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Ref: 2025-0121

2nd May 2025

Royal College of Physicians response to Regulation 28 report to prevent future deaths

Dear Mr Walker,

The Royal College of Physicians (RCP) notes with concern the content of the Regulation 28 report for the prevention of future deaths related to the death of Chloe Elizabeth Burgess. We send our sincere condolences to the family of Ms Burgess.

This regulation 28 report is addressed to the RCP, and we have consulted cardiovascular and pharmacology experts, as well as liaising with the Royal Pharmaceutical Society to appropriately respond.

We note the matters of concern raised in this report, particularly that the potential dangers of the combination of amitriptyline, paroxetine and ivabradine are not widely appreciated and do not trigger an alert on the prescribing software used in primary care and/or by pharmacists. We also note that Chloe was known to have an electrical conducting abnormality of the heart, left bundle branch block an intraventricular conduction defect, which is in the BNF, lists as a 'caution' with the use of Ivabradine. Ivabradine | Drugs | BNF | NICE.

Our experts noted that whist ivabradine is a pacemaker current (If) inhibitor, used for the symptomatic management of heart-related chest pain and heart failure, it is also used for inappropriate sinus tachycardia.

We note that neither paroxetine or amitriptyline are listed as drugs interacting with ivabradine in the BNF Ivabradine | Interactions | BNF | NICE. The BNF is the recommended

nationally used prescribing aid. This is often used as a reference source for prescribing software and is overseen by the joint formulary committee.

Interactions between drugs which increase the concentration of ivabradine are well recognised and do appear in the BNF. Pharmaceutical colleagues also note that Stockley's Drug Interactions table, accessed via the Medicines Complete website does not show a "life-threatening or contraindicated combination" between amitriptyline and ivabradine. It does suggest, on a theoretical basis, that "dosage adjustment or close monitoring is needed" as "the risk of QT-interval prolongation with amitriptyline might be exacerbated by bradycardia caused by ivabradine. If concurrent use is unavoidable, monitor cardiac effects (e.g. heart rate) closely."

We note your concerns regarding the potential dangers related to failure to metabolise amitriptyline which can, incrementally, lead to toxicity, and the need for those prescribing to have full understanding of the potential interactions. The interaction by which paroxetine is predicted to increase the concentration of amitriptyline is also well recognised and included in the BNF Amitriptyline | Interactions | BNF | NICE / Paroxetine | Interactions | BNF | NICE. Pharmacology colleagues consulted noted that ivabradine is metabolised by a different enzyme from amitriptyline and are not aware of it increasing the concentration of amitriptyline. As ivabradine slows the heart, they note that there is a theoretical risk of QT-interval prolongation (changes in the electrical coordination within the heart) with amitriptyline which might be exacerbated by bradycardia caused by ivabradine and may increase the likelihood of arrhythmias in drugs which increase the QT interval on the ECG. This is supported by ongoing research, referenced below[1].

The Royal Pharmaceutical Society, as joint publishers of the BNF have advised that pharmacokinetic (drug metabolism) interactions are included within the BNF, but that all theoretical compound effects of combinations of medications through their mode of action cannot be included. Furthermore, prescribing software for primary care and pharmacies is provided by independent commercial organisations, who will choose which reference materials they use to inform alerts. This software and its application is currently not regulated.

It is the role of all prescribers to understand the overarching mechanisms of action of medicines they may prescribe, and where similar actions occur by more than one medicine, or might exacerbate pathology in individual patients, particular caution or monitoring should be instituted. It is important that they do not rely on prescribing software, but use recognised reference materials.

The Royal College of Physicians works closely with the Royal Pharmaceutical Society, the British Pharmacological Society and NHS England Chief Pharmacists. We will discuss this case at our next Patient Safety Committee and Joint Medicines Safety Working Group, to explore whether further action should be taken informed by this case.

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[1] hERG potassium channel blockade by the HCN channel inhibitor bradycardic agent ivabradine - PubMed

hERG potassium channel inhibition by ivabradine requires channel gating - PubMed

hERG potassium channel inhibition by ivabradine may contribute to QT prolongation and risk of torsades de pointes - PubMed

Royal College of Physicians

Yours sincerely,

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Clinical Vice President, Royal College of Physicians