BEST in Mental Health
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Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

"Does Quetiapine and/or Olanzapine increase the risk of blood clots in adults of working age?"

Clarification of question using the *PRO* structure

Patients:	Adults of working age
Risk factor:	Prescription of Quetiapine and/or Olanzapine
Outcome:	Development of blood clots

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Clinical and research implications

Data from one, large and generally well conducted retrospective case control study indicated that current antipsychotic use may be linked with an increased risk of venous thromboembolism (VTE), within the first 30 days after the start of treatment. No increased risk was found for previous exposure to antipsychotic drugs (more than 60 days before the start of the study). The VTE risk associated with current use appeared to vary between individual antipsychotic drugs and neither all atypical antipsychotics nor olanzapine specifically were found to be associated with increased risk of VTE, however, it should be noted that the numbers of participants in individual drug and exposure time categories was often small.

Although the base population from which this study was sampled was large, a still larger dataset is need to adequately explore the relationship between the duration of use of antipsychotic drugs and risk of VTE and how this may vary between individual drugs; it is important to ensure that there are adequate numbers of study participants for each drug and exposure combination assessed.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified one large retrospective study, which used conditional logistic regression analysis of data from the Clinical Practice Research Datalink (CPRD) to assess the relationship between exposure to antipsychotic drugs and the risk of venous thromboembolism (VTE), and to assess the effects of dose and duration of use. The base population, from which participants included in this study were samples, comprised adults who had filled at least one prescription for an antipsychotic drug between 1998 and 2012. The study included 4,026 participants: 868 cases who were diagnosed, between 1998 and 2012 with VTE (including deep vein thrombosis (DVT), and pulmonary embolism (PE)) which required anticoagulant treatment or which was fatal; 3,158 controls, matched by age, sex, general practice, calendar time and length of medical history. Current exposure to antipsychotic drugs was stratified by typical and atypical antipsychotics and by individual drug, where sufficient data were available. Individual drug exposure data were reported for olanzapine, but not for quetiapine.

Main findings

The study found that current antipsychotic use (within 60 days before index date or after index date) was associated with a small, but not statistically significant increase in the risk of VTE relative to non-exposure; no other exposure durations were associated with increased risk. When data for current exposure were analysed by individual antipsychotic drug, only prochlorperazine was found to be associated with a statistically significant increased risk of VTE (adjusted odds ratio (aOR) 2.18 (95% CI: 1.47 to 3.25)). Neither all atypical antipsychotics nor olanzapine specifically were found to be associated with increased risk of VTE. When data for current antipsychotic use were further stratified into current new use (0 to 30 days) and current long-term use (more than 30 days), only current new use was found to be associated with a statistically significant increased risk of VTE (aOR 3.21 (95% CI: 1.64 to 6.29)).

Author's conclusions

Ishiguro (2014) - The risk of VTE with typical and atypical antipsychotics varies with type of drug and is highest just after starting the drug.

Reliability of conclusions/Strength of evidence

Data from one, generally well conducted retrospective case control study indicated that new, current antipsychotic use may be associated with an increased risk of VTE, within the first 30 days after initiation of treatment. However, it should be noted that only 36 of the participants included in this analysis were classified as new current users of antipsychotics.

What do guidelines say?

Neither National Institute for Health and Care Excellence (NICE) nor Searching of Scottish Intercollegiate Guidelines Network (SIGN) guidelines comment on the risk association between Quetiapine and/or Olanzapine and developing blood clots in adults of working age.

Date question received: 18/03/2015
Date searches conducted: 23/03/2015
Date answer completed: 27/04/2015

References

Cohort / Case control studies

Ishiguro, C., Wang, X., Li, L., & Jick, S. (2014). Antipsychotic drugs and risk of idiopathic venous thromboembolism: a nested case–control study using the CPRD. *Pharmacoepidemiology and Drug Safety*, *23*(11), 1168-1175.

Zornberg, G. L., & Jick, H. (2000). Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study. *The Lancet*, *356*(9237), 1219-1223. - **EXCLUDED – Earlier study from the same group, using the same data source.**

Results

Case-control studies

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Ishiguro et al. (2014)	*Participants*: Base population: Adults in the Clinical Practice Research Datalink (CPRD) who had filled at least one prescription for an antipsychotic drug between 1998 and 2012. Cases: Adult UK residents aged 20-59, from the base population, who were diagnosed between 1998 and 2012 with venous thromboembolism (VTE) (which includes deep vein thrombosis (DVT) and pulmonary embolism (PE)), which required anticoagulant treatment or which was fatal. Potential cases were excluded if they had other causes for VTE in the 3 months prior to the index date (lower-limb injury, invasive surgery, severe trauma, and pregnancy). People with important clinical risk factors (history of cancer (except non-melanoma skin cancer), renal failure, epilepsy, insulin-dependent diabetes mellitus, multiple sclerosis, myocardial	*Base population:* 810,308 *Total participants*: 4,026 (n=868 cases And n= 3,158 controls)	This retrospective study aimed to assess the relationship between exposure to antipsychotic drugs and the risk of VTE and to assess the effects of dose and duration of use. Of the 4,026 participants included in the study, 375 were classified as current antipsychotic users (0 to 60 days), 106 were classified as recent users (61 to 120 days) and 3545 were classified as non-users (all other exposures including never use). Data were analysed using conditional logistic regression. Each potential confounder was assessed for independent association with antipsychotic drug exposure and risk of VTE. Although none of them affected the crude association of antipsychotic drug exposure and risk of VTE by 10% or more, all potential confounders were retained in the final model to estimate adjusted ORs (aORs). Current antipsychotic use (within 60 days before index date or after index date) was associated with a small, but not statistically significant, increase in the risk of VTE relative to non-exposure (no use or use >120 days before index date); aOR 1.26 (95% CI: 0.97 to 1.63). Recent use (61-120 days	The research question was clearly defined. Controls were randomly selected from the same data set from which cases were taken and matched by age, sex, general practice, calendar time and length of medical history.

	infarction, cerebral vascular accident, other cardiovascular disease, alcohol abuse, or drug abuse) at any time before the index date were also excluded. Controls: Adults UK residents aged 20-59 from the base population, with up to four controls for each case randomly selected, and matched by age, sex, general practice, calendar time and length of medical history. *Risk factor*: Use of typical or atypical antipsychotic medication (including Olanzapine & Quetiapine). Current exposure was defined as receipt of a prescription whose filled use extended to within 60 days before the index date or beyond the index date. Current exposure was sub-divided by duration of use, typical or atypical antipsychotic and potency of typical antipsychotic. Recent and past exposures were defined as receipt of a prescription whose filled use extended to within 61–120 and 121–365 days before the index date, respectively. All other exposures, including never use of antipsychotics before the		before index date was not associated with increased risk; aOR 1.04 (95% CI: 0.65 to 1.67). Current new use (<30 days since first recorded prescription) was associated with a statistically significant increase in the risk of VTE relative to non-exposure; aOR 3.21 (95% CI: 1.64 to 6.29). Current longer term use (≥30 days since first recorded prescription) was not associated with increased risk; aOR 1.09 (95% CI: 0.82 to 1.44). When the risks associated with individual antipsychotic drugs, for current use relative to non-exposure, were considered, only prochlorperazine (aOR 2.18 (95% CI: 1.47 to 3.25)) and risperidone (aOR 1.83 (95% CI: 0.88 to 3.81)) were associated with increased risk of VTE; for risperidone, the association did not reach statistical significance. Neither all atypical antipsychotics nor olanzapine specifically were found to be associated with increased risk of VTE.	The study was a retrospective analysis in which the outcome was defined by a previously determined diagnosis. Statistical analysis was robust and potential confounders were considered in the analyses.

	index date, were classified as non-exposed. *Covariates:* The following potential confounders were considered in the analysis: smoking status; BMI; history of hypertension, hyperlipidemia, phlebitis, schizophrenia, bipolar disorder, depression, and other psychoses prior to the index date; current use of oestrogen containing drugs, or antidepressant drugs. *Study design:* Case-control study using the Clinical Practice Research Datalink (CPRD) to identify participants.			
Zornberg et al. (2000)	**EXCLUDED – Earlier study from the same group, using the same data source**			

Risk of bias:

Case-control studies

	RISK OF BIAS (ASSESSED USING SIGN GUIDANCE FOR CASE-CONTROL STUDIES)					
	Question (clearly focussed)	**Subject selection (taken from comparable populations, loss to follow-up)**	**Outcome assessment (reliable, blinded to exposure)**	**Confounding (accounted for in design and analysis)**	**Statistical analysis (reporting of confidence intervals)**	**Overall assessment**
Ishiguru (2014)	☺	☺	☺	☺	☺	☺

☺ Low risk ☹ High risk ? Unclear risk

Search details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	antipsychotic thrombosis	4	0
	olanzapine thrombosis	2	0
	quetiapine thrombosis	2	0
	antipsychotic blood clot	1	0
	olanzapine blood clot	0	0
	quetiapine blood clot	1	0
	antipsychotic embolism	3	0
	olanzapine embolism	1	0
	quetiapine embolism	1	0
DARE	1 (quetiapine or olanzapine) IN DARE194 2 (seroquel OR "seroquel XR") IN DARE 2 3 (zyprexa OR olasek OR ziprexa OR symbyax) IN DARE 1 4 ("blood clot*" or thrombosis or thrombus) IN DARE 877 5 MeSH DESCRIPTOR Thrombosis EXPLODE ALL TREES 1014 6 MeSH DESCRIPTOR Embolism EXPLODE ALL TREES 274 7 (Embolism) IN DARE 414 8 #1 OR #2 OR #3 194 9 #4 OR #5 OR #6 OR #7 1649 10 #8 AND #9 0	0	0
Primary studies			
CENTRAL	#1 quetiapine or olanzapine 3075 #2 "blood clot*" or thrombosis or thrombus 14300 #3 MeSH descriptor: [Thrombosis] explode all trees 5298 #4 MeSH descriptor: [Embolism and Thrombosis] explode all trees 5889	3	0

	#5 #2 or #3 or #4 16015 #6 #1 and #5 8		
PsycINFO	1. PsycINFO; QUETIAPINE/; 1533 results. 2. PsycINFO; exp OLANZAPINE/; 3052 results. 3. PsycINFO; (seroquel OR "seroquel XR").ti,ab; 87 results. 4. PsycINFO; (zyprexa OR olasek OR ziprexa OR symbyax).ti,ab; 41 results. 5. PsycINFO; 1 OR 2 OR 3 OR 4; 4353 results. 6. PsycINFO; exp EMBOLISMS/ OR exp THROMBOSES [+NT]/; 944 results. 7. PsycINFO; "blood clot*".ti,ab; 93 results. 8. PsycINFO; (thrombus OR thrombosis).ti,ab; 1056 results. 9. PsycINFO; embolism*.ti,ab; 485 results. 10. PsycINFO; 6 OR 7 OR 8 OR 9; 1866 results. 11. PsycINFO; 5 AND 10; 12 results.	12	0
Embase	12. EMBASE; exp OLANZAPINE/; 26064 results. 13. EMBASE; (seroquel OR "seroquel XR").ti,ab; 227 results. 14. EMBASE; (zyprexa OR olasek OR ziprexa OR symbyax).ti,ab; 129 results. 15. EMBASE; 1 OR 12 OR 13 OR 14; 32071 results. 16. EMBASE; exp EMBOLISMS/ OR exp THROMBOSES [+NT]/; 0 results. 17. EMBASE; "blood clot*".ti,ab; 8250 results. 18. EMBASE; (thrombus OR thrombosis).ti,ab; 160985 results. 19. EMBASE; embolism*.ti,ab; 55404 results. 20. EMBASE; 16 OR 17 OR 18 OR 19; 206757 results. 21. EMBASE; 15 AND 20; 91 results. 22. EMBASE; exp THROMBOEMBOLISM/; 349902 results. 23. EMBASE; 20 OR 22; 398092 results. 24. EMBASE; 15 AND 23; 396 results. 25. EMBASE; random*.ti,ab; 944560 results. 26. EMBASE; factorial*.ti,ab; 24340 results. 27. EMBASE; (crossover* OR cross-over*).ti,ab; 72213 results.	38	2

	28. EMBASE; placebo*.ti,ab; 209470 results. 29. EMBASE; (doubl* ADJ blind*).ti,ab; 147898 results. 30. EMBASE; (singl* ADJ blind*).ti,ab; 15352 results. 31. EMBASE; assign*.ti,ab; 252929 results. 32. EMBASE; allocat*.ti,ab; 89701 results. 33. EMBASE; volunteer*.ti,ab; 184037 results. 34. EMBASE; CROSSOVER PROCEDURE/; 41811 results. 35. EMBASE; DOUBLE BLIND PROCEDURE/; 118316 results. 36. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 362270 results. 37. EMBASE; SINGLE BLIND PROCEDURE/; 19622 results. 38. EMBASE; 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37; 1495395 results. 39. EMBASE; 24 AND 38; 38 results.		
Medline	2. MEDLINE; QUETIAPINE/; 0 results. 13. MEDLINE; exp OLANZAPINE/; 0 results. 14. MEDLINE; (seroquel OR "seroquel XR").ti,ab; 139 results. 15. MEDLINE; (zyprexa OR olasek OR ziprexa OR symbyax).ti,ab; 69 results. 16. MEDLINE; 12 OR 13 OR 14 OR 15; 203 results. 17. MEDLINE; exp EMBOLISMS/ OR exp THROMBOSES [+NT]/; 180276 results. 18. MEDLINE; "blood clot*".ti,ab; 7058 results. 19. MEDLINE; (thrombus OR thrombosis).ti,ab; 119466 results. 20. MEDLINE; embolism*.ti,ab; 43541 results. 21. MEDLINE; 17 OR 18 OR 19 OR 20; 247012 results. 22. MEDLINE; 16 AND 21; 0 results. 23. MEDLINE; (Quetiapine OR Olanzapine).ti,ab; 8256 results. 24. MEDLINE; 14 OR 15 OR 23; 8288 results. 25. MEDLINE; 21 AND 24; 36 results.	36	0

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