A Reasonable Alternative to Clozapine in the Chronically Relapsing Smoking Patient? A Retrospective Analysis

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ABSTRACT

Background: Clozapine levels are severely decreased by cigarette smoke hydrocarbons. A new agent that is unaffected by smoking is paliperidone palmitate.

Objective: The purpose of this study is to retrospectively evaluate hospital readmission and time until readmission for patients prescribed paliperidone palmitate intramuscular injection (PP) as an alternative to oral clozapine for patients with severe schizophrenia who resume smoking following discharge. A secondary analysis was performed to determine whether smoking status alone affects hospital readmission rates in both smoking and nonsmoking clozapine-treated patients.

Methods: This was a retrospective analysis of all patients who were positive for smoking at admission and readmission who were prescribed clozapine and PP. Smokers were identified by concurrent orders for nicotine replacement. Readmission rates and time until readmission were determined. Data were analyzed utilizing nonparametric statistical methods.

Results: A total of 133 subjects were identified, including 108 smokers in PP group, 18 smokers in clozapine group, and 7 nonsmoking clozapine patients. Readmission rates were statistically significant between smokers in the clozapine and PP groups, with significantly lower readmission rates in the PP group ($p = .004$). In the sub-analysis, hospital readmissions between smokers and nonsmokers in the clozapine group were statistically significant ($p = .027$). Results may be influenced by use of a single hospital site, limits of a retrospective analysis, and variation in pharmaceutical preparation.

Conclusion: PP may be a reasonable alternative to clozapine in severe schizophrenia for patients who continually resume smoking following discharge. Smoking may also be an important predictor of decompensation in smokers prescribed clozapine. A further prospective study is warranted.

Key Words—adherence, clozapine, paliperidone, readmission, smoking

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Tobacco smoking poses considerable health risks, contributing to the development of cancer, heart disease, and pulmonary diseases.¹⁻³ As suggested by guidelines of The Joint Commission (TJC), many hospitals and mental health facilities have moved to a “smoke-free” policy, prohibiting tobacco smoking within these institutions.^{4,5} The rationale behind these policies is noble, encouraging wellness and discouraging negative health behaviors.

Smokers who present to these institutions for either medical or psychiatric concerns are frequently offered nicotine replacement products to prevent nicotine withdrawal and craving during their admission. Nicotine replacement has been shown to aid in smoking cessation; however, many resume smoking behavior following discharge.⁶ This problem is particularly significant in the schizophrenia population. Patients diagnosed with schizophrenia experience quit rates

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that are 2 to 3 times lower than in the general smoking population.⁷ Additionally, it has been estimated that approximately 80% of patients suffering with schizophrenia smoke cigarettes, with some estimates of smoking behavior as high as 90% in this population.^{7,8} This smoking burden can contribute not only to the potential for the development of significant health problems but leads to disproportional economic problems in this population.⁹ Empiric evidence has shown that tobacco smoking may be used to self-medicate symptoms of schizophrenia, side effects of antipsychotics, or cognitive deficits, which may represent a further barrier to cessation.¹⁰

Another concern in regard to smoking is the drug-smoking interactions that induce metabolism of some medications. The specific concern for this interaction involves the hydrocarbons contained in cigarette smoke. These hydrocarbon compounds induce hepatic CYP 450 1A2 isoenzyme, leading to decreases in serum drug levels of some antipsychotic agents.¹¹⁻¹³ Estimates state that this enzyme is fully induced in patients smoking as few as 7 cigarettes per day.⁷ CYP 1A2 induction occurs within 10 to 12 hours of exposure to an inducer and may take approximately 1 to 2 weeks to normalize once the inducer is discontinued.¹⁴ The interaction may lead to negative outcomes in patients with schizophrenia, and smoking reduction strategies may also be insufficient to mitigate the interaction in this population.^{15,16} Clozapine is an oral agent that produces a major drug-smoke interaction, yet it is utilized in severe or treatment-resistant schizophrenia. It has also been recommended as a possible second option in patients with inadequate response to an initial antipsychotic agent, intolerable side effects with the trial of the first agent, or patients with aggression or the presence of suicidality. Additionally, smoking status can be considered a patient-specific consideration for treatment choice.¹⁷ The drug requires close monitoring for the development of neutropenia and also carries risks for the induction of seizures, myocarditis, or orthostasis.¹⁸ Clozapine serum drug levels are profoundly impacted and smoking can decrease clozapine drug levels by as much as 50%, leading to psychiatric decompensation.^{13,19} Since many hospital units are now “smoke-free” environments, stabilization may occur in an environment that does not correlate with the patient’s circumstances outside of the hospital where smoking resumption is likely. It has been proposed that a strategy for managing this interaction if the patient resumes smoking is to increase the clozapine dose by 50% over 2 to 4 weeks after discharge.^{20,21}

Stabilized, smoking patients taking clozapine as outpatients may be exposed to a different set of risks. In the event of a medical admission to the “smoke-free” hospital environment, smokers are typically offered nicotine replacement products. During the period in which the patients are free from smoke hydrocarbons, the serum drug levels of clozapine may increase. It has been suggested that downward dose adjustment of as much as 40% should be made during the first week of admission.²² If the dose reduction is overlooked, patients may encounter severe adverse reactions such as orthostasis, tachycardia, somnolence, fatigue, and potentially seizures as a result of rapidly increasing clozapine levels.²³⁻²⁷

An agent that is approved for the treatment of schizophrenia that does not interact with cigarette smoke hydrocarbons is paliperidone.²⁸ Paliperidone is a first-line atypical antipsychotic US Food and Drug Administration (FDA)–approved for the treatment of schizophrenia or schizoaffective disorder. It is available as a daily oral formulation or as the monthly long-acting intramuscular injectable palmitate salt.²⁹ The drug, which is 9-OH-risperidone, is an active metabolite of risperidone. Most antipsychotics, except for ziprasidone or paliperidone, are prone to serum drug level decreases due to enzyme induction.³⁰ As an active metabolite, the CYP450 1A2 interaction is avoided; thus, if smoking resumption occurs, there will be minimal impact on serum drug levels. Therefore, paliperidone may mitigate the risk of toxic serum drug levels following admission to a smoke-free facility.

In an effort to find a reasonable alternative antipsychotic agent to clozapine in smokers with comparable psychiatric stability, we chose to investigate hospital readmission and time-until-readmission outcomes for smoking patients taking either clozapine oral tablets or paliperidone palmitate injection (PP). Literature has also shown that there may be improved time until discontinuation when using first-generation long-acting injectable antipsychotic medications in schizophrenia and schizoaffective disorder.³¹ Further, more recent literature has shown the superiority of PP compared to oral atypical antipsychotics in delaying the time until treatment failure; however, clozapine was not included as an option in this study.³² PP was also selected since long-acting injectable antipsychotics have shown improved quality of life and improved pharmacoeconomic outcomes compared to oral antipsychotics.³³⁻³⁵

OBJECTIVE

Since clozapine was not utilized in the Alphas et al study as a comparator to PP, the authors decided

to investigate existing patient data for clozapine and PP prescribed patients for whom continuous positive smoking status was a patient-related consideration.²⁹ The purpose of this study is to evaluate patient readmission and time-until-readmission outcomes for paliperidone palmitate intramuscular injection (PP) as a reasonable alternative to oral clozapine for patients with severe schizophrenia who find it difficult or impossible to cease smoking following hospital discharge. A secondary analysis was performed to investigate whether smoking status alone affects hospital readmission rates in clozapine-treated patient. The study was performed and approved in accordance with the ethical standards of both the hospital and university Institutional Review Boards regarding human experimentation.

METHODS

A retrospective chart review was performed for all subjects diagnosed with schizophrenia who were ordered and administered either clozapine or PP from January 2012 to January 2015 in a large tertiary university teaching hospital. The hospital serves medical and mental health needs for an urban population as part of university health system. A convenience sample of smokers was identified from these subjects by concurrent orders for and administration of nicotine replacement products during admission as a surrogate marker of outpatient smoking status. Therefore, subjects include smoking patients administered PP or clozapine while admitted during this 3-year timeframe. Nonsmoking clozapine-treated patients were also identified for secondary analysis. All subjects were admitted for either psychiatric or medical/psychiatric admission, medical/psychiatric admission being defined as a medical admission requiring psychiatry consult and subsequent psychiatric care. Following subject identification, readmission and time until readmission data were collected from the hospital electronic medical record. Collected data included age, gender, and smoking status (on admission and readmission). GAF (Global Assessment of Function) score on admission, discharge, and readmission was collected to determine subject functionality as an estimate of illness severity. Additional collected data included the discharge dose of the corresponding antipsychotic on discharge and possible readmission and time until hospital readmission.

Data were analyzed using IBM SPSS 22.0 (IBM Corp., Armond, NY). Due to non-normal sample distribution, nonparametric statistics were used at a priori significance of $\alpha = 0.05$ and confidence level of 0.95. Independent sample Mann-Whitney U tests for GAF score and medication dose analysis were performed

for the nonparametric continuous data. Fisher's exact test was employed for the determination of readmission between groups of nominal data. A one-sample Kolmogorov-Smirnov test was performed to analyze the difference in mean dose of clozapine on discharge and readmission in the subanalysis. Time until readmission was analyzed using Cox proportion hazard model with GAF scores on admission and discharge as a covariate to account for illness severity.

RESULTS

There were 133 medical records that met inclusion criteria; 108 smokers prescribed PP (mean dose, 175.9 mg every month) and 18 smokers prescribed clozapine (mean dose, 381.9 mg daily) during the study period. There were 7 subjects prescribed clozapine who were determined to be nonsmokers for subanalysis (mean dose, 412.5 mg daily). GAF scores on admission, discharge, and any readmissions were comparable between smoking clozapine and PP subjects, signifying a statistically similar level of functional impairment at each juncture. Readmissions between subjects included 9/18 clozapine subjects (50.0%) compared to 18/108 PP subjects (16.7%), the rate of which was determined to be statistically significant, favoring PP ($p = .004$). However, time until readmission was comparable between drugs via Cox proportional hazards model ($p = .425$). Demographics and results in smoking subjects prescribed clozapine or PP are summarized in Table 1.

In the subanalysis comparing smoking and nonsmoking clozapine-treated subjects, baseline demographics and illness severity were similar. There were no statistical differences in the discharge dose of clozapine between smokers and nonsmokers nor was there a statistical difference between mean dose of clozapine on discharge and readmission. Following discharge, 9 smokers (50% of the smoking subjects) were readmitted to the hospital: 2 for a psychiatric reason and 7 for medical/psychiatric reasons. Each of these subjects was subsequently treated in psychiatry during their admission, and none of these readmissions were determined to be due to complications of clozapine treatment. No nonsmokers were readmitted to the hospital during the study period. All-cause readmission comparison between smokers and nonsmokers was statistically significant ($p = .027$). A summary of the distribution of clozapine readmissions and dose adjustments based upon smoking status can be seen in Table 2.

Subjective findings of the study found reluctance to adjust doses upon admission to account for the change in smoking status. Only 2 smokers prescribed

Table 1. Comparison of smoking clozapine and smoking paliperidone palmitate subjects

Demographics	Clozapine	Paliperidone palmitate	<i>p</i>
Subjects, <i>N</i>	18	108	
Gender, male/female, <i>n/n</i>	13/5	68/40	
Age, years ^a	48.12 ± 8.20	41.88 ± 11.49	ns
GAF score, admission ^a	31.25 ± 14.36	24.69 ± 5.29	ns
GAF score, discharge ^a	48.75 ± 6.29	50.71 ± 3.19	ns
Dose on discharge, (clozapine mg/day; PP mg/month)	381.94 ± 203.24	177.87 ± 35.36	
No. (%) of readmissions ^b	9 (50.0)	18 (16.7)	.004
GAF score, readmission ^a	35.00 ± 10	28.89 ± 5.30	ns
Time until readmission, months ^c	5.85 ± 5.33	6.14 ± 4.72	ns

Note: Values given are mean ± SD, unless otherwise indicated. GAF = Global Assessment of Function.

^aIndependent sample Mann-Whitney U.

^bFisher's exact test.

^cCox proportional hazard [95% CI for Exp(B)]; *p* = .972 [0.908-1.042] admission GAF and *p* = .002 [0.905-1.087] discharge GAF.

Table 2. Results of subanalysis of clozapine smokers and clozapine nonsmokers

	Smokers	Nonsmokers	<i>p</i>
Subjects, <i>N</i>	18	7	
Gender, male/female, <i>n/n</i>	13/5	4/3	
Age, years ^a	46.22 ± 7.81	53.00 ± 7.59	ns
GAF score, admission ^a	31.25 ± 14.36	37.14 ± 16.95	ns
GAF score, discharge ^a	48.75 ± 6.29	48.21 ± 10.30	ns
Discharge clozapine dose, mg/day ^a	381.94 ± 203.24	412.50 ± 160.08	ns
No. of readmissions ^b	9	0	.027
GAF score, readmission	35 ± 10	N/A	
Readmission clozapine dose, mg/day ^c	363.89 ± 164.46	N/A	ns
Gender readmitted, male	6	N/A	
Time until readmission, months	5.85 ± 5.33	N/A	

Note: Values given are mean ± SD, unless otherwise indicated. GAF = Global Assessment of Function; N/A = not applicable.

^aIndependent sample Mann-Whitney U.

^bFisher's exact test.

^cOne sample Kolmogorov-Smirnov.

clozapine had a decrease in clozapine dose upon readmission to the smoke-free hospital environment to account for the change in smoking status. One of these subjects had serum clozapine and norclozapine levels drawn. There were no medical events or comorbidities as a result of failure to adjust clozapine doses.

CONCLUSION

Because of similarities on admission, discharge, readmission, and demographics, coupled with the

much lower readmission rate, PP may prove to be a reasonable alternative for the management of schizophrenia in the patient who chronically relapses to smoking behavior following discharge. Further prospective study of PP as a reasonable alternative treatment to clozapine is warranted in patients who are unwilling to cease smoking or find it extremely difficult to quit. Our findings suggest that, based on similar demographics, functionality, and need for nicotine replacement on readmission, alternative treatments

to clozapine for the treatment of severe schizophrenia in smokers would be very helpful to improve long-term positive psychiatric outcomes. PP may prove to be one of these options. A future direction is to prospectively determine whether PP is just such a viable option. Additionally, providing intensive smoking cessation interventions during the inpatient treatment phase for smokers prescribed clozapine may help to improve long-term stability. Introducing a smoking cessation model earlier in the treatment continuum may prove to be advantageous following discharge in terms of psychiatric stability as well as overall positive health outcomes.

Improved adherence from the use of long-acting injectable formulations as seen in the recent literature by Alphs et al may be an alternative explanation for the lower readmission rates.³² In this work, patients prescribed oral atypical antipsychotics (not including clozapine) were found to have decreased time until treatment failure with oral antipsychotics compared to PP. Our results suggest that the readmission rates of smokers prescribed PP were statistically lower than the readmission rates of smokers prescribed clozapine. This finding may be interpreted as improved adherence with treatment when using a long-acting injectable antipsychotic agent or possibly a longer duration of illness in clozapine-treated patients. Despite these findings, the severity of the smoke–clozapine interaction cannot be overlooked in the current work. PP was chosen as a comparator agent due to both its status as an active metabolite of risperidone, the avoidance of a smoke–drug interaction, and as a long-acting antipsychotic agent. The dosage form difference may have played a role as a limitation to the study, and further prospective studies should be performed to investigate the interaction's role in adherence.

In the secondary analysis of clozapine-treated smokers compared to nonsmokers, smoking status may be an important risk factor in itself for decompensation and rehospitalization. In our sample, only clozapine-treated smokers were readmitted to the hospital. While the number of subjects in the subanalysis groups was small and no definitive conclusions can be drawn from the data, this finding may shed light on the importance of smoking cessation in clozapine-treated patients and add credence to the performance of future research emphasizing the importance of smoking cessation initiation very early in the treatment continuum.

Due to the limitations of a retrospective review and findings from a single hospital site within a specified time frame, a prospective, ongoing study in multiple sites may produce more clinically relevant

and generalizable findings. The use of GAF scores used in clinical practice as a part of the former DSM-IV-TR axis diagnosis may not fully correlate with results of assessment scales employed in prospective clinical trials such as Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS). Additionally, the non-normal distribution of data required the employment of nonparametric statistical methods. A possible explanation for the small clozapine sample may be the reluctance of patients to consent to phlebotomy testing, patient fear of metabolic side effects from the drug, or physician hesitance in utilizing clozapine. This may have led to the use of alternative antipsychotic agents. A larger, normalized sample distribution may provide stronger evidence for the recommendation of PP in the smoking population. A further limitation to the results was the inability to determine the lifetime chronicity of schizophrenia treatment in subjects, because data were only available during the prespecified time frame. Lastly, patient readmission to hospitals outside of the current site was not possible and created a further limitation to the generalizability of results.

We chose not to include oral paliperidone in this analysis due to the extremely low number of patients prescribed this medication during the study period. It was utilized to determine tolerability of paliperidone prior to long-acting administration; risperidone oral tablets were also administered as part of the tolerability challenge. Additionally, mean doses of each drug may not be considered therapeutically equivalent or interchangeable. Therefore caution should be exercised in the application of these results.

The findings of this retrospective review infer that, based upon similar functionality on admission and discharge, further prospective study of PP as a reasonable alternative to clozapine for patients with schizophrenia that continually resume smoking following discharge is warranted. The lack of CYP450 1A2 induction of PP may be an important consideration in the long-term psychiatric outcomes of patients suffering from schizophrenia. Variability in serum drug levels as a result of the smoke hydrocarbon induction of the enzyme in patients taking clozapine may lead to psychiatric decompensation despite adherence with medications. Conversely, a stable, smoking clozapine-treated patient may be vulnerable to untoward adverse effects following admission to a smoke-free environment. Utilizing PP following discharge from the acute hospital environment could also provide a window to initiate smoking cessation interventions without exposing

the patient to unnecessary risks. A future prospective study regarding the use of PP in chronic smokers and the effect of intensive smoking cessation treatment during the acute inpatient admission is planned.

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