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Title Page

Title

Emerging Drugs Network of Australia: a toxicosurveillance system of illicit and emerging drugs in the Emergency Department

Running Title

Emerging Drugs Network of Australia

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Acknowledgments

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Author Contributions

All lead authors contributed to the study design and development of the national minimum dataset. JLS drafted the manuscript, which all authors have revised and approved.

Competing Interests

None declared.

Ethics Approval

Ethics approval under National Mutual Acceptance has been granted by the South Metropolitan Health Service Human Research Ethics Committee (RGS0000003673).

Keywords

Emergency medicine; toxicology; illicit drug use; novel psychoactive substances; harm reduction

TITLE

Emerging Drugs Network of Australia: a toxicosurveillance system of illicit and emerging drugs in the Emergency Department.

ABSTRACT

Objective

The unprecedented rise in synthetic drugs, many containing unknown toxic agents, has made timely analytical diagnosis more difficult, and has reduced the confidence of clinicians providing Emergency Department (ED) management to this population of patients. This has also impacted the quality of evidence informing harm reduction responses. The Emerging Drugs Network of Australia (EDNA) brings together emergency physicians, toxicologists and forensic laboratories to establish a standardised ED toxicosurveillance system in Australia.

Methods

Blood analysis of intoxicated patients will be conducted by forensic laboratories to enable precise identification of the substances causing acute toxicity. This will be linked with clinical data collected at the time of ED presentation to enable analysis of the clinical effects and outcomes associated with different illicit and emerging drugs. Toxicological and clinical data collected across sentinel sites will align with a nationally endorsed minimum dataset.

Results

EDNA's collaborative network will establish a national system of surveillance and reporting of illicit and emerging drugs causing acute toxicity. Standardisation of data collection recorded in a national clinical registry will provide more robust data on epidemiology and associated harms. This will facilitate the translation of clinical and toxicological evidence into timely, appropriate harm reduction and policy.

Conclusion

Our work represents a collaborative response to calls for more sophisticated data on emerging drug trends in Australia. EDNA will improve coordination between clinicians and analytical services by way of its standardised approach to surveillance and reporting.

KEYWORDS

Emergency medicine; toxicology; illicit drug use; novel psychoactive substances; harm reduction

MAIN TEXT

Introduction

Illicit drug use is a challenge to emergency departments (EDs) and associated harms are increasing. Rapid emergence of new synthetic drugs,[1,2] and increasing illegal manufacturing and non-medicinal use of pharmaceuticals,[3,4] have made effective detection, clinical management and public health responses difficult. This is a dynamic global phenomenon, with approximately one new novel psychoactive substance (NPS) emerging weekly. Since 2009, over 1000 individual NPS have been reported to the United Nations Office of Drug Control Early Warning Advisory on NPS (UNODC EWA).[4] Increasing interest in online and app-based drug markets, and shifts towards easily transported, cheaper and higher potency substitutes are of particular concern.[5,6] Australia is vulnerable to these trends given the absence of standardised surveillance systems to rapidly detect, monitor and disseminate timely information on new and emerging drugs.

In EDs, toxicology tests are not routinely performed on illicit drug-related presentations. This is noteworthy because our data indicate that 6.9% of ED presentations are illicit drug-related, and 9.2% of all ED presentations have a history of illicit drug use.[7] Unfortunately, this occurs in a context already limited by reporting and coding systems (i.e. ICD codes) that fail to capture the diversity of drugs causing acute toxicity.[7,8] Presentations are often coded based on clinical features rather than the drug involved. This carries important implications on the quality of data available on overdose and drug toxicity, and has resulted in a substantial underestimation of healthcare resource utilisation related to illicit drugs.[7] Targeted research in

this group, including laboratory confirmation of drugs, would provide much needed insight into the drugs involved in ED presentations, their clinical patterns of toxicity and associated harms.

The inability to measure these drugs in hospitalisations or deaths in a rapid manner has also precluded Australia's involvement in important global networks such as the UNODC EWA.[2,9] Growing international evidence highlights the need for multidisciplinary approaches and improved collaboration between EDs, forensic laboratories and public health authorities to enable earlier identification of drug-related threats.[2,8,10-14] This has led to the development of early warning systems (EWS) in several regions and globally.[2,9] The demonstrated evidence of these systems to facilitate rapid exchange and validation of information between agencies and inform tactical responses to emerging drug problems has led to them to be regarded as international best practice.

In Australia, proof-of-concept work in the Western Australian Illicit Substance Evaluation (WISE) study established the feasibility of this approach.[15] Access to state-of-the-art analytical instrumentation and expertise provided by ChemCentre WA enabled identification of the specific drugs causing harm, their quantitative levels and associated clinical effects across more than 600 ED patients. Similar approaches with varying methodology have also been successfully implemented by the EDNA Investigator team in South Australia (South Australian Drug Early Warning System - Admission Blood Psychoactive Substance Testing),[16] NSW (Prescription, Recreational and Illicit Substance Evaluation - PRISE)[17] and Victoria (Emerging Drugs Network of Australia VIC).

Lessons learnt from these state-based initiatives and similar projects overseas[11,13,14,18] highlight the importance of collaborative effort and approaches that standardise data collection, surveillance and reporting of illicit drug-related presentations. For example, NSW has already made significant progress as part of PRISE to enable rapid translation of toxicology results from patients requiring ICU care, into drug alerts disseminated by the NSW Ministry of Health.[19]

This paper outlines the methodological approach taken to establish a national ED based toxicosurveillance system in Australia. The Emerging Drugs Network of Australia (EDNA) brings together emergency physicians, toxicologists and forensic laboratories, with assistance from existing specialist networks such as state poisons information centres, the Toxicology And Poisons Network Australasia, and the Toxicology Specialist Advisory Group. EDNA will build a national repository of clinical and toxicological data on illicit and emerging drugs involved in ED presentations, including their clinical effects, treatment approaches and outcomes. We aim to:

1. Develop standardised testing protocols with high sensitivity to identify new and emerging NPS, detect changes in patterns of use and identify highly toxic psychoactive substances;
2. Determine clinical patterns of toxicity associated with the illicit drugs and NPS involved in ED presentations, and how these relate to outcomes, including resource implications.
3. Support EWS responses in each state by sharing clinical and toxicological information across key agencies to inform public health and harm reduction policy.

Methods

Study Design and Setting

This is a national multi-centre prospective toxicosurveillance system of illicit drug-related ED presentations. The intention is for EDNA to serve as an ongoing national surveillance system. The initial three years of the project (2021-2023) will prioritise implementation of uniform mechanisms to collect, store and analyse blood samples from eligible patients; and clinical data collection by EDs using a nationally endorsed dataset. The network of sentinel hospitals and forensic laboratories contributing to EDNA are presented in Figure 1. Where sufficient resources and capacity exist, additional EDs will be recruited in each state to increase the representativeness of surveillance data.

Population and Ethical Considerations

Patients presenting with severe and/or unusual clinical features associated with stimulant, hallucinogenic or opioid poisoning and/or patients presenting as part of a suspected cluster of poisonings, and where a blood test and/or intravenous cannulation is required as part of usual care, will be sought for inclusion into the registry. As part of EDNA, a cluster is defined as two or more cases with: (i) exposure to the same substance; AND (ii) geographically or situationally co-located; AND (iii) ED presentations within 48 hours of each other. Patients will be excluded from the registry if intravenous access is not required as part of usual care, or if the treating clinician considers symptoms are predominantly related to causes other than acute illicit drug effects (e.g. pure alcohol intoxication).

Ethics approval under National Mutual Acceptance has been granted by the South Metropolitan Health Service Human Research Ethics Committee (RGS0000003673) for the establishment of EDNA's de-identified national registry. This includes waiver of consent as per Section 2.3.10 of the National Statement on Ethical Conduct in Human Research, 2007 (updated 2018).[20] It will be impracticable to obtain consent from eligible patients under

the influence of illicit drugs as they are intoxicated and of altered mental state and thus, are unable to provide valid consent at the time of enrolment. Following patients post-discharge presents a privacy risk for those who do not wish to divulge that they had potentially taken illegal drugs. Finally, the de-identified nature of the registry means there will be no ability to identify or obtain retrospective consent of any patient.

Data Collection and Management

EDNA will collect a nationally endorsed minimum dataset of illicit drug use involved in ED presentations at sentinel hospitals. Blood samples from eligible patients will be collected as soon as possible after arrival in the ED. Detailed protocols for sample collection and storage have been published.[15,16] Samples collected in the context of a suspected cluster of poisonings will be sent for immediate analysis to the relevant forensic laboratory. Confirmation of the agent(s) involved in the ED presentations will be made available to the lead local clinical investigator.

Clinical information relating to the current episode of acute toxicity will be collected retrospectively from medical records within one month of the patient's presentation. This approach was considered essential to reduce the burden on emergency clinicians and improve data quality and completeness. Data collection will be overseen by lead clinical investigators in each state, and supported by a national data manager.

EDNA's minimum dataset will capture key demographic, drug exposure, clinical and outcome variables associated with acute illicit drug and NPS toxicity. Each sentinel site will enter required minimum data into a secure, online data management system (REDCap) to enable web-based submission to the national registry. The national registry will be housed on

a secure server at Curtin University and managed by the Health Research and Data Analytics Hub. During this process, a unique REDCap identifier will be assigned to each patient record to ensure no identifiable information is held in the national registry. A data dictionary and collection guide will ensure consistent data collection and interpretation of clinical parameters across sites. When possible, elements and metadata specifications will align with existing national standards and terms (i.e. National Health Data Dictionary).

Sample Testing Protocols

Samples submitted to laboratories will be tested for a broad range of licit and illicit drugs, including synthetic cannabinoids, cathinones, designer opioids and other NPS. Most NPS can only be detected using specialised equipment and analytical expertise in forensic laboratories to rapidly identify previously unreported compounds. Specialised analytical instrumentation will be used such as Liquid Chromatography – Triple Quadrupole Mass Spectrometry (LCMS-QQQ), Liquid Chromatography – Quadrupole Time of Flight Mass Spectrometry (LCMS-QTOF) and Gas Chromatography – Triple Quadrupole Mass spectrometry (GCMS-QQQ), which provide capability to detect low dose – high potency drugs such as NBOMe and fentanyl analogues. De-identified toxicology results will then be linked to the patient's REDCap identifier to enable analysis of the clinical effects and outcomes associated with different illicit and emerging drugs.

The scope of substances included in testing protocols will provide high sensitivity to identify new and emerging NPS, changes in patterns of use and identify highly toxic psychoactive substances. Quantitative levels of substances detected will be carried out for cases of interest such as unusual clinical presentations or clusters of poisonings.

Statistical Analysis

EDNA's toxicosurveillance system will require sufficient data and time to develop complex analyses. This is particularly true given the unique characteristics of our population (illicit drug users requiring emergency care), setting (sentinel EDs) and exposure of interest (illicit drugs, including identification of new and low prevalence NPS). Initial analyses will be predominantly descriptive, including tabulating demographic characteristics (age and sex) and for specific drugs. This will also enable reporting of key outputs such as the number and type of new NPS identified from toxicological analyses.

Geographical and time trends in drugs identified will be examined annually. Patterns in clinical features (e.g. temperature, conscious state), management (e.g. use of sedation) and outcomes (e.g. discharged home, admitted to ICU) will be explored between drug groups using chi-square test or Fisher's exact test (dichotomous variables) or logistic regression (continuous variables) to identify potential associations. Examination of outcomes will also enable exploration of resource implications for different drugs, such as length of stay (LOS) in ED and LOS in hospital, using truncated negative binomial regression.

Results

A conceptual roadmap detailing research activities, outputs and outcome indicators in the context of EDNA's primary research aims is provided in Figure 2. This high-level schematic links research activities (what we will do) with intended outcomes (what we will achieve) at a national level. Outcome indictors listed under each aim will provide a more granular approach to monitoring and reporting progress towards each aim.

Clinical data relating to acute toxicity from the drug exposure, and a standardised approach to blood sampling and analysis, will provide a systematic and robust means of collecting, monitoring and analysing patient-level data across the country. Together, these elements form the basis of EDNA's national minimum dataset; an agreed set of data elements for mandatory collection and reporting by sentinel sites. The scope of EDNA's national minimum dataset is outlined in Table 1 (Appendix 1).

Discussion

EDNA represents a coordinated national response to calls for more sophisticated data on emerging drug trends. The Prime Ministerial National Ice Taskforce and the accompanying Council of Australian Governments National Ice Action Strategy both called for better data on emerging drug trends to inform treatment approaches and harm reduction strategies such as an EWS.[21] Recommendations put forward by the Victorian Parliament's Inquiry into drug law reform include (Recommendation 7), "establish an early warning system to enable analysis, monitoring and public communications about new psychoactive substances and other illicit substances of concern."[22] Similarly, the WA Methamphetamine Taskforce's Recommendation 53: "Department of Health continues the WA Illicit Substance Evaluation Study as an ongoing valuable EWS for rapid identification and reporting of conventional and novel psychoactive drugs causing toxicity in patients."[23] Finally, recommendations from a recent Coronial Inquest into the death of six patrons at music festivals in NSW: "That the NSW Department of Health contributes to the Emerging Drugs Network of Australia by sharing the information that is obtained through the NSW Health's enhanced surveillance in ED and ICU settings."[24] This recommendation was supported by the NSW Special Commission of Inquiry into crystal methamphetamine and other amphetamine type stimulants.[25]

From a clinical standpoint, our novel approach of utilising a specific blood test to identify the causative agent(s) of illicit drug poisonings will enable clinicians to draw a parallel between patients' symptoms and specific substance(s) detected from forensic analysis. This is a unique opportunity to evaluate current management approaches. Evidence of best practice in this area is limited, and is critical to building the confidence and capacity of clinicians to intervene more effectively.[12]

Standardised protocols for collecting, storing and analysing blood samples will provide forensic laboratories with a unique opportunity to continuously update their drug profiling database. Historically, progress in this field has been hampered by variations in testing methodologies and drug nomenclature across jurisdictions, and limited information sharing between laboratories. Now, information sharing at a national level has commenced under the banner of EDNA, through the Toxicology Specialist Advisory Group.[26] This preliminary work has resulted in the development of an extensive library of emerging drugs of concern and the methods required to improve detection. Over time, this will support the development, validation and routine use of new analytical techniques.

The key advantage of EDNA will be the translation of clinical and toxicological evidence into timely and appropriate public health and harm reduction responses. Collaborations between local EDs and forensic laboratories will provide a vital mechanism for disseminating objective information to frontline services and public health authorities on emerging drug-related threats. Information sharing to the general public and user groups will be supported by strong partnerships with key health authorities in each jurisdiction, community-based services

and consumer representatives. This means that information will be made available across the entire spectrum: from individual drug users to government policy.

It will also inform the development of the National Prompt Response Network, which is a unique data sharing platform being developed by the National Centre for Clinical Research on Emerging Drugs to provide a comprehensive, evidence-base of illicit and emerging drug use and associated community level impacts. This system intends to draw information from Police, Coronial data, user groups and the general public.

Conclusion

EDNA will integrate clinical and laboratory data to strategically identify the drugs responsible for acute harm in multiple Australian jurisdictions. The national distribution of EDNA collaborators will support rapid information sharing across the country to and from users, clinicians and health authorities. Finally, EDNA's collaborative national approach will support coordinated local and national substance use public health policy.

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Author Contributions

All authors contributed to the study design and development of the national minimum dataset. JLS drafted the manuscript, which all authors have revised and approved.

Competing Interests

None declared.

Ethics Approval

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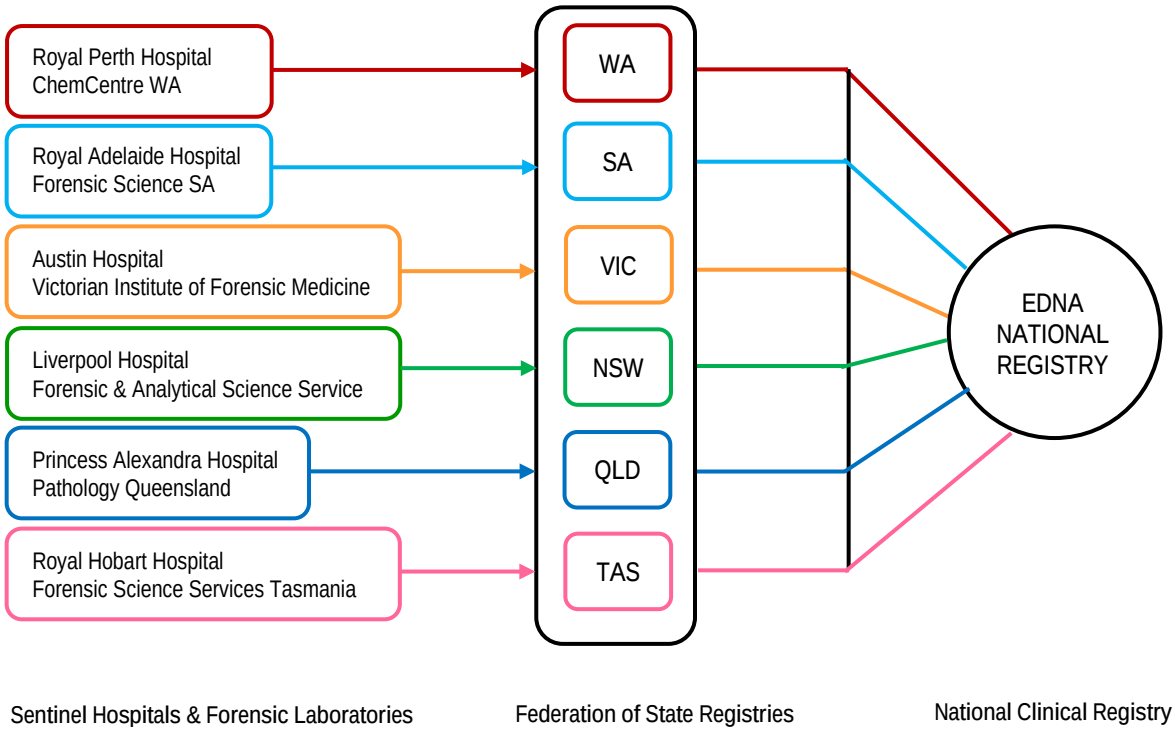

Figure 1. Sentinel Hospitals and Forensic Laboratories Contributing to EDNA

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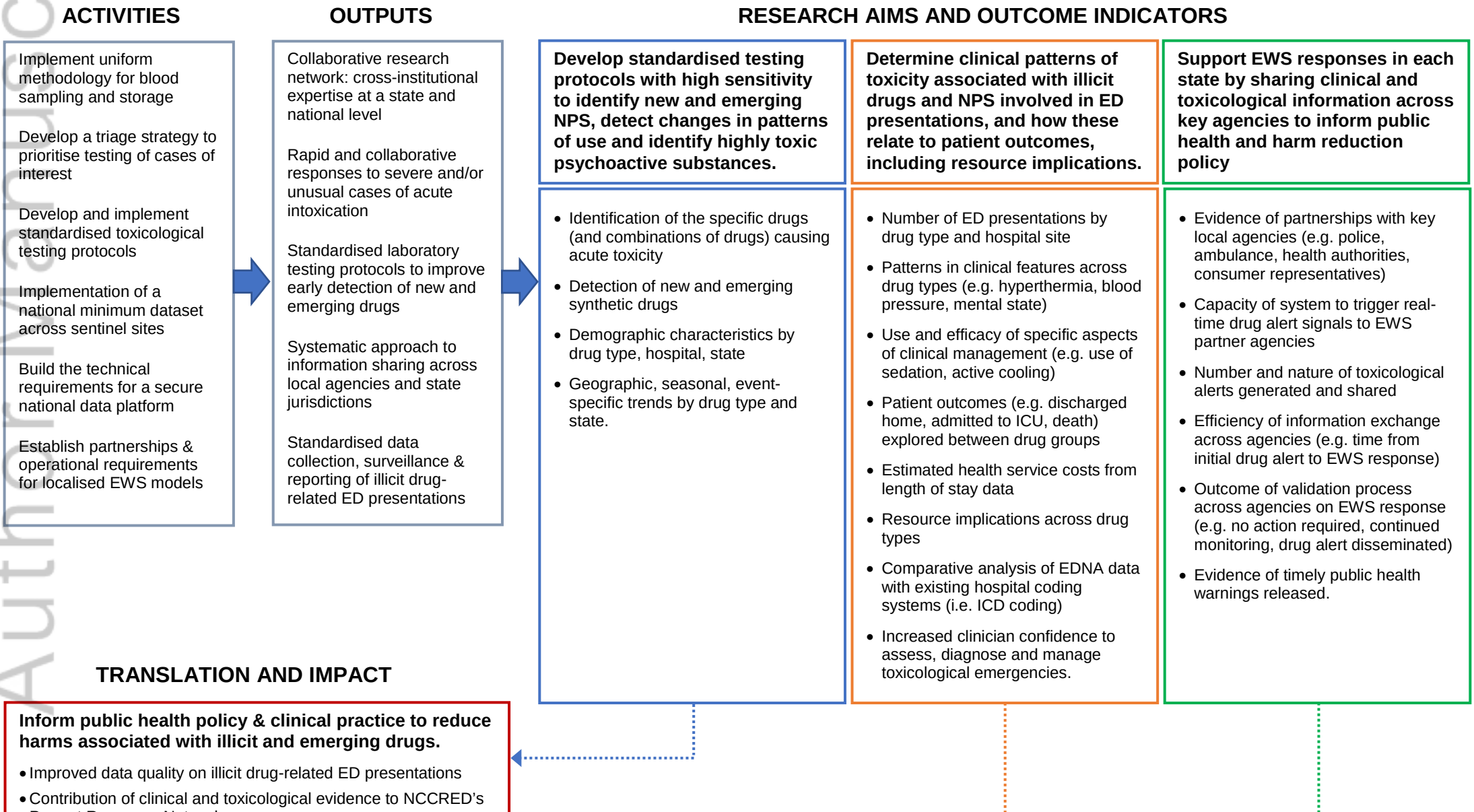

Figure 2. EDNA Outcomes Measurement Framework

Table 1. EDNA National Minimum Dataset – Key Data Elements

REDCap Instrument	Data Element
ED Presentation	Triage date / time Age (years) Sex (checkbox) Mode of arrival to ED (checkbox) Australasian Triage Scale (checkbox) Patient part of cluster* (checkbox)
Drug Exposure	Source of reported drug exposure • Patient self-report (checkbox) • Other source(s) (e.g. friend/family; paramedic; police) (checkbox) Patient reported drug use for intent of self-harm (checkbox) Setting of drug use (checkbox) Postcode of drug use if known Reported drug exposure(s) (checkbox) Route of administration for drug exposure (checkbox) Known regular medications (text)
First Recorded Observations	Setting of first recorded observations (e.g. pre-hospital or hospital) (checkbox) First observations pre sedation / pharmaceutical intervention (checkbox) First recorded vitals: • Respiratory rate (value) • Heart rate (value) • Systolic BP (value) • Diastolic BP (value) • Temperature (value) • GCS (E/V/M scores = auto-calculated total) Pupil size (value) Blood sugar level (value) Mental state (pre-hospital or at presentation – prior to pharmaceutical intervention)

Worst recorded complications related to drug exposure – first 24 hrs of acute toxicity	Hyperthermia (≥ 38°C) (checkbox) → if Y, max temp (value) Hypothermia (≤ 35°C) (checkbox) → if Y, min temp (value) Tachycardia (HR ≥100bpm) (checkbox) → if Y, max heart rate (value) Bradycardia (HR ≤ 60bpm) (checkbox) → if Y, min heart rate (value) Arrhythmia (checkbox) → if Y, specify type (text) Cardiac Arrest (checkbox) Hypertension (SBP ≥ 160mmHg) (checkbox) → if Y, max systolic BP (value) Hypotension (SBP ≤ 90mmHg) (checkbox) → if Y, min systolic BP (value) Hyperventilation (RR ≥ 30brpm) (checkbox) → if Y, max resp rate (value) Hypoventilation (RR ≤ 6brpm) (checkbox) → if Y, min resp rate (value) Apnoea (checkbox) Minimum GCS (pre-sedation) → (E/V/M scores = auto-calculated total) Seizure (checkbox) Other clinical features: • Clonus (checkbox) → if Y, number of beats (value) • Vomiting (checkbox) • Diarrhoea (checkbox) • Urinary retention (checkbox) • Abnormal sweating (checkbox) • Dystonia (checkbox) • Hypertonia (checkbox) • Hyperreflexia (checkbox)
Biochemical or Organ Injury	Acute kidney injury (creatinine ≥ 1.5 x baseline or peak level ≥ 120umol/L males and 100umol/L females) → if Y, peak creatinine (value) Acute liver injury (ALT ≥ 1000) → if Y, ALT / AST (value) Rhabdomyolysis (CK ≥ 1000) → if Y, peak creatinine kinase (value) Aspiration pneumonia/pneumonitis (checkbox) Hypoxic brain injury (checkbox) Persistent psychotic symptoms ≥ 24 hrs (checkbox) Other Complication (specify) → if Y, specify other complications (text)
Management	**Pre-hospital interventions** (checkbox options listed) - CPR - Adrenaline - Intubation - IV Dextrose - Droperidol - Ketamine - Benzodiazepines → if Y, specify type (checkbox) - Morphine - Naloxone → if Y, specify route of administration (checkbox) + total dose (value) - Olanzapine - Physical restraint - None provided - Other

	Hospital – pharmaceutical (checkbox) • If Y to Benzodiazepines, specify type (checkbox) • If Y to Naloxone, specify route of administration (checkbox) • If Y to Naloxone, specify total dose *in first hour* (value) **Hospital – non-pharmaceutical** (checkbox options listed) - CPR - Activated charcoal - Active cooling - Dialysis for renal support - Dialysis for toxin elimination - ECMO - Intubation - Non-invasive ventilation - Physical restraint - Whole bowel irrigation - None provided - Other
Outcome	ED Disposition (checkbox) ED discharge date / time ED LOS (hours - calculated value) ICU admission (checkbox) → if Y: • ICU admission date / time • ICU discharge date / time • ICU LOS (hours - calculated value) Hospital discharge date / time (if relevant) Hospital LOS (calculated value) (if relevant) Final discharge location (checkbox)
Analytical Results (laboratory)	Ethanol Concentration (value and unit) Name of drug(s) detected from lab results Concentration level(s) if available (e.g. GHB)

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All lead authors contributed to the study design and development of the national minimum dataset. JLS drafted the manuscript, which all authors have revised and approved.

Competing Interests

None declared.

Ethics Approval

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