Published in final edited form as:

Schizophr Res. 2018 September ; 199: 420–421. doi:10.1016/j.schres.2017.12.019.

Lymphoma following clozapine exposure: more information needed

Jonathan G. Leung, PharmD,

Department of Pharmacy, Mayo Clinic, Rochester, MN; Mayo Clinic – Rochester, 1216 Second Street SW, Rochester MN 55902

Jason N. Barreto, PharmD,

Department of Pharmacy, Mayo Clinic, Rochester, MN; Mayo Clinic – Rochester, 1216 Second Street SW, Rochester MN 55902

Carrie A. Thompson

Division of Hematology, Department of Internal Medicine, Mayo Clinic – Rochester, 200 First Street SW, Rochester, MN 55905

Keywords

clozapine; leukemia; lymphoma

To the Editor:

Clozapine is the drug of choice for treatment resistant schizophrenia and has demonstrated superiority to other antipsychotics; however, its adverse event profile precludes use as a first line agent.(Meltzer, 2012) The carcinogenicity of clozapine remains unknown due to conflicting data. A systematic review concluded that antipsychotics as a class cannot be considered carcinogenic in humans, despite rodent data suggesting the contrary.(Fond et al., 2012) Notably, authors highlight that clozapine, specifically, may be associated with an increased risk of leukemia. Nielsen and colleagues investigated the incidence of acute myeloid leukemia (AML) in patients with schizophrenia or schizoaffective disorder receiving clozapine versus no clozapine exposure. Adjusted for sex and age, the authors reported that patients who had received clozapine had a greater risk of developing AML (HR 8.31 CI: 2.02-34.23).(Nielsen and Boysen, 2010) Any putative mechanism of how clozapine may increase the risk of leukemia is unknown but hypotheses include cytotoxic effects on

Corresponding Author: Jonathan G. Leung, PharmD, Psychiatric Clinical Pharmacist, Department of Pharmacy, Mayo Clinic, Rochester, 1216 Second Street SW, Rochester MN 55902, leung.jonathan@mayo.edu, Phone: 507-266-7400, Fax: 507-255-7556.

Contributors

JGL and JNB designed the study and wrote the protocol. JGL wrote the first draft of the manuscript and all authors reviewed and contributed content to the final draft. All authors contributed to and have approved the final manuscript.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of interest

None

bone marrow stroma cells and nitrenium ions formed by clozapine oxidation which act as free radical and interact with DNA.(Fond et al., 2012)

In addition to leukemia, multiple case reports have been published describing patients on clozapine developing lymphoma.(Ali et al., 2014; Chamberlain et al., 2015; Frieri et al., 2008; Hundertmark and Campbell, 2001) This observation was the rationale for a recent retrospective evaluation at a large community mental health center, which reported that 5 of 221 patients (2%) over 11 years who were prescribed clozapine developed lymphoma. (Meltzer, 2016)

Based on this available data we aimed to determine the incidence and assess the risk of any hematologic malignancy in patients with schizophrenia or schizoaffective disorder exposed to clozapine compared to those never exposed to clozapine. Following approval by the Mayo Clinic and Olmstead Medical Center investigational review boards we accessed the Rochester Epidemiologic Project (REP) database. The population of Olmsted County (from which REP data is derived) is representative of the population of Minnesota, of the Upper Midwest and of a large segment of the entire US population. The REP database was used to conduct a search for patients with ICD-9 codes for schizophrenia or schizoaffective disorder (295-295.9) and hematologic malignancies (200-208.92) between 1990 and 2014. A description of the REP database and methodology is well defined in other studies.(Rocca et al., 2012) As of 2015, the REP contained information on approximately 550,000 individuals. Patients under the age of 18 or who had a Minnesota Research Authorization status of ineligible (i.e. non-consenting) were excluded. Using query tools, REP data identified 205 of 1955 patients with an ICD-9 code for schizophrenia or schizoaffective disorder as being exposed to clozapine. For ICD-9 codes associated with hematologic malignancy, 37 of 1955 patients were found. However, individual medical records of patients with a hematological malignancy and schizophrenia or schizoaffective disorder were reviewed to assess if exposures to clozapine had occurred prior to the hematologic malignancy and no such cases were found. Following this negative finding, an IRB modification was approved to use the “Expanded REP” database.

The Expanded REP contains approximately 1.8 million unique individual patients in 27 counties of Minnesota but over a shorter time period. The Expanded REP is not usually accessed before REP because it cannot guarantee that all health care encounters are accounted for and thus not used for incidence studies. The Expanded REP data contained an additional 50 patients with a diagnosis of schizophrenia or schizoaffective disorder and a hematologic disorder (between 2010 and 2015) as well as and clozapine prescription information (2003-2015). Using this data set 4 cases were elucidated of patients with schizophrenia or schizoaffective disorder who developed lymphoma following an exposure to clozapine. Statistical analysis was not performed due to the limited number of cases. Table 1 contains a summary of the cases reviewed.

In conclusion, we were not able to find any cases of hematologic malignancy following clozapine exposure utilizing a database containing detailed patient information from one county in Minnesota. Exploration of the Expanded REP, in 27 counties, with information from a shorter time interval revealed 4 cases. The rarity of cases involving hematology

malignancy (specifically lymphoma and not leukemia) in patients with schizophrenia or schizoaffective disorder detected within the Expanded REP compels future investigations utilizing a larger national database. Such future research would be needed at this time to suggest a possible association between malignancy and clozapine exposure, if any.

Acknowledgment

This study was made possible using the resources of the Rochester Epidemiology Project, which is supported by the National Institute on Aging of the National Institutes of Health under Award Number R01AG034676. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health

References:

- Ali MS, Lehmann-Waldau F, Taikato RM, 2014 Continuation of clozapine in a patient with lymphoma. *Aust N Z J Psychiatry* 48(11), 1066–1067.
- Chamberlain FE, Walsh N, Falkowski J, 2015 Chemotherapy for Hodgkin's lymphoma in a patient receiving clozapine for treatment-resistant schizophrenia: use of the Mental Capacity Act 2005. *BJPsych Bull* 39(6), 305–307. [PubMed: 26755992]
- Fond G, Macgregor A, Attal J, Larue A, Brittner M, Ducasse D, Capdevielle D, 2012 Antipsychotic drugs: pro-cancer or anti-cancer? A systematic review. *Med Hypotheses* 79(1), 38–42. [PubMed: 22543071]
- Frieri T, Barzega G, Bada A, Villari V, 2008 Maintaining clozapine treatment during chemotherapy for non-Hodgkin's lymphoma. *Prog Neuropsychopharmacol Biol Psychiatry* 32(6), 1611–1612. [PubMed: 18606485]
- Hundertmark J, Campbell P, 2001 Reintroduction of clozapine after diagnosis of lymphoma. *Br J Psychiatry* 178, 576.
- Meltzer HY, 2012 Clozapine: balancing safety with superior antipsychotic efficacy. *Clin Schizophr Relat Psychoses* 6(3), 134–144. [PubMed: 23006238]
- Meltzer M, 2016 Lymphoma developing during clozapine therapy. *Aust N Z J Psychiatry* 50(5), 498–499.
- Nielsen J, Boysen A, 2010 Clozapine treatment associated with increased risk of acute myeloid leukemia (AML). *Schizophr Res* 123(2-3), 270–272. [PubMed: 20850952]
- Rocca WA, Yawn BP, St Sauver JL, Grossardt BR, Melton LJ 3rd, 2012 History of the Rochester Epidemiology Project: half a century of medical records linkage in a US population. *Mayo Clin Proc* 87(12), 1202–1213. [PubMed: 23199802]

Table 1

Cases Characteristics

Patient gender/RE P case?	Age at clozapine initiation*	Age at onset of lymphoma	Type of Lymphoma	Comment
Man/yes	25	45	Follicular Lymphoma	Clozapine was discontinued at the age of 46 following concerns it would interact with azathioprine (started for a newly diagnosed mixed connective tissue disorder).
Man/yes	48	55	Burkitt lymphoma	Clozapine was discontinued following a decline in ANC to $0.27 \times 10^9/L$ after methotrexate as part of the CODOX-M chemotherapy. No clozapine rechallenge occurred after recovery of ANC.
Man/yes	40	45	Chronic lymphocytic leukemia/ well differentiated lymphocytic lymphoma	Opted observation for CLL due to adherence concerns. Clozapine discontinued at age 54 due to concerns for contributing to cognitive disorder and severe orthostatic hypotension.
Woman/no	30	39	Follicular Lymphoma	Treated with bendamustine and rituximab initially for 6 cycles with concomitant clozapine with no aberrant ANC values (checked weekly). Four months after completion of chemotherapy the patient was found to have an ANC of $0.54 \times 10^9/L$ and clozapine subsequently discontinued. Patient was successfully rechallenged with clozapine ~6 months later following psychiatric decompensation.