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EVIDENCE BASED CASE REPORT

Pulmonary embolism in a patient taking clozapine

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A 45 year old man with schizophrenia began experiencing auditory hallucinations at the age of 25. These were well controlled for several years by a monthly intramuscular injection of haloperidol decanoate. One year after he switched to oral haloperidol, the intensity of the hallucinations increased and included a voice commanding him to end his life. Concerns for his safety led to a brief admission to psychiatric hospital. When he had to return to hospital within a month, the inpatient psychiatrist inferred a loss of response to haloperidol and encouraged the patient to switch to clozapine. Six months later he was brought to an emergency department in an acute confusional state after a clozapine overdose. The drug was discontinued and his mental status improved rapidly, but investigation of acute dyspnoea showed bilateral pulmonary emboli. The patient was not overweight and had no history of recent surgery, trauma to the legs, or malignancy, but he was a heavy smoker. Laboratory tests for hypercoagulable states had negative results. He was treated with intravenous heparin and then oral warfarin and was transferred to a psychiatric unit for resumption of treatment with clozapine.

I (VHS) received a call from a physician in training who had admitted the patient to the psychiatric unit. She wondered about a possible association between clozapine and thromboembolism. I consulted with a colleague (TWL) who, like me, had not heard of this risk. The patient was expected to be in hospital for two more weeks, which gave us some time to consider alternative drugs.

Asking a question

The most pressing area of uncertainty was determining whether clozapine had anything to do with this patient's pulmonary emboli and if so, whether alternative drugs posed less of a risk.[1] We formulated a structured question: in a patient with schizophrenia who does not have any risk factors for venous thromboembolism (patient), does clozapine (intervention) versus other antipsychotic medications (comparison) increase the risk of pulmonary embolism (outcome)? We began with our two favourite desk references: the handbook of psychopharmacotherapy,[2] which made no mention of thromboembolic complications for clozapine, and a subscription online database (www.micromedex.com), which included several case reports of pulmonary emboli, all in people without known risk factors. The 2007 *Physicians' Desk Reference*, commonly used in the United States, had a cryptic entry noting "18 cases of fatal PE in association with clozaril therapy as of 1993" with an unreferenced incidence of "1 death per 3,450 person years of use [or] 27.5 times (95% Confidence Interval 17.1-42.2)" the risk in a matched sample matched for age and sex.[3] This raised our level of concern, but as we lacked adequate information to assess validity, quantify risk, or know whether this applied to our patient we decided to search the clinical literature.

Accessing the evidence

Randomised controlled trials provide the most valid evidence to assess comparative effects of drugs. Such trials, however, are usually not big enough or long enough to detect rare or delayed risks. Meta-analyses of data from randomised controlled trials can increase this power to detect rare events. Failing this, observational data can provide valuable information on risk, but are more prone to bias.

We thus used a hierarchical search strategy (box) based on that given by Haynes et al.[4] We started searching "secondary" sources for critically appraised summaries of high quality evidence before proceeding to the primary databases. The box details our strategy and rationale for selecting studies for more detailed review. On discovering the dearth of randomised studies or even prospective, controlled data we looked for any quantitative evidence (beyond suggestive case reports) estimating the risk for pulmonary emboli for any antipsychotic drug.

Appraising the evidence

We submitted the three selected studies to a structured appraisal (table).[8] Clozapine first became available for use in the United States in 1989. Given concerns about agranulocytosis, all prescriptions were monitored through a national clozapine registry. Walker et al's 1997 cohort study of this registry compared 67 072 current versus former clozapine users followed from 1991 to 1993 for mortality due to various causes, including pulmonary embolism.[6] The researchers

calculated standardised (for age, sex and race) mortality rates (SMR)[9] for various causes, using US population mortality rates from 1985-8 (the most recently available) as a comparator. The SMR for pulmonary embolism was 30 per 100 000 person years. This was close to the estimate we had found in the *Physicians' Desk Reference*, and reading this paper helped contextualise that number.

Firstly, there was a small absolute risk (19 cases of pulmonary embolism in 85 399 person years of follow-up). Although there was no control group, comparisons were made between current and past users of clozapine. Secondly, although mortality from pulmonary embolism seemed to be about fivefold (relative risk of 5.2) in current compared with past users, the rarity of this event precluded estimating a (presumably wide) confidence interval that would include the possibility of no difference. We preferred to err on the side of caution (assuming that the relative risk was significantly larger than 5.2), presuming under-reporting of pulmonary embolism on death certificates and the large number of case reports implicating clozapine in people without other risk factors for pulmonary embolism.

Thirdly, overall mortality rates were lower in current versus former clozapine users, and this was attributed mostly to the lower risk of suicide (relative risk 0.17, 95% confidence interval 0.10 to 0.30). Ironically, our patient had used clozapine in an overdose attempt. Finally, this study challenged clinical intuition, reporting higher standardised mortality rates (deaths per 100 000 person years) from circulatory causes than suicides (106 *v* 39) and more actual deaths from pulmonary embolism than agranulocytosis (18 *v* 2) in current users.

Structured appraisal of studies quantifying the risk for idiopathic pulmonary embolus in adults with schizophrenia taking antipsychotic drugs

	Walker 1997 (cohort study of national registry)[6]	Parkin 2003 (case-control study)[5]	Zornberg 2000 (case-control study)[7]
Are the results valid?			
Were the patients and controls similar?	Yes. Internal control (current *v* past users)	Not adequately reported. Analysis adjusted for oestrogen exposure. Controls were randomly selected from age and sex matched cohort	No. Controls had higher rates of hypertension, smoking, and current oral contraceptive use
Were outcomes and exposures measured in the same way?	Yes. Outcome of fatal pulmonary embolus determined by review of death certificates.	Yes. Outcome of fatal pulmonary embolus determined by necropsy in most patients	Yes. Extracted from UK general practice research database. Outcome of venous thromboembolism requiring hospitalisation for anticoagulation determined by one of several objective tests
Was follow-up long enough and complete?	Mean days of observation was over two months in both groups of interest; 92% had usable death certificates	At least 1 month of exposure, maximum duration of exposure of 3 months	At least 1 month of exposure and mean duration of follow-up of 6. 8 years
Does the association satisfy simple rules for causation:			
Temporal relationship correct?	Yes	Yes	Yes
Dose-response?	No data	No data	No
"Dechallenge-rechallenge"?	No data	No data	No data
Biological plausibility?	Increase in weight and sedation from clozapine might increase risk for pulmonary embolus	None proposed	None proposed
What are the results?			
How strong is the association between exposure and outcome (risk ratios or odds ratios)?	Standardised mortality risk ratio for current versus past clozapine users 5.25 (based on 18 *v* 1 deaths due to pulmonary embolus)	Adjusted odds ratios for current versus no exposure to antipsychotics	Adjusted odds ratios for current versus no exposure to first generation antipsychotics
		Lower potency: 20.8	Lower potency: 24.1
		Any (first generation) antipsychotic: 13.3	Higher potency: 3.3
How precise is the estimate of risk (95% confidence intervals)?	Not reported	Lower potency: 1.7 to 259.0	Lower potency: 3.3 to 172.7
		Any antipsychotic: 2.3 to 76.3	Higher potency: 0.8 to 13.2
How relevant are the results?			
Are the results applicable to this patient?	Yes. He would have met entry criteria for this study	Yes. Cases and controls had no known risk factors for venous thromboembolism	Yes. Cases and controls had no known risk factors for venous thromboembolism
What is the magnitude of risk to this patient?	Given lack of confidence intervals, cannot estimate maximum risk for clozapine	Study suggests lower risk for high potency typical antipsychotics	Study suggests lower risk for high potency typical antipsychotics
Patient's preferences? Alternatives?	See text		

Two case-control studies had careful ascertainment of cases and excellent follow-up.[5 7] Parkin et al used a New Zealand national death registry to identify adults under age 60 and without established risk factors and tracked deaths caused by pulmonary embolism between 1990 and 1998.[5] Zornberg and Jick defined cases as all venous thromboembolic events requiring hospitalisation for anticoagulation and drew participants from the UK general practice research database of three million patients.[7] None of the observational data can provide definitive evidence of a casual [causal?]link, and both the latter studies evaluated only first generation antipsychotics. Nevertheless, both provided usable evidence, implicating lower potency first generation antipsychotics as worse offenders, with the odds ratio for higher potency first generation antipsychotics such as haloperidol reassuringly overlapping 1.

Applying the evidence and assessing the outcome

We presented the patient with the possibility that clozapine might increase his risk for pulmonary emboli. He then revealed that for the past year he had been erratically adherent to his oral haloperidol. In this light, the judgment that his hallucinations were refractory to haloperidol (an indication for clozapine) on his previous admission seemed wrong. Given no evidence to support any reduced risk with the second generation antipsychotic medications and some data indicating a lower risk with haloperidol, we supported his decision to return to monthly injections of this drug.

Over the next three months the patient resumed his previous dose of haloperidol decanoate. The warfarin was discontinued after six months, when follow-up investigations for hypercoagulable states proved negative. Eighteen months later, the patient was free of recurrent thromboembolic events and at his psychiatric baseline.

Searching for the evidence

Step 1: Search secondary resources for relevant controlled trials

Resources: *Clinical Evidence* (www.clinicalevidence.org); *Evidence Based Mental Health* (http://ebmh.bmj.com); Cochrane Library (www.cochrane.org)—focused on the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and Cochrane Central Register of Controlled Trials

Search term: "clozapine"

Rationale: We examined abstracts of two relevant systematic reviews of randomised controlled trials comparing clozapine to first and second generation antipsychotics. Neither reported on thromboembolic complications. Few of the included trials extended beyond three months.

Step 2: Search a primary database (Medline) for observational studies using the PubMed Clinical Query search tool (www.ncbi.nlm.nih.gov/entrez/query/static/clinical.shtml)

Settings: "broad, sensitive" and search terms "cloza*" and "pulmonary embol*" within the category of "etiology"

Rationale: We selected two studies[5 6] that quantified risk for pulmonary embolism in patients taking any antipsychotic drug, and scanned several case reports of pulmonary embolism in patients without other known risk factors. Because we had not yet found any studies comparing risk for clozapine and other antipsychotics, we extended our search.

Step 3: Search, more comprehensively, Medline and EMBASE using the OVID interface

Search terms: "pulmonary embolus" (MESH and keyword) combined with "antipsychotic" (MESH and keyword)

Rationale: We selected one additional study that quantified risk for pulmonary embolism, albeit only for first generation antipsychotic drugs.[7]

Auditing the process

We could not find an answer to our specific question, but our use of a structured approach showed "actionable" information about a previously underappreciated risk (an informal poll at our clinic confirmed a general ignorance of reported associations between antipsychotic medications and pulmonary emboli). Favoured sources of prescription information (manuals, *Physicians' Desk Reference*) proved less useful than primary databases.[10] The entire process took about five hours. The strongest limitation to informed decision making was that limited post-marketing surveillance data were available for comparing the risk of various drugs.

This systemic problem requires clinicians to be alert to unexpected risks, even of established treatments.[11]

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