



Investigation report

Potential under-recognised risk of harm from the use of propranolol

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Medication, Communication and decision making

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Executive Summary

Introduction

This investigation explores the under recognised toxicity of propranolol in overdose. Propranolol is used to treat a number of medical conditions, including migraine, cardiovascular problems and the physical effects of anxiety. There has been a steady rise in the number of propranolol prescriptions issued to NHS patients. Between 2012 and 2017 there was a 33% increase in the number of deaths reported as being linked to propranolol overdose, with 52 deaths recorded as having been linked to propranolol overdose in 2017.

The reference event

Emma was diagnosed with anxiety from the age of 11. During her teens she had been prescribed propranolol for a year to treat the physical symptoms of her anxiety. Propranolol belongs to a group of drugs called beta blockers. In February 2016, Emma visited her General Practitioner (GP) with symptoms of migraine and was prescribed propranolol to help with migraine prevention.

In March 2017, Emma went to a new GP practice with symptoms of depression and anxiety. She described having suicidal thoughts and was prescribed antidepressant medication (citalopram) and given advice on how to access mental health services. She continued to be prescribed propranolol for her migraine and citalopram for depression throughout 2017.

One day in January 2018, Emma called 999 at 19:00 hours to report that she had taken an overdose of propranolol and citalopram. She was alert and responsive at the time of the call. Emma should have received a Category 3 ambulance response[1] in line with the emergency triage system operated by the Ambulance Trust and the national ambulance response programme. However, a local variation in practice at the Ambulance Trust meant that she instead received a higher, Category 2 ambulance response[2].

An ambulance arrived at the scene at 19:56 hours; the crew found Emma awake but unable to speak or move. Her condition deteriorated rapidly and advanced life support efforts were commenced to resuscitate her. She was taken to hospital at 20:59 hours and arrived at 21:09 hours. Further efforts were made to resuscitate Emma, but these were not successful. Emma was pronounced dead at 21:33 hours.

The national investigation[3]

The Healthcare Safety Investigation Branch (HSIB) received a notification from the Ambulance Trust concerning the potential under-recognised risk of propranolol toxicity. The notification highlighted the potential for patients who had overdosed on propranolol to rapidly deteriorate before receiving medical assistance.

The investigation into the reference event reviewed the care Emma received from her GP practice, and during the ambulance response and emergency treatment of her overdose. After gathering additional information and assessing the incident against HSIB's investigation criteria, the Chief Investigator authorised a national investigation.

The national investigation reviewed relevant national guidance and clinical practice. It also considered research and safety literature relating to propranolol and toxicity, engaged with national subject matter advisors, and consulted with professional bodies.

The investigation focused on:

- the potential for clinicians across the healthcare system to not recognise the risk of propranolol toxicity and the potential for it to cause rapid deterioration when taken in large quantities
- the handling of propranolol overdose calls made to the ambulance service, and ambulance response times
- understanding the emergency treatment options for patients who have overdosed on propranolol.

Findings

Primary care

- Propranolol is a cardiac medication but is now predominantly prescribed for the treatment of migraine or anxiety.
- Propranolol is widely used by many patients without incident and with clinical benefit.
- There is a specific group of patients who may be at an increased risk of using propranolol for self-harm because they have co-existing migraine, depression or anxiety.

- Current guidance for prescribing propranolol does not contain sufficient warnings regarding the potential severe toxicity of propranolol when taken in overdose.
- Current awareness of the potential impact of propranolol in overdose is limited and hinders the ability of prescribers to exercise clinical judgement when choosing to prescribe propranolol.
- There is a lack of published research and guidance on how propranolol may interact with antidepressant medication when taken in overdose.
- Propranolol is licensed for use to treat anxiety symptoms, as reflected in the British National Formulary[4], but clinical guidance regarding when and how it should be used in practice is not available from the National Institute for Health and Care Excellence.

Ambulance response

- There are variations in how ambulance triage systems may categorise calls concerning specific medication overdose.
- Cases of overdose are complex due to the many variable factors relating to the patient and the medication taken. Current ambulance triage systems are not able to account for this complexity.
- Automatic re-categorisation of overdose calls may not be effective or efficient in ensuring the sickest patients receive access to the quickest and most effective care.
- There are variations in the level of clinical input provided to help determine the correct category of ambulance response to calls involving overdose.
- Intervention by clinicians in the ambulance control room can help to identify and address specific complexities encountered in overdose cases and assist in an appropriate ambulance response being provided.

Emergency care

- Secondary care in hospital is required to ensure that a patient can receive the appropriate range of treatments to address propranolol toxicity.
- Current guidance for ambulance crews may not be effective in ensuring that patients who have taken an overdose receive timely hospital care.
- There are limited treatment options available to ambulance crews to help them treat patients who may have taken a propranolol overdose.
- Current guidance available to emergency department clinicians could be more clearly communicated to aid in the emergency response.

HSIB makes the following Safety Recommendations

Safety recommendation R/2020/068:

It is recommended that the British National Formulary reviews and updates guidance on the use of propranolol in the treatment of anxiety and the advice provided for beta blocker overdose.

Safety recommendation R/2020/069:

It is recommended that the National Institute for Health and Care Excellence reviews and updates guidance on the use of propranolol in the treatment of anxiety and migraine, with particular reference to the toxicity of propranolol in overdose.

Safety recommendation R/2020/070:

It is recommended that the Royal College of General Practitioners supports its members in identifying the potential risk of prescribing propranolol to patients in at-risk groups.

Safety recommendation R/2020/071:

It is recommended that the Royal Pharmaceutical Society supports its members in identifying the potential risk of prescribing propranolol to patients in at-risk groups.

Safety recommendation R/2020/072:

It is recommended that PrescQIPP CIC supports its subscribers to identify the potential risk of prescribing propranolol to patients in at-risk groups.

Safety recommendation R/2020/073:

It is recommended that NHS England/NHS Improvement evaluates current approaches to the clinical oversight of overdose calls within ambulance control rooms and leads on work to develop a national framework to describe the requirements for appropriate clinical oversight of overdose calls.

Safety recommendation R/2020/074:

It is recommended that the Association of Ambulance Chief Executives works with the National Poisons Information Service to review its guidance on the treatment and transportation of patients known to have taken an overdose of propranolol or other beta blocker medication.

HSIB makes the following Safety Observations

Safety observation O/2020/058:

Electronic prescribing systems used in primary care may benefit from alerts that prompt clinicians about the potential risks of prescribing propranolol to people in certain patient groups.

Safety observation O/2020/059:

Further research into possible interactions between propranolol and Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants in overdose would be beneficial.

Safety observation O/2020/060:

National resuscitation guidance may benefit from further specific information concerning the additional challenges and treatment options available for other types of medication overdose.

Safety observation O/2020/061:

Paramedics would benefit from the ability to access TOXBASE when responding to emergency calls.

Safety observation O/2020/062:

It may be beneficial for the format of TOXBASE guidance to be reviewed to consider whether guidance documents may be better presented to allow clinicians to quickly and more easily interpret key steps in the treatment of overdose.

HSIB notes the following SafetyActions**Safety action A/2020/020:****Safety action by the Medicines and Healthcare products Regulation Agency (MHRA)**

The MHRA is reviewing the information in the Summary of Product Characteristics (a legally required document detailing a medicine's properties and officially approved conditions of use) for propranolol-containing products relating to overdose and interactions with other medicines. It is also seeking advice from relevant experts on the need to review whether the balance of benefits and risks of propranolol remains favourable in patients presenting with physical symptoms of anxiety.

Safety action A/2020/021:

Safety action by NHS England/NHS Improvement

In March 2019, NHS England wrote to ambulance trusts in England regarding the management of cases where patients have self-harmed and are at risk of suicide. This included specific reference to patients who may have taken an overdose of medication. The letter acknowledged that there were varying models in place for the management of these cases and that it was imperative that such patients be provided with appropriate input and support from clinicians at an early stage.

NHS England requested that all ambulance services review their processes to ensure that robust clinical oversight was in place in control rooms to monitor patients who have self-harmed and are having suicidal thoughts, particularly those who have been allocated an initial Category 3 or 4 ambulance response. In regard to overdose, NHS England said that, when on a call, consideration should be given to the type of overdose and quantity of medication taken, which might necessitate the need to upgrade a call for clinical reasons.

1 Background and context

1.1 Propranolol

1.1.1 Propranolol is in a class of medications known as beta blockers (beta adrenergic blocking agents). Propranolol is licenced in the UK to treat a number of medical conditions, including migraine, cardiovascular problems[5] and the physical effects of anxiety. Propranolol changes the way the body responds to certain nerve impulses and reduces blood pressure by slowing the heart rate (by blocking the action of adrenaline, a hormone produced in the adrenal glands). Propranolol is able to enter the brain and may help to relax blood vessels in the brain, hence its use to treat migraine.

1.1.2 Propranolol can rapidly cause significant chemical damage to the heart when taken in overdose; typical effects include profound bradycardia (slow heart rate), hypotension (low blood pressure) and reduced electrical activity in the heart. Beta blockers can also impact on the central nervous system and the body's ability to process sodium, a chemical essential to the functioning of the body. This may lead to fatigue, reduced consciousness levels, confusion, hallucinations, seizures, and coma. Symptoms of beta blocker overdose are usually apparent within one to two hours of medication being ingested and may result in the rapid deterioration of a patient's condition. Propranolol is recognised as being one of the most challenging overdoses to treat (Resus, 2019) and urgent emergency medical intervention may be required.

1.2 National Institute for Health and Care Excellence (NICE)

1.2.1 NICE guidance (2012) recommends that propranolol is used as a first-line preventative medication for migraine headaches. NICE guidance on the treatment of anxiety (NICE, 2011a) and wider guidance on common mental health problems (NICE, 2011b) do not provide guidance on the use of propranolol to treat symptoms of anxiety.

1.2.2 NICE guidance (2009) and Clinical Knowledge Summaries (2015) provide guidance on the management of depression in adult patients. A range of treatment options are available. Routinely these include advice on psychological therapies and access to antidepressant medication. NICE guidance advises General Practitioners (GP) to take into account the toxicity of prescribed medicines if a patient is deemed to be at risk of suicide. A similar statement is included in NICE guidance (2004) for the management of cases where patients are at risk of self-harm.

1.3 The British National Formulary (BNF)

1.3.1 The BNF is the UK pharmaceutical reference source. It advises that propranolol can be used for the prophylactic (preventative) management of migraine (BNF, 2019d). The BNF specifies the dose for the prevention of migraine in adults as being between 80 milligrams (mg) and 240mg per day.

1.3.2 The BNF also provides information on the licenced use of propranolol for the treatment of two physical symptoms of anxiety. For anxiety tachycardia (rapid heartbeat), it suggests a dose of 10mg to 40mg three to four times a day. For anxiety with symptoms such as palpitation, sweating and tremor, the suggested dose is 40mg once daily, increased if necessary to three times a day.

1.4 Medicines and Healthcare products Regulatory Agency (MHRA)

1.4.1 The MHRA is responsible for the licensing of medicines in the UK, ensuring they meet statutory standards of safety, quality and efficacy. The MHRA's remit includes the approval of the Summary of Product Characteristics (SmPC) and Patient Information Leaflets (PIL), which are legal documents approved as part of the marketing authorisation of every medicine.

1.4.2 The MHRA operates the Yellow Card Scheme; a UK system for collecting and monitoring information on suspected adverse drug reactions (ADRs). The purpose of the scheme is to provide an early warning that the safety of a product may require further investigation. As of August 2019, a total of 42 reports of overdose have been reported in association with propranolol (describing overdose, intentional overdose or prescribed overdose). After taking into account duplicate reports, the MHRA advised the investigation that there have been a total of 27 unique reports of propranolol overdose.

1.4.3 The Yellow Card Scheme relies on voluntary reporting of suspected ADRs by health professionals and patients. There is also a legal obligation for pharmaceutical companies to submit serious ADR reports involving the use of their drugs.

1.5 Citalopram

1.5.1 Citalopram is in a class of medications known as selective serotonin reuptake inhibitors (SSRIs). These medications are used in the treatment of depression. It is thought that SSRIs work by increasing the serotonin available in the brain. Citalopram is used in the treatment of depressive illness. The BNF (2019a) specifies treatment of between 20mg and 40mg per day for adults.

1.6 National Poisons Information Service (NPIS) and TOXBASE

1.6.1 NPIS is a national service, approved by the UK Departments of Health and Social Care and commissioned by Public Health England, that provides expert advice on all aspects of acute and chronic poisoning. NPIS also provides a 24-hour-a-day telephone advice service staffed by specialists in toxicology[6] and supported by consultant toxicologists. The service is able to provide toxicology information to clinicians and is suggested as a source of advice in more complex poisoning cases.

1.6.2 NPIS provides TOXBASE, an online resource that is intended to be the primary resource for healthcare professionals seeking advice on poisoning or overdose. TOXBASE is available to NHS Trusts via password-protected access. TOXBASE also provides a smartphone app.

1.7 NHS England Ambulance Response Programme (ARP)

1.7.1 The ARP was established in 2015. Its stated aim was to increase the operational efficiency of ambulance services while maintaining a focus on the clinical needs of patients. Three objectives were stated to be central to the programme (NHS England, 2018b):

- prioritising the sickest patients, to ensure they receive the fastest response
- driving clinically and operationally efficient behaviours, so the patient gets the response they need first time and in a clinically appropriate timeframe
- putting an end to unacceptably long waits by ensuring that resources are distributed more equitably among all patients.

1.7.2 ARP conducted large-scale clinical trials within English ambulance services and issued final ARP guidance to ambulance services in July 2017. It established new ambulance response categories and the average response times expected for each. These are:

- Category 1: For calls to people with immediately life-threatening and time-critical injuries and illnesses. These will be responded to in a mean average time of seven minutes, with at least 90% of calls receiving a response within 15 minutes.
- Category 2: For emergency calls, such as cases of stroke or chest pain, which may require rapid assessment and/or urgent transport. These will be responded to in a mean average time of 18 minutes, with at least 90% of calls receiving a response within 40 minutes.
- Category 3: For urgent calls which require treatment and transport to an acute setting (such as a hospital emergency department). The aim is for at least 90% of calls to receive a response within 120 minutes.
- Category 4: For less urgent calls where some patients may also be given advice over the telephone or referred to another service. The aim is for at least 90% of calls to receive a response within 180 minutes.
- Category 5: For calls which require clinical assessment but not an ambulance response. The aim is for at least 90% of calls to receive a call back from a clinician within 180 minutes.

In April 2019, NHS England and NHS Improvement merged to become a single organisation. This report refers to them as individual organisations when mentioning their activities/ publications up to April 2019, and jointly as 'NHS England/NHS Improvement' (NHSE/I) for those after April 2019.

1.8 Emergency triage systems

1.8.1 There are currently two triage systems (systems for assessing the urgency of patients' needs in order to prioritise a response) that are approved for use in English ambulance services and linked to ARP standard response times.

1.8.2 The Advanced Medical Priority Dispatch System (AMPDS)[7] is used by approximately half of English ambulance services. AMPDS uses a method approved by the International Academy of Emergency Medical Dispatch. Descriptions of symptoms reported by callers are assigned to a code, which in turn allows a suitable category ambulance response to be provided.

1.8.3 NHS Pathways is used by the remaining English ambulance trusts. This is the same programme that provides the Clinical Decision Support System (CDSS) used in NHS 111 call centres. The system is needs based, meaning that life-threatening problems assessed at the start of the call trigger ambulance responses, progressing through to less urgent conditions which require a less urgent response in other healthcare settings.

1.8.4 Both systems map their triage codes (the types of conditions which can be identified) to the ARP datasets and have been endorsed by the Association of Ambulance Chief Executives (AACE) via its National Ambulance Service Medical Directors Group, and approved by its Emergency Call Prioritisation Advisory Group. As triage tools, both systems predominantly rely on the symptoms or circumstances reported at the time of the call to determine the category of ambulance response.

1.8.5 NHS England acknowledges that a continual review of these datasets is necessary in order to develop a robust evidence base for ambulance response categorisation. It is also necessary to ensure that ambulance trusts commit to sharing information and evidence regarding clinical prioritisation, particularly where an ambulance trust may vary its category of ambulance response from the approved dataset, to ensure that the evidence base for any such variation can be considered in a national context.

1.9 Resuscitation guidance

1.9.1 The Resuscitation Council (UK) provides guidance for clinicians on cardiopulmonary resuscitation (CPR) and advanced life support, including guidance on performing CPR before a patient arrives in hospital (pre-hospital resuscitation) (2015).

1.10 Joint Royal Colleges Ambulance Liaison Committee (JRCALC) guidance

1.10.1 Clinical practice guidance for paramedics and other ambulance staff within UK ambulance services is based on the UK Ambulance Services Clinical Practice Guidelines document (AACE, 2019)[8]. This is produced by the JRCALC and endorsed by the AACE.

1.10.2 Where established national clinical guidelines exist, for example regarding CPR, these are reflected in the JRCALC guidance, with further specific additions relevant to paramedic staff to help them manage cases where patients require treatment.

2 The Reference event

2.1 Background

2.1.1 Emma was first diagnosed with anxiety when she was 10 years old. Her family report that she was a “perfectionist” and high academic achiever who was prone to worry.

2.1.2 At the age of 16, Emma was referred for cognitive behavioural therapy (CBT)[9] to treat her anxiety. Aged 18, Emma visited her General Practitioner (GP) practice because she was having panic attacks. She was prescribed propranolol to treat the physical symptoms of her anxiety and was also advised to see her university counsellor.

2.1.3 Also at the age of 18, Emma developed migraine headaches. She was advised that the propranolol she was receiving for her anxiety may help to prevent the migraine and she was later prescribed additional medication to treat the onset of migraine symptoms. Emma continued to take propranolol for her anxiety until she was 19 years old, when Emma stopped taking this medication.

2.1.4 Aged 22, Emma again reported problems with migraine to her GP. She was prescribed propranolol as a migraine prophylaxis (preventative). She ultimately received a repeat prescription for 240mg a day, which is the BNF-recommended maximum dose of this medication.

2.2 Primary care

2.2.1 In February 2017, having moved into a new flat, Emma changed her GP practice. On 9 March 2017, she attended her first GP appointment at the new practice (‘the Practice’).

2.2.2 At the appointment she reported that she was anxious, depressed, and said that she had begun to have suicidal thoughts. Her GP assessed her condition and noted that Emma was able to make good eye contact, was not delusional, had protective factors (such as her family and friends), and was able to access counselling services through her employer. She was considered at low risk of suicide or self-harm.

2.2.3 Emma was prescribed sertraline (an antidepressant). Alongside this medication, Emma continued to receive her repeat prescription for propranolol to treat her migraines. Emma was also given advice on how to contact local NHS mental health services, and was given a review appointment with the GP for two weeks’ time.

2.2.4 On 21 March 2017, Emma attended her review appointment and reported that she was “doing much better...feeling much brighter” and had not had any further suicidal thoughts. Emma and her GP discussed accessing counselling or using a mindfulness app on her smartphone.

2.2.5 On 4 April 2017, Emma attended another review appointment with her GP. Her low mood had improved, and she had had no suicidal thoughts. She reported that she was still woken by anxiety on occasions but felt she could manage this better than before. Emma reported some side effects from the sertraline and the GP switched her to a different antidepressant, citalopram. She received a repeat prescription for this medication at the BNF-recommended dose of 20mg per day.

2.2.6 On 21 April 2017, Emma attended for a further review. She reported feeling better on citalopram, but that she was still anxious. The GP still considered Emma to be at low risk of suicide and made a plan to review her care in three to four weeks. She was again given details on counselling services, how to access the local NHS mental health crisis team, and how to access the Improving Access to Psychological Therapy (IAPT)[10] programme.

2.2.7 On 20 June 2017, Emma attended her final appointment at the Practice. She stated that her mood occasionally fluctuated and she was again given advice on how to access IAPT and CBT resources. Emma reported that she had “tried some [therapy] methods with benefit” and that she felt she had needed antidepressants in order to “push forward”. The GP reviewed her propranolol and citalopram medication, and suggested that Emma attend for a further appointment in September 2017.

2.2.8 Emma booked a further appointment at the Practice for an unknown reason on 14 August 2017. She did not attend this appointment and there is no record of a review appointment being booked.

2.2.9 By September 2017, Emma’s family report that she was feeling better and more confident. Emma was a clinical scientist and she was able to travel to New Zealand by herself for her professional development, working in hospitals in Auckland, Wellington and Christchurch.

2.2.10 Emma continued to receive repeat prescriptions of citalopram and propranolol from the Practice in August, November and December 2018.

2.3 Ambulance response

2.3.1 On 24 January 2018 at 19:00 hours, Emma called the ambulance service via 999 to report that she had taken an overdose. Emma was alone in her flat and was alert and able to answer the call handler’s questions. She told the call handler, “I have taken an overdose of pills; I don’t think I meant to do it really.” She did not report any problems breathing and stated that she had taken an overdose of “propranolol and citalopram...about 10 minutes ago”.

2.3.2 Emma was given instructions to make sure that an ambulance crew could access her flat. She was advised to avoid eating or drinking and to “rest in the most comfortable position” until the ambulance crew arrived.

2.3.3 At 19:06 hours, an ambulance was requested for dispatch to Emma as a Category 2 call. At 19:16 hours, an ambulance was allocated to the call but was then redirected to another Category 2 call by dispatchers. At 19:43 hours, another ambulance was dispatched to the call and arrived with Emma at 19:56 hours. The ambulance crew consisted of a paramedic and an ambulance technician. Emma was found on her bed in a collapsed state; her eyes were open, but she was unable to speak or move.

2.3.4 At 20:00 hours a series of clinical observations including pulse rate, respiratory rate, blood pressure, oxygen saturations (the level of oxygen in the blood), blood sugar level, temperature, Glasgow Coma Scale (GCS) score[11] and an electrocardiograph (ECG)[12] were recorded. Emma's oxygen saturations were low (92%) compared with normal ranges in an otherwise well adult ($\geq 94\%$) and her GCS was reduced (8/15). The attending paramedic determined that the ECG showed a normal heart rate. Emma was administered oxygen and her oxygen saturations improved to 100%.

2.3.5 The ambulance crew tried several times to insert a cannula (a narrow tube through which medication or fluids can be administered straight into a vein) but had difficulties doing so. While doing this, the crew observed that Emma had several small seizures and it was decided to not delay her transport to hospital. The ambulance technician returned to the ambulance to collect a stretcher to move Emma to the ambulance.

2.3.6 At 20:15 hours Emma became profoundly bradycardic (her heart rate slowed down) and no palpable pulses were present. At this stage cardiac arrest was diagnosed and the paramedic started cardiopulmonary resuscitation (CPR). When the ambulance technician returned with the stretcher a request was made by the ambulance crew for a second ambulance to attend.

2.3.7 During the resuscitation attempt, ventilations (assistance with breathing) were provided via a self-inflating bag-valve-mask with supplemental oxygen administered at a rate of 15 litres per minute. Emma's airway was suctioned to remove any fluids and the paramedic inserted an oropharyngeal airway[13]. Intravenous adrenaline was administered at 20:20 hours followed by a second dose at 20:25 hours. At 20:27 an intravenous infusion of fluids was commenced.

2.3.8 A second ambulance arrived at 20:35 hours. Attempts were subsequently made by both paramedics to insert a laryngeal mask airway[14] to provide a more reliable means of ventilating Emma, but these efforts were not successful. Efforts were also made to use an endotracheal tube[15]. Both paramedics were unable to visualise the vocal cords to pass the tube and therefore an oropharyngeal airway was reinserted and ventilations recommenced using a bag-valve-mask. Two further doses of adrenaline were administered intravenously at 20:35 and 20:45 hours.

2.3.9 At 20:59 hours the ambulance crew commenced transfer to a nearby emergency department. They made a priority call while en route to alert the receiving hospital staff to the imminent arrival of a patient in cardiac arrest. CPR was performed throughout the transfer and a final dose of adrenaline was given to Emma intravenously at 21:07 hours. The ambulance arrived at the hospital at 21:09 hours.

2.4 Emergency department care

2.4.1 On arrival at the emergency department, Emma was transferred to the resuscitation area. She was seen by a consultant in emergency medicine. The consultant noted that Emma's airway was being maintained by an oropharyngeal airway, but Emma had no central pulse and her pupils were dilated.

2.4.2 Emma was considered to be in PEA[16] arrest. Emma was intubated[17] to enable high doses of oxygen to be administered to her lungs via a ventilator. An arterial blood gas test[18] was also carried out to determine the impact the PEA arrest was having on Emma's physiology and to aid with further resuscitation treatment, including consideration of the possible reversible causes of the cardiac arrest.

2.4.3 Emma received eight cycles of advanced life support of two minutes in length. Emma also received:

- four doses of adrenaline
- intralipid: this is a fat emulsion that is used in a range of overdoses and is thought to bind drugs to help reduce the amount of 'free' drug within the body
- glucagon: this increases the amount of calcium available to the system and strengthens cardiac contractions
- sodium bicarbonate: propranolol acts to block the sodium available for cardiac contraction. Sodium bicarbonate is administered specifically to combat this blocking effect.

2.4.4 An ultrasound scan[19] was performed to help determine whether there was any activity in Emma's heart. This confirmed that, despite the efforts to treat Emma, there was no cardiac activity. Arterial blood gas results also showed profound changes in Emma's pH levels and lactate[20]. These results were suggestive of a prolonged resuscitation effort and further indicated a poor prognosis from the resuscitation. Emma was pronounced dead at 21:33 hours, 78 minutes after the ambulance crew's initial attempts at CPR had begun.

3 Involvement of the Healthcare Safety Investigation Branch

3.1 Notification of the reference event

3.1.1 The Healthcare Safety Investigation Branch (HSIB) received a notification from the Ambulance Trust raising concern about a possible unrecognised risk to patients due to the toxicity of propranolol. The concern focused on the potential for the health of patients overdosing on propranolol to rapidly deteriorate before they were able to receive medical assistance.

3.2 Decision to investigate

3.2.1 Following a detailed scoping investigation, HSIB's Chief Investigator authorised a full investigation as the safety issue met the following criteria:

Outcome impact – What was, or is, the impact of the safety issue on people and services across the healthcare system?

3.2.2 Between 2012 and 2017 there was a 33% increase in the number of deaths reported as being linked to propranolol overdose, with 52 deaths recorded as having been linked to propranolol overdose in 2017.

3.2.3 When taken in overdose, propranolol can act rapidly to significantly decrease the heart rate and blood pressure while simultaneously impacting on the body's ability to process sodium, leading to seizures, confusion or coma. In such cases urgent emergency medical intervention is required.

Systemic risk – How widespread and how common a safety issue is this across the healthcare system?

3.2.4 Since 2012 there has been a 34% increase in propranolol prescriptions, with 4,694,616 prescriptions provided to patients by 2016. In the year 2017/2018 the UK National Poisons Information Service received 354 enquiries regarding propranolol toxicity.

3.2.5 The safety issue impacts many clinical settings, including prescribing in primary care settings, ambulance response and treatment, and emergency medical treatment in the emergency department. Some ambulance services have identified this safety issue and made local variations to ambulance response times to account for the increased risk of rapid deterioration in the health of patients overdosing on propranolol.

Learning potential – What is the potential for an HSIB investigation to lead to positive changes and improvements to patient safety across the healthcare system?

3.2.6 Initial consideration by HSIB highlights that only local-level action has been taken to address this issue in ambulance response, which although adequate, may impact upon other areas of the system. Investigating the safety issue from a broader perspective to include primary care, emergency medical treatment and clinicians' awareness of propranolol toxicity could result in systemic safety improvements. This may also lead to a broader understanding of the systems and processes in place to identify and respond to other medicines that may result in rapid deterioration in overdose.

3.2.7 The following safety issues were identified during the HSIB initial investigation and formed the basis of the wider investigation:

- There is the potential for clinicians across the healthcare system to not recognise the risk of the toxicity of propranolol and the potential for it to cause rapid deterioration in patients when taken in large quantities.
- The handling of propranolol overdose calls and ambulance response times varies between ambulance services.
- There is variation in the understanding of the emergency treatment options for patients who have overdosed on propranolol.

3.2.8 The investigation report focuses on the harmful effects of propranolol in overdose. However, it is important to note that other beta blocker medications may also be used for the prevention of migraine.

4 Primary Care

4.1 Analysis and findings from the local investigation

Propranolol awareness

4.1.1 The investigation spoke with the staff and principal GP at Emma's General Practitioner (GP) practice (*'the Practice'*). They explained to the investigation that they had never been involved in a case of propranolol overdose and had not understood the significant impact such an overdose may have on a patient.

4.1.2 The principal GP explained that in the course of considering whether to prescribe propranolol they would have regard to guidance in order to assist them in their decision making. This would routinely include National Institute for Health and Care Excellence (NICE) guidance and Clinical Knowledge Summaries, and British National Formulary (BNF) guidance. The principal GP had examined these resources following the reference event and found that they did not contain any specific guidance on the potential risks of propranolol when taken in

overdose, its use in patients who may be depressed or at risk of suicide, or any potential interactions with SSRI antidepressants (selective serotonin reuptake inhibitor antidepressants – see 1.5.1).

4.1.3 Staff told the investigation that the Practice used an electronic patient record system. These systems have the ability to provide alerts to clinical staff relating to specific medications or diagnoses to help clinicians to make prescribing decisions. There was no such alert within the Practice's system for the prescribing of propranolol when linked to a diagnosis of depression or risk of self-harm.

Medications

4.1.4 Emma was initially prescribed propranolol for her migraines in February 2016. This was in line with NICE and BNF guidance. Emma was then prescribed sertraline in March 2017, before this was switched to citalopram in April 2017. Both medications were prescribed by staff in line with NICE and BNF guidance.

4.1.5 Citalopram is also recommended for use in panic disorders by the BNF (2019a). The principal GP told the investigation that they were conscious that citalopram may also help to alleviate symptoms of anxiety in patients. The investigation's GP subject matter advisor (GP SMA) advised that it would be considered a responsible approach to polypharmacy (the use of several medications at the same time) if a GP was able to treat both the patient's migraine and depression, and assist in the treatment of her known anxiety problems, with as few medications as possible.

4.1.6 Emma was receiving prescriptions for both propranolol and citalopram at the time of her death. The Practice estimated that approximately 10-15% of its patients with anxiety or depression would be receiving propranolol, either for the treatment of migraine or where propranolol was being used alongside citalopram to treat symptoms of panic disorder in line with BNF guidance. The investigation's GP SMA stated that they would expect to see a similar proportion of patients on these medications in other GP practices.

4.1.7 Between February 2016 and her death in January 2018, Emma was receiving 160 x 40mg propranolol tablets every time she collected her repeat prescription. This was calculated to allow Emma a 28- to 42-day supply of propranolol, depending on whether she needed to adjust her dose to the maximum level to treat a migraine. Emma was also receiving a prescription for citalopram at 56 x 20mg tablets and she received a 56-day supply on each repeat prescription. These doses were in line with NICE and BNF guidance.

4.1.8 The principal GP told the investigation that they can make a professional decision to limit a supply of a medication in each prescription if they are concerned that a patient is at risk of self-harm. Certain medications also routinely have their supply limited due to known risks of

misuse or impact in overdose (for example, tricyclic antidepressants (NHS, 2009), an older class of antidepressants which also act to reduce the sodium available to the body). Emma's improving condition meant that Practice staff had no concerns that Emma may self-harm or misuse her medications.

4.1.9 The investigation's GP SMA advised that GPs may exercise discretion regarding the period for which repeat prescriptions can be issued. British Medical Association guidance states that GPs can prescribe medicines for intervals they feel are clinically appropriate (British Medical Association, 2018), taking into account the patient's condition and their compliance with treatment.

4.1.10 The Practice's policy was for repeat prescriptions to be issued for a six-month period before requiring a patient's case to be reviewed. Local commissioning guidance in place for the Practice also included consideration for medications to be prescribed and dispensed in supplies of up to 56 days at a time for suitable patients. The investigation's GP SMA confirmed that such longer prescription lengths may often be issued by GPs, particularly for people managing long-term conditions or people who may struggle to attend or pay for more frequent repeat prescriptions.

4.1.11 Practice staff told the investigation that they had not come across a case where the supply of propranolol was limited, either during their training or in discussion with colleagues. The principal GP perceived that for the majority of patients this was an effective treatment with limited cause for concern.

4.1.12 Emma collected repeat prescriptions for propranolol in June 2017, twice in August 2017, and then in November 2017 and December 2017. Emma also received prescriptions for citalopram in June 2017, twice in August 2017, and in December 2017. An analysis of the repeat prescriptions shows that Emma was not stockpiling or overusing these medicines.

4.1.13 Emma routinely received 6.4 grams (g) of propranolol in every repeat prescription. Fatal overdoses have been recorded where patients have ingested 2g (Suarez et al, 1988) or more of propranolol. Emma did not have to stockpile her medication in order to take a fatal dose of propranolol which had been prescribed in line with relevant national guidance and professional practice.

Access to support

4.1.12 NICE (2015a) advises that patients should be seen within specific timescales once depression is suspected. Emma was seen and assessed in line with this guidance. The GP recorded in the final consultation note that Emma was 'doing well' and that she was accessing support.

4.1.13 In addition to local access to NHS mental health services, the Practice offered therapeutic listening therapy and had a local arrangement in place with a counsellor. The Practice had agreed to let a room to a counsellor in return for them offering reduced-price services. This meant that patients were able to access private counselling sessions at discounted rates. Emma would have been aware of these services and discussions setting out the mental health support available are recorded in her medical records.

4.1.14 The Practice explained that Emma's August 2017 appointment had been the first appointment she had failed to attend. This did not raise any concerns with staff and would not have triggered any formal process to follow up with Emma to identify the reason for her non-attendance.

4.1.15 The Practice further explained that patients often missed appointments for a variety of reasons and that this instance did not appear unusual. This comment was supported by the investigation's GP SMA who advised that patients missing appointments in primary care was a relatively common issue that may be caused by a variety of reasons (Oliver, 2019).

4.1.16 The Practice also explained that it relied on patients to book review appointments when these were required, as the computer systems would not automatically generate them. Given the timescales involved, staff did not routinely book a review appointment at the same time as a patient consultation, as it may not be convenient for patients to have an appointment made so far in advance. Instead, staff expected patients to contact the Practice to ensure a review was booked.

4.1.17 The investigation's GP SMA commented that it would be common and understandable practice to allow ongoing prescriptions for a patient who was felt to be in remission from their illness, pending their next formal review. Emma's next formal review would be required in January 2018 and she would have needed to see her GP before any further prescriptions would have been issued.

4.1.18 In response to the incident, the Practice has developed a range of safety actions (see below) in an effort to enhance the care provided to patients. In addition, Emma's family was keen to stress the high level of care and support their daughter received from staff at the Practice.

HSIB notes the following local safety actions

Safety action A/2020/022:

- The Practice developed new guidance for patients new to antidepressants. This prompts its GPs to arrange patient reviews at: two weeks, more frequently over the

first three months, a three-month follow-up, and then a further follow-up in six to 12 months.

Safety action A/2020/023:

- The Practice now schedules patient reviews at 12-month intervals in advance for patients with mental health needs.

Safety action A/2020/024:

- The Practice carried out an audit of all patients on antidepressants and invited them for a review appointment. The Practice now sends text/call reminders to patients who do not attend appointments and also have depression.

Safety action A/2020/025:

- The Practice has limited repeat prescriptions for antidepressants to a three-month period and now limits prescription of propranolol to a 28-day supply for patients who also have depression.

Safety action A/2020/026:

- The Practice has developed a new depression scoring and screening tool to build on the existing good practice followed during Emma's case, and ensures this approach is adopted consistently in future patient consultations.

Safety action A/2020/027:

- The Practice has reorganised the main display board in the waiting area to focus on mental health support.

4.2 Analysis and findings from the wider investigation

Propranolol use

4.2.1 Propranolol is a relatively common prescription that is provided in primary care. Data[21] shows a steady increase in the number of propranolol prescriptions issued to patients since 2014, from 340,958 in May 2014 to 474,233 in July 2019 (Figure 1).

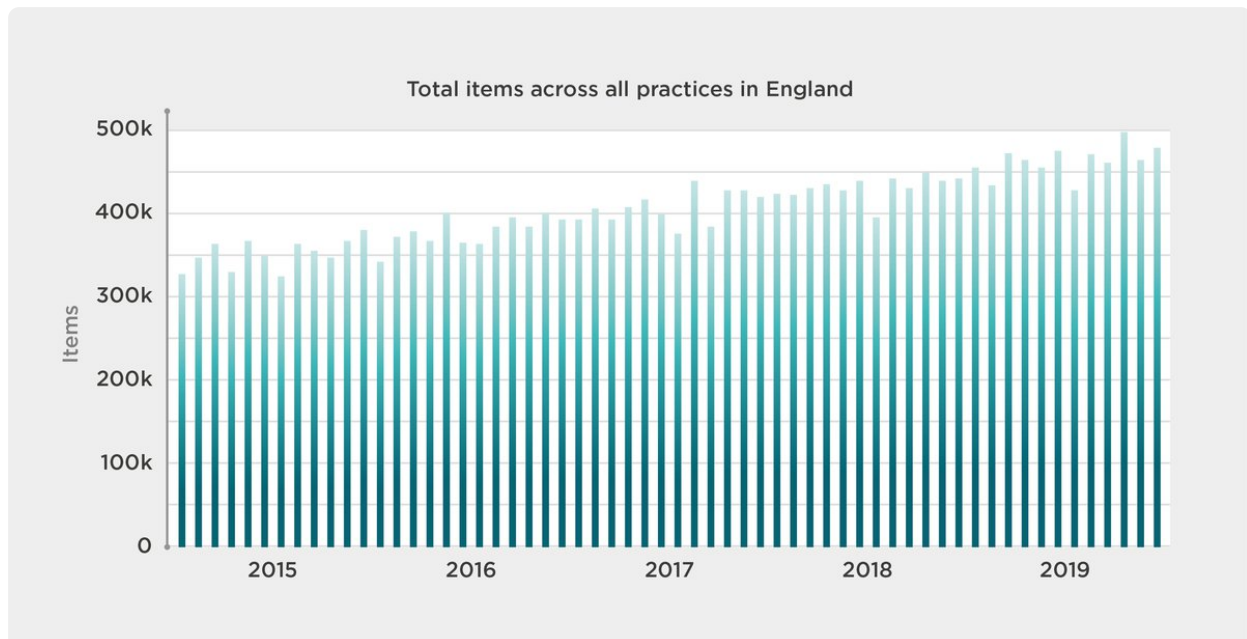


Fig 1 Prescriptions of propranolol issued, May 2014 to July 2019

4.2.2 The investigation has been unable to access any data to demonstrate the medical reason for these prescriptions. NHS England information (NHS, 2019a) explains that propranolol used to be a popular treatment for hypertension (high blood pressure) but is now only considered for use when other, more effective medicines have been ineffective in controlling a patient's blood pressure.

4.2.3 Pharmacy and medical subject matter advisors have also informed the investigation that propranolol is increasingly being used in the treatment of migraine and anxiety. Information from the Medicines and Healthcare products Regulatory Agency (MHRA)[22] also supports that the most commonly searched for indications for propranolol are migraine and anxiety symptoms.

4.2.4 Given the decreasing use of propranolol in the treatment of hypertension, it is likely that the overall increase in its use reflects the increasing use of propranolol in non-cardiac conditions, such as migraine and anxiety.

4.2.5 Both the BNF and NICE guidance provide information on the use of propranolol to prevent migraine. The relief of situational anxiety and generalised anxiety symptoms is a licenced indication (approved reason for use) for some propranolol products. The BNF confirms that propranolol is licensed for use in the treatment of physical symptoms of anxiety. However, NICE guidance on the treatment of anxiety (NICE, 2011a) and wider guidance on common mental health problems (NICE, 2011b) does not refer to propranolol or how and when it may be used in practice to treat patients with these symptoms.

4.2.6 Maudsley Prescribing Guidelines[23] (Abel et al, 1999) list propranolol under 'depression and anxiety' as a treatment that is less well tolerated or has a weaker evidence base.

4.2.7 Since the earliest paper published on propranolol and anxiety in 1966, the investigation can identify only one systematic review and meta-analysis of the literature (Steenen et al, 2016) in regard to the use of propranolol to treat anxiety. The systematic review found that 'the quality of evidence for the efficacy of propranolol at present is insufficient to support the routine use of propranolol in the treatment of any of the anxiety disorders'.

Current guidance on propranolol toxicity

4.2.8 In England, guidance on overdose of propranolol and beta blockers is set out within a range of sources.

4.2.9 NICE guidance (2012) and the Clinical Knowledge Summary on the use of propranolol for migraine (NICE, 2019) do not contain any reference to the risks of propranolol in overdose.

4.2.10 The BNF contains information on the risks of medications in overdose. For propranolol, the symptoms of overdose are listed as including light-headedness, dizziness, fainting, and that heart failure may be precipitated or exacerbated. For beta blocker poisoning more broadly, the BNF adds that patients may have a slow heart rate and that 'acute massive overdosage' should be managed in hospital.

4.2.11 Primary care patient record systems may also contain information that prompts prescribers to the possible risks of prescribing certain medications.

4.2.12 According to NICE (2015b), these clinical decision support tools are defined as 'an active, computerised intervention that occurs at the time and location of prescribing, to support prescribers with decision-making'.

4.2.13 For example, some systems will identify when 'depression' has been entered as a patient diagnosis and issue an alert stating that amitriptyline (a class of antidepressant medication) is indicated in depression but is not recommended due to the risk in overdose. However, the investigation concluded that alerts are not routinely present in electronic systems for the prescribing of propranolol to a similar patient group.

4.2.14 A detailed discussion of the use of such systems is contained in the Healthcare Safety Investigation Branch (HSIB) investigation, Electronic Prescribing and Medicines Administration Systems and Safe Discharge (HSIB, 2019).

HSIB makes the following Safety Observation

Safety observation O/2020/058:

Electronic prescribing systems used in primary care may benefit from alerts that prompt clinicians about the potential risks of prescribing propranolol to people in certain patient groups.

4.2.15 The MHRA includes guidance in the Summary of Product Characteristics (SmPC) document on the use of a medicine, including warnings and precautions for prescribers and patients (medicines.org.uk, 2018). The SmPC is the basis of information for healthcare professionals on how to use a medicinal product safely and effectively. It is not in the remit of the SmPC to give general advice on the treatment of particular medical conditions, but aspects of treatment that relate specifically to use of the medicinal product or its effects should be mentioned.

4.2.16 SmPC guidance is updated via monitoring of the MHRA's Yellow Card Scheme reports (see 1.4.2). The guidance provided on propranolol overdose recognises the risk of cardiovascular and neurological[24] impacts on patients and the potential need for treatment in intensive care where a significant impact on cardiac function is observed.

HSIB notes the following Safety Action**Safety action A/2020/020:****Safety action by the Medicines and Healthcare products Regulation Agency (MHRA)**

The MHRA is reviewing the information in the Summary of Product Characteristics (a legally required document detailing a medicine's properties and officially approved conditions of use) for propranolol-containing products relating to overdose and interactions with other medicines. It is also seeking advice from relevant experts on the need to review whether the balance of benefits and risks of propranolol remains favourable in patients presenting with physical symptoms of anxiety.

4.2.17 Other sources of information are also available to prescribers and patients to advise them on medications and any potential overdose risks. One popular resource for clinicians provides a blanket warning of the need to visit an emergency department in the case of any overdose of any medication (Patient.info, 2017).

4.2.18 Information from the National Poisons Information Service (NPIS) is provided via TOXBASE (see 1.6). TOXBASE provides guidance on the treatment options for propranolol overdose. This includes commentary on the range of toxic doses recorded for propranolol. TOXBASE advises of the circumstances in which patients should be referred for medical assessment. Within the advice provided is an '*alert for hospital doctors*' to advise that propranolol is potentially very toxic and clinicians managing patients who have overdosed on propranolol are encouraged to discuss serious cases with TOXBASE.

4.2.19 Data on the use of TOXBASE suggests that primary care clinicians may be accessing this information resource less regularly than those in acute services, with only 6% of TOXBASE user sessions being recorded by clinicians in primary care (NPIS, 2017). This is likely to be due to the types of services contacted first by patients who have taken an overdose; emergency departments and ambulance services are the most frequent users of TOXBASE.

4.2.20 The investigation's GP SMA commented that it is unlikely that a prescriber would regularly access TOXBASE to determine the potential impacts of a medication in overdose during the prescribing process.

4.2.21 The investigation found that the range of sources regularly accessed by clinicians at the point of prescribing may not consistently recognise the potential serious impacts of propranolol in overdose, which have been identified by academic studies in other countries.

4.2.22 A 1996 study (Reith et al.) considered poisoning deaths reported in Newcastle, Australia between 1987 and 1995. Propranolol was the only beta blocker associated with death and seizures when taken in overdose. The study also identified that propranolol was over represented in beta blocker poisoning and was taken by a younger age group.

4.2.23 A 1997 study (Love et al) of data from the United States (US) identified that propranolol was implicated as a cause of death in a disproportionately high percentage of deaths reported from beta blocker toxicity. A further study from the US identified propranolol as the main drug associated with beta blocker toxicity (Menke et al, 2015).

4.2.24 There is a need to ensure that guidance regularly accessed by prescribers accurately reflects the potential risks of propranolol. This can help to enable clinicians to reach appropriate prescribing decisions for vulnerable groups of patients who may require propranolol to treat a medical condition.

HSIB makes the following Safety Recommendation

Safety recommendation R/2020/068:

It is recommended that the British National Formulary reviews and updates guidance on the use of propranolol in the treatment of anxiety and the advice provided for beta blocker overdose.

Link between migraine and mental health

4.2.25 NICE guidance (2012) prompts clinicians to consider whether medicines are appropriate to be prescribed according to the patient's preference, comorbidities (other illnesses or conditions they have at the same time) and risk of adverse events. For certain medications more specific warnings are provided.

4.2.26 For example, the NICE Clinical Knowledge Summary on depression (2015) identifies that tricyclic antidepressants have potentially fatal cardiovascular effects when taken in overdose and that overdose can also cause sedation, coma, hypotension, and seizures. NICE guidance does not contain any specific reference to the danger of adverse events arising from overdose of propranolol. The investigation's emergency medicine subject matter advisor (emergency medicine SMA) highlighted that the mechanism by which propranolol acts on the body in overdose and the potential severity of its impact is very similar to tricyclic antidepressants.

4.2.27 Studies have demonstrated that people who have migraine are over two and a half times more likely have depression compared with people who do not have migraine (Breslau, 1988; Lipton et al, 2000; Zwart et al, 2003; Minen et al, 2016). Depression is one of the most common psychiatric comorbidities in patients with migraine, with up to 47.9% of patients with migraine also reporting that they have depression (Antonaci et al, 2011).

4.2.28 More than half of patients with migraine will also meet the criteria for at least one anxiety disorder in their lifetime (Minen et al, 2016). Anxiety disorders are two to five times more prevalent in patients with migraine than in the general population (Breslau, 1988). Patients with generalised anxiety disorder are at increased risk of migraine, and patients with migraine are at increased risk of generalised anxiety disorder (McWilliams et al, 2004).

4.2.29 Given the link between migraine, depression and anxiety there is the potential for an increased chance that patients seeing a medical professional about either migraine or anxiety will be receiving propranolol alongside treatment for depression.

4.2.30 There is a significantly increased risk of suicide in patients with depression (Bachmann, 2018). This may pose an increased risk that propranolol may be used in overdose by patients whose depression includes thoughts of self-harm.

4.2.31 Current NICE guidance (2009) does not provide advice on interventions in the event that a patient being treated for depression does not attend for a planned follow-up appointment.

HSIB makes the following Safety Recommendation

Safety recommendation R/2020/069:

It is recommended that the National Institute for Health and Care Excellence reviews and updates guidance on the use of propranolol in the treatment of anxiety and migraine, with particular reference to the toxicity of propranolol in overdose.

4.2.32 The investigation was told that the common use of propranolol within primary care, and the relative infrequency with which any GP may come across a serious adverse reaction, meant that there may be a lack of awareness of the risks posed by propranolol use for patients in certain groups. This was supported by comments received by the investigation from the Royal College of General Practitioners.

4.2.33 The investigation spoke with a number of GPs about their knowledge of the toxic effects of propranolol. Clinicians told the investigation that pressures on their time meant that they were unlikely to be able to access the broad range of information sources highlighted above. Instead, there were key resources that they would frequently refer to in order to aid prescribing decisions. These typically included the BNF and NICE Clinical Knowledge Summaries.

4.2.34 GPs told the investigation that the risk of severe effects in overdose was better understood for other medicines, such as tricyclic antidepressants. For these medicines, the risk of toxicity in overdose is specifically referred to in NICE guidance (2009) which helps practitioners to reach prescribing decisions.

4.2.35 Reports of deaths from propranolol overdose are increasing and every clinician that spoke to the investigation reflected that they perceive there to be an increase in the number of propranolol overdoses being seen.

4.2.36 Between 2012 and 2017 there has been a 33% increase in the number of patients reported to have died due to propranolol overdose, with 52 people recorded as having died due to propranolol overdose in 2017 (Office for National Statistics (ONS), 2018b). Of these 52 people, 67% (35) were women. Young women have also been seen to be at greater risk of death from propranolol overdose (Love et al, 1997).

Fig 2 ONS data on number of deaths linked to propranolol per year, 1993-2017

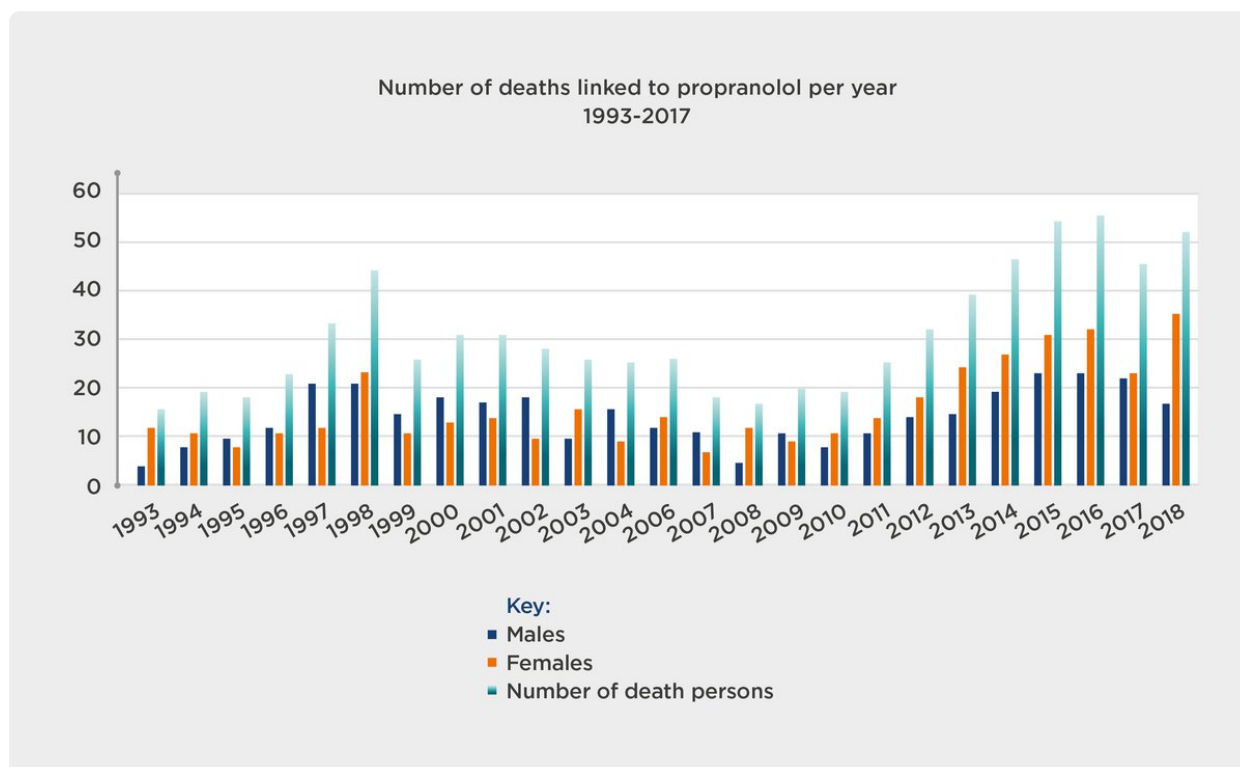


Fig 2 ONS data on number of deaths linked to propranolol per year, 1993-2017

4.2.37 The investigation found that there was a lack of awareness among GPs about propranolol toxicity and how this may impact on patients at greater risk of self-harm. This was in part due to the limited guidance available to GPs and also the relative infrequency with which they have encountered propranolol overdose.

HSIB makes the following Safety Recommendation

Safety recommendation R/2020/070:

It is recommended that the Royal College of General Practitioners supports its members in identifying the potential risk of prescribing propranolol to patients in at-risk groups.

4.2.38 A growing number of pharmacists in primary care are regularly involved in prescribing and dispensing medication (NHS England, 2019). The NHS Long Term Plan (NHS, 2019c) commits to increasing the number of pharmacists within primary care. Pharmacists are likely to have a growing role in primary care medicines safety and would also benefit from an increased awareness of the potential risk linked to propranolol prescribing identified in this report.

HSIB makes the following Safety Recommendation

Safety recommendation R/2020/071:

It is recommended that the Royal Pharmaceutical Society supports its members in identifying the potential risk of prescribing propranolol to patients in at-risk groups.

4.2.39 In addition to GP and pharmacist professional groups, there are a range of other stakeholders who may be involved in decisions relating to primary care prescribing. These include clinical commissioning groups (CCGs) and local medicines safety leads. These groups would also benefit from an increased awareness of the potential risk linked to propranolol prescribing identified in this report.

4.2.40 PrescQIPP CIC is an NHS-funded not-for-profit organisation that supports quality, optimised prescribing for patients. It provides guidance and support on prescribing to a large community of NHS professionals, with CCGs and commissioning support units among its subscribers, supporting the vast majority of the UK patient population. PrescQIPP CIC aims to share knowledge and expertise to ensure that prescribing professionals have access to the highest quality resources and information.

HSIB makes the following Safety Recommendation**Safety recommendation R/2020/072:**

It is recommended that PrescQIPP CIC supports its subscribers to identify the potential risk of prescribing propranolol to patients in at-risk groups.

4.2.41 As evidenced in the reference event, if a patient who is receiving propranolol is also being treated for depression they may be taking an SSRI antidepressant such as citalopram (see 1.5). NICE (2009) advises that patients with depression who require medication should receive SSRI antidepressants as a first-line treatment option because they have a low toxicity in overdose. Of the SSRI medications that may be recommended, citalopram is seen to be the most toxic in overdose (Hawton et al, 2010), with SSRI medication noted to cause coma, seizures and irregular heartbeat in overdose (NHS, 2019d).

4.2.42 NICE guidance reflects that SSRI medication is contraindicated where a patient is known to have QT interval[25] prolongation or where they are taking medication known to prolong QT interval. QT interval prolongation is a heart rhythm problem where the heart's electrical system takes longer than normal to reset between beats (NHS, 2019b). Both citalopram and

propranolol may prolong the QT interval when taken in overdose (Farhangi and Sansone, 2003). In addition, both citalopram and propranolol have been noted to cause arrhythmia (irregular heartbeat) and convulsions in overdose (BNF, 2019c).

4.2.43 The BNF recognises that citalopram is contraindicated when used with sotalol (another beta blocker), noting that manufacturers advise against using two or more medications that are known to prolong the QT period (BNF, 2019b). Although sotalol may be more effective than propranolol in suppressing heart rhythm disturbance (Deedwania, 1997) both medicines can be used to treat the same cardiac conditions.

4.2.44 When taken in overdose together, propranolol and citalopram may work in conjunction to increase the impact on a patient due to the similar nature in which they present in overdose. Medicines.org.uk (2018) advises that the development of cardiovascular complications is more likely if other cardioactive drugs (drugs that affect the heart) are also ingested.

4.2.45 An American online resource (Drugs.com, 2019) identifies that using propranolol together with citalopram may increase the effects of propranolol. It identifies that there have been reports of patients using beta blockers who have subsequently developed bradycardia (slow heart beat), hypotension (low blood pressure), and complete heart block (electrical signals cannot pass normally within the heart). The MHRA summary of product characteristics (SmPC) also advises that a different SSRI medication (fluvoxamine) can increase the concentration of propranolol in the system and lead to bradycardia.

4.2.46 However, the investigation has been unable to find any significant body of academic or professional literature that has considered in depth any potential risks relating to the reaction of SSRI antidepressants and beta blockers.

HSIB makes the following Safety Observation

Safety observation O/2020/059:

Further research into possible interactions between propranolol and Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants in overdose would be beneficial.

5 Ambulance response

5.1 Analysis and findings from the local investigation

The triage system

5.1.1 The Ambulance Trust used the Advanced Medical Priority Dispatch System (AMPDS) to help call handlers triage emergency calls. This system is used by half of the ambulance services in the UK and is drawn from a wider international AMPDS system.

5.1.2 When Emma called the ambulance service via 999 at 19:00 hours the call was transferred to an Ambulance Trust emergency call handler. These staff are non-clinical (not trained medical professionals) and receive training on how to use AMPDS in order to gather information from patients and ensure that the correct category of ambulance response is provided.

5.1.3 The call handler first asked if Emma was breathing. Emma confirmed that she was and that she was calling for herself. The call handler then asked Emma what had happened. Depending on the answer to this question, a range of cards (algorithms) can be selected in AMPDS to guide the call handler through a triage process, resulting in a decision on the priority of the call and the call category to which it should be allocated.

5.1.4 Emma confirmed that she had taken an overdose and this directed the call handler to use AMPDS Card 23: Overdose/Poisoning (Ingestion). This deals specifically with overdose calls and requires the call handler to ask a range of questions. On the recording of the call, Emma is heard to be alert and responsive to questions during the call and she reported that she was breathing normally.

5.1.5 The call handler was prompted to ask Emma what substance she had taken. The response to this question influences the category of ambulance that is dispatched to a call. If a caller confirms that they have taken any of the following medications, a Category 2 ambulance would be dispatched:

- cocaine or methamphetamine
- tricyclic antidepressants
- opioids, such as heroin or morphine
- an acid or an alkali.

5.1.6 An overdose of any other named drug or substance would routinely be assessed as requiring a Category 3 ambulance response.

5.1.7 The Ambulance Trust confirmed that during a call reporting overdose, the caller is also asked to confirm the time they may have taken the overdose. However, the Ambulance Trust did not routinely collect other information on medications. The investigation was told that this was due to the complexities of determining tablet size, dosages, amounts and any interactions between other medicines; this information would not routinely impact on the category of ambulance allocated to a call by the AMPDS system.

Clinical review

5.1.8 The investigation observed that there were paramedic staff available within the control room at the Ambulance Trust to provide advice and guidance on the categorisation and dispatch of calls. They were also able to review calls that were awaiting ambulance dispatch.

5.1.9 Call handling staff and dispatchers told the investigation that they could raise specific concerns with the clinical team if they felt a call required further clinical insight. The clinical team could then assist in considering whether a call needed to be re-categorised. However, this relied on call handling and dispatch staff identifying any clinical issues for escalation.

5.1.10 The clinical team told the investigation that the majority of their time was spent reviewing Category 4 calls to determine whether an ambulance was required or whether a more urgent resource was needed. This was with a view to ensuring appropriate ambulance resource could be allocated to either upgrade a response to these calls or to provide advice for home treatment options.

Category of ambulance response

5.1.11 The investigation identified that during Emma's call, the call handler asked an additional question not contained within the guidance for the algorithm. When Emma confirmed she had taken an overdose of propranolol and citalopram the call handler asked, "Do you use them as antidepressants?" When Emma confirmed that she did, the call handler triaged the call under the 'tricyclic antidepressant' code and a Category 2 ambulance was provided.

5.1.12 The investigation team spoke to the call handler to understand why this deviation occurred. The call handler was a woman who was approximately the same age as Emma. She disclosed that she had some personal experience of these medications and understood that propranolol could be used to treat anxiety and was often used in conjunction with antidepressants. It was this personal experience that led the call handler to ask if Emma took her medications for depression and to subsequently categorise Emma's call as Category 2.

5.1.13 The call handler requested an ambulance for Emma at 19:06 hours. When Emma's call was passed to the dispatch operator, they made routine checks to determine the availability of an ambulance for a Category 2 response.

5.1.14 The investigation identified that an ambulance had initially been allocated to Emma's call at 19:16 hours. However, this ambulance had been diverted to another Category 2 call. The other call had involved repeated contact from clinicians at a mental health unit reporting a patient with significant bleeding. The investigation team discussed this scenario with dispatch operators, who understood from these calls that there may be a patient with severe bleeding

who required immediate medical attention. On this basis, the dispatcher asked the ambulance initially intended for Emma to divert to this call, as it was within the locality and no other ambulance resource was available.

5.1.15 The ambulance that attended Emma's call was allocated to the call at 19:43 hours and arrived at her flat at 19:56 hours. In total, it took an ambulance 52 minutes to arrive in response to Emma's call. This is in excess of the mean target time (18 minutes) and 90% rate (40 minutes) set for Category 2 ambulance response. The call fell within the 10% of Category 2 calls that may not receive a response within these target times.

5.1.16 Data from the Ambulance Trust shows that on the day of Emma's call it received a total of 2,062 emergency calls, of which 1,197 were Category 2. Due to this level of demand, the mean response time for the ambulance service on that day was 25 minutes (versus a target of 18 minutes) and the 90% rate was 52 minutes (versus a target of 40 minutes).

5.1.17 The Ambulance Trust explained that ongoing problems with ambulance response times are well recognised nationally when considering the resource available. The Ambulance Trust's response times for Category 2 calls in January 2018 were in line with national average data compiled by NHS England (2018a).

5.1.18 The investigation did not consider in more detail the topic of ambulance resourcing and response times as this fell outside of the investigation's remit. However, future HSIB investigation's will likely consider current ambulance resourcing and response times in more detail.

5.1.19 It is important to note that had a Category 3 ambulance been dispatched (as should have happened under the AMPDS system), Emma should have received a response within two hours. On the day in question, the Ambulance Trust's Category 3 90% response time was two hours and 24 minutes. This was better than the England-wide average at that time.

5.1.20 Given the rapid deterioration in Emma's condition, any further delay in the ambulance response may have resulted in Emma dying in her home before an ambulance could arrive. The investigation was made aware of similar incidents at other ambulance trusts where this had occurred following dispatch of a Category 3 ambulance to calls concerning propranolol overdose.

First-party callers

5.1.21 Emma had been identified as a first-party caller, meaning that she was calling on her own behalf. Emma was also alone at the time of her call; there was no one else with her in her flat. Once a request for an ambulance was made the emergency call handler provided ‘*safety netting*’ advice²⁶ to Emma, which was to call back if her condition worsened. The call handler then ended the call.

5.1.22 Safety netting advice may not have been effective for Emma due to the rapid deterioration that propranolol overdose can induce, which can include confusion and loss of consciousness. Given this, it may not have been possible for Emma to contact the Ambulance Trust again when her condition deteriorated.

5.1.23 The Ambulance Trust explained that due to demand on the service, call handlers could not stay on the line with all callers until an ambulance arrived. The Ambulance Trust also explained that at the time of Emma’s call it had set criteria for calls where it would expect call handlers to stay on the line. These included calls where:

- pre-arrival instructions were required (for example, directions to a third party for conducting cardiopulmonary resuscitation (CPR))
- a patient was unconscious
- a patient was having multiple seizures
- a defibrillator²⁷ was present and needed to treat a patient
- a caller had threatened suicide/self-harm or violence.

5.1.24 Emma’s call did not fall within these categories. She was alert and orientated at the time of her call and was not threatening suicide or self-harm; she had already taken an overdose of medication.

HSIB notes the following local Safety Action

Safety action A/2020/028:

The Ambulance Trust has amended its call handling policy to offer more discretion to call handlers as to when they can choose to stay on the phone with a first party caller who has taken an overdose.

Propranolol re-coding

5.1.25 The investigation was informed by senior managers at the Ambulance Trust that, following Emma's call, it had introduced a local policy for dealing with propranolol overdose, which has been in place since 1 February 2018.

5.1.26 The variation to the call handling policy was intended to adapt the AMPDS categorisation to ensure that any callers reporting a propranolol overdose were categorised as a Category 2 call. This action was taken due to the organisation's increased awareness of the potential of a propranolol overdose to lead to rapid deterioration. The variation stated that propranolol should be treated as a tricyclic antidepressant and triaged as a Category 2 call.

5.1.27 The Ambulance Trust explained that it could not make variations to the AMPDS software or triage algorithms in order to reflect the variation to its call handling policy. Instead, the variation had been issued to emergency call handler team leaders via email. This was then cascaded to call handlers via email and at team briefings. The investigation saw that the variation to the call handling policy had also been also printed out and placed in a shared paper folder in the control room that the call handlers could access.

5.1.28 The Ambulance Trust also had an internal intranet that contained guidance documentation on tricyclic antidepressants. This identified medications that fell within this class to help alert call handlers to named drugs. Propranolol had not been added to this list in line with the local variation as it is not a tricyclic antidepressant.

5.1.29 The investigation ran a test call with one of the call handlers in the Ambulance Trust control room using the narrative of the reference event patient's call, to determine what category of ambulance would be dispatched. The call proceeded in the same manner as Emma's call until the call handler asked what medications had been taken.

5.1.30 The call handler was not familiar with propranolol and explained that it would be normal practice for call handlers to rely on Ambulance Trust guidance or use internet searches to try to find out what a medication was. In this case, on searching, the call handler identified propranolol as a beta blocker. The call handler recognised citalopram as an antidepressant and searched the list of tricyclic antidepressants to see if citalopram was present. As an Selective Serotonin Reuptake Inhibitor (SSRI) medication, citalopram was not on this list. Based on this understanding of these medications, the call handler assigned a Category 3 ambulance to the test call.

5.1.31 Data from the Ambulance Trust suggested that an average of four calls a month contained mention of propranolol overdose, compared to an average of 1,496 calls per month where overdose of a range of other medications and substances was raised. The relative rarity of specific overdose calls may have made it challenging for emergency call handlers to recall guidance without further prompts or support from the computer systems they use.

HSIB notes the following local Safety Action

Safety action A/2020/029:

The Ambulance Trust has recognised the limitation of the local variation to its call handling policy and raised a case with the AMPDS dispatch academy to ask that propranolol be added to the list of medicines within AMPDS that can be coded as a Category 2 response.

5.2 Analysis and findings from the wider investigation

Triage systems

5.2.1 Patients calling 999 who reported overdose and symptoms similar to those reported by Emma would routinely receive a Category 3 ambulance response in line with the AMPDS or NHS Pathways systems.

5.2.2 The investigation noted that both the AMPDS and NHS Pathways datasets are capable of allocating higher category call responses to overdose calls depending on the physical signs and/or symptoms reported at the time of the call. For example, if the call concerns a patient who is unconscious or having difficulty breathing, a Category 2 ambulance would be dispatched. Within the NHS Pathways dataset, if a caller who had taken an overdose reported being hot to the touch or pale in colour then a Category 2 ambulance could also be dispatched.

5.2.3 The NHS Pathways dataset does not prompt emergency call handlers to ask what medication a caller may have taken. If this information is offered, it would not affect the category of ambulance dispatched via the NHS Pathways system by an emergency call handler. The ability to provide a higher category of ambulance response in NHS Pathways is based on the physical symptoms reported by the caller, not on any known risk of deterioration of the patient's condition due to medication overdose.

5.2.4 The AMPDS dataset does allow for a Category 2 ambulance response to be dispatched to patients where a caller reports an overdose of a specific category of medication. The investigation engaged with the Ambulance Trust and subject matter advisors to understand the rationale for this variation. The variation was seen to emerge from the specific concerns and knowledge of clinical deterioration arising from overdose of certain groups of medication.

5.2.5 This reasoning is reflected in the AMPDS dataset and guidance provided to call handlers. For example, the algorithm for tricyclic antidepressants recognises that these medications can cause collapse and unconsciousness very quickly, even when a caller is seemingly alert.

5.2.6 AMPDS guidance for emergency call handlers does identify that overdose of cardiac medications can lead to collapse and unconsciousness very quickly. However, calls concerning these medications are not automatically re-categorised within the AMPDS system. In addition, the guidance does not direct call handling staff to the increased use of propranolol (and beta blocker medications) in the management of migraine or their use in anxiety. This may limit call handlers' ability to identify that propranolol is a cardiac medication and that the case may need to be escalated to a clinical colleague.

Variation in ambulance response to propranolol overdose

5.2.7 The investigation aimed to identify what, if any, variation existed within ambulance services when considering how ambulance trusts may handle emergency calls concerning an overdose of propranolol, or overdose more broadly.

5.2.8 To do so, the investigation requested information from English ambulance services. Responses were received from eight English ambulance services. To allow a broader UK comparison, information was also gathered from ambulance services in Scotland, Wales and Northern Ireland.

5.2.9 The information returned to the investigation demonstrated significant variation in practice among UK ambulance services. All ambulance services apart from the Ambulance Trust in the reference event confirmed that reports of overdose involving propranolol would not be automatically upgraded to a Category 2 ambulance response. Instead, the responses reflected a range of approaches for dealing with overdose calls in general.

5.2.10 Many of the responses received included varying guidance on when overdose calls would be alerted to clinical staff. These included a range of responses:

- A response facilitated only on the AMPDS or NHS Pathways data set with no clinical review.
- Systems whereby calls concerning overdose may be alerted to clinical staff for review (for example, where an ambulance response was delayed).
- Systems whereby all calls concerning overdose would be alerted to clinical staff for review and potential re-categorisation (for example, by flagging such calls to clinical colleagues).

5.2.11 The data received revealed that there was no consistent approach to the way overdose calls may be handled, what information may be requested, or what (if any) clinical review was indicated. A review identified that there were significant differences in the clinical resource available to NHS ambulance services and how they were used (NHS Improvement, 2018).

5.2.12 In addition, the investigation found no nationally agreed approach to the circumstances in which a first-party caller who was alone would be kept on the line by emergency call handling staff. The reference event demonstrated that operational pressures may require call handlers to terminate calls and provide safety netting advice.

5.2.13 The rapid deterioration in a patient's condition that can follow a propranolol overdose, and overdose of other medications, may mean that safety netting advice cannot always be effective in these patient groups. No specific national guidance is provided as to the potential risk posed to these patients.

Information collected from callers about overdose

5.2.14 The investigation found that the range of information collected from callers reporting an overdose by emergency call handlers in AMPDS and NHS Pathways may routinely be limited to the nature of the drug taken. The investigation team observed that the time a patient took a drug may also be collected, but that this did not directly impact on the categorisation of a call within the AMPDS or NHS Pathways dataset.

5.2.15 No further prompts were incorporated into the AMPDS or NHS Pathways dataset to encourage emergency call handlers to collect other information about the nature of the overdose. Even where further information may be collected, there was no mechanism to enable this to influence the categorisation of ambulance response determined by the datasets. Emergency call handlers were unable to override categorisation decisions but could add additional notes of their call should this assist in any clinical review.

5.2.16 Overdose is recognised to be a complex medical problem, with multiple variables impacting on the potential severity of the symptoms a patient may experience (NICE, 2017). A study considering overdose in Wales (John et al, 2016) identified that over 54% of patients who had requested medical help had ingested two or more medications, making consideration of the potential pharmacological impact of the overdose even more challenging because of the interaction between drugs.

5.2.17 The National Institute for Health and Care Excellence (NICE) Clinical Knowledge Summary on poisoning and overdose (2017) provides guidance for medical professionals in first contact with patients who may have taken an overdose, to help them to identify cases of potentially serious poisoning. The Clinical Knowledge Summary provides guidance on the information required to determine the appropriate clinical response to an overdose. This includes gathering information on:

- the age, weight, and sex of the person
- past medical history, medication and factors that could impact on the effect of overdose

- the amount and types of medicine taken
- when and how the medicine was taken.

5.2.18 This information is not routinely collected within current AMPDS or NHS Pathways datasets. The investigation was told by subject matter advisors that it would be extremely challenging for the datasets to account for the range of variables that may exist in cases of overdose.

5.2.19 If a patient who had taken an overdose visited an emergency department, the range of information identified above would be sought to determine the appropriate clinical response. However, if an overdose patient contacted an ambulance service call centre this information would not routinely be collected. Instead, the process of determining the individual impact on a patient of the medications they may have taken may not begin until a paramedic crew arrived.

Re-categorisation of propranolol overdose

5.2.20 In line with the safety action taken by the Ambulance Trust, the investigation has considered whether the ability to re-categorise propranolol as a Category 2 ambulance response could be effective. This would require amendments to the AMPDS and NHS Pathways but would allow for an enhanced response to be easily identified and dispatched.

5.2.21 However, subject matter advisors and ambulance trusts have stressed to the investigation the impact that re-categorising ambulance response times for specific conditions can have on the broader ability for ambulance services to provide services in line with the Ambulance Response Programme (ARP) (see 1.7). The ARP has undergone external evaluation (NHS England, 2018b) to assess its impact on increasing the operational efficiency of ambulance services while maintaining a focus on the clinical needs of patients.

5.2.22 Subject matter advisors have highlighted that, without appropriate evaluation, the re-categorisation of responses to specific conditions can have a direct impact on the ability to respond to other emergencies. For example, the investigation was told by subject matter advisors that if propranolol was automatically categorised as a Category 2 ambulance response then the additional resource required to meet this priority would need to be drawn from the existing resources available to the ambulance service. There is currently no additional resource available within the NHS to allow for additional paramedic crews and response vehicles to assist in responding to these calls.

5.2.23 Automatic re-categorisation of specific overdose calls also does not account for the individual variation seen within overdose calls. This can make overdose calls challenging to assess accurately within current datasets.

5.2.24 Data from the Office for National Statistics (ONS, 2018a) also identifies that there are a range of other medications linked to patient deaths that also do not currently require automatic re-categorisation. For these medications, the same challenges exist in terms of the ability for information to be accurately collected and considered within the clinical context of the patient requiring an ambulance response.

5.2.25 Not all callers will require a higher category ambulance response due to the individual variations seen in overdose. Inappropriate categorisation of ambulance resources directly impacts on the ability for ambulance services to provide appropriate ambulance responses to other patients. In the context of the ARP's aims, such an approach may not target the sickest patients and may not be clinically or operationally efficient.

Clinical review

5.2.26 Paramedic staff are routinely available in the emergency call centre to supplement the emergency call handling team. In addition, mental health nursing support may also be available to help manage cases where callers have specific mental health needs.

5.2.27 The investigation observed control rooms where clinical staff were involved in screening or handling emergency calls. Where this was the case, clinicians were able to override the ambulance response category generated by the datasets. This was to account for the clinical skills of these staff and to allow clinical decision making to be incorporated into the triage process.

5.2.28 The investigation spoke with clinicians in ambulance control rooms who explained that they may override the system-generated ambulance response category in overdose cases where they had specific concerns about the amount and type of medication taken. A similar approach could also be applied to broader categories of calls that "just do not sound right" based on a clinician's experience and where they may have a clinical suspicion that a more or less serious problem may be the issue.

5.2.29 AMPDS guidance to emergency call handlers reflects broader guidance within the NICE Clinical Knowledge Summary (2017) in stating that information obtained from patients who have deliberately taken an overdose may be misleading and should be treated with clinical suspicion. In addition, NICE advises that, as self-poisoning is often impulsive, medications may have been taken from the first available source a person can access. This may not be their own medication, which can make it challenging for callers to describe what they have taken. Also, many people may be unable to explain the exact amount of medication they have taken.

5.2.30 Further interaction between patients and trained clinicians may help to overcome these challenges. In such circumstances, patients calling 999 may be able to undergo a more in-depth clinical consultation where required. This may help to identify more accurately the nature of the overdose and consider the complexities of the way in which such an overdose may affect that patient.

5.2.31 The investigation observed that the experience and knowledge available to clinicians within the control room helped them to proactively assess the potential risks posed to a patient by the medications they may have taken. Some ambulance trusts have also developed tools (for example, a specific overdose / poisons algorithm) to help clinicians identify factors that may put patients at a higher risk of serious complications from overdose.

5.2.32 Clinical review can help to ensure that the complex symptoms and effects of overdose can be holistically considered on a patient-by-patient basis. Such additional scrutiny may help to ensure that a more tailored response can be provided to overdose calls than is currently possible via current ambulance response algorithms. Clinical review may also aid the provision of appropriate safety netting advice. This would allow clinicians to use their professional judgement to determine whether a caller needs to be kept on the line or could be provided with advice to call back if their condition deteriorated.

5.2.33 Studies of NHS 111 services (Sen et al, 2019) have demonstrated that the clinical screening of calls can reduce the number of emergency department attendances recommended to patients. This may create greater efficiencies within the system by allowing suitable safety netting advice and the category of ambulance provided to be based more accurately on a patient's clinical presentation and known risks of deterioration. Such an approach would be in line with the stated aims of the ARP.

HSIB notes the following Safety Action

Safety action A/2020/021:

Safety action by NHS England/NHS Improvement

In March 2019, NHS England wrote to ambulance trusts in England regarding the management of cases where patients have self-harmed and are at risk of suicide. This included specific reference to patients who may have taken an overdose of medication. The letter acknowledged that there were varying models in place for the management of these cases and that it was imperative that such patients be provided with appropriate input and support from clinicians at an early stage.

NHS England requested that all ambulance services review their processes to ensure that robust clinical oversight was in place in control rooms to monitor patients who have self-harmed and are having suicidal thoughts, particularly those who have been allocated an initial Category 3 or 4 ambulance response. In regard to overdose, NHS England said that, when on a call, consideration should be given to the type of overdose and quantity of medication taken, which might necessitate the need to upgrade a call for clinical reasons.

5.2.34 The current action taken by NHS England can help to encourage ambulance trusts to learn from current best practice. However, without further guidance to aid a shared understanding of the expectations for clinical support for calls concerning overdose, there remains a risk that significant local variation will continue to exist within English ambulance trusts. This is contrary to the stated aims of the Ambulance Response Programme (ARP).

HSIB makes the following Safety Recommendation

Safety recommendation R/2020/073:

It is recommended that NHS England/NHS Improvement evaluates current approaches to the clinical oversight of overdose calls within ambulance control rooms and leads on work to develop a national framework to describe the requirements for appropriate clinical oversight of overdose calls.

6 Emergency treatment

6.1 Analysis and findings from the local investigation

Ambulance response

6.1.1 Emma's mother felt strongly that Emma could have been advised to attend her local emergency department immediately. The local emergency department was located approximately four miles from her home and would have been around a 15-minute journey by car or taxi. The family felt that this may have allowed Emma to access emergency treatment more rapidly.

6.1.2 The Ambulance Trust explained that where a patient is deemed to require transport to an emergency department for definitive treatment, a double-crewed ambulance (an ambulance with a two-person crew) is the preferred option. The Ambulance Trust stated that rapid

response vehicles (which are single-crewed) are typically sent to incidents where immediate on-scene clinical intervention is required (for example, cardiac arrest or anaphylaxis²⁸, which are Category 1 calls). A rapid response vehicle would only routinely be considered for other categories of call where the standard response time to an incident had been exceeded.

6.1.3 When Emma's call exceeded the standard response time the dispatch operator tried to find additional ambulance resources that could attend the call. Rapid response vehicles were not available during this period because they had been allocated to other emergency calls. When a double-crewed ambulance became available it was allocated to Emma's call.

Ambulance treatment

6.1.4 When the ambulance arrived on the scene the ambulance crew carried out an initial assessment in line with national clinical guidance (Association of Ambulance Chief Executives, 2019) (referred to as the Joint Royal Colleges Ambulance Liaison Committee (JRCALC) guidance) to consider Emma's airway, adequacy of breathing, circulatory status and any neurological disability. The ambulance crew also took steps, in line with JRCALC guidance, to identify Emma's bradycardia and seek to establish whether there were disturbances in her heart rhythm using an electrocardiograph (ECG).

6.1.5 Emma's condition quickly deteriorated following the ambulance crew's arrival and she went into cardiac arrest at approximately 20:15 hours. This was approximately 85 minutes after Emma reported taking the overdose to the emergency call handler. This is in line with the time period within which propranolol is noted to act on the body in overdose and the rapid deterioration that can occur.

6.1.6 The investigation's paramedic subject matter advisor (paramedic SMA) explained that cardiac arrest in the pre-hospital setting is frequently complicated by environmental constraints such as location and space, alongside a lack of immediate recourse to additional clinical support.

6.1.7 The ambulance crew carried out cardiopulmonary resuscitation (CPR) as directed by JRCALC guidance. The paramedic SMA noted that CPR by a single ambulance crew consisting of two staff is unlikely to be effective due to fatigue and the technical and cognitive demands of providing advanced life support. In addition, it is unlikely that effective CPR could have been continued when moving Emma to the ambulance if only two staff were present at the scene.

6.1.8 The investigation was told that the manual handling associated with using a trolley bed requires two staff, which would preclude the provision of ongoing CPR chest compressions. The additional complication caused by the paramedics being unable to establish an advanced

airway using tracheal intubation or a laryngeal mask airway (see 2.3.8) also meant that at least one member of staff would have been dedicated to maintaining basic airway support and bag-valve-mask ventilation during transfer to the ambulance.

Emergency department care

6.1.9 The emergency department team had considered TOXBASE (see 1.6) as a source of information to treat Emma's symptoms; TOXBASE guidance had been printed and was evident in Emma's medical records.

6.1.10 Expert opinion provided to the Coroner suggested that due to the volume of propranolol ingested by Emma, and the test results observed in the emergency department, Emma's overdose may not have been survivable despite the efforts of staff to resuscitate her.

6.2 Analysis and findings from the wider investigation

Paramedic education

6.2.1 In the UK, the training required to become a registered paramedic is delivered by the Health and Care Professions Council (HCPC) in accordance with an approved syllabus guided by the professional body, the College of Paramedics (2013).

6.2.2 Pharmacology (the study of how drugs and how they work in the body) is a core component of the paramedic education programme. This extends to an understanding of the basic pharmacological action of common drug classes such as beta blockers. The paramedic SMA advised that it would be unusual for an undergraduate paramedic curriculum to address the specifics of propranolol overdose.

Paramedic guidance

6.2.3 JRCALC includes guidance on the treatment of overdose and poisoning. In the case of any airway, breathing or circulation problems, the guidance suggests that a time-critical transfer to hospital should take place, with ongoing corrective action to address airway and breathing problems taking place on the way.

6.2.4 The paramedic SMA advised that there is a challenge facing paramedics in determining the point at which a patient should be taken to hospital. The investigation was told that good-quality CPR must be maintained to ensure that the patient is able to survive the journey to hospital, where any acute poisoning can be further treated. However, in cases of overdose, there is the potential for toxicity from medications to act on the patient and further their deterioration while life support efforts are underway.

6.2.5 Resuscitation Council (UK) guidance (2015) provides limited examples of where additional steps or caution may be required to help facilitate resuscitation. This includes reference to resuscitation being required as a result of opioid or cocaine overdose.

6.2.6 JRCALC provides additional guidance to paramedics on the treatment options available to address toxicity from a range of other medications while resuscitation efforts take place. This includes providing additional treatment to help counteract the effects of a drug, such as the need to administer naloxone (a medication used to block the effects of opioids) in cases of paracetamol compound drug overdose (for example, where tablets may also contain codeine (an opioid)). It also includes guidance on the potential risks associated with specific overdoses, advising, for example, that tricyclic antidepressant overdose can lead to convulsions and rapid physical change.

6.2.7 Beta blockers, and propranolol specifically, are identified as a common drug that may be taken in overdose. Specific guidance from JRCALC in regard to the treatment of beta blocker overdose advises that this may cause bradycardia, hypotension, dizziness and confusion. No specific warning is given in regard to the potential rapid deterioration that may result from propranolol overdose.

6.2.8 Guidance on the management of beta blocker overdose focuses on how to manage any potential slow heart rate in line with JRCALC guidance on cardiac rhythm disturbances. This guidance states that efforts should be made to establish an ECG and take steps to manage the slow heart rate before potentially transferring patients for further care.

6.2.9 The investigation considered the interventions available to paramedics when seeking to manage a slow heart rate or carrying out resuscitation that may help to address the underlying toxicity.

6.2.10 The drug glucagon is advocated as an emergency treatment for beta blocker overdose (Truhlar et al, 2015). Glucagon is referenced in JRCALC guidance, but only in relation to its use in hypoglycaemia (low blood sugar) at a dose of 1mg (glucagon is supplied in 1mg vials). Ambulance services that have engaged with the investigation have explained that routinely two vials of this medication would be available to an ambulance crew.

6.2.11 In order to treat beta blocker overdose glucagon must be administered intravenously at relatively high dosages (Bailey, 2003). It would typically require up to 10mg to begin treatment in a patient weighing 70kg. These quantities of glucagon are not routinely carried in the majority of UK ambulance services.

6.2.12 Other treatments that may be considered in the context of propranolol overdose include administration of sodium bicarbonate (Truhlar et al, 2015) and intralipid (Sebe et al, 2015) (see 2.4.3). Sodium bicarbonate is administered specifically to combat sodium channel blockade, a

particular feature of propranolol overdose which affects the generation of electrical impulses within the heart. Intralipid may be used in a variety of drug overdoses, including beta blocker overdose. Neither sodium bicarbonate nor intralipid are routinely carried by ambulance crews and paramedics would require additional guidance to facilitate their administration.

6.2.13 When considering the need to carry additional medications to combat specific overdose symptoms, there is a need to acknowledge the limited space and resource available to ambulance crews. The equipment carried by UK ambulances is intended to enable paramedics to respond to a broad range of medical conditions. The need to carry additional specialist medications would be challenging given the range of conditions that may be encountered by ambulance crews. Typically, medical treatment to address the toxic effects of propranolol is only available in secondary care settings, such as hospitals and specialist centres.

6.2.14 JRCALC guidance does not currently include information about the rapid deterioration that may result from overdose of propranolol. Guidance on rapid deterioration is provided for other medicines. For example, advice about tricyclic antidepressant overdose contains warnings about the ability for this medication to lead to rapid change in a patient's condition. The investigation's emergency medicine subject matter advisor (emergency medicine SMA) highlighted that the mechanism by which propranolol acts on the body in overdose and the potential severity of its impact is very similar to tricyclic antidepressants.

6.2.15 Also, JRCALC guidance does not advise on the potentially time-critical transfer required for patients who have taken a propranolol overdose. Such advice is provided in other circumstances, such as penetrating trauma injuries. These are recognised to require medical interventions that are not available to ambulance crews. In such cases, the advice given is not to stay on the scene to resuscitate a patient and instead to take patients immediately to hospital for treatment.

6.2.16 The investigation found that although ambulance crews are able to respond to specific symptoms of propranolol overdose (for example, slow heart rate), they are unable to begin active treatment of its toxic effect on the body. In such circumstances, rapid transport to the nearest emergency department is required in order to allow appropriate treatment to begin as quickly as possible.

HSIB makes the following Safety Recommendation

Safety recommendation R/2020/074:

It is recommended that the Association of Ambulance Chief Executives works with the National Poisons Information Service to review its guidance on the treatment and transportation of patients known to have taken an overdose of propranolol or other beta blocker medication.

HSIB makes the following Safety Observation

Safety observation O/2020/060:

National resuscitation guidance may benefit from further specific information concerning the additional challenges and treatment options available for other types of medication overdose.

6.2.17 Giving paramedic crews access to the TOXBASE mobile app would provide further opportunities for paramedics to understand the potential risks and treatment options for specific types of overdose.

HSIB makes the following Safety Observation

Safety observation O/2020/061:

Paramedics would benefit from the ability to access TOXBASE when responding to emergency calls.

Overdose presentations to the emergency department

6.2.18 The investigation's emergency medicine SMA commented that overdose is a relatively common reason why patients present to an emergency department.

6.2.19 The Royal College of Emergency Medicine curriculum (RCEM, 2015) includes treatment of poisoning and refers to beta blockers specifically as one of the common poisonings that clinicians need to be aware of. It also refers to the need for clinicians to access the National Poisons Information Service (NPIS) and TOXBASE to seek guidance on the management of poisoning cases.

6.2.20 The investigation's emergency medicine SMA confirmed that TOXBASE would be expected to be the first point of reference for emergency department clinicians treating a suspected poisoning or overdose. NPIS also provides a 24-hour telephone service supported by expert toxicology staff that can provide advice and guidance to clinicians.

6.2.21 TOXBASE guidance states that, in the presence of cardiac arrest, propranolol overdose may require prolonged resuscitation attempts. It goes on to mention specific interventions that clinicians could consider for a conscious patient who has taken an overdose. It includes consideration of:

- bicarbonate (to help with abnormalities seen on the ECG)
- intravenous fluids (to help manage low blood pressure)
- ionotrope or vasopressors (to help manage blood pressure)
- atropine (to help manage slow heart rate)
- glucagon (which increases the amount of calcium available to the system and strengthens heart contractions)
- high-dose insulin (suggested to increase the strength of muscle contractions in the heart)
- intralipid (a fat emulsion thought to bind drugs to help reduce the amount of 'free' drug within the system).

6.2.22 The above represents a complex series of medical interventions that may be required to treat a range of signs and symptoms encountered in propranolol overdose and includes a number of medication dosage recommendations.

6.2.23 The investigation's emergency medicine SMA commented that the way TOXBASE information is laid out, both online and when printed out, is complex. This could mean that important information about treatment options for propranolol overdose is hard to locate in the guidance and could be overlooked.

6.2.24 In the reference case, TOXBASE guidance was followed appropriately. However, in a high-stress and high cognitive load environment (such as a resuscitation) it is easy to miss important detail (Angerer and Weigl, 2015) and omissions or errors are more likely to occur (Staal, 2004).

6.2.25 TOXBASE guidance also includes an '*alert box*' to encourage direct telephone consultation with NPIS toxicology experts to try and mitigate this risk. However, in addition, pictorial algorithms are in use in other areas of medicine (Resuscitation Council (UK), 2015) to help simplify and standardise complex interventions (Podgorolec et al, 2002) and help to reduce cognitive load. This may also help to further ensure clinicians are able to easily interpret the necessarily complex guidance contained within TOXBASE.

HSIB makes the following Safety Observation

Safety observation O/2020/062:

It may be beneficial for the format of TOXBASE guidance to be reviewed to consider whether guidance documents may be better presented to allow clinicians to quickly and more easily interpret key steps in the treatment of overdose.

7 Summary of findings, safety recommendations, safety observations and safety actions

7.1 Findings

Primary care

- Propranolol is a cardiac medication but is now predominantly prescribed for the treatment of migraine or anxiety.
- Propranolol is widely used by many patients without incident and with clinical benefit.
- There is a specific group of patients who may be at an increased risk of using propranolol for self-harm because they have co-existing migraine, depression or anxiety.
- Current guidance for prescribing propranolol does not contain sufficient warnings regarding the potential severe toxicity of propranolol when taken in overdose.
- Current awareness of the potential impact of propranolol in overdose is limited and hinders the ability of prescribers to exercise clinical judgement when choosing to prescribe propranolol.
- There is a lack of published research and guidance on how propranolol may interact with antidepressant medication when taken in overdose.
- Propranolol is licensed for use to treat anxiety symptoms, as reflected in the British National Formulary , but clinical guidance regarding when and how it should be used in practice is not available from the National Institute for Health and Care Excellence.

Ambulance response

- There are variations in how ambulance triage systems may categorise calls concerning specific medication overdose.

- Cases of overdose are complex due to the many variable factors relating to the patient and the medication taken. Current ambulance triage systems are not able to account for this complexity.
- Automatic re-categorisation of overdose calls may not be effective or efficient in ensuring the sickest patients receive access to the quickest and most effective care.
- There are variations in the level of clinical input provided to help determine the correct category of ambulance response to calls involving overdose.
- Intervention by clinicians in the ambulance control room can help to identify and address specific complexities encountered in overdose cases and assist in an appropriate ambulance response being provided.

Emergency care

- Secondary care in hospital is required to ensure that a patient can receive the appropriate range of treatments to address propranolol toxicity.
- Current guidance for ambulance crews may not be effective in ensuring that patients who have taken an overdose receive timely hospital care.
- There are limited treatment options available to ambulance crews to help them treat patients who may have taken a propranolol overdose.
- Current guidance available to emergency department clinicians could be more clearly communicated to aid in the emergency response.

HSIB makes the following Safety Recommendations

Safety recommendation R/2020/068:

It is recommended that the British National Formulary reviews and updates guidance on the use of propranolol in the treatment of anxiety and the advice provided for beta blocker overdose.

Safety recommendation R/2020/069:

It is recommended that the National Institute for Health and Care Excellence reviews and updates guidance on the use of propranolol in the treatment of anxiety and migraine, with particular reference to the toxicity of propranolol in overdose.

Safety recommendation R/2020/070:

It is recommended that the Royal College of General Practitioners supports its members in identifying the potential risk of prescribing propranolol to patients in at-risk groups.

Safety recommendation R/2020/071:

It is recommended that the Royal Pharmaceutical Society supports its members in identifying the potential risk of prescribing propranolol to patients in at-risk groups.

Safety recommendation R/2020/072:

It is recommended that PrescQIPP CIC supports its subscribers to identify the potential risk of prescribing propranolol to patients in at-risk groups.

Safety recommendation R/2020/073:

It is recommended that NHS England/NHS Improvement evaluates current approaches to the clinical oversight of overdose calls within ambulance control rooms and leads on work to develop a national framework to describe the requirements for appropriate clinical oversight of overdose calls.

Safety recommendation R/2020/074:

It is recommended that the Association of Ambulance Chief Executives works with the National Poisons Information Service to review its guidance on the treatment and transportation of patients known to have taken an overdose of propranolol or other beta blocker medication.

HSIB makes the following Safety Observation

Safety observation O/2020/058:

Electronic prescribing systems used in primary care may benefit from alerts that prompt clinicians about the potential risks of prescribing propranolol to people in certain patient groups.

Safety observation O/2020/059:

Further research into possible interactions between propranolol and Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants in overdose would be beneficial.

Safety observation O/2020/060:

National resuscitation guidance may benefit from further specific information concerning the additional challenges and treatment options available for other types of medication overdose.

Safety observation O/2020/061:

Paramedics would benefit from the ability to access TOXBASE when responding to emergency calls.

Safety observation O/2020/062:

It may be beneficial for the format of TOXBASE guidance to be reviewed to consider whether guidance documents may be better presented to allow clinicians to quickly and more easily interpret key steps in the treatment of overdose.

HSIB notes the following Safety Actions

Safety action A/2020/020:

Safety action by the Medicines and Healthcare products Regulation Agency (MHRA)

The MHRA is reviewing the information in the Summary of Product Characteristics (a legally required document detailing a medicine's properties and officially approved conditions of use) for propranolol-containing products relating to overdose and interactions with other medicines. It is also seeking advice from relevant experts on the need to review whether the balance of benefits and risks of propranolol remains favourable in patients presenting with physical symptoms of anxiety.

Safety action A/2020/021:

Safety action by NHS England/NHS Improvement

In March 2019, NHS England wrote to ambulance trusts in England regarding the management of cases where patients have self-harmed and are at risk of suicide. This included specific reference to patients who may have taken an overdose of medication. The letter acknowledged that there were varying models in place for the management of these cases and that it was imperative that such patients be provided with appropriate input and support from clinicians at an early stage.

NHS England requested that all ambulance services review their processes to ensure that robust clinical oversight was in place in control rooms to monitor patients who have self-harmed and are having suicidal thoughts, particularly those who have been allocated an initial Category 3 or 4 ambulance response. In regard to overdose, NHS England said that, when on a call, consideration should be given to the type of overdose and quantity of medication taken, which might necessitate the need to upgrade a call for clinical reasons.

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9 Endnotes

[1] The aim is for at least 90% of calls to receive a response within 120 minutes.

[2] A mean response time of 18 minutes and at least 90% of calls to receive a response within 40 minutes.

[3] The national investigation concluded in October 2019. Owing to the UK general election and the wishes of the family the planned publication of the report was delayed until February 2020. All information in the report is correct as of the conclusion of the national investigation in October 2019.

[4] The British National Formulary (or BNF) is the UK reference for prescribing, dispensing and administering medicines.

[5] Problems relating to the circulatory system, including the heart and blood vessels.

[6] The branch of science concerned with the nature, effects, and detection of poisons. A consultant toxicologist is a medical professional who specialises in this field.

[7] Sometimes referred to as the Medical Priority Dispatch System (MPDS).

[8] At the time of the reference event the 2016 JRCALC guidance would have been applicable to ambulance crews attending propranolol overdose calls. There is no significant variation in this regard between the 2016 version and the 2019 guidance referenced in this report.

[9] CBT is a talking therapy that can help manage problems by changing the way patients think and behave.

[10] IAPT services provide evidence-based treatments for people with anxiety and depression.

[11] The Glasgow Coma Scale is used to assess patients in a coma. Scores range from fully conscious (15/15) to unconscious (3/15).

[12] A test to check the heart's rhythm and electrical activity.

[13] This consists of a curved plastic device with an integral bite-block designed to support the tongue and maintain an open airway.

[14] This device consists of a single tube with an elliptically shaped inflatable mask. The tube is inserted via the mouth and is positioned just above the vocal cords. When the mask component is inflated it creates a seal, enabling oxygen to be delivered via the trachea (windpipe) into the lungs.

[15] This involves visualising the vocal cords and passing a tube, with or without an inflatable cuff, directly through the vocal cords and into the trachea. It is a more technically challenging procedure but has the advantage that when the cuff is inflated the trachea is protected from further contamination by any fluids or other debris and ventilations may be delivered directly to the lungs.

[16] Pulseless electrical activity: this is a type of cardiac arrest where there is some electrical activity on the ECG but no pulse or cardiac output can be felt.

[17] The process of inserting a tube, called an endotracheal tube, through the mouth and then into the airway.

[18] A test that measures the levels of oxygen, carbon dioxide and other chemicals in blood from an artery, and the pH level (acidity) of the blood.

[19] A procedure that uses high-frequency sound waves to create an image of part of the inside of the body.

[20] Normal pH values are between 7.35 and 7.45; Emma's was 6.65. Normal lactate values are less than 2 millimoles per litre (mmol/L); Emma's was 20mmol/L.

[21] Data available via <https://openprescribing.net/chemical/0204000R0/>

[22] Data provided to the investigation by the MHRA via MedDRA. MedDRA is the medical dictionary developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use to enable the sharing of regulatory information about medical products.

[23] A referenced prescribing guideline for psychiatric (mental illness) medications.

[24] Relating to the brain and nervous system.

[25] The time between the Q wave and the T wave on the electrocardiogram. The Q wave indicates the electrical activity start of the major contraction of the heart, and the T wave indicates the resetting (repolarisation) of the heart's electrical system at the end of the heartbeat.

[26] Advice to a patient on what to do or who to contact if their symptoms get worse, for example.

[27] A device used to deliver an electric shock to the heart of a patient in cardiac arrest, to help the heart re-establish its rhythm.

[28] A serious allergic reaction.

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