SAFER MEDICATION USE

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Propranolol in the treatment of anxiety

Aim of this publication

Propranolol is increasingly used for the treatment of anxiety. However, several recent critical incidents have raised concerns that there may still be a lack of awareness amongst prescribers over the risks associated with propranolol in overdose. This report aims to raise awareness of the potential toxicity of propranolol in overdose and highlight a specific group of patients who may be at an increased risk of using propranolol for self-harm. It is recommended that this information is cascaded to ICB medicines safety groups and medicines safety officers to determine actions required within their systems.

Background

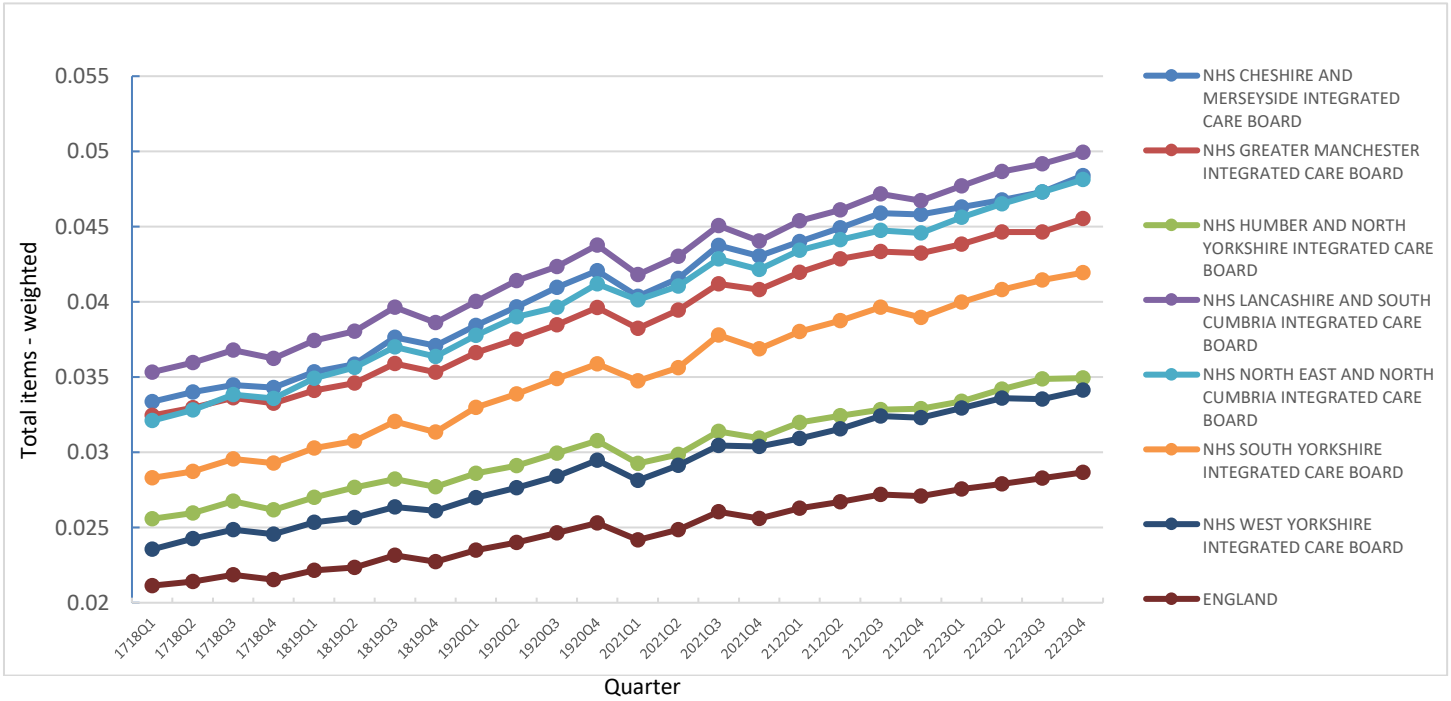
Propranolol is a non-cardioselective beta-adrenergic antagonist (beta-blocker) which has been used for the treatment of hypertension and heart rhythm disturbances for many years, but it is now more commonly prescribed for migraine prophylaxis and anxiety.[1,2] In recent years there has been a substantial rise in the number of propranolol prescriptions being issued in primary care.[3] Propranolol is an effective and safe drug when taken as prescribed and is widely used in primary care.[2] However, on TOXBASE propranolol has an alert highlighting that it is potentially very toxic in overdose, and it is important that it is prescribed appropriately, especially in those at risk of self-harm.[4] Although individual response after overdose varies greatly, propranolol can lead to rapid deterioration in patients that requires urgent medical intervention, and it is recognised as one of the most challenging overdoses to treat.[2,4] Prescribers need to be aware of the risk of toxicity of propranolol and the potential severe clinical outcomes following overdose.

In 2020, the UK Healthcare Safety Investigation Branch (HSIB) published a report on the potentially under recognised toxicity of propranolol in overdose., and risks when taken alongside antidepressants.[2] The report made a series of recommendations to various national organisations to ensure the safe use of propranolol and the most effective response and treatment to any overdose calls. However, current prescribing information and systems (where these are in place) do not always contain sufficient warnings regarding the potential severe toxicity of propranolol in overdose or the appropriateness of prescribing to individuals at risk of self-harm.

Increasing propranolol prescribing

Data extracted from ePACT2 show that over the last six years propranolol prescribing in primary care in England has increased by 36% when weighted for list size (figure 1).[3] Over the same period, there was a markedly greater increase in propranolol prescribing across all seven Integrated Care Systems (ICs) in the North of England, in particular, in the North East and North Cumbria, and the South Yorkshire ICSs which showed an increase of 50% and 48%, respectively. It should be noted that these data include prescribing of propranolol for any indication.

Figure 1. Propranolol prescribing for the North of England ICSs (total Items weighted by list size, Apr 2017- Mar 2023)

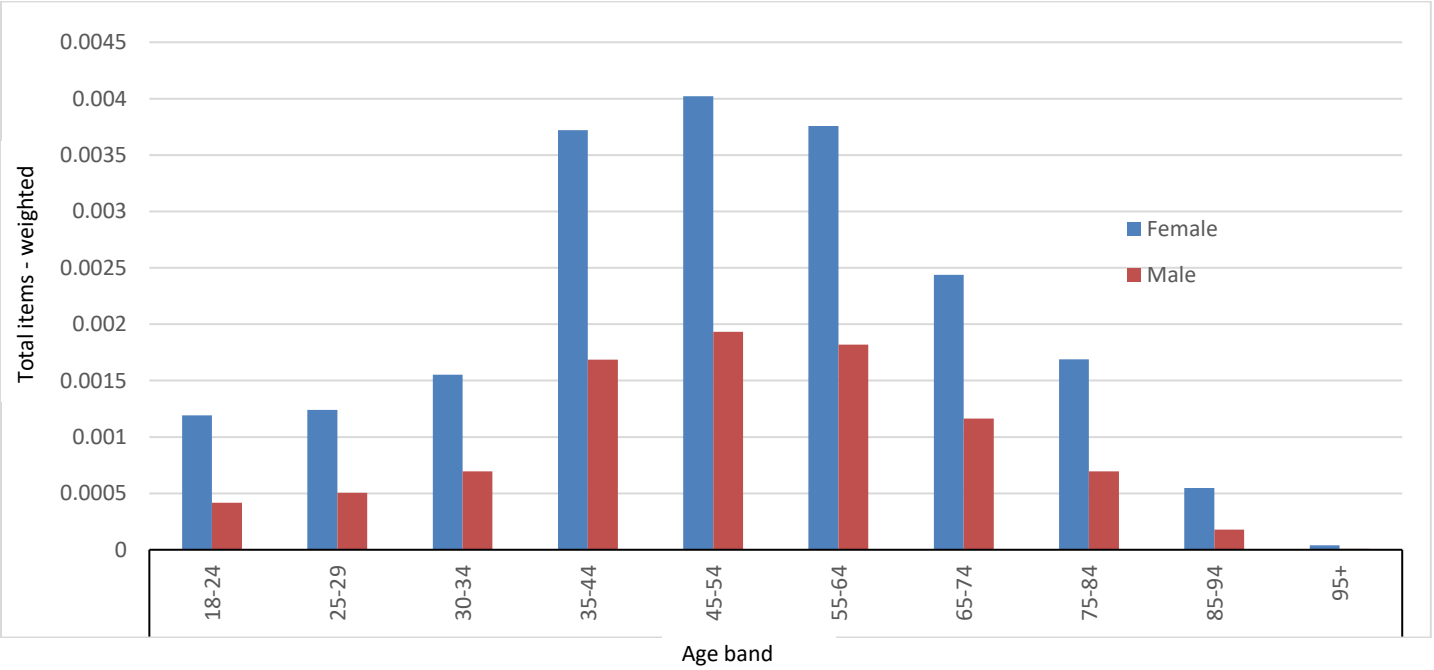


Anxiety disorders are the most common psychiatric disorders in UK general practice, and there has been a substantial increase in the recording of both anxiety diagnoses and symptoms between 2003 and 2018.[5] The overall recorded incidence in females was nearly twice that of males, and there was a marked increase in the incidence in younger age groups (18–34 years). The Health Foundation COVID-19 impact inquiry report shows pandemic restrictions had a significant impact on mental health and the ability of people to access health care and support networks, with women and younger people amongst those having fared the worst.[6]

Looking at the most recent propranolol prescribing data for England (Q3 23/24), the rates of prescribing in females were over twice that of males across all age groups (figure 2).[3] Similar trends were seen across all seven ICs in the North of England (data not shown). Although some of this prescribing will have been for other indications, the observed use of propranolol in those aged under 35 years is consistent with a previously reported rise in the primary care prescribing of beta-blockers for the treatment of anxiety in younger age groups.[5] Whether this reflects increased primary care presentation, wider awareness of anxiety among GPs, increasing severity of symptoms, or a greater acceptance of medication, is unclear.

A recent study using qualitative interviews explored GPs' views of prescribing beta-blockers for people with anxiety (n=17).[7] It found that GPs often viewed beta-blockers as a low-risk option compared to antidepressants, particularly in young adults where they might have concerns about risk of suicidal ideation or increased risk of self-harm. Some GPs explained that patients sometimes wanted an immediate improvement in their symptoms which GPs thought beta-blockers could potentially offer. Furthermore, some patients seemed more willing to try beta-blockers than antidepressants, as they did not perceive them as 'mental health drugs' and therefore potentially more acceptable and less stigmatising.

Figure 2. Propranolol prescribing by gender and age in England (total items weighted by age band list size, Oct 2017- Dec 2023)



Propranolol in the treatment of anxiety

Anxiety disorders are managed predominantly within primary care.[5,8] NICE Guidance (CG113) on generalized anxiety disorder (GAD) and panic recommends a stepped-care approach based on severity of symptoms and functional impairment, as well as consideration of comorbidities, patient preferences, and previous treatment.[9] If comorbidities such as depression are present, the primary disorder should be treated first. Serotonin Reuptake Inhibitors (SSRIs) are effective for a range of anxiety disorders and are suitable first-line treatments. If this is ineffective another SSRI or a SNRI may be offered. If SSRIs and SNRIs are contraindicated or not tolerated, pregabalin may be considered (with cautions). Benzodiazepines should not be offered for the treatment of GAD in primary care, except as a short-term measure during crises (maximum duration 2-4 weeks), and only by prescribers expert in their use. Antipsychotics should not be prescribed for the treatment of GAD in primary care.

Low dose propranolol, (usual dose 40-80mg per day in divided doses) is licensed for the relief of situational anxiety and GAD.[10] It may be useful for some patients exhibiting prominent somatic symptoms such as tachycardia, sweating and tremor. However, propranolol is not featured in NICE Guidance on the treatment of GAD and there are currently no clinical guidelines detailing when and how it should be used for anxiety.[9] Propranolol will not treat the underlying psychological symptoms of anxiety, such as worry, tension, or fear. Therefore, in GAD where worry is a particular feature the use of propranolol would not be routinely recommended.

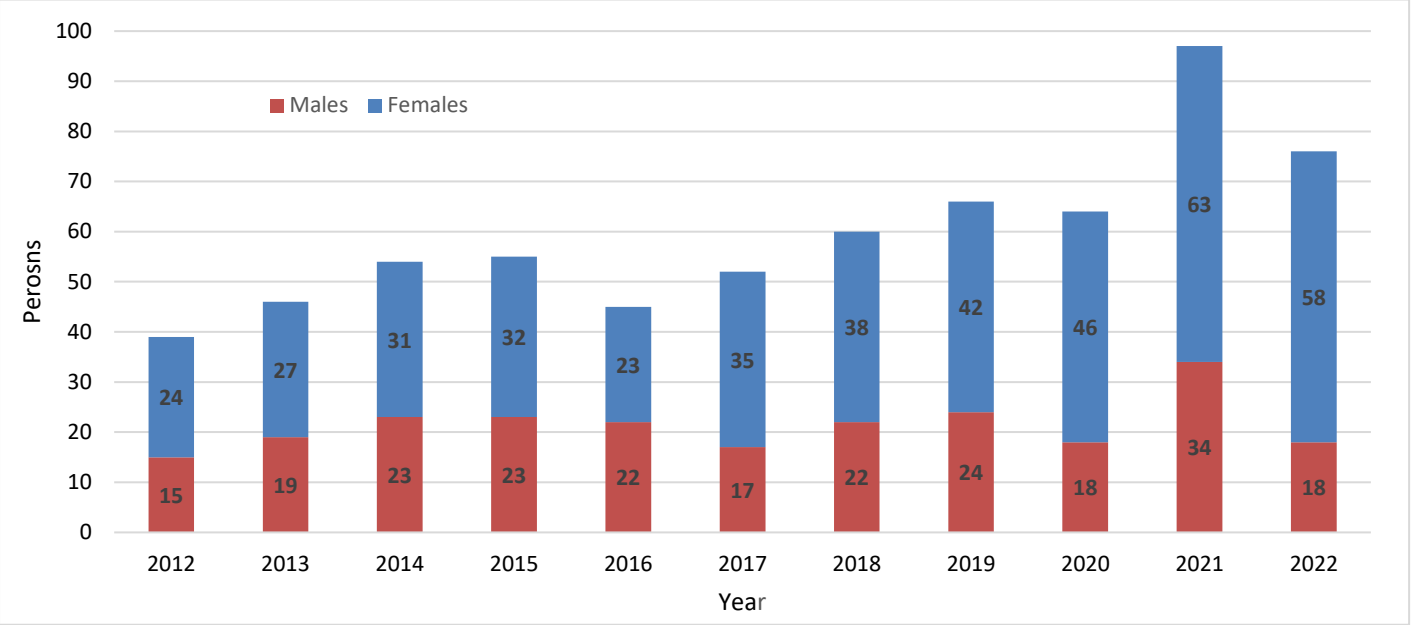
Due to the potentially severe consequences in overdose, caution should be used when prescribing propranolol for the treatment of anxiety. Before prescribing propranolol a full patient centred risk assessment, including history of suicidal thinking and self-harm should be undertaken to ensure that it is used appropriately. Propranolol should be initiated at low doses and gradually increased until the desired therapeutic effect is achieved. The lowest possible dose should be used for the shortest possible time. Regular follow up should be arranged to monitor treatment progress with suitable precautions maintained in at-risk populations to minimise adverse outcomes. A number of services may be available within primary care networks via social prescribing link workers to support people with mild anxiety and issues that may be contributing to it. Referral to specialist mental health services outside of primary care should be considered for complex and severe anxiety difficulties, or if there is a high risk of self-harm.[9]

Propranolol and the risk of self-harm

For this report, self-harm is defined as any intentional act of self-poisoning or injury carried out by an individual, irrespective of the of degree of suicidal intent or other motives.

National data shows that between 2012 and 2022 there was a 95% increase in deaths reported as being linked to propranolol overdose, with 76 deaths recorded in 2022 (figure 3).[11,12] In 2023/24, there have been six Prevention of Future Death Reports involving an intentional overdose of propranolol.[13] Two of these incidents involved an overdose of propranolol which had been prescribed in primary care for the physical symptoms of anxiety.

Figure 3. Number of drug-poisoning deaths where propranolol was mentioned on the death certificate in England and Wales registered between 2012 and 2022.



The National Poisons Information Service (NPIS) has conducted a series of studies examining the prevalence and circumstances surrounding propranolol overdoses. In a prospective analysis of propranolol exposures reported to NPIS between June 2019 and May 2020 a total of 171 enquiries were received regarding 164 patients, of whom 50% had taken a deliberate overdose of prescribed propranolol.[14] More than half of those who took a deliberate overdose had been prescribed propranolol for anxiety, of whom 30% had taken previous overdoses. Co-ingestion with one or more SSRI antidepressants occurred in 10% of these patients. In a further study, intentional overdoses involving propranolol were reported in 301 patients (67% female) between January 2022 and December 2022.[15] Propranolol was the patient's own medication in at least 62% of cases, and of the 132 cases in which the indication was recorded, 89% had been prescribed propranolol for anxiety. Of these, at least 42% were known to have taken deliberate overdoses previously. A retrospective review explored the demographics of fatal propranolol overdoses reported to NPIS between 2017 and 2021.[16] Over the five-year period a total of 46 fatalities were reported, with 57% of them being in young adults below the age of 40, and 77% of these being females. Almost half of all cases involved co-ingestion of an antidepressant, and in 89% of cases cardiac arrest occurred prior to contact with NPIS.

Data from the most recent NPIS annual report (2022-23) shows that propranolol was the eighth most commonly viewed product page on TOXBASE online with 21,787 views (UK only).[17] In total, NPIS received 459 enquires involving propranolol in 2022-23. Of these, 318 patients had taken an intentional propranolol overdose and 12 people died as a result. Propranolol was a prescribed medication in 173 cases, of which 108 were prescriptions to manage anxiety.

Identifying people at potentially increased risk of self-harm

People of all ages and from all social and cultural backgrounds may harm themselves and identification of individuals who may be particularly vulnerable can be difficult. Self-harm is rarely caused by a single circumstance or event and in any individual case multiple factors are usually involved.[18] The triggers that may increase an individual's risk of taking actions to harm themselves or attempt suicide commonly include difficult personal or social circumstances, past trauma (including abuse, neglect or loss), or social or economic deprivation.[18,19] For each person the contributing circumstances are individual, but some groups who may be at particularly increased risk of self-harm are young people, those experiencing mental health problems such as depression, anxiety, eating disorders, personality disorder, and alcohol or drug misuse. People with neurodivergent conditions (ADHD, autism), prisoners, veterans from the armed forces, some cultural minority groups, and people from sexual minorities (LGBT) are also found to be at greater risk of self-harming behaviours.[18,19] Young people who identify as female are up to five times more likely to self-harm than those who identify as male, though completed suicide is more prevalent among males.[18] Repetition of self-harm is particularly common in young people and represents the single strongest predictor of a future suicide attempt.[20]

It is essential that a holistic and person-centred assessment of all patients is undertaken before considering pharmacological treatment for individuals with anxiety. Details should be gathered about previous contact with psychiatric services, relevant psychosocial factors, severity of any comorbid depression or neurodivergence, and crucially feelings of hopelessness and suicidal ideation. The person's own history is vital as these factors may not previously have been disclosed, recorded, or diagnosed.

Where particularly vulnerable individuals are identified, appropriate help and intervention should be offered. In many instances the means to self-harm such as medication may be easily accessible in the immediate environment, which poses a greater risk of impulsive overdose. Whilst no medication can be considered safe taken in this context, certain medications such as propranolol pose a much greater risk of harm, or death, and prescribers should very carefully explore the risks and benefits of such treatment with the person, particularly if they are deemed to be at increased risk of self-harm. It is important to consider the potential toxicity of all prescribed medicines including those prescribed by other services and be mindful of quantities supplied on a prescription.

Recommendations

- ICBs should cascade this information to all providers via effective routes, such as Medication Safety Officers and medicines safety groups, who will determine the appropriate actions to be undertaken for their patients across their systems. This may include a local review of current propranolol prescribing practises, and communication of the risks described here via electronic prescribing systems and decision aids.
- Encourage Yellow Card Reporting of all suspected adverse drug reactions to propranolol including overdose to the MHRA as described below.

Practice points.

- Where psychological treatments have not been successful SSRIs are suitable first-line treatments for anxiety. If this is ineffective consider another SSRI or a SNRI. If SSRIs and SNRIs are contraindicated or not tolerated, pregabalin may be considered – however, this carries its own risks and prescribing should only be undertaken following a careful exploration of the risks and benefits, and with close monitoring and review.
- Low dose propranolol is licensed for the relief of situational anxiety and GAD, but it is not featured in NICE Guidance. Propranolol may be useful for some patients exhibiting prominent somatic symptoms such as tachycardia, sweating and tremor. However, it does not treat the underlying psychological causes of anxiety and therefore, in GAD where worry is a particular feature its use is not routinely recommended.
- Propranolol is known to cause severe toxicity in overdose and prescribers should carefully explore the risks and benefits of treatment in those who may be at an increased risk of self-harm.
- A full history and continuous assessments must be performed to ensure that propranolol is used correctly, with appropriate precautions maintained in at-risk populations to minimize adverse outcomes. Be alert to suicidal ideation and assess suicide risk, especially in young people, those with comorbid mental health problems, people with neurodivergent conditions, and those with a history of alcohol or drug misuse.
- Where particularly vulnerable individuals are identified, appropriate help and intervention should be offered at the earliest point.
- When prescribing propranolol for anxiety, use the lowest effective dose for the shortest possible time, review the quantity supplied and perform a risk assessment at every contact. Prescribers should be especially vigilant when prescribing propranolol in patients already taking an antidepressant (and vice-versa).
- If discontinuing propranolol, cautiously reduce the dose being mindful of withdrawal symptoms and encourage patients to safely dispose of any propranolol tablets if they are no longer required.

Urgent referral for medical assessment is required for all patients who have taken propranolol to self-harm, ingested a potentially toxic dose or who are symptomatic irrespective of the dose ingested. If reporting a suspected overdose to the emergency services, it is essential to inform them of the involvement of propranolol.

TOXBASE or the UK National Poisons Information Service must be consulted if there is any doubt regarding the degree of risk, or about management.

When should suspected adverse drug reactions be reported to the MHRA?

All serious suspected adverse drug reactions (ADRs) to propranolol including overdose should be reported to the MHRA via the Yellow Card Scheme (www.yellowcard.gov.uk).

An ADR is defined as serious when it is fatal, life-threatening, disabling or incapacitating, results in or prolongs hospitalisation, congenital abnormalities are observed or where the ADR is considered medically significant.

The Yellow Card Centre Northern and Yorkshire can provide support and guidance on any ADR related enquiry or completion of a Yellow Card. Information is available via our website (www.rdtc.nhs.uk).

References

1. Srinivasan A V. Propranolol: A 50-year historical perspective. *Ann Indian Acad Neurol*. 2019;22(1). doi:10.4103/aian.AIAN_201_18
2. Healthcare Safety Investigation Board. *Potential Under-Recognised Risk of Harm from the Use of Propranolol. Healthcare Safety Investigation I2018/022.* https://www.hsib.org.uk/documents/214/hsib_report_potential_under_recognised_risk_harm_propranolol.pdf
3. NHS BSA. ePACT2. https://www.nhsbsa.nhs.uk/access-our-data-products/epact2
4. National Poisons Information Service. TOXBASE: Propranolol. https://www.toxbase.org/
5. Archer C, MacNeill SJ, Mars B, Turner K, Kessler D, Wiles N. Rise in prescribing for anxiety in UK primary

care between 2003 and 2018: a population-based cohort study using Clinical Practice Research Datalink. *British Journal of General Practice*. 2022;72(720):e511-e518. doi:10.3399/BJGP.2021.0561
6. Suleman M, Sonthalia S, Webb C, et al. Unequal pandemic, fairer recovery: The COVID-19 impact inquiry report. Published online July 6, 2021. doi:10.37829/HF-2021-HL12)
7. Archer C, Kessler D, Wiles N, Chew-Graham CA, Turner K. Exploring GPs' views on beta-blocker prescribing for people with anxiety disorders: a qualitative study. *Br J Gen Pract*. Published online June 10, 2024. doi:10.3399/BJGP.2024.0091
8. Parker EL, Banfield M, Fassnacht DB, Hatfield T, Kyrios M. Contemporary treatment of anxiety in primary care: a systematic review and meta-analysis of outcomes in countries with universal healthcare. *BMC Fam Pract*. 2021;22(1). doi:10.1186/s12875-021-01445-5
9. NICE. Generalised anxiety disorder and panic disorder in adults: management | Guidance and guidelines |. *NICE clinical guideline 113 guidance.nice.org.uk/cg113*. 2011;(113).
10. Summary of Product Characteristics. Propranolol 10 & 40mg Film-coated tablets. https://www.medicines.org.uk/emc
11. Office for National Statistics. Number of drug-poisoning deaths where propranolol was mentioned on the death certificate, England and Wales, registered between 1993 and 2017.
12. Office for National Statistics. Number of drug-poisoning deaths, by age, where propranolol was mentioned on the death certificate, England and Wales, registered between 2016 and 2022.
13. Courts and Tribunals Judiciary. Prevention of Future Deaths. https://www.judiciary.uk/prevention-of-future-death-reports/
14. Williams HA, Henke D, Jagpal PS, Ferner RE, Sandilands EA. A 1-year prospective analysis of propranolol exposures reported to the UK National Poisons Information Service (NPIS)'. *Clin Toxicol*. 2021;59:557.
15. Williams H, Jagpal P, Bradberry S, Sandilands EA, Gray LA, Thanacoody RHK. A one-year prospective survey of propranolol exposures to UK National Poisons Information Service.' Clinical Toxicology, 62(sup1), 1–135.
16. Williams H, Jagpal P, Sandilands E, Gray L, Thanacoody R, Bradberry S. 1456: Fatal propranolol overdoses reported to the UK National Poisons Information Service (NPIS) over 5 years 01/01/2017–31/12/2021. *Emergency Medicine Journal*. 2022;39(12):A979-A979. doi:10.1136/EMERMED-2022-RCEM2.30
17. UK Health Security, Agency. *National Poisons Information Service Report 2022 to 2023*. https://www.npis.org/Download/NPIS report 2022-23.pdf
18. Royal College of Psychiatrist. Suicide and Risk : Helping People Who Self-Harm. *Policy*. Published online 2010.
19. NICE. Clinical Knowledge Summaries. Self-harm. Last revised in November 2023. Accessed September 24, 2024. http://cks.nice.org.uk/
20. Bennardi M, McMahon E, Corcoran P, Griffin E, Arensman E. Risk of repeated self-harm and associated factors in children, adolescents and young adults. *BMC Psychiatry*. 2016;16(1). doi:10.1186/s12888-016-1120-2