APA Hyperlipidemia

Antipsychotic-Induced Hyperlipidemia Among People with Schizophrenia

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INTRODUCTION

- The newest antipsychotic agents exhibit superior safety in terms of extrapyramidal side effects compared to conventional antipsychotics.
- Recent evidence from the literature has suggested an association between the use of these agents and the development of metabolic abnormalities, including hyperlipidemia.
- We used a large health care database to determine the independent contribution of these agents to the development of hyperlipidemia, while adjusting for other risk factors.

DEFINING ANTIPSYCHOTIC EXPOSURE

- Exposure was defined as receipt of antipsychotic monotherapy during the 12 weeks prior to the development of hyperlipidemia in the case (or the same time period in the control). To determine the effect of longer exposure durations, we did a parallel analysis where exposure was defined with respect to medications received up to 52 weeks prior to the onset of hyperlipidemia.
- Second generation drugs included clozapine, olanzapine, quetiapine, and risperidone. First generation drugs included chlorpromazine, fluphenazine, loxapine, pimozide, promazine, trifluoperazine, haloperidol, perphenazine, prochlorperazine, and thioridazine.

METHODS

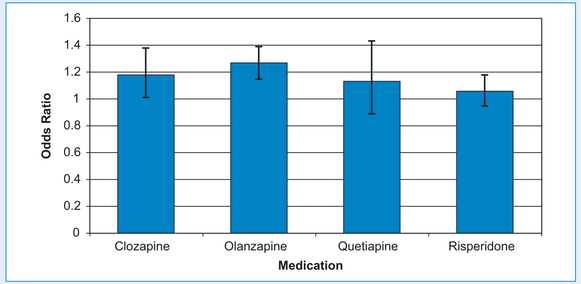
- This case-control study was based on data derived from the California Medicaid (i.e., Medi-Cal) system during 1997-2000. This database included 129,341 patients with schizophrenia.
- To be a case, patients had to have schizophrenia (ICD-9: 295) and hyperlipidemia (ICD-9: 272.0-272.4) subsequent to schizophrenia, be 18 years or older, and be on only one antipsychotic medication during the 12- or 52-week period prior to their hyperlipidemia diagnosis.
- Cases and controls had to be continuously eligible for Medicaid benefits during the 12- or 52-week period prior to hyperlipidemia onset in the case.
- Conditional logistic regression assessed the risk of exposure to four second generation agents, controlling for ethnicity and exposure to other hyperlipidemia-inducing medications (beta-blockers and thiazide diuretics, loop diuretics, anticonvulsants, and protease inhibitors).
- The reference group for all comparisons was comprised of patients on first generation antipsychotic therapy.

RESULTS

- 4,371 cases were matched to 8,052 non-hyperlipidemic controls (people with schizophrenia matched on gender and age ± 3 years).
- Using a 12-week period prior to hyperlipidemia onset, exposure to clozapine (OR=1.18, 95% CI: 1.01-1.38) or olanzapine (OR=1.27, 95% CI: 1.15-1.39) significantly increased the risk of developing hyperlipidemia compared to first generation antipsychotics.
- The odds ratios for exposure to risperidone (OR=1.06, 95% CI: 0.95-1.18) and quetiapine (OR=1.13, 95% CI: 0.89-1.43) were not significantly greater than 1.
- African-American ethnicity was a significant risk factor for development of hyperlipidemia (OR=1.19, 95% CI: 1.07-1.32) as was unknown ethnicity (OR=1.22, 95% CI: 1.11-1.33). Exposure to beta-blockers and thiazide diuretics (OR=1.46, 95% CI: 1.29-1.65), loop diuretics (OR=1.40, 95% CI: 1.14-1.72), or protease inhibitors (OR=1.95, 95% CI: 1.12-3.40) also increased risk.
- Lengthening the exposure period from 12 to 52 weeks prior to hyperlipidemia onset decreased the sample size but otherwise had no appreciable effect on the results.

RESULTS

Figure 1. Adjusted Risk of Hyperlipidemia for Selected Second Generation Antipsychotics (12-week exposure period)



*Matched for age and gender; adjusted for ethnicity, and exposure to beta-blockers and thiazide diuretics, loop diuretics, anticonvulsants, and protease inhibitors. Reference is any first generation antipsychotic.

Table 1. Characteristics of Cases and Controls (12-week exposure period)

Characteristic	Cases (n=4,371) Mean	SD	Controls (n=8,052) Mean	SD	Test Stat.	P
Age						
Mean (SD)	42.69[a]	12.29	43.53	12.47		
Min	18		18			
Max	96		95			
	N	**%**	**N**	**%**		
Gender						
Male	2281[a]	52.18	4136	51.37		
Female	2090	47.82	3916	48.63		
Ethnicity						
White	2251	51.51	4478	55.63	19.32[b]	<.0001
Hispanic	74	1.69	129	1.60	0.15	0.70
African-American	761	17.41	1320	16.40	2.10	0.15
Others	47	1.08	81	1.01	0.13	0.71
Unknown	1237	28.31	2042	25.37	12.60	0.0004
Concomitant Medications						
Beta-blockers and thiazide diuretics	517	11.83	688	8.54	34.87	<.0001
Loop diuretics	185	4.23	250	3.10	10.66	0.001
Anticonvulsants	520	11.90	885	10.99	2.32	0.128
Protease Inhibitors	28	0.64	25	0.31	7.27	0.007
Exposed to Antipsychotics						
First Generation Drugs	1811	41.43	3639	44.95	14.21	0.0002
Clozapine	320	7.32	566	7.03	0.36	0.55
Olanzapine	1260	28.83	2028	25.19	19.29	<.0001
Quetiapine	118	2.70	217	2.69	0.0002	0.99
Risperidone	862	19.72	1622	20.14	0.32	0.57

Note: Cases were patients 18 years or older who developed hyperlipidemia after being diagnosed with schizophrenia. Controls were patients 18 years or older who were diagnosed with schizophrenia but not hyperlipidemia. See text for details.

[a] Statistical comparisons of the matching variables for all cases and all controls are inappropriate because each case was matched to a different number of controls.

[b] χ^2 test with 1 degree of freedom.

RESULTS

Table 2. Parameter Estimates For Conditional Logistic Regression Model Predicting Development of New-Onset Hyperlipidemia in Patients With Schizophrenia Exposed to One of Four Different Second Generation Antipsychotics (12-week exposure period)

Variable	Parameter Estimate	S.E.	Chi-Square	P	Odds Ratio	95% Lower	95% Upper
Atypical Antipsychotics							
Clozapine (n=886)	0.16	0.08	4.28	0.04	1.18	1.01	1.38
Olanzapine (n=3288)	0.24	0.05	23.35	<.0001	1.27	1.15	1.39
Quetiapine (n=335)	0.12	0.12	0.94	0.33	1.13	0.89	1.43
Risperidone (n=2484)	0.06	0.05	1.16	0.28	1.06	0.95	1.18
Ethnicity							
Hispanic (n=203)	0.21	0.15	1.84	0.18	1.23	0.91	1.66
African-American (n=2081)	0.17	0.05	10.06	0.00	1.19	1.07	1.32
Other Ethnicity (n=128)	0.16	0.19	0.66	0.42	1.17	0.80	1.70
Unknown Ethnicity (n=3279)	0.20	0.05	18.37	<.0001	1.22	1.11	1.33
Hyperlipidemia-Inducing Medications							
Beta-blockers and thiazide diuretics (n=1205)	0.38	0.06	34.30	<.0001	1.46	1.29	1.65
Loop diuretics (n=435)	0.33	0.11	10.15	0.00	1.40	1.14	1.72
Anticonvulsants (n=1405)	0.08	0.06	1.75	0.19	1.09	0.96	1.22
Protease Inhibitors (n=53)	0.67	0.28	5.63	0.02	1.95	1.12	3.40

Note. Reference group for clozapine, quetiapine, olanzapine, and risperidone was all other first generation antipsychotics.

DISCUSSION/CONCLUSION

- In a large population of low-income, publicly-financed patients with schizophrenia, exposure to clozapine and olanzapine, but not risperidone or quetiapine, was associated with a significantly increased risk of developing hyperlipidemia when compared to first generation antipsychotic medications.
- These effects were not due to age, gender, ethnicity, or concomitant exposure to other medications. African-American ethnicity, as well as exposure to concomitant medications were significant, independent risk factors. More research needs to be done to quantify the personal and societal risk/benefit ratio associated with use of these medications.
- Decisions concerning selection of antipsychotic medications should reflect known efficacy, other safety issues, tolerability, and cost. In practice, the relative weights assigned to these factors will likely differ with the clinical and financial context of the treatment.
- Given the increased baseline risk of cardiovascular disease among people with schizophrenia, the benefits of prescribing olanzapine or clozapine for a given individual should be weighed against the possibility of increased cardiovascular risk.
- When olanzapine or clozapine is prescribed, clinicians should consider the appropriateness of periodic screening of lipid levels.

REFERENCES

Meyer JM. Novel antipsychotics and severe hyperlipidemia. *J Clin Psychopharmacol*. Aug 2001;21(4):369-374.

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