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Original Article

Clozapine-associated pulmonary embolism: presenting features and outcomes, UK pharmacovigilance data, 1990–2022

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Background

Pulmonary embolism is said to be more common in clozapine-treated patients than either in patients treated with other antipsychotics or in the general population.

Aims

To explore clinical features and outcomes of clozapine-related pulmonary embolism in the UK.

Method

We studied UK Yellow Card reports recorded as clozapine-related respiratory, thoracic and mediastinal disorders, 1990–2022.

Results

Of 474 unique reports of people with clozapine-associated pulmonary embolism, 339 (59% male) remained after applying strict exclusion criteria. Of these, 164 patients (48%) died. The mean clozapine dose was 336.7 (range 25–1000) mg d^{-1} ($N = 126$). There was no difference in dose between the fatal and non-fatal outcomes. The median age at onset of pulmonary embolism was 45 years (range 21–82 years; $N = 309$). The median duration of clozapine treatment until onset was 2.9 years (range 2 days–22.7 years; $N = 306$). Sixty-five (39%) non-fatal and 36 (22%) fatal emboli occurred within 1 year of treatment. People who died were more likely to be obese (adjusted odds ratio 2.61; 95% CI 1.44–4.91) and to be noted as sedentary (adjusted odds ratio 6.07; 95% CI 1.58, 39.9). The 3 year moving average of cases was 0–5 per year, 1990–1999, 26 in 2010 and 16 in 2022. There was no change in the proportion of deaths by year of report ($p = 0.41$).

Conclusions

Clozapine-related pulmonary embolism is a significant concern with a high fatality rate. This risk necessitates a proactive approach to not only prevention, but also early recognition and management.

Keywords

Clozapine; pulmonary embolism; venous thromboembolism; adverse drug reactions; pharmacovigilance.

Clozapine is the most effective antipsychotic for treatment-refractory schizophrenia (treatment-resistant schizophrenia, TRS). However, its use is limited by a significant adverse drug reaction (ADR) profile, including the risk of agranulocytosis, myocarditis, clozapine-induced gastrointestinal hypomotility (CIGH) and metabolic syndrome, which necessitate regular monitoring through blood tests and clinical evaluation. Clozapine-associated pulmonary embolism is a further life-threatening complication.

Pulmonary embolism and clozapine

The incidence of pulmonary embolism in patients treated with clozapine is higher compared not only to the general population, but also to those given other antipsychotics.[1–4] In a clozapine registry study (67 072 patients, 1991–1993), the absolute risk of death from pulmonary embolism was 5.2 times higher among current as compared to past patients using clozapine.[1] Overall mortality has been estimated at 30%.[5–7] However, much of the evidence has been derived from high-level pharmacovigilance or registry data, with limited clinical details about presentations.[8] A review on clozapine-related thromboembolic events identified 28 relevant studies or case reports published since 2000, with a combined total of 42 patients.[7]

UK clozapine product licensing mandates robust reporting of ADRs through the UK Medicine and Healthcare products Regulatory Agency (MHRA) Yellow Card scheme. To study the demographics, risk factors and outcomes of clozapine-related pulmonary embolism, we examined MHRA clozapine-related Yellow Card reports recorded as respiratory, thoracic and mediastinal disorders, 1990–2022.

Method

We studied reports to the Yellow Card scheme recorded as respiratory, thoracic and mediastinal disorders as per the Medical Dictionary for Regulatory Activities (www.meddra.org), where clozapine was a suspected agent and pulmonary embolism was a documented ADR, 1990–2022 inclusive. Data were extracted using a pre-specified data-extraction form. Where available, the following data were recorded: date of reported event; age (year); gender; weight (kg); smoking status; pregnancy status; hormonal contraceptive use; pulmonary embolism event characteristics, such as date of onset, treatment and outcome; duration of clozapine treatment and clozapine dosage at time of report of pulmonary embolism (mg d^{-1}); presence of concomitant respiratory ADRs; results of relevant clinical investigations; use of other antipsychotic medications; clinical commentary; and other information, such as the presence of acute illness or use of 'sedentary' as a descriptor.

To limit the analysis to instances where clozapine use was the primary risk factor for pulmonary embolism, presentations in which the following risk factors were noted were excluded from the final clozapine-related pulmonary embolism cohort: long-haul

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travel, such as an intercontinental flight, that was described as 'recent' or documented as having taken place in the 4 weeks before the development of deep vein thrombosis (DVT) or pulmonary embolism; recent trauma; recent surgery; active malignancy; a strong family history of venous thromboembolism (VTE); thromboembolism that had occurred while the person was not taking clozapine; prescription of anticoagulants for unspecified reasons; or a blood clotting disorder. We also excluded presentations where the person was admitted to hospital for a potentially thrombogenic acute medical problem at the time, or was described as 'bed-bound' or otherwise immobilised in an older age residential care facility. We excluded presentations where clinical commentary indicated the absence of pulmonary embolism. We included presentations in which the person was described as having a sedentary lifestyle. Extracted data including clinical case commentary were reviewed independently by two co-authors (SE-P and RN) to assess for presence of exclusion criteria, and discrepancies were resolved by consensus.

Data analysis

The clozapine-related pulmonary embolism cohort was analysed by the following: age; gender; presence of obesity (body mass index $\geq$30 kg m^{-2}); clozapine dose at diagnosis of pulmonary embolism; duration of clozapine treatment before onset of pulmonary embolism; clinical details at presentation; and co-prescribed antipsychotic medication. Demographic and clinical covariates of patients who died were compared with those who either had recovered or were recorded as 'not yet recovered'. Comparisons were made using Mann–Whitney *U*-tests for continuous variables and Fisher's exact tests for categorical variables. Odds ratios for death by duration of treatment and additional risk factors for pulmonary embolism were estimated using logistic regression models adjusted for age and gender. The age of the patient was mean-centred for analyses.

The 3 year moving average series for total pulmonary embolism presentations and deaths were computed to smooth out year-on-year variations. A linear trend in the proportion of deaths was analysed using an extended beta regression model for outcomes that include 0 and 1.[9] A two-sided Type-I error of 0.05 was used to assess significance and analyses were conducted in R version 4.3.2 for Windows (R Statistical Foundation, Vienna, Austria; https://cran.r-project.org/) on the GNU Emacs editor version 27.1 for Windows (https://lists.gnu.org/archive/html/emacs-devel/2020-08/msg00237.html).

Results

There were 3676 (1344 fatal) clozapine-related Yellow Card reports within the respiratory, thoracic and mediastinal disorders class (Supplementary Table 1 available at https://doi.org/10.1192/bjp.2025.10422). Pulmonary embolism was the second most reported ADR (474 unique reports, 250 deaths) after dyspnoea (886 reports). (N.B. Pneumonia is associated with clozapine use, but is not a recognised ADR term per se.)

After applying the exclusion criteria, 339 people with suspected clozapine-induced pulmonary embolism (59% male; Table 1) remained. Of these patients, 164 (48.4%) died, while 167 people were reported as having either recovered or not yet recovered (for 8 people outcome was not recorded). The median age at onset of pulmonary embolism was 45 (range 21–82) years. Additional antipsychotics were prescribed to 77 (22.7%) people, most commonly amisulpride (8.8%) followed by aripiprazole (4.4%).

Clozapine dose was documented for 126 patients (37.2%) (mean 336.7 ± 171.5 mg (s.d.), range 25–1000 mg d^{-1}). Plasma clozapine and *N*-desmethylclozapine (norclozapine) concentrations were seldom recorded (4 and 1% of patients, respectively), and were not studied further. The median duration of clozapine treatment until onset of pulmonary embolism was 2.9 years (range:

Table 1 Summary data: clozapine-related pulmonary embolism, UK pharmacovigilance reports, 1990–2022

(a) Male versus female					
(i) Non-fatal	*N*	Male (*N* = 98)	*N*	Female (*N* = 69)	Test[a]
		Median (range)		Median (range)	
Age (year)	84	41.0 (22–75)	64	45.0 (23–82)	0.581
Dose (mg d^{-1})	44	337.5 (25–675)	15	275.0 (125–475)	0.245
Duration of treatment (year)[b]	80	1.9 (0.0–22.7)	62	0.7 (0.0–17.0)	0.088
Body weight (kg)	19	102.0 (63.0–180.0)	7	83.9 (50.9–118.0)	0.056
Sudden onset	3	–	1	–	0.643
Other antipsychotics co-prescribed	24	–	12	–	0.340
(ii) Fatal	*N*	Male (*N* = 99)	*N*	Female (*N* = 65)	Test[a]
		Median (range)		Median (range)	
Age (year)	92	44.0 (25–77)	61	50.0 (25–79)	0.073
Dose (mg d^{-1})	37	350.0 (75–800)	30	300.0 (100–1000)	0.104
Duration of treatment (year)[b]	96	5.1 (0.1–20.5)	64	3.8 (0.0–19.5)	0.230
Body weight (kg)	35	100.0 (70.0–215.0)	24	102.0 (54.0–153.0)	0.350
Sudden onset	25	–	9	–	0.114
Other antipsychotics co-prescribed	26	–	15	–	0.714
(b) Non-fatal versus fatal	*N*	Non-fatal (*N* = 167)	*N*	Fatal (*N* = 164)	Test[a]
		Median (range)		Median (range)	
Age (year)	148	43.5 (22–82)	153	46.0 (25–79)	0.035
Dose (mg d^{-1})	59	300.0 (25–675)	67	300.0 (75–1000)	0.186
Duration of treatment (year)[b]	142	1.3 (0.0–22.7)	160	4.4 (0.0–20.5)	<0.001
Body weight (kg)	26	97.9 (50.9–180.0)	59	102.0 (54.0–215.0)	0.864
Obese (body mass index $\geq$30 kg m^{-2})	21	–	42	–	0.003
Sedentary	2	–	11	–	0.011
Sudden onset	4	–	34	–	<0.001
Smoker	19	–	25	–	0.334
Other antipsychotics co-prescribed	36	–	41	–	0.516

a. Test for differences between groups. Mann–Whitney *U*-test for age, duration, dose and weight; Fisher's exact test for the remainder.
b. Duration of clozapine treatment before pulmonary embolism onset.

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Table 2 Clozapine-related pulmonary embolism, UK pharmacovigilance reports 1990–2022: risk of death by clinical and demographic factors

Variable	Unadjusted odds ratio (95% CI)	Adjusted[a] odds ratio (95% CI)
Duration of treatment (2-year increment)	1.11 (1.02, 1.22)	1.10 (1.00, 1.21)
Clozapine dose (100 mg d^{-1} increment)	1.22 (0.99, 1.54)	1.25 (0.99, 1.62)
Obesity (body mass index ≥30 kg m^{-2})	2.39 (1.36, 4.33)	2.61 (1.44, 4.91)
Smoking	1.40 (0.74, 2.69)	1.34 (0.69, 2.62)
Sedentary	5.93 (1.56, 38.73)	6.07 (1.58, 39.91)
Age (5-year increment)	1.11 (1.01, 1.22)	1.11 (1.01, 1.22)
Male gender	1.07 (0.69, 1.66)	1.22 (0.76, 1.94)

a. Adjusted by age and gender; age adjusted by gender; gender adjusted by age; age mean-centred.

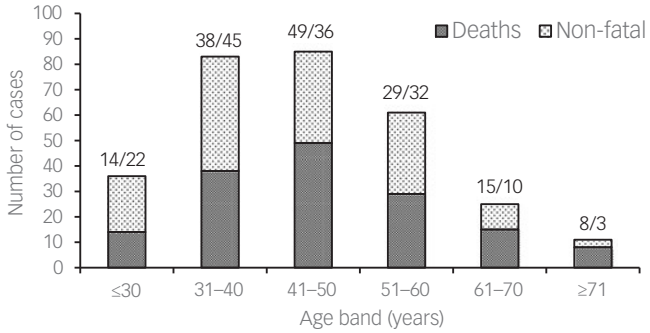

Fig. 1 Clozapine-related pulmonary embolism, UK pharmacovigilance reports 1990–2022 by age band.

2 days–22.7 years; $N = 306$). Sixty-five (38.9%) non-fatal and 36 (22.0%) fatal episodes occurred within the first year of treatment. Four patients were prescribed contraceptives. There were no instances where the patient was recorded as being either pregnant or postpartum.

Clinical presentation

The clinical features reported most frequently were dyspnoea ($N = 26$), chest pain (25), vomiting (5) and dizziness (3). In the deaths, pulmonary embolism was often only discovered on autopsy, although the deceased may have reported symptoms consistent with VTE before death. For example, over a period of 2 weeks, a male in-patient in his 40s experienced difficulties mobilising because of dyspnoeic episodes. This was attributed to anxiety by staff. He was later found dead in his room, with autopsy identifying DVT and pulmonary embolism as the cause of death. Similarly, a man in his 50s became short of breath and dizzy while out walking. He was taken to hospital by ambulance, where he was diagnosed with a panic attack and discharged. He was found dead at home 2 days later and pulmonary embolism and DVT were discovered post-mortem. Another man who was in his 20s died 1 month after starting clozapine. He had been complaining of leg pain, chest pain, nausea and vomiting and dizziness, but the significance of these symptoms was not recognised. He collapsed and died, with the autopsy identifying underlying DVT and pulmonary embolism as the cause of death.

People who died were more likely to be obese (adjusted odds ratio 2.61; 95% CI 1.44–4.91) and to be noted as sedentary (adjusted odds ratio 6.07; 95% CI 1.58, 39.91) (Table 2). Pulmonary embolism presentations were reported most commonly for people aged 30–50 years (Fig. 1). Even patients younger than 40 years old had mortality rates of 44%. The 3 year moving average of reported presentations increased from 0–5 per year, 1990–2000, to 26 in 2011, before falling to 16 in 2022 (Fig. 2). There was no evidence of a change in the proportion of deaths by year of report ($p = 0.41$).

Discussion

Ever since the introduction of chlorpromazine, reports of suspected antipsychotic-related VTE have emerged, especially in people taking clozapine and low-potency first-generation antipsychotics.[1–4,10] A meta-analysis published in 2020 found the use of *any* antipsychotic was associated with a relative risk of 3.69 (1.23–11.07) for pulmonary embolism.[11] Another systematic review found fatal pulmonary embolism to be seven times more frequent amongst people taking antipsychotic medication, with clozapine being the agent implicated most commonly.[4]

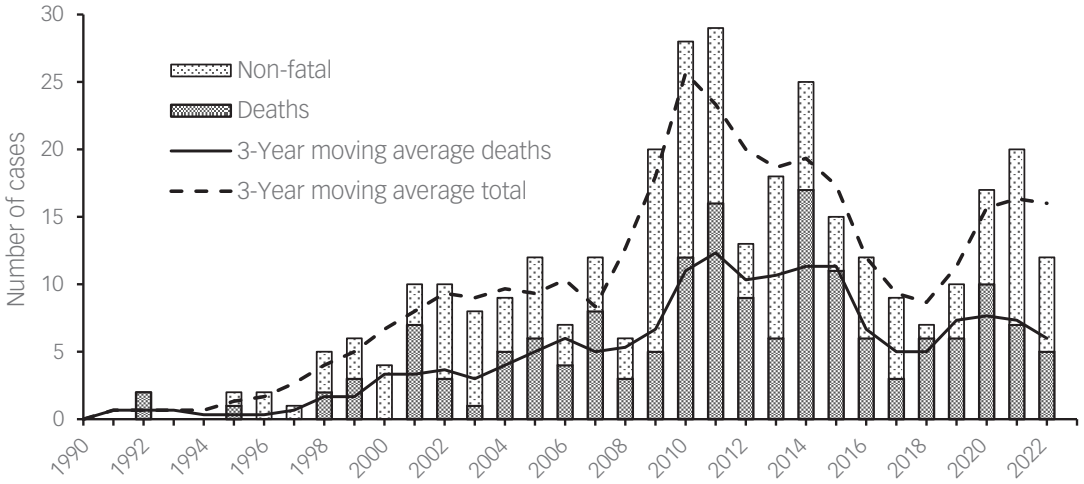

Fig. 2 Clozapine-related pulmonary embolism, UK pharmacovigilance reports 1990–2022 by year.

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The Uppsala Monitoring Centre, the designated World Health Organization Collaborating Centre for International Drug Monitoring, holds a global database of individual case safety reports (ICSRs) related to suspected ADRs. A Bayesian confidence neural network is used to detect safety signals. Overall, these data show statistically significant signals for pulmonary embolism and clozapine, olanzapine, risperidone, haloperidol and quetiapine, indicating these agents are associated with increased rates of pulmonary embolism. Clozapine has been implicated in over twice as many patients as any other antipsychotic (Supplementary Table 2).

In 2009, the MHRA issued a report that drew attention to the risk of VTE with antipsychotic medication.[12] Of 146 UK reports of suspected antipsychotic-related pulmonary embolism, 89 (61%) were attributed to clozapine. The MHRA recommended that the 'summary of product characteristics' for antipsychotic medications be updated to include warnings about VTE to raise awareness for healthcare professionals and patients. However, we would suggest that further education is required because our study revealed cases of clozapine-related pulmonary embolism detected on autopsy after signature symptoms such as chest pain, dyspnoea, dizziness and painful swollen calves had been disregarded by clinical care staff.

Epidemiology of clozapine-related pulmonary embolism

The epidemiology of clozapine-related pulmonary embolism differs from that of pulmonary embolism within the general community. Patients in our study were relatively young (median age 45 years). In the general population, VTE is predominantly a disease of older age, being rare before age 50,[13] with peak incidence occurring after age 60. Second, in 70% of patients no other identifiable minor risk factors for pulmonary embolism were recorded, whereas in the general population it is thought that fewer than 30% of cases of pulmonary embolism develop idiopathically.[14] Lastly, the case fatality rate in patients with clozapine-related pulmonary embolism in our study was 48%. This compares unfavourably with the estimated 28-day mortality of 11% in an ambulatory general population-based cohort with first-episode VTE.[15]

To put these data in context, the number of deaths attributed to clozapine-related pulmonary embolism is higher than those occurring with many of its better known ADRs. For example, as of 2021, eight cases of clozapine-associated agranulocytosis that led to death had been reported in the UK.[16] Between 2010 and 2019, there were 25 deaths at most associated with myocarditis in people taking clozapine,[17] compared to the 92 clozapine-related pulmonary embolism fatalities that were reported to the Yellow Card scheme over that same period (Supplementary Table 1).

People prescribed clozapine may have worse pulmonary embolism outcomes because of the presence of comorbidities, late presentation or diagnostic overshadowing. While this study was not designed to analyse case commentaries thematically, a pattern was noted whereby a person presented with features of pulmonary embolism that were either dismissed or misattributed to mental health symptoms, with pulmonary embolism identified only on autopsy. However, the relatively high fatality rate in our study may have been influenced by detection bias because non-fatal pulmonary embolism cases may have gone undiagnosed/unreported.

The data suggest that clozapine-related pulmonary embolism presents in relatively young adults and is often fatal. This aligns with the results of smaller studies examining clozapine and pulmonary embolism. In an audit of 42 reports of patients taking clozapine at VTE onset, the mean age was 42 years;[14] 32.5% of the patients died. Pulmonary embolism occurring after 3 weeks of clozapine was described in a 51-year-old woman in the absence of any risk factors for VTE.[18] Pulmonary embolism in a 34-year-old man during a retrial of clozapine after developing rhabdomyolysis has also been reported,[19] with the only identified risk factors for pulmonary embolism being obesity and a history of smoking.

In our study, the median duration of clozapine treatment was 2.9 years (range 2 days–22.7 years) before pulmonary embolism onset, whereas in a further case series most events occurred within 6 months of clozapine initiation.[7]

Limitations

Yellow Card data in general may be susceptible to bias from changes in ADR reporting practices that occur over time. Publicity and media attention can influence reporting rates, leading to temporary spikes in ADR reporting that may not accurately reflect underlying incidences.[20] Changes in prescribing practices, patient demographics and comorbidities can also skew the safety profile of a drug over time.[20–22] Pharmacovigilance data may also suffer from underreporting. It is estimated that only about 5% of ADRs are reported to pharmacovigilance centres.[23] However, in the UK, clozapine post-marketing surveillance is unusually comprehensive because its product licence mandates that all patients are registered with a supplier that collates ADR notifications and reports them to the Yellow Card scheme. Nonetheless, clozapine Yellow Card ADR reporting rates have been shown to be incomplete.[24–26]

There were some 14 000 people prescribed clozapine in the UK in 2001 (Novartis, personal communication to RJF, 2001). In November 2019, the corresponding figure was 37 301.[27] Thus, whilst reports of suspected clozapine-induced pulmonary embolism increased up to 2011, the number of people taking clozapine also increased during this time. The absence of an accurate denominator of people exposed to clozapine thus makes it impossible to calculate annual incidence rates of clozapine-related pulmonary embolism. Lastly, some risk factors for pulmonary embolism, such as smoking and obesity, are likely to have been underreported – some 65 and 50% of men and of women, respectively, prescribed clozapine in the UK and Ireland were recorded as smokers at the time of blood sampling in one large audit.[28]

Mechanism of clozapine-related pulmonary embolism

The anticholinergic effects of clozapine may lead to reduced mobility and an increased risk of thrombosis. In vitro studies have shown that clozapine can alter platelet aggregation and coagulation pathways[29] and affect fibrin formation,[30] potentially contributing to a prothrombotic state. Obesity, commonly associated with clozapine use, is a risk factor for pulmonary embolism (hazard ratio 2.5, 95% CI, 1.1–5.5).[31] Obstructive sleep apnoea and metabolic syndrome, common clozapine-associated ADRs, are also established risk factors for VTE.[32] However, a study of adults starting antipsychotic treatment for the first time, which presumably did not include clozapine, found the risk of VTE in people initiating antipsychotic treatment did not seem to be related to the risk of either sedation or metabolic adverse events.[33]

Recognition

Clinicians, including mental health clinicians, need to be familiar with presentations of DVT and pulmonary embolism so they can recognise them early and take prompt action. In the general population, the mortality rate of acute pulmonary embolism reduces from up to 30% when left untreated to around 8% when appropriately diagnosed and managed.[34] Greater awareness of another common clozapine-related ADR, CIGH, seems to have

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improved outcomes for patients, with publicity aimed at raising concern about this problem having been linked to a decline in CIGH-related morbidity and mortality reported to the MHRA.[35]

The classic symptoms of pulmonary embolism include dyspnoea, pleuritic chest pain, cough and haemoptysis, but these are present in less than half of people.[34] The most common feature is sudden-onset or worsening resting dyspnoea. However, people may also present with progressive exercise-induced dyspnoea. More than one-half of patients experience chest pain, but this can be difficult to distinguish from angina. Other presentations of pulmonary embolism can include cough (approximately 20% of patients), haemoptysis (a consequence of lung infarction, 7%) and syncope (14%). Signs of DVT include leg swelling and pain. The diagnostic challenge is compounded by the fact that typical symptoms of pulmonary embolism overlap with other common conditions, such as myocardial infarction, pneumonia, respiratory failure and heart failure. Therefore, a high index of suspicion is essential.

The diagnosis of pulmonary embolism is based on assessment of clinical likelihood, electrocardiogram (ECG), chest X-ray, laboratory investigations (primarily D-dimer and markers of cardiac injury and overload), imaging techniques, most commonly computed tomography pulmonary angiogram (CTPA) or ventilation-perfusion scintigraphy, and echocardiography. The use of clinical prediction rules, such as the Wells score, helps stratify patients into low, intermediate or high probability categories for pulmonary embolism.[36] However, standard VTE risk stratification questionnaires are not directly applicable to psychiatric patient populations.[37]

The D-dimer test is a sensitive, but non-specific marker of fibrin degradation.[38] A negative D-dimer test effectively rules out pulmonary embolism in low-risk patients; however, for patients with intermediate or high probability of pulmonary embolism, imaging is warranted.[39,40] The CTPA is the imaging modality of choice because of its high sensitivity and specificity.[41] Ventilation-perfusion scanning is an alternative, particularly in patients with contraindications to the CTPA, such as allergy to contrast media or renal impairment, but this can be difficult to interpret if there is comorbid lung disease. There is no evidence supporting serial D-dimer measurement.

Prevention

Preventive strategies include promoting physical activity, supporting smoking cessation, managing metabolic syndrome, minimising weight gain and considering prophylactic anticoagulation in high-risk patients, especially those with either previous VTE or multiple VTE risk factors.[42] The National Institute for Health and Care Excellence (NICE) guideline does not support the routine use of either oral aspirin or subcutaneous low molecular weight heparin in psychiatric in-patients, but does support using pulmonary embolism risk factor identification.

Increased effort to record risk factors, such as smoking status, in clozapine-related pulmonary embolism ADR reports could help indicate prevention strategies. The potential benefits and risks of continuing clozapine in patients who develop pulmonary embolism should be carefully weighed, and alternative antipsychotic therapies may be considered if the risk is deemed too high.

Research needs

An approach that could be considered is co-treatment with a glucagon-like peptide-1 receptor agonist. In 15 patients prescribed clozapine, subcutaneous semaglutide (once weekly, 36 weeks) led to significantly greater weight loss compared with 16 patients given placebo, without affecting either psychotic symptoms or blood clozapine concentrations.[43] Whilst this has not been tested as a strategy to prevent pulmonary embolism in such patients, it is plausible that it could reduce incidence through mitigation of risk factors and could also help reduce any comorbid complications of obesity, such as obstructive sleep apnoea.

Clinical implications

Pulmonary embolism is a serious and potentially life-threatening condition. The increased risk in clozapine-treated patients necessitates a proactive approach to not only prevention but also early recognition and management. Close monitoring for clinical features suggestive of pulmonary embolism is essential, particularly during the initial months of clozapine therapy when the risk appears highest. Regular assessment of body weight, metabolic parameters and mobility will help identify those at increased risk. Clinicians should maintain a high index of suspicion, particularly in those with additional risk factors, such as obesity, smoking, a sedentary lifestyle or a personal/family history of VTE. Data from the Uppsala Monitoring Centre show that other antipsychotics, including olanzapine, risperidone, haloperidol and quetiapine, are also associated with increased rates of pulmonary embolism, and similar precautions should be taken when using these medications. Research into the mechanism of, and risk mitigation strategies for, antipsychotic-related pulmonary embolism is essential to improve patient outcomes.

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Supplementary material

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Data availability

The authors confirm that summaries of the data supporting the findings of this study are available within the article. The primary data are not publicly available owing to reasons of patient confidentiality and can only be obtained by direct application to the Medicine and Healthcare products Regulatory Agency (MHRA).

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Author contributions

S.E.-P., R.N. and S.A.H. planned the study, evaluated the data and helped write the paper, A.H.M.K. performed the statistical analyses, C.J. and L.W. extracted the data, A.N. helped write the paper and R.J.F. initiated the study and helped write the paper.

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Declaration of interest

None.

Ethical standards

The study was approved by the MHRA Ethics Committee (Study Number AYCD044). To preserve anonymity, identifying demographic data were removed from the MHRA data and age translated into ranges.

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