figure 1). Most decedents were male (n=279, 62.8%) and the median age of death was 43 years old (range 1 to 94 years) (Table 1). Deaths mostly occurred at home (n=332, 74.8%), or in hospital 73 (16.4%,). Most deaths were associated with pharmaceutical agents only (n=342, 77.0%), 55 (12.4%) with an illicit agent only and 47 (10.6%) with a combination of pharmaceutical and illicit agents. A total of 213 (48.0%) deaths were associated with a single drug. There was a total of 99 unique specified drugs associated with these deaths: 89 pharmaceutical and 10 illicit agents. The median number of agents causing death was 2 (range 1 to 11).

Hospital presentations with drug overdose

We included 11,907 presentations with overdose relating to 21,296 drug overdoses to HATS (Figure 2). Most people overdosing were female (n=7671, 64.4%) and the median age was 34 years old (range <1 to 99 years) (Table 1). Most overdoses were associated with a pharmaceutical agent only (n=11,208, 94.1%). There were 408 (3.4%) overdoses that were associated with an illicit agent only and 291 (2.4%) with a combination of pharmaceutical and illicit agents. There were a total of 6632 (55.7%) overdoses with a single drug. HATS recorded drugs differently to NCIS, including combination products and varying dosages of certain products, precluding direct comparison, however, there was a total of 509 listed drug components associated with the overdoses; 490 pharmaceutical and 19 illicit agents. The median number of agents in overdose was 1 (range 1 to 14). Within the 11,907 admissions, there were 24 deaths. Eight of these deaths did not appear within the NCIS study population: of these, four deaths were

presumptively matched in NCIS, while four could not be identified and were presumably not referred to or investigated by the Coroner.

Fatal Toxicity Index and Case Fatality

For our primary analyses, the median FTI was 5.38 deaths/DDD/100y and CF was 4.26%. The weighted FTIs and CFs for individual products and for drug classes can be found in supplementary information (Supplementary 3). The correlation between weighted FTI and CF for all 81 individual drugs implicated in a drug death where both FTI and CF was available was strong (Spearman's rho 0.64, P<0.001), and very strong for the single drug deaths in our secondary analysis (Spearman's rho 0.96, P<0.001). Sensitivity analyses in which we excluded overdoses with drugs in which the presentation to hospital was not primarily with drug toxicity had minimal effect on the FTI and CF for individual drugs in both primary and secondary analyses.

Class analyses

Opioids (excluding heroin) had a significantly greater relative lethal toxicity than the median of all drugs, with a FTI of 40.3 (35.2-45.4) deaths/DDD/100y and CF of 12.4% (11.0-13.9) overall (Figure 3a). Of the opioid class, confidence intervals for dextropropoxyphene, pethidine and pholcodine were particularly wide and so were omitted from Figure 3. The FTI for methadone appears to be substantially greater than other opioids but this is associated with under capture of dispensings and so difficult to interpret (see limitations). The FTI and CF for methadone (146.7 (107.8-185.7) deaths/DDD/100y and 29.4% (22.7-36.0)), morphine (85.4 (62.1-108.6) deaths/DDD/100y and 36.9 (29.0-44.8)) and fentanyl (62.5 (29.5-95.5) deaths/DDD/100y and 47.1 (29.0-65.3)) were significantly greater than the median of

other opioids. Fentanyl appeared to have a relatively higher CF than FTI (Figure 3b). Conversely, oxycodone appeared to have a relatively higher FTI than CF (Figure 3b). Prescribed opioids appear to have similar CF in multiple compared to single agent overdose. However, methadone, oxycodone and morphine may be more toxic in multiple agent deaths as measured by FTI (Figure 4a & b).

Antidepressants had a low relative fatal toxicity, with an overall FTI and CF of 2.5 (2.0-3.0) deaths/DDD/100y and 2.5% (2.0-3.0) respectively. However, TCAs had a much higher FTI and CF (14.51 (9.74-19.29) deaths/DDD/100y and CF 7.1% (4.8-9.3) respectively) compared to other subclasses of antidepressants (Figure 3c). Overall FTI and CF for antipsychotics was 7.9 (5.5-10.3) deaths/DDD/100y and 1.72% (1.2-2.24) respectively. The confidence intervals for FTI and CF for individual antipsychotics were generally wide but point estimates for clozapine (50.10 deaths/DDD/100y and 15.51%) were higher than other antipsychotics and olanzapine had the lowest point estimate for FTI and CF (1.0 deaths/DDD/100y and 3.3%) (Figure 3d). Quetiapine and pericyazine had relatively higher FTIs than CFs (Figure 3d). Quetiapine also appeared to be substantially more toxic in multiple agent overdose compared to single (Figure 4d). Benzodiazepines had a similar overall case fatality to antidepressants but a higher FTI (6.7 (5.6-7.8) deaths/DDD/100y).

Heroin was the most toxic illicit drug with a CF of 26.4% (19.1-33.7) and had a greater CF when taken as a single agent. Amphetamines had a case fatality that was significantly greater than the average CF of all other drugs combined at 8.5% (5.8-11.2) (Figure 5).

DISCUSSION

In this sixteen-year population level study we have summarised poisoning deaths and overdoses within the Greater Newcastle Hunter Area. We have measured the relative toxicity of all drugs taken in overdose in terms of risk of death at the point of prescribing (fatal toxicity index) and at the point of overdose (case fatality) and focused on classes of drugs commonly prescribed and taken in overdose. With some notable exceptions, FTI and CF are well correlated for all deaths and for deaths involving a single agent some drugs and drug classes appear to be more toxic when taken in combination with other drugs.

The demographics of people overdosing and dying from overdose in terms of age and sex have remained relatively constant over the last two decades [16].

Of the classes of interest, opioids were the most toxic in terms of FTI and CF. Differences within the opioid class in terms of FTI and CF may partially be accounted for by differences in potencies at the mu opioid receptor [17] but this does not explain why morphine was more toxic than oxycodone. This may be a metabolite issue as heroin is rapidly metabolized to morphine, which may lead to a misattribution of causality [18]. While the FTI for methadone is difficult to interpret, the CF was high relative to other opioids, which is consistent with previous studies [19-21]. The relative toxicity of opioids in our study was slightly different to a whole of population Finnish study, in which methadone had the highest FTI, followed by oxycodone and then tramadol [19]. This may reflect national differences in prescribing practices, drug use (including diversion and misuse) or may be a consequence of differing methodology, as the Finnish study did not attempt to weight multiple drug overdoses to account for causality.

The observation that fentanyl has a higher CF relative to FTI indicates it may be more toxic at the point of overdose rather than prescribing. Since around 2006, there have been increases in fentanyl prescribing and deaths in Australia, some of which may be accounted for by increasing diversion and illicit use [22, 23]. The relatively high toxicity of opioids is concerning given opioid dispensing in Australia has increased 15-fold (500,000 to 7.5 million) between 1992 and 2012 with proportionate increases in harms measured by deaths and hospitalisations [24].

The finding that TCAs have the highest FTI and CF of all of the antidepressants is consistent with previously studies in which other antidepressants have >10-fold lower lethal toxicity [8, 19, 25]. Our finding that clozapine was the most toxic antipsychotics is consistent with previous studies [11] and its toxicity profile; causing more sedation and hypotension when taken in overdose, particularly in non-adherent or treatment naive patients [26]. A previous study concluded that the FTI of antipsychotics was inversely related to potency at D2 receptors, implying that actions on other receptors may be more important, however, this analysis did not include atypical agents [11]. The finding that olanzapine has the lowest relative toxicity of all antipsychotics was consistent with previous European studies [19, 27]. The recent escalation in prescribing of atypical antipsychotics in the Australian community, with high rates of 'off label' use and polypharmacy [28-30] in patients who may be at increased risk of overdose is concerning given their higher than average relative toxicity. This is particularly the case for quetiapine, which is frequently found in psychotropic polypharmacy and appears to be a more toxic in multiple agent overdoses [28]. The finding that benzodiazepines have a relatively low fatal toxicity but are more toxic in multiple agent deaths is consistent with previous studies [9, 10, 31].

It is unsurprising that heroin is the most toxic illicit drug but the finding that amphetamines have higher than average relative toxicity is of concern given the increasing use of methamphetamine in Australia and globally amongst people who already use illicit drugs [32, 33]. Our findings are similar to previous studies that estimated relative toxicity using measures of drug availability (number of users as determined by household surveys, number of seizures by law enforcement agencies and estimates of the market size) as the denominator as well as the propensity of drugs to cause deaths as single causative agents [18, 34]. Our observation that the point estimate for cannabis CF was greater that amphetamines and MDMA likely relates to coronial misattribution of causality; cannabis may have been found on postmortem toxicology analysis is unlikely to cause death [18].

Limitations

Previous studies have found that toxicological cause of death on coronial reports on may not always be accurate. This may be the result of misattribution of causality to metabolites or because of post mortem redistribution causing spuriously high concentrations [27, 35]. We attempted to account for the metabolite issue in this study. Furthermore, in the setting of multiple agent poisonings, limited attempts were made by coroners to identify causative agents. For example paracetamol and morphine could be listed as equally associated with a death, an implausible combination given the different time courses of lethality. This study did not systematically evaluate the quality of the coroner's reports with respect to cause of death and each drug was assumed to be equally weighted in causing death. Some drugs commonly prescribed and taken in

overdose such as pregabalin were notably absent from Coronial reports as they are not part of the standard postmortem toxicology assay.

We assumed that prescribing in the Hunter region reflects national prescribing patterns, and this was found to be the case in previous studies [36]. The use of DDD for many of these drugs as measures of exposure, in particular opioids and psychotropics, can be inaccurate if the therapeutic dose range is wide [14, 37]. Prescribing also goes un-recorded in ASM data for medicines dispensed within the hospital system or as part of the S100 scheme, leading to a spuriously lower denominator and hence an overestimation of FTI for these medicines. This is particularly the case for buprenorphine and methadone, which are both S100 medicines when prescribed for opioid use disorder. Furthermore, FTI cannot be calculated for non-prescription medicines. In these situations, CF is the preferred estimate of relative fatal toxicity where corresponding overdose data is available. FTI and CF represent an average of all people prescribed a drug or taking the drug in overdose and so do not account for individual level predictors of death at the point of prescribing or overdose.

CONCLUSION

This study has allowed the estimation of the lethal toxicity of agents commonly taken in overdose by calculating FTI and CF and has explored the correlation and limitations of these measures. Expanding this study to a larger population would increase the power of this technique but is limited by missing information on overdose numbers. While FTI and CF are reasonably well correlated, the FTI estimates the risk of death from the point of dispensing and so is relevant to medicines policy makers and prescribers. CF estimates risk of death at point of overdose and so is relevant to prescribers when

assessing overdose risk, emergency physicians and toxicologists when managing overdoses, and public health policy makers in mitigating overdose risk.

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Conflict of interest: There are no competing interests to declare

References

1. Descotes, J. and F. Testud, *Toxicovigilance: a new approach for the hazard identification and risk assessment of toxicants in human beings.* Toxicology and Applied Pharmacology, 2005. **207**(2): p. 599-603.
2. Meyboom, R.H., et al., *Pharmacovigilance in perspective.* Drug Safety, 1999. **21**(6): p. 429-447.
3. Wilce, H. and S. Kings Cross, *Temazepam capsules: what was the problem?* Australian Prescriber, 2004. **27**: p. 58-59.
4. Bateman, N.D. and E.A. Sandilands, *European Medicines Evaluation Agency bans dextropropoxyphene: a landmark decision for clinical toxicology?* Clinical Toxicology, 2009. **47**(8): p. 782-783.
5. Corcoran, P., et al., *Use of analgesics in intentional drug overdose presentations to hospital before and after the withdrawal of distalgesic from the Irish market.* BMC Pharmacology and Toxicology, 2010. **10**(1): p. 6.
6. Dawson, A.H., et al., *Acute human lethal toxicity of agricultural pesticides: a prospective cohort study.* PLoS medicine, 2010. **7**(10): p. e1000357.
7. Buckley, N.A. and P.R. McManus, *Can the fatal toxicity of antidepressant drugs be predicted with pharmacological and toxicological data?* Drug Safety, 1998. **18**(5): p. 369-381.
8. Cassidy, S. and J. Henry, *Fatal toxicity of antidepressant drugs in overdose.* British medical journal (Clinical research ed.), 1987. **295**(6605): p. 1021.
9. Geulayov, G., et al., *Relative toxicity of benzodiazepines and hypnotics commonly used for self-poisoning: An epidemiological study of fatal toxicity benzodiazepines.* Clinical Toxicology, 2003. **41**(7): p. 975-980.

11. Buckley, N. and P. McManus, *Fatal toxicity of drugs used in the treatment of psychotic illnesses.* The British Journal of Psychiatry, 1998. **172**(6): p. 461-464.

12. Mellish, L., et al., *The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers.* BMC Research Notes, 2015. **8**(1): p. 634.

13. Whyte, I.M., N.A. Buckley, and A.H. Dawson, *Data collection in clinical toxicology: are there too many variables?* Clinical Toxicology, 2002. **40**(3): p. 223-230.

14. Islam, M., et al., *Twenty‐year trends in benzodiazepine dispensing in the Australian population.* Internal Medicine Journal, 2014. **44**(1): p. 57-64.

15. Rossi, S., S. Hurley, and A. Vitry, *Australian medicines handbook*. 2018, Adelaide: Australian Medicines Handbook Pty Ltd.

16. Buckley, N.A., et al., *A prospective cohort study of trends in self‐poisoning, Newcastle, Australia, 1987–2012: plus ça change, plus c'est la même chose.* Medical journal of Australia, 2015. **202**(8): p. 438-442.

17. Volpe, D.A., et al., *Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs.* Regulatory Toxicology and Pharmacology, 2011. **59**(3): p. 385-390.

18. King, L.A. and J.M. Corkery, *An index of fatal toxicity for new psychoactive substances.* Journal of Psychopharmacology, 2018. **32**(7): p. 793-801.

19. Ojanperä, I., P. Kriikku, and E. Vuori, *Fatal toxicity index of medicinal drugs based on a comprehensive toxicology database.* International Journal of Legal Medicine, 2016. **130**(5): p. 1209-1216.

20. Pilgrim, J.L., M. McDonough, and O.H. Drummer, *A review of methadone deaths between 2001 and 2005 in Victoria, Australia.* Forensic Science International, 2013. **226**(1-3): p. 216-222.

21. Handley, S. and R. Flanagan, *Drugs and other chemicals involved in fatal poisoning in England and Wales during 2000–2011.* Clinical Toxicology, 2014. **52**(1): p. 1-12.

22. Roxburgh, A., et al., *Trends in fentanyl prescriptions and fentanyl‐related mortality in A ustralia.* Drug and alcohol review, 2013. **32**(3): p. 269-275.

23. McKeown, H.E., et al., *Is Australia ready for fentanyl?* Science & Justice, 2018. **58**(5).

24. Blanch, B., S. Pearson, and P. Haber, *An overview of the patterns of prescription opioid use, costs and related harms in Australia.* British Journal of Clinical Pharmacology, 2014. **78**(5): p. 1159-66.

25. Koski, A., E. Vuori, and I. Ojanperä, *Newer antidepressants: evaluation of fatal toxicity index and interaction with alcohol based on Finnish postmortem data.* International Journal of Legal Medicine, 2005. **119**(6): p. 344-348.

26. Reith, D., et al., *Features and toxicokinetics of clozapine in overdose.* Therapeutic Drug Monitoring, 1998. **20**(1): p. 92-97.

27. Griffiths, C. and R. Flanagan, *Fatal poisoning with antipsychotic drugs, England and Wales 1993-2002.* Journal of Psychopharmacology, 2005. **19**(6): p. 667-674.

28. Brett J, K.E., Daniels B, Buckley NA, Schneider C, Nassir A, Zoega H, McLachlan AJ, Pearson SA., *Psychotropic medication use in Australia, 2007 to 2015: Changes in annual incidence, prevalence and treatment exposure.* Australian & New Zealand Journal of Psychiatry, 2017. **51**(10): p. 990-9.

29. Brett, J., et al., *Psychotropic polypharmacy in Australia, 2006 to 2015: a descriptive cohort study.* British Journal of Clinical Pharmacology, 2017. **83**(11): p. 2581-8.

30. Berling, I., N.A. Buckley, and G.K. Isbister, *The antipsychotic story: changes in prescriptions and overdose without better safety.* British Journal of Clinical Pharmacology, 2016. **82**(1): p. 249-254.

31. Buckley, N., et al., *Relative toxicity of benzodiazepines in overdose.* Brittish Medical Journal 1995. **310**(6974): p. 219-221.

32. Degenhardt, L., et al., *Crystalline methamphetamine use and methamphetamine‐related harms in Australia.* Drug and Alcohol Review, 2017. **36**(2): p. 160-170.

33. Chomchai, C. and S. Chomchai, *Global patterns of methamphetamine use.* Current Opinion in Psychiatry, 2015. **28**(4): p. 269-274.

34. King, L.A. and J.M. Corkery, *An index of fatal toxicity for drugs of misuse.* Human Psychopharmacology: Clinical and Experimental, 2010. **25**(2): p. 162-166.

35. Dwyer, P. and I. Jones, *Fatal self-poisoning in the UK and the paracetamol/dextropropoxyphene combination.* Human & Experimental Toxicology, 1984. **3**(1 suppl): p. 145s-174S.

36. Buckley, N.A., et al., *Correlations between prescriptions and drugs taken in self-poisoning. Implications for prescribers and drug regulation.* Medical Journal of Australia, 1995. **162**(4): p. 194-197.

37. Karanges, E.A., et al., *Trends in opioid utilisation in Australia, 2006‐2015: Insights from multiple metrics.* Pharmacoepidemiology and Drug Safety, 2017.

Table 1: Demographics of National Coronial System (NCIS) study population and Hunter Area Toxicology Service (HATS) study populations.

	NCIS Demographics (n=444 deaths)	HATS Demographics (n=11907 admissions)
	n (%)	n (%)
Gender		
Male	279 (62.8)	4211 (35.4)
Female	165 (37.2)	7671 (64.4)
Transgender	0	25 (0.2)
Age (years)		
≤ 25	31 (7)	3516 (29.5)
> 25 to ≤ 35	96 (21.6)	2773 (23.3)
> 35 to ≤ 45	123 (27.7)	2662 (22.4)
> 45 to ≤ 55	125 (28.2)	1793 (15.1)
> 55	69 (15.5)	1163 (9.8)
Death location		
At Home	332 (74.8)	NA
In Hospital	73 (16.4)	NA
Other	39 (8.8)	NA

Figure 1: Flow diagram of poisoning death study population derived from National Coronial Information System

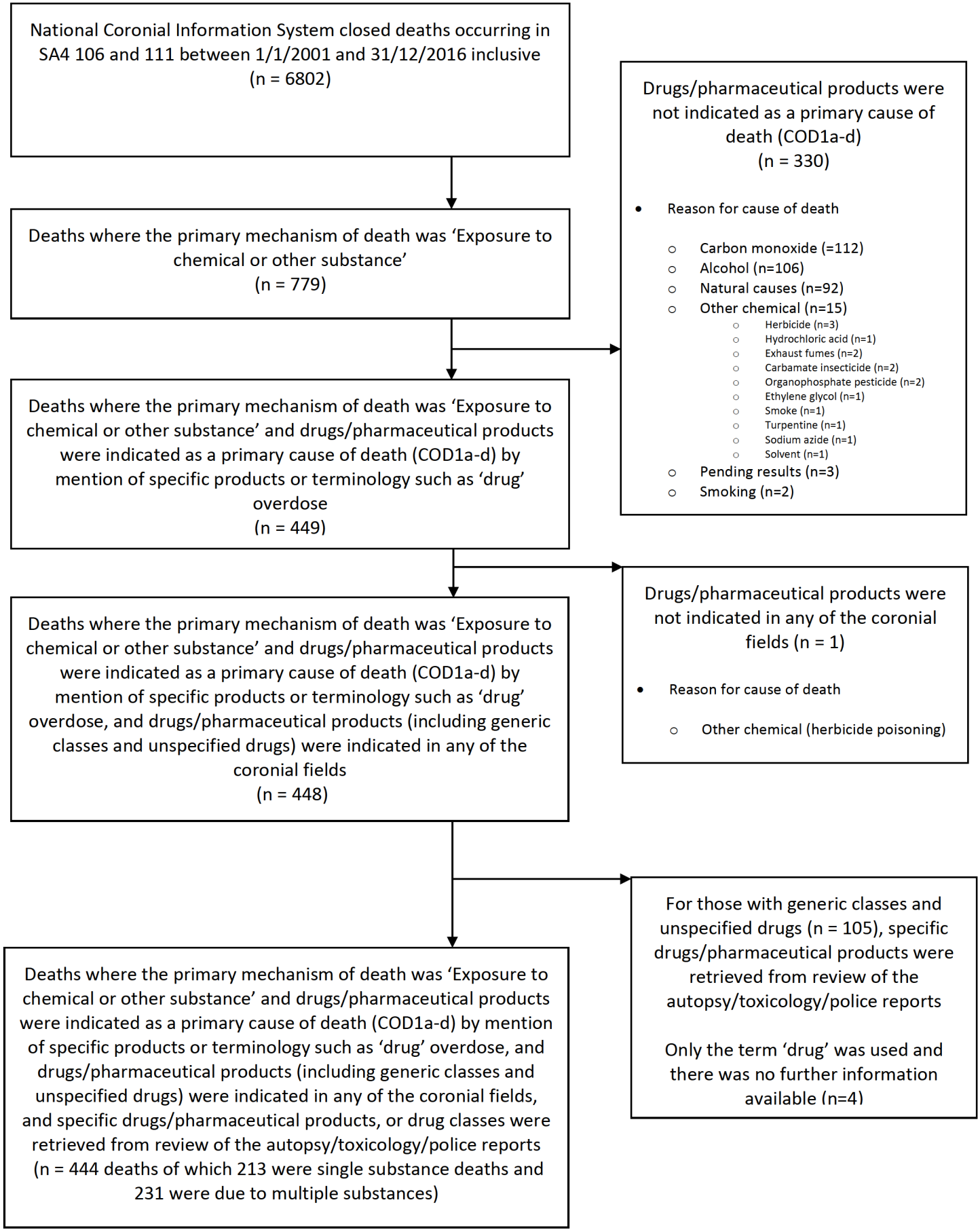
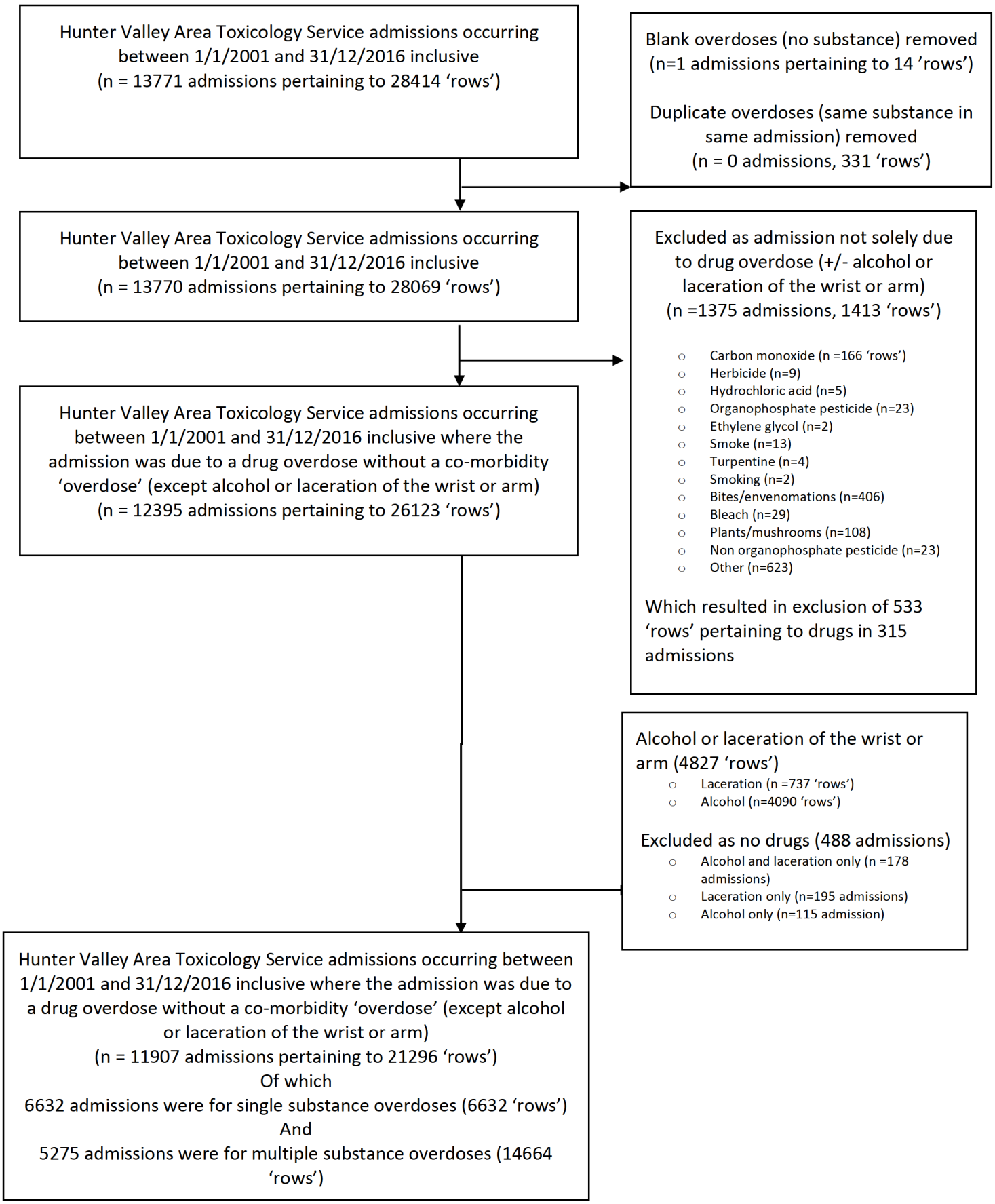


Figure 2: Flow diagram of overdose study population derived from Hunter Area Toxicology Service



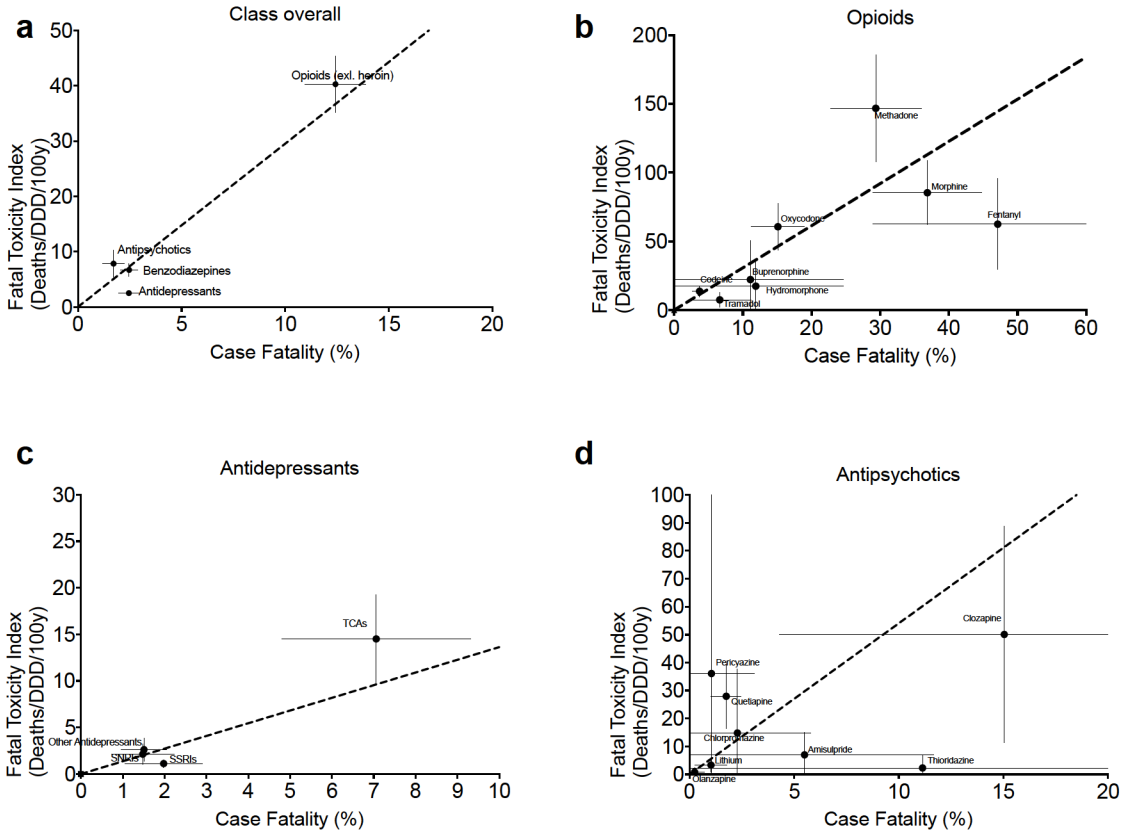


Figure 3: Fatal Toxicity Index (FTI) versus Case Fatality (CF) for (a) Class overall, (b) Opioids, (c) Antidepressants and (d) Antipsychotics. Dashed lines represent extrapolations of the median FTI and CF for each class in question.

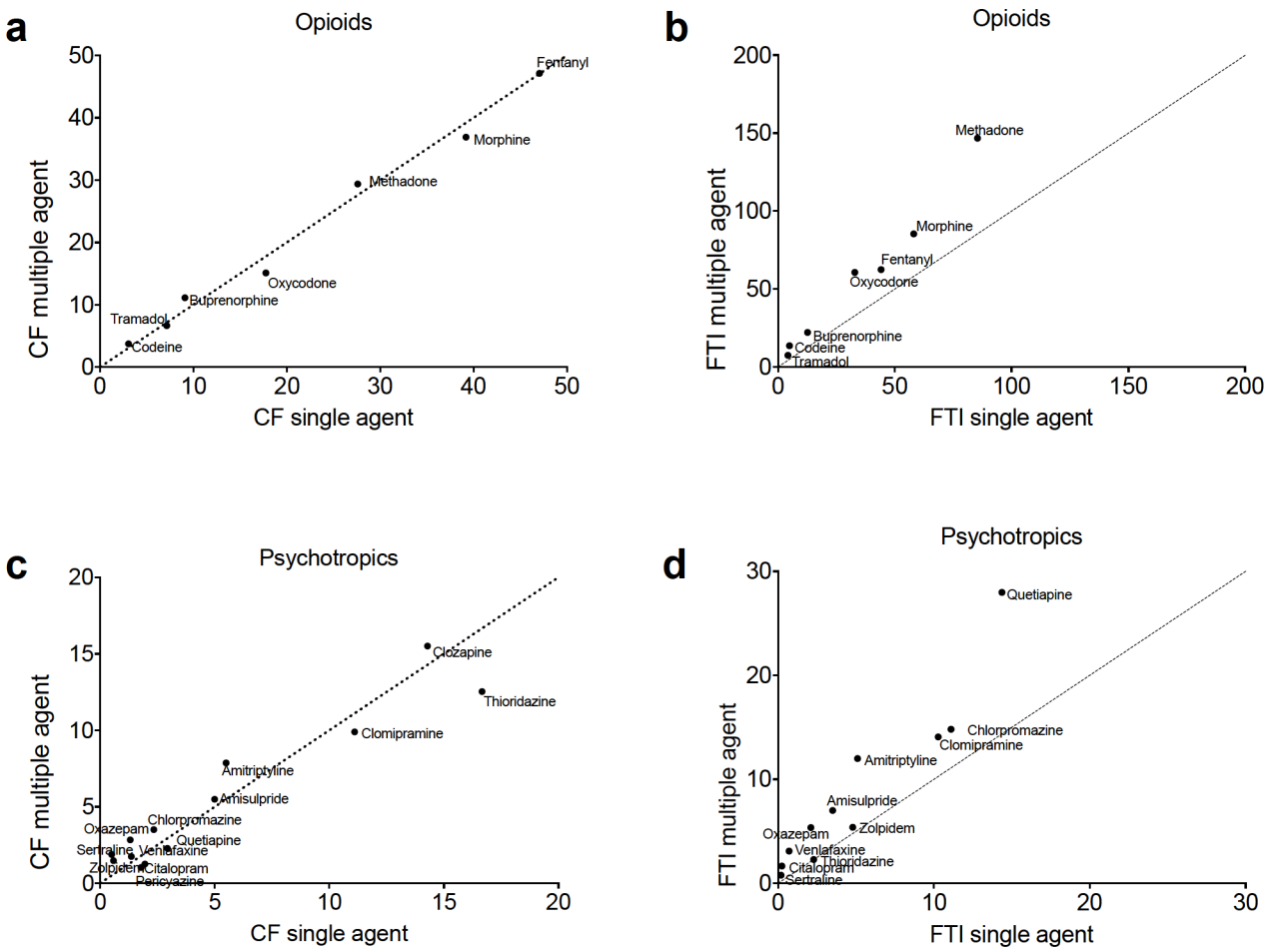


Figure 4: Multiple agent versus single agent case fatality (CF) and fatal toxicity index (FTI) for (a)&(b) Opioids and (b)&(c) Psychotropics.

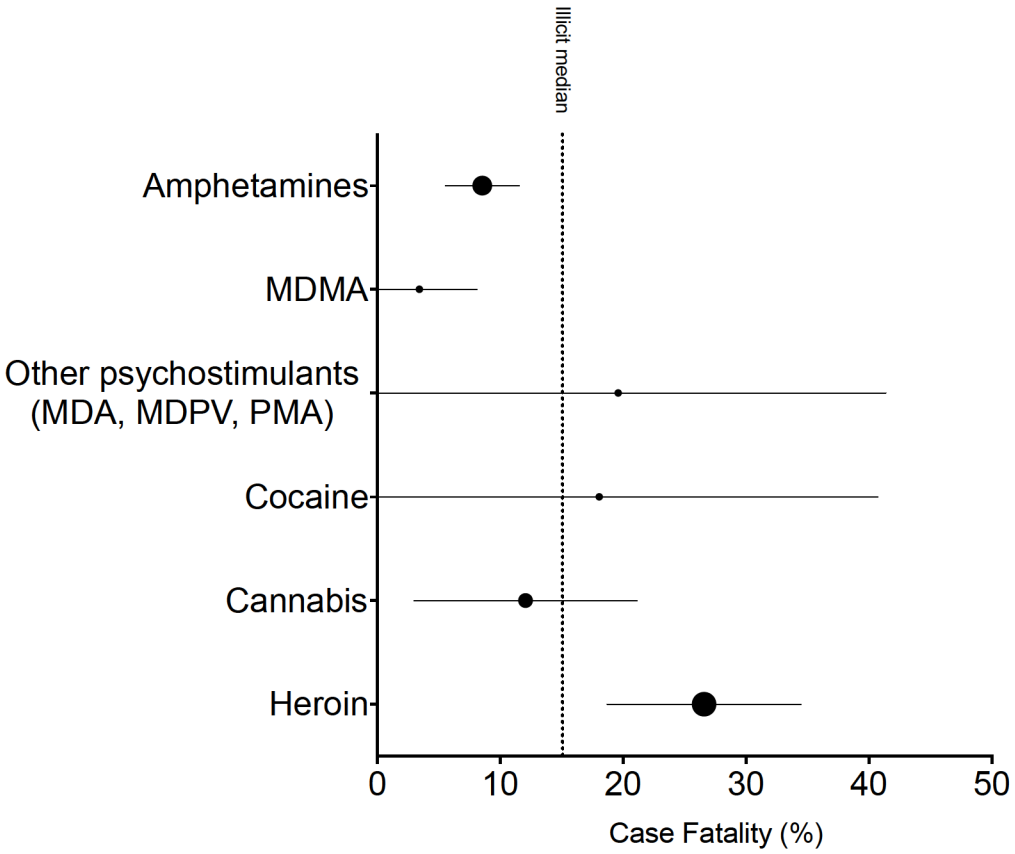


Figure 5: Case fatality for illicit substances.
Size of point proportional to number of deaths.