# **⊘**SciMedCentral

# **Case Report**

# Clozapine and Neuroleptic Malignant Syndrome: Case Report and Risk Analysis of Monotherapy vs. Combination Therapy

### **Andrew Farah\***

Department of Psychiatry, UNC Healthcare, USA

#### Abstract

#### Traditionally, patients who are considered treatment-resistant, or who present with more severe symptoms, are often considered for clozapine therapy. The combination of clozapine with another SGA, or on FGA, is also commonly utilized for such severe cases, and may be considered standard-of-care given the prevalence of these strategies.

The following case report involves a chronically symptomatic schizophrenic who developed NMS on a combination of long acting injectable aripiprazole and clozapine. A review of the literature regarding clozapine associated NMS in combination with other agents vs. monotherapy indicates that, at least based on case reports, it is possible that combination clozapine-aripiprazole therapy may convey a higher risk of NMS than either agent as monotherapy.

# **CASE REPORT**

A 28-year-old male with a nine-year history of paranoid schizophrenia, and no prior history of NMS, was receiving aripiprazole for seven months, his usual dose being 400 mg a month. He had received 600 mg every three weeks for two subsequent doses due to his lack of response at 400 mg a month, thought related to his metabolism of the parent compound, and/ or his obesity and large stature, but his insurance refused to approve such high, frequent dosing, and he was returned to 400 mg a month for four months prior to his inpatient presentation. Despite medication compliance and ACT team involvement, he never reported a resolution of delusional thinking, and was hospitalized after he began confronting neighbors and making bizarre statements that were driven by his paranoia. Further, his parents specifically requested a trial of clozapine. Clozapine was started on day one of his hospital stay, 12 days after his latest aripiprazole injection. By day eight of hospitalization, clozapine was escalated to 200 mg daily, and by the following evening, the patient developed obtundation, confusion, was oriented to person only. He was noted to also have an oral fever of 101.9, and tachycardia ranging from 112-124, yet no general muscle stiffness on exam. Creatinine phosphokinase level was 1846 U/L, and reached a high of 4238 one day later. All oral medications were discontinued except as needed lorazepam, and he was transferred to the medical ward for supportive care.

The patient received intravenous hydration, as needed lorazepam, and supportive measures. He recovered within

ten days, and was challenged upon return to psychiatry with a trial of brexpiprazole. The dose was escalated to 4 mg twice a day by week two, with better symptom control. The patient remains on the combination of aripiprazole 400 mg monthly and brexpiprazole 4 mg bid, six months after discharge. This patient's NMS is typical of clozapine-induced NMS in that it followed rapid escalation of dose, he had no stiffness, and a brief low-grade fever that resolved within eight hours.

#### DISCUSSION

Early hopes that clozapine would be devoid of the risk of neuroleptic malignant syndrome (NMS) were dispelled with the first case report in 1986 [1]. However, some authors have suggested that NMS associated with second generation antipsychotics (SGA) is characterized by a lower rate of occurrence, and a lesser degree of clinical severity than first generation (FGA0 cases [2,3]. The consensus that SGA-induced NMS is associated with less frequent lethal outcomes has been disputed, and a recent chart review also challenged the notion that SGA's are less likely to cause NMS. The authors noted in particular the risks associated with poly pharmacy, and with aripiprazole. [4]. Further, clozapine-, aripiprazole- and amisulpride-induced NMS may present with atypical features more frequently than cases of other SGA-associated NMS. The atypical features reported include less intense extra pyramidal symptoms, and/or a lower degree fever. It has also been noted that 5.5% of reported cases of SGA-NMS were lethal, thus, the mortality rate seems to be much lower for SGA-NMS than

JSM Clinical Pharmaceutics

#### \*Corresponding author

Andrew Farah, Department of Psychiatry, UNC Healthcare, USA, Tel: 336-878-6000, Email: brian.farah@ unchealth.unc.edu

Submitted: 17 August 2017

Accepted: 25 September 2017

Published: 27 September 2017

ISSN: 2379-9498

#### Copyright

© 2017 Farah

OPEN ACCESS

#### Keywords

Clozapine

• Neuroleptic malignant syndrome

*Cite this article:* Farah A (2017) Clozapine and Neuroleptic Malignant Syndrome: Case Report and Risk Analysis of Monotherapy vs. Combination Therapy. J Clin Pharm 3(1): 1013.

## **⊘**SciMedCentral

previous estimates of 10-20 % among cases of FGA-NMS [5]. Yet it is more likely that the lower mortality rates with SGA use simply reflect greater clinician awareness, and a trend towards earlier detection and intervention. It is a fair assumption that the majority of NMS cases are not reported to manufacturers nor submitted to journals as case reports. Thus, relying on the case report literature may be easily criticised for not reflecting true rates. An unremarkable case that resolves with prompt discontinuation of the offending agent and supportive care would contribute nothing new to the literature. Thus, it is possible that case reports disproportionately represent those incidences involving more than one antipsychotic or atypical feature, due to the uniqueness of those cases. Therefore, accepting that the true occurrence will always remain unknowable, we have only the literature and manufacturers' databases for what insights can be discerned. Of the 47 case reports of clozapine associated-NMS, 13% were administered lithium as well, while 11% were coadministered another mood stabilizer or anticonvulsant (such as valproate agents, carbamazepine, oxcarbazepine, or lamotrigine). Further, one prior review (when there were 36 known cases of clozapine induced NMS) found that 50% of those patients had experienced at least one prior episode of NMS [5]. Though NMS has been reported with the co-administration of clozapine with olanzapine, risperidone, haloperidol, orziprasidone, (and one report involved the co-administration of clozapine with haloperidol, divalproex, and fluphenazine decanoate) aripiprazole seems to covey a heightened risk of NMS when combined with clozapine [5-9]. The combination of clozapine and aripiprazole has induced NMS in five case reports, including the above [10-25]. Of the eighteen reported cases of aripiprazole associated-NMS, 5 involve clozapine co-administered with aripiprazole (29.4%), the above case likely being the second reported with aripiprazole long acting injectable and clozapine. One of those cases involved a combination of clozapine, aripiprazole, and lithium [7]. Aripiprazole (oral) co-administered with risperidone account for one case report, while combination oral aripiprazole and olanzapine another, and the remaining eleven involve aripiprazole monotherapy. Of all case reports of clozapine associated-NMS, 11 of 47, or 23%, involve combination therapy with other antipsychotics, 5 of those 11 (45.5%) involving clozapine and aripiprazole, (2 LAI and 3 oral). Whether combining clozapine with FGA or SGA agents truly magnifies the risk of NMS is worthy of further investigation, however based on the limited sample of published cases, chart review literature, and manufacturer data, combination therapy appears to convey a higher risk of NMS than either agent administered as monotherapy.

Further, data suggests that aripiprazole and clozapine may convey a heightened risk of NMS when co-administered, as 29% of aripiprazole-associated NMS case reports involve its combination with clozapine. Further chart review studies may help confirm this finding, and may also help determine if there is a bias towards reporting cases of combination therapy.

#### **REFERENCES**

 Pope HG JR, Cole JO, Choras PT, Fulwiler CE. Apparent neuroleptic malignant syndrome with clozapine and lithium. J Nerv Ment Dis. 1986; 174: 493-495.

- 2. Trollor JN, Chen X, Chitty K, Sachdev PS. Comparison of neuroleptic malignant syndrome induced by first- and second-generation antipsychotics. Br J Psychiatry. 2012; 201: 52-56.
- Nakamura M, Yasunaga H, Miyata H, Shimada T, Horiguchi H, Matsuda S. Mortality of neuroleptic malignant syndrome induced by typical and atypical antipsychotic drugs: a propensity-matched analysis from the Japanese Diagnosis Procedure Combination database. J Clin Psychiatry. 2012; 73: 427-430.
- 4. Su YP, Chang CK, Hayes RD, Harrison S, Lee W, Broadbent M, et al. Retrospective chart review on exposure to psychotropic medications associated with neuroleptic malignant syndrome. ActaPsychiatr Scand. 2014; 130: 52-60.
- Belvederi Murri M, Guaglianone A, Bugliani M, Calcagno P, Respino M, Serafini G, et al. Second-Generation Antipsychotics and Neuroleptic Malignant Syndrome: Systematic Review and Case Report Analysis. Drugs in R&D. 2015; 15: 45-62.
- Minfeng Cheng, Huaying Gu, Liangrong Zheng, Houliang Wang, Zhiyong Zhong, Shenglin Wen, et al. Neuroleptic malignant syndrome and subsequent clozapine-withdrawal effects in a patient with refractory schizophrenia. Neuropsychiatr Dis Treat. 2016; 12: 695-697.
- G. van Rooijen, M. Strypet, A. Maat, D.S Scheepens, M.S. Oudijn, K.E. Klopper, et al. Early introduction of clozapine after neuroleptic malignant syndrome may prevent malignant catatonia: a case report. European Neuropsychopharmacology, 2017; 27: 91-92.
- 8. Lochhead JD, Nelson MA, Schneider AL. Risks and Benefits of Rapid Clozapine Titration. Ment Ill. 2016; 8: 6457.
- Sharma R, Kashyap R. Successful treatment of a complicated case of neuroleptic malignant syndrome with a higher dose of bromocriptine and lorazepam. Jl Postgrad Med Ed Res. 2016; 49:88-90.
- 10.Patel MJ, Brunetti L. Neuroleptic malignant syndrome secondary to aripiprazole initiation in a clozapine-intolerant patient. Am J Health Syst Pharm. 2010; 7: 1254-1259.
- 11.Brunelle J. Aripiprazole and neuroleptic malignant syndrome. J ClinPsychoparhmacol. 2007; 27: 212-214.
- 12. Daniel Molina, Leslie E. Tingle, Xiaohui Lu. Aripiprazole as the causative agent of neuroleptic malignant syndrome: a case report. Prim Care Companion. J Clin Psychiatry. 2007; 9: 148-150.
- Kang SG, Lee HJ, Lee MS, Kim L, Park JS. Atypical neuroleptic malignant syndrome associated with aripiprazole. J ClinPsychopharm. 2006; 26: 534.
- Rodriguez OP, Dowell MS. A case report of neuroleptic malignant syndrome without feverin a patient given aripiprazole. J Okla State Med Assoc. 2006; 99: 435-438.
- 15. Chakraborty N, Johnson T. Aripiprazole and neuroleptic malignant syndrome. Int Clin Psychoparnmacol. 2004; 19: 351-353.
- 16.Ping-Tao Tseng, Yi-Chung Chang, Chih-Hua Chang, Hung-Yu Wang, Yu-Shian Cheng, Ching-Kuan Wu, et al. Atypical neuroleptic malignant syndrome I patients treated with aripiprazole and clozapine: a case series study and short review. Int J Psychiatry Med. 2015; 49: 35-43.
- 17. Chen YT, Su KP, Chang JP. Early detection and management of atypical neuroleptic malignant syndrome secondary to aripiprazole. Schizophr Res. 2011; 132: 97-98.
- 18.Ali S, Pearlman RL, Upadhyay A, Patel P. Neuroleptic malignant syndrome with aripiprazole andlithium: a case report. J Clin Psychopharmacol. 2006; 26: 434-436.
- 19.Gahr M. Neuroleptic malignant syndrome with aripiprazole in Huntington's disease.MovDisord. 2010; 25: 2475-2476.

# **⊘**SciMedCentral

- 20. Marshall PB, Mellman TA, Nguyen SX. Neuroleptic malignant syndrome with the addition of aripiprazole to olanzapine. Am J Psychiatry. 2008; 165: 1488-1489.
- 21.Evcimen H. Neuroleptic malignant syndrome induced by low dose aripiprazole in first episode psychosis. J Psychiatr Prract. 2007; 13: 117-119.
- 22. Seksan Srephichit, Richard Sanchez, James A. Bourgeois. Neuroleptic malignant syndrome and aripiprazole in an antipsychotic-naive patient. J Clin Psychopharmacol. 2006; 26: 94-95.
- 23.Duggal HS, Kithas J. Possible neuroleptic malignant syndrome with aripiprazole and fluoxetine.Am J Psychiatry. 2005; 162: 397-398.
- 24. Dassa D. Neuroleptic malignant syndrome with the addition of aripiprazole to clozapine. Progress in Neuropsychopharmacologic Biology and Psychiatry. 2010; 34: 427-428.
- 25. Ananth J, Parameswaran S, Gunatilake S, Burgoyne K, Sidhom T. Neuroleptic malignant syndrome and atypical antipsychotic drugs. J Clin Psych. 2004; 65: 464-470.

#### **Cite this article**

Farah A (2017) Clozapine and Neuroleptic Malignant Syndrome: Case Report and Risk Analysis of Monotherapy vs. Combination Therapy. J Clin Pharm 3(1): 1013.