Institution: The University of Edinburgh		
Unit of Assessment: 1		
Title of case study: I: A shorter treatment regimen for patients with paracetamol overdose reduces adverse drug reactions and saves NHS resources		
Period when the underpinning research was undertaken: 2010 – 2019		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
James Dear	Chair of Clinical Pharmacology	2005 – present
Nick Bateman	Honorary Professor	1998 – present
Michael Eddleston	Personal Chair of Clinical Toxicology	2005 – present
David Webb	Christison Chair of Therapeutics and Clinical Pharmacology	1990 – present
Alasdair Gray	Chair of Emergency Medicine	2001 – present
Period when the claimed impact occurred: 2015 – 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Underpinning Research: UoE-led research developed "SNAP", a shorter 12-hour treatment regimen with the antidote acetylcysteine for paracetamol overdose, and in a randomised clinical trial found it to result in fewer adverse drug reactions (ADRs) and be as effective at preventing liver injury as the standard 21-hour treatment.

Significance and Reach of Impact: TOXBASE, the UK's primary authority on poisoning cases, was updated to recommend SNAP in April 2020, meaning that all hospital admissions for paracetamol overdose can now be treated according to the SNAP regimen; by December 2020, the SNAP entry on TOXBASE had been accessed 3,913 times from 185 hospitals across the UK. The SNAP regimen has been in routine use in 100% of health boards in mainland Scotland since July 2020.

The SNAP regimen reduces the rate of ADRs from 11% to 2%, meaning that ADRs were averted in 352 patients among the 3,913 patients for whom the TOXBASE entry was accessed. Use of SNAP is also associated with a shorter length of hospital stay, freeing NHS beds sooner and resulting in cost savings of GBP180 per patient. With SNAP now available to use for all 50,000 annual paracetamol overdose admissions, this can translate to NHS savings of up to GBP9,000,000 every year.

2. Underpinning research

The Challenge: Current treatment against paracetamol overdose is effective but problematic

Paracetamol (acetaminophen) overdose is one of the most common reasons for emergency hospital attendance and the leading cause of acute liver failure in the Western world. In the UK, it results in over 50,000 acute hospital admissions and is the direct cause of death of more than 200 people per year.

Patients admitted to hospital are treated with the antidote acetylcysteine (NAC). This was shown in the 1970s to be highly effective at preventing liver injury, and essentially the same 21-hour treatment regimen has been used ever since, even though no formal dose-ranging studies had ever been undertaken to define the optimal dosing strategy.

Despite its effectiveness, the 21-hour treatment regimen is known to carry major disadvantages: first, it is associated with a high incidence of ADRs, typically nausea, vomiting

and anaphylactoid reactions. Second, medication errors can occur because the regimen is complex, consisting of three different sequential weight-related doses of NAC. Third, the length of the treatment leads to significant hospital bed occupancy (around 47,000 bed days per year in England alone).

Shorter treatment regimen "SNAP" results in fewer ADRs

To address these problems with the 21-hour regimen**,** University of Edinburgh researchers used pharmacokinetic modelling to develop a shorter 12-hour NAC regimen, called the Scottish and Newcastle Anti-emetic Pre-treatment for Paracetamol Poisoning ("SNAP") regimen. This was designed to deliver the same total licensed dose of NAC as the 21-hour regimen, but without the very high early blood NAC concentrations that are associated with ADRs [3.1].

The SNAP regime was tested in a UoE-led double-blind randomised controlled trial in three UK acute clinical units (Edinburgh, Newcastle and Aberdeen). The team randomised 222 patients to either the 21-hour regimen or the new SNAP regimen, and recorded the number of ADRs observed. The results showed that vomiting, retching and the need for antihistamines (to quell anaphylactoid reactions) at 2 hours were significantly reduced in the SNAP regimen compared with the 21-hour regimen (in 39/108 patients in SNAP group, versus 71/109 in the 21-hour group; $p<0.0001$) [3.2].

SNAP regimen is safe in routine clinical use

Following the trial, in 2015–16 the SNAP regimen was introduced into routine clinical practice in three Toxicology Centres of Excellence in the UK (Edinburgh, Newcastle and St Thomas' Hospital London). To assess the safety and efficacy of the SNAP regimen in this setting, the UoE team carried out an observational study comparing patient outcomes before and after the introduction of the SNAP regimen (n=1,488 before and 1,852 after).

This study found that the proportion of patients experiencing ADRs fell from 11% (163 patients) during the 21-hour regimen to 2% (37 patients) after the SNAP regimen was introduced. Thus, the use of SNAP prevented 167 ADRs that would have been expected if the 21-hour protocol had been used throughout. Importantly, there were no differences between the groups in liver function or other toxicity measures. Follow-up data gathered from the Scottish cohort using data linkage revealed that there were no cases of liver failure or death in any patients from either group, within 30 days of discharge [3.3].

Thus, in routine clinical use, the SNAP regimen shows equivalent efficacy in preventing liver injury to the standard 21-hour NAC regimen, while producing fewer adverse reactions in a shorter treatment time.

3. References to the research

[3.1] Thanacoody, HKR, Gray, A, Dear, JW, Coyle, J, Sandilands, EA, Webb, DJ, Lewis, S, Eddleston, M, Thomas, SH & Bateman, DN 2013, 'Scottish and Newcastle antiemetic pre-treatment for paracetamol poisoning study (SNAP)' *BMC Pharmacology & Toxicology*, vol. 14, pp. 20. doi: 10.1186/2050-6511-14-20

[3.2] Bateman, DN, Dear, JW, Thanacoody, HKR, Thomas, SH, Eddleston, M, Sandilands, EA, Coyle, J, Cooper, JG, Rodriguez, A, Butcher, I, Lewis, SC, Vliegenthart, ADB, Veiraiah, A, Webb, DJ, Gray, A. 2014, Reducing adverse effects from intravenous acetylcysteine treatment of paracetamol poisoning: a randomised controlled trial. *Lancet*. 383: 697-704. doi: 10.1016/S0140-6736(13)62062-0

[3.3] Pettie, JM, Caparrotta, T, Hunter, R, Morrison, E, Wood, DM, Dargan, PI, Thanacoody, HKR, Thomas, S, Elamin, MEMO, Francis, B, Webb, D, Sandilands, EA, Eddleston, M & Dear, J. 2019, 'Safety and efficacy of the SNAP 12 hour acetylcysteine regimen for the treatment of paracetamol overdose', *EClinicalMedicine*. doi: 10.1016/j.eclinm.2019.04.005

Funding: Scottish Chief Scientist Office (grant no CZB/4/722) for the SNAP trial

4. Details of the impact

Impact on clinical guidelines: SNAP was added to TOXBASE

The UK's primary clinical guidelines for treating all poisoning cases are published by the National Poisons Information Service (NPIS; the National Institute for Health and Care Excellence guideline on poisoning redirects to the NPIS website). NPIS maintains an online clinical toxicology database TOXBASE and its associated smartphone application, which is available to all clinicians in the UK and had 12,015 subscribers in 2018 [5.1]. On the 15th of April 2020, the SNAP regimen was added to TOXBASE as a protocol option for treating paracetamol overdose [5.2].

Impact on clinical practice

Following the update to TOXBASE, the SNAP regimen is now available to treat all cases of paracetamol overdose presenting at any UK hospital. Between the update on the 15th of April and the end of the REF period on the 31st of the December 2020, the SNAP dosing section of TOXBASE was accessed 3,913 times from 185 hospitals across the UK [5.3a, b, e]; the locations of accesses are illustrated below in **Figure 1**. In addition, within the same time period, the SNAP entry was accessed 162 times from 14 overseas countries, including the Republic of Ireland, Brazil, Australia, Poland and the Czech Republic [5.3c–e].

It is important to note that the number of accesses to the TOXBASE site is a significant underestimation of the true number of times the regimen has been used to treat a patient. Many hospitals produce hard copies of protocols for their staff to refer to and, once healthcare professionals have become accustomed to using the regimen, they may not need to log into the database each time they use it. For example, the Royal Infirmary of Edinburgh has accessed the SNAP page on TOXBASE only 3 times since it became live, but has used the regimen to treat all 412 paracetamol overdoses seen in that time [5.3e].

Figure 1.
Geographical spread of UK hospitals who have accessed the SNAP page of TOXBASE between the 15th of April and the 31st of December 2020

Source: NPIS [5.3]

By summer 2020, the SNAP regimen was in routine use in 100% of hospitals in mainland Scotland, and thus is being used to treat all approximately 5,700 annual admissions for paracetamol overdose in Scotland [5.4]. A consultant in the Greater Glasgow and Clyde health

board noted: "*Since* [summer 2020], *it's been very successful. The juniors and nursing staff prefer using it and patients have a shorter length of stay and fewer adverse reactions*." [5.4c].

Notably, 11 hospitals serving major UK cities including Manchester, Bristol and Nottingham had already adopted the SNAP regimen *prior* to the TOXBASE update. First among these were the Royal Infirmary of Edinburgh (September 2015), St Thomas' Hospital London (June 2016) and Royal Victoria Infirmary in Newcastle (October 2016); these 3 hospitals had by June 2018 treated a combined 2,246 patients according to the SNAP regimen [3.3]. They were followed by the Pennine Acute Hospital (serving Manchester; December 2018), North Bristol (May 2018), City Hospital Birmingham (summer 2019), Barnsley Hospital (December 2018), Chesterfield Royal Hospital (August 2018), Derby Royal (August 2018), Crosshouse Hospital Kilmarnock (summer 2019) and NHS Highland (summer 2019) [5.5].

Impact on health & welfare

Since the SNAP regimen reduces the rate of ADRs from 11% of patients to 2% [3.3] its adoption means that patients are less likely to experience highly unpleasant episodes of nausea, vomiting and anaphylactoid reactions. Thus, if the 3,913 UK accesses to the SNAP entry on TOXBASE each represented the presentation in the Emergency Department of a single patient, approximately 78 of these would have ADRs when treated with the SNAP regimen, whilst 430 patients would have experienced ADRs had they been treated with the 21-hour regimen instead. Thus, ADRs were averted in 352 patients in this calculation alone. The true number of averted ADRs will be significantly higher, given that clinicians do not need to access TOXBASE to use the SNAP regimen every time an overdose presents, but will likely refer to a printed copy kept in the Emergency Department.

The averted ADRs not only reduce the distress experienced by patients but also alleviate the additional burden that ADRs place on NHS resources through requiring nursing time to care for unwell patients and administer antihistamines.

Economic impact: Use of SNAP reduces length of hospital stay

Use of the SNAP regimen saves NHS resources through shortening the length of time patients stay in hospital. A formal health economic assessment was undertaken to quantify this reduction. The assessment used data from a clinical audit of all admissions for paracetamol overdose at the Royal Infirmary of Edinburgh, and compared two time periods: before the SNAP regimen was introduced (29th December 2014 to 26th September 2015, n=373), and after SNAP was introduced (27th September 2015 to 26th June 2016, n=450) [5.6]. Pricing categories based on Health Resource Group codes were assigned to patients depending on length of stay and presence or absence of adverse events.

This assessment found that the 21-hour regime was associated with more patients staying in hospital for longer than 24 hours (the threshold typically used to denote "long stay"; **Figure 2** [5.6]). Together with a lower number of adverse events recorded, the shorter length of stay associated with the SNAP regimen was found to lead to an estimated saving of GBP180.33 per patient. Extrapolating this to the approximately 50,000 patients treated annually in the UK [5.7], suggests that, once implemented at a national scale, use of the SNAP regimen could result in NHS savings of up to GBP9,016,000 every year [5.6].

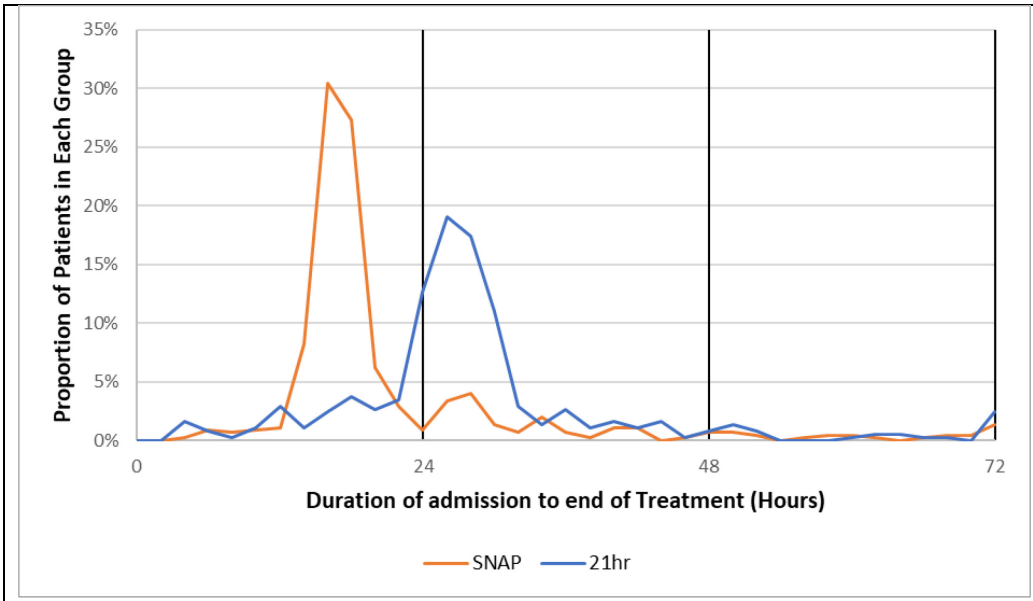

Figure 2: Length of hospital stay in patients treated with SNAP (orange) versus patients treated with the 21-hour regime (blue). Approximately 2/3 of the 21-hour regimen group exceeded the 24-hour threshold stay typically used to denote a "long stay", compared with only 1/5 in the SNAP group [5.6].

5. Sources to corroborate the impact

[5.1] NPIS Annual report 2017–18, p. 21

[5.2] Screenshot from TOXBASE Twitter, 15th April 2020

[5.3] Accesses to the TOXBASE SNAP entry
a. Record of UK accesses by hospital, 15/04/2020– 19/08/2020
b. Record of UK accesses by hospital, 20/08/2020– 31/12/2020
c. Record of overseas accesses by hospital, 15/04/2020– 19/08/2020
d. Record of overseas accesses by hospital, 20/08/2020– 31/12/2020
e. Letter from TOXBASE Manager, confirming the authenticity of the spreadsheets

[5.4] Emails from all health boards in mainland Scotland

[5.5] Emails attesting to the use of SNAP prior to TOXBASE update:
a. Pennine Acute Hospital, Manchester
b. North Bristol
c. Barnsley, Chesterfield, Nottingham Queen's Medical Centre and Derby Royal
(Kilmarnock and Highland are included as [5.4a] and [5.4h])

[5.6] Formal health economic assessment of cost-savings achieved through use of SNAP

[5.7] Narayan H, Thomas S, Eddleston M, Dear J, Sandilands E, & Bateman N. Disproportionate effect on child admissions of the change in medicines and healthcare products regulatory agency guidance for management of paracetamol poisoning: an analysis of hospital admissions for paracetamol overdose in England and Scotland. *British Journal of Clinical Pharmacology*. 2015. doi:10.1111/bcp.12779