Trends Journal of Sciences Research, 2018, Volume 3, Issue 3, 104-115
http://www.tjsr.org/journal/index.php/tjsr
DOI: 10.31586/PharmaceuticalHealth.0303.01

Comparative Effectiveness of Smoking Cessation Medications among Schizophrenic Smokers

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Research Article

Open Access

How to cite this article: Wu, I., Chen, H., Bordnick, P., James Essien, E., Johnson, M., J Peters, R., Vadhariya, A., & Abughosh, S. (2018). Comparative Effectiveness of Smoking Cessation Medications among Schizophrenic Smokers. *Trends Journal Of Sciences Research*, *3*(3), 104-115. https://doi.org/10.31586/PharmaceuticalHealth.0303.01

Received: September 04, 2018

Accepted: October 05, 2018

Published: October 05, 2018

Abstract **Objective**: To examine which medication could lead to a higher short and long term smoking abstinence in patients with schizophrenia.
Methods: A retrospective cohort study was conducted using General Electric (GE) medical records database (1995 – 2011). The cohort consisted of adult smokers with diagnosis of schizophrenia newly initiating cessation medication. Short term and long term outcomes of cessation were measured at 3 weeks and 1 year. Descriptive and chi-square analyses were used to determine the frequencies and associations of patient characteristics with the abstinence outcomes. Logistic regression models were carried out to determine the predictors of short term and long term abstinence.
Results: The cohort consisted of 3,976 patients. Abstinence rate was highest for Varenicline, followed by Bupropion, NRT, and lastly combination at week 12. At one year, abstinence rate was highest for Varenicline, followed by combination, NRT, and lastly Bupropion. Age, race, household locations and receiving counseling were associated with abstinence. No significant differences were found between cessation medications.
Conclusions: There were no statistically significant differences in quitting with type of cessation medication. Predictors of better abstinence identified included older age, white race, western household location. These factors should be considered when designing future interventions for schizophrenic population as this minority population may need more tailored approaches to achieve a successful cessation outcome.

Keywords: *Comparative effectiveness, Smoking cessation, Schizophre*

1. Introduction

Schizophrenic patients have a higher smoking prevalence as compared to the general population: 72% - 90% vs. 23%[1]. Previous studies have also shown they tend to be heavy smokers [2], to have higher dependence level and much lower cessation rates[3,4]. The high prevalence can be possibly due to self-medication effect as tobacco may be used to alleviate some of the symptoms in schizophrenia [5,6]. However, there is increasing evidence that a majority of smokers with schizophrenia want to quit smoking.[7]

The available cessation pharmacotherapies include nicotine replacement therapy (NRT), Bupropion SR, and the most recent approved Varenicline [8,9]. The FDA suggested regimen for smoking cessation is usually 12 weeks long. Of the various nicotine medications sold, the gum and patch are the most frequently used. Nicotine gum is available in 2-mg and 4-mg doses. The 2-mg gum is recommended for patients smoking <25 cigarettes/day; the 4-mg gum is recommended for

patients smoking more than that. Bupropion was originally approved by the FDA for treating depression under brand name Wellbutrin® in 1996 [10]. In the following year, FDA approved the same ingredients but under trade name Zyban® for smoking cessation [3]. The drug therapy Varenicline was approved in 2006 and was new during the period of this study[9].

Studies that have been conducted among schizophrenic smokers regarding smoking abstinence were with small sample sizes and all were in rigorously controlled RCT patterns [11-19]. Our objective was to examine which medication could lead to a higher smoking abstinence for both short and long term. Aside from medications, we also identified other predictors of successful quitting.

2. Material and Methods

2.1. Data source

The data used for this study was extracted from the General Electric Centricity Electronic Medical Record (GE EMR) database. The Centricity EMR database is used by >20,000 clinicians and contains longitudinal ambulatory electronic health data for >7.4 million patients, including demographic, vital signs, laboratory results, medication list entries, prescriptions, and diagnoses. What made GE EMR an appropriate tool for our analysis is that it is enriched by some forms of NRTs are OTCs which cannot be captured using administrative claims data.

2.2. Study population

We included patients who were enrolled between 12/13/1995 to 10/31/2011. Patients aged <18 years old or those who received Wellbutrin® (Bupropion SR) for depression 6 months prior to index date were excluded. We identified patients with a diagnosis of schizophrenia or schizoaffective disorder (ICD-9 code 295.00-295.99) [20].

After identifying the population, we constructed a series of new-user cohort of patients who had newly initiated using cessation medications. Only the first exposure to each of the medication was examined so we can be sure quitting is not affected by the previous cessation product. Since cessation medications are usually being prescribed for three months [21], we used 3-month for drug treatment window. For individual who were exposed to two different medications, we then examined if the 2nd was within 3 months from the first one. If not, then he/she was classified as having monotherapy, and belonged to the drug group he/she got exposed to first. If the patient was exposed to more than one medication that's within 3 months, then he/she stayed in the combination group. Unlike claims data, in EMR, we could not be certain the second cessation medication was a switch over or an add-on as medication stop dates were missing for many records. Thus patients with multiple therapies within a 3 –month window could either be on combination therapy, or could have made multiple attempts to quit within the time frame.

2.3. Short term outcome - 12 weeks (up to 16 weeks)

Though most of the medications are for 12 weeks, we observed our short term outcome up to 16th week because the medication may last longer for some patients if they are not perfectly adherent due to reasons such as forgetfulness etc. Three observation windows for smoking status were constructed: (1) status obtained the next day of index - day 60, (2) status obtained day 61-90, and (3) status obtained day 91 - 120. If a smoker had smoking status recorded in all three windows, then we took the observation preference as window #2, #3, and then window #1.

2.4. Long term outcome – 1 year

Two models were analyzed: (1) only patients who quit at the 12th week, and (2) all patients irrespective of whether they quit or not at week 12. We took the smoking status that's closest to day 365 from index date. Only the observations within one year were examined. We did not extend the observation for another month because we believed it is very likely to have an immediate effect on quitting for their second exposure.

2.5. Logistic regression models

Logistic regression models were identified, and the dependent variables were the smoking status at three different outcomes as previously mentioned: (model 1a) Quitting at 12th week, (model 1b) Quitting at 1 year among those who quit at week 12, and (model 2) Quitting at 1 year (regardless of the smoking status at week 12).

The independent variable of primary interest was the cessation product used. However demographic variables such as age, race, gender, that were included in the models included: age, race, gender. BMI was added to the model due to the known relationship between quitting and weight gain[22]. Region, payment type, specialty group were added to control for any practice related variables associated with prescription of certain cessation medications. Additionally the smoking addiction level, smoking counseling and exposure to medications that might affect smoking status (nortriptyline, buspirone, clonidine, naltrexone, mecamylamine, or rimonabant), comorbidity index (D'Hoore), and severity of mental disorder (having antipsychotic injections) were also added to the model. We added an extra variable for model 1b and model 2: having an exposure to any of the cessation product between week 16 - year 1 (yes/no), and another variable for model 2: quit smoking at week 12 (yes/no).

Level of nicotine dependence was inferred from their dosages. If their starting dose for nicotine patch was 21mg/day or nicotine gum 4mg/piece then they were classified as high addiction; on the other hand, if nicotine patch was 7 or 14mg, or nicotine gum 2mg/piece, then they were classified as low addiction. However, Bupropion or Varenicline users were all classified as high addiction because doses were fixed for all smokers.

Descriptive and chi-square analyses were used to determine the frequencies and associations of patient characteristics with the abstinence outcomes. Multiple logistic regression models were carried out to determine the predictors of successful cessation. All variables with p-value <0.2 in chi-sq as well as the possible confounding variables were included in the logistic models. Characteristics like age, gender, and race were included regardless of the significant results in chi-sq. Interaction terms were tested as well. All statistical analyses were carried out using SAS statistical package version 9.3.

3. Results

3.1. Baseline Sample Characteristics

From the inception of GE data, we found a total of 49,175 patients were diagnosed with schizophrenia or schizoaffective disorder. About 10% of them got at least one cessation medication (n=4,504, 9.16%). Individuals <18 years old or those who received antidepressants Bupropion (Wellbutrin®) 6 months prior to index date were dropped. This brought us down to a total of 3,976 patients. Figure 1 shows how the sample size reduced by applying each inclusion and exclusion criteria.

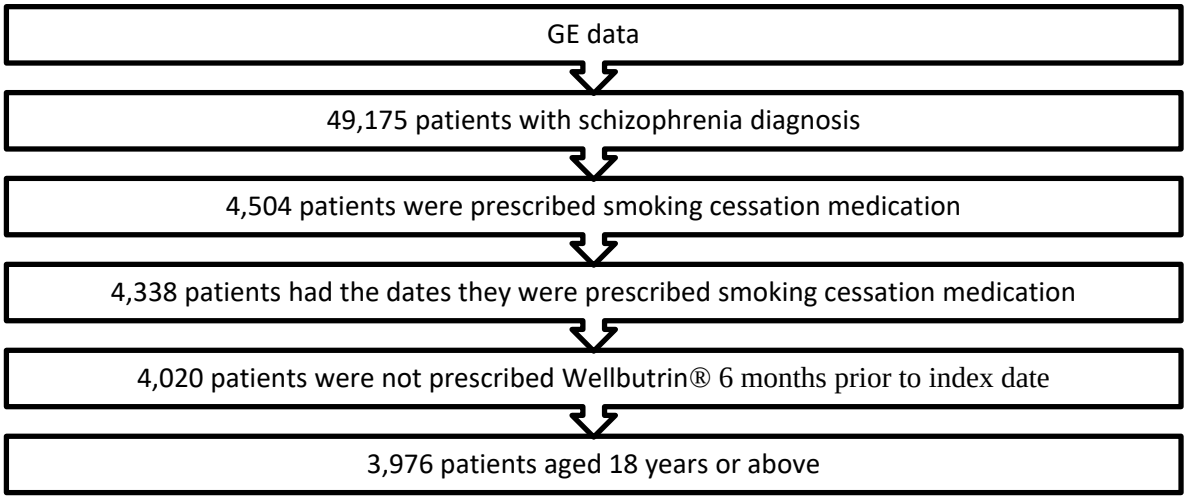

Figure 1. Our study cohort

3.2. Cohort distribution

Slightly more than half were male (n=2,141, 53.85%), close to half were whites (n=1,805, 45.40%), and majority were with high addiction level (n=3,202, 80.53%). Most of them had stable mental states (n=3,881, 97.61%). Slightly more than

half (n=2,045, 53.62%) of the users were under Medicare or Medicaid coverage. The mean age was 45.40 years old (±SD: 11.51). Most of the cessation medications were prescribed by their primary physicians (n=3,858, 97.03%) and about 40% of patients had received smoking counseling (n=1,606, 40.39%). Patient characteristics are presented in Table 1.

As shown in Table 1, NRT was the most commonly used (n=2,590, 65.14%) compared to Bupropion SR (n=89, 2.24%) and Varenicline (n=1,164, 29.28%). A portion of patients were prescribed two medications within 3-month window: NRT + Varenicline (n=112, 2.82%) and NRT + Bupropion (n=21, 0.53%). No records were found for any individual to receive Bupropion and Varenicline during the same period. Due to small sample size of those who got more than one medication, we grouped them together into "combination group" in further logistic regressions.

Table 1. Abstinence at week 12 (or 16) and year 1 among schizophrenic smokers who were prescribed any smoking cessation medication

Characteristics	Total Frequency (Percentage)	Model 1a Abstinence at week 12 or 16 (n=235, 18.02%)		Model 1b Abstinence at year 1 among those quit at week 12 or 16 (n=170, 75.22%)		Model 2 Abstinence at year 1, regardless of quitting at week 12 or 16 (n=346, 17.20%)	
		N (%)	p-value	N (%)	p-value	N (%)	p-value
Demographics							
Sex							
Female	1,835 (46.15%)	111 (17.99%)	0.9778	77 (71.30%)	0.1910	170 (17.86%)	0.4570
Race							
Blacks	622 (15.64%)	19 (10.27%)	**0.0025***	12 (63.16%)	0.4207	29 (9.93%)	**0.0010***
Whites	1,805 (45.40%)	112 (17.53%)		85 (77.27%)		188 (19.26%)	
All others	1,549 (38.96%)	104 (21.67%)		73 (72.26%)		129 (17.34%)	
Region							
Midwest	1,089 (27.41%)	76 (19.34%)		54 (75.00%)		88 (15.20%)	
Northeast	1,278 (32.17%)	69 (14.20%)	**<0.0001***	45 (67.16%)	0.1996	120 (16.19%)	**0.0024***
South	927 (23.33%)	34 (14.05%)		29 (85.29%)		65 (16.33%)	
West	679 (17.09%)	56 (30.60%)		42 (79.25%)		73 (24.83%)	
BMI							
Normal (BMI<25)	1,483 (37.30%)	83 (19.53%)		65 (80.25%)		123 (18.25%)	
Overweight (25<=BMI<30)	874 (21.98%)	44 (15.17%)	0.3187	35 (81.40%)	0.1132	77 (16.81%)	0.6707
Obesity (BMI>=30)	1,619 (40.72%)	108 (18.34%)		70 (68.63%)		146 (16.59%)	
Insurance							
Medicare or Medicaid	2,045 (53.62%)	129 (18.78%)	0.2834	102 (79.69%)	0.2153	200 (19.32%)	**0.0057***

Clinical factors							
Had antipsychotic injectables 1 year prior to index date Yes	95 (2.39%)	7 (18.42%)	0.9481	6 (85.71%)	0.5136	12 (23.53%)	0.2248
Smoking Cessation Related							
Addicted to nicotine Yes	3,202 (80.53%)	196 (18.61%)	0.2546	139 (73.94%)	0.3196	284 (17.39%)	0.6313
Cessation Medication Varenicline NRT Bupropion SR Combination	1,164 (29.28%) 2,590 (65.14%) 89 (2.24%) 133 (3.35%)	73 (21.04%) 153 (17.43%) 4 (18.18%) 5 (8.77%)	0.1300	57 (78.08%) 113 (73.86%) n/a n/a	0.4914	112 (20.07%) 215 (16.09%) 5 (14.29%) 14 (16.87%)	0.2038
Cessation Rx given by specialty care physician? Yes	118 (2.97%)	11 (30.56%)	**0.0472***	7 (70.00%)	0.6957	9 (20.93%)	0.5119
Received any medication that might affect smoking status anytime 6 months prior to index date Yes	180 (4.53%)	9 (14.52%)	0.4619	n/a	n/a	16 (14.52%)	0.8878
Smoking counseling received anytime one year prior to index date Yes	1,606 (40.39%)	102 (14.51%)	**0.0004***	73 (73.74%)	0.6482	146 (14.50%)	**0.0013***
Had the 2nd cessation exposure within 1 year among those who quit at month 3 or 4 Yes	n/a	n/a	n/a	36 (58.06%)	**0.0002***	101 (19.42%)	0.1182
Abstinence at week 12 Yes	n/a	n/a	n/a	n/a	n/a	175 (74.47%)	**<0.0001***
Total frequency for model 1a=3,976; Total frequency for model 1b=226; Total frequency for model 2=3,976; ***P<0.05**							

3.3. Abstinence at the three timelines

Among the 3,976 cohort, approximately 1/3 had smoking status recorded at week 12 (n=1,304, 32.80%) and 235 of those quit smoking (18.02%). Average smoking status was assessed at 66.72 days after the medication exposure. Abstinence rate was highest for Varenicline (21.04%), followed by Bupropion SR (18.18%), NRT (17.43%), and lastly combination

(8.77%). Among the 235 schizophrenic patients who quit smoking at week 12, we continued follow up time until one year and found almost 3/4 of their quitting behavior sustained (n=170, 75.22%).

Among the 3,976 cohort, approximately half had smoking status recorded at year 1 (n=2,012, 50.60%) and 346 of those quit smoking (17.20%). Average smoking status was assessed at 209.52 days after the medication exposure. Abstinence rate was highest for Varenicline (20.07%), followed by combination treatment (16.87%), NRT (16.09%), and lastly Bupropion (14.29%).

3.4. Logistic regression for model 1a

Logistic regression results are presented in Table 2. In the multivariate models, we found that older adults were more likely to quit (OR=1.02, 95% CI=1.01 – 1.03). As compared to Blacks, Whites (OR=1.83, 95% CI=1.04 – 3.20) and all other races (Asians, Hispanics, Multi-races, and Indian Americans) (OR=2.13, 95% CI=1.19 – 3.79) were more likely to quit smoking. Those whose household locations were in the west part of U.S. were also more likely to achieve quitting as compared to those in the Midwest (OR=2.18, 95% CI=1.39 – 3.41). No significant differences were found between cessation medications. Individuals who had received smoking counseling were actually less likely to quit (OR=0.67, 95% CI=0.49 – 0.92).

Table2. Logistic regression models for quitting at week 12 (or 16) and year 1 among schizophrenic smokers

	Model 1a - Abstinence at week 12-16		Model 1b - Abstinence at year 1 among those who quit at week 12 -16		Model 2 - Abstinence at year 1 (regardless of quitting at week 12 -16)	
Characteristics	Unadjusted ORs	Adjusted ORs (c=0.653)	Unadjusted ORs	Adjusted ORs (c=0.883)	Unadjusted ORs	Adjusted ORs (c=0.881)
Demographics						
Sex						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.01 (0.76 – 1.34)	1.07 (0.79 – 1.44)	1.50 (0.82 – 2.75)	1.49 (0.74 – 3.03)	0.92 (0.73 – 1.16)	0.82 (0.54 – 1.24)
Age (years)	1.01 (0.99 – 1.03)	**1.02 (1.01 – 1.03)***	1.01 (0.99 – 1.04)	1.01 (0.98 – 1.04)	1.01 (0.99 – 1.02)	1.02 (0.99 – 1.04)
Race						
Blacks	Reference	Reference	Reference	Reference	Reference	Reference
Whites	**1.86 (1.11 – 3.12)***	**1.83 (1.04 – 3.20)***	1.99 (0.71 – 5.58)	2.05 (0.60 – 7.02)	**2.17 (1.43 – 3.28)***	1.58 (0.78 – 3.20)
All others	**2.42 (1.44 – 4.08)***	**2.13 (1.19 – 3.79)***	1.78 (0.63 – 5.02)	1.77 (0.50 – 6.28)	**1.91 (1.24 – 2.92)***	1.41 (0.67 – 2.97)
Region						
Midwest	Reference	Reference	Reference	Reference	Reference	Reference
Northeast	**0.69 (0.49 – 0.99)***	0.88 (0.59 – 1.31)	0.69 (0.33 – 1.43)	0.60 (0.24 – 1.51)	1.08 (0.80 – 1.46)	1.32 (0.76 – 2.31)
South	0.69 (0.44 – 1.06)	0.94 (0.58 – 1.53)	1.94 (0.66 – 5.75)	1.50 (0.44 – 5.18)	1.09 (0.77 – 1.55)	1.52 (0.79 – 2.92)
West	**1.84 (1.24 – 2.75)***	**2.18 (1.39 – 3.41)***	1.28 (0.55 – 2.99)	1.43 (0.49 – 4.24)	**1.85 (1.31 – 2.62)***	1.86 (0.96 – 3.62)
BMI						
Normal (BMI<25)	Reference	Reference	Reference	Reference	Reference	Reference
Overweight (25<=BMI<30)	0.74 (0.50 – 1.10)	0.78 (0.51 – 1.19)	1.08 (0.42 – 2.77)	0.92 (0.32 – 2.66)	0.91 (0.67 – 1.24)	1.07 (0.62 – 1.84)

Obesity (BMI>=30)	0.93 (0.68 – 1.28)	1.04 (0.74 – 1.47)	0.54 (0.27 – 1.08)	0.62 (0.28 – 1.38)	0.90 (0.69 – 1.16)	0.66 (0.41 – 1.07)
Insurance Not Medicare/Medicaid Medicare or Medicaid	Reference 1.18 (0.88 – 1.57)	Reference 1.16 (0.85 – 1.58)	Reference 1.50 (0.79 – 2.83)	Reference 1.53 (0.75 – 3.15)	Reference **1.41 (1.11 – 1.79)***	Reference 1.28 (0.84 – 1.95)
Clinical factors						
Comorbidty Index	0.97 (0.89 – 1.05)	0.92 (0.84 – 1.01)	0.95 (0.80 – 1.12)	1.15 (0.92 – 1.45)	0.94 (0.88 – 1.01)	0.94 (0.83 – 1.07)
Had antipsychotic injectables 1 year prior to index date No Yes	Reference 1.03 (0.45 – 2.37)	Reference 1.02 (0.44 – 2.40)	Reference 2.02 (0.24 – 17.09)	Reference 1.22 (0.12 – 12.40)	Reference 1.50 (0.78 – 2.90)	Reference 1.71 (0.57 – 5.13)
Smoking Cessation Related						
Addicted to nicotine No Yes	Reference 1.25 (0.86 – 1.81)	Reference 1.07 (0.71 – 1.62)	Reference 0.65 (0.27 – 1.55)	Reference 0.59 (0.21 – 1.64)	Reference 1.08 (0.80 – 1.46)	Reference 0.89 (0.51 – 1.55)
Cessation Medication Varenicline NRT Bupropion SR Combination	Reference 0.80 (0.58 – 1.09) 0.84 (0.28 – 2.54) **0.37 (0.14 – 0.94)***	Reference 0.89 (0.63 – 1.27) 1.04 (0.33 – 3.34) 0.38 (0.15 – 1.00)	Reference 0.80 (0.41 – 1.54) n/a n/a	Reference 0.63 (0.29 – 1.42) n/a n/a	Reference **0.77 (0.60 – 0.99)*** 0.67 (0.26 – 1.75) 0.81 (0.44 – 1.49)	Reference 0.95 (0.59 – 1.54) 1.58 (0.38 – 6.59) 0.78 (0.25 – 2.40)
Cessation Rx given by specialty care physician? No Yes	Reference 2.06 (0.99 – 4.23)	Reference 2.09 (0.97 – 4.48)	Reference 0.76 (0.19 – 3.04)	Reference 0.45 (0.09 – 2.20)	Reference 1.29 (0.61 – 2.70)	Reference 0.50 (0.15 – 1.63)
Received any medication that might affect smoking status anytime 1 year prior to index date No Yes	Reference 0.77 (0.38 – 1.57)	Reference 0.96 (0.46 – 2.04)	n/a	n/a	Reference 0.97 (0.56 – 1.67)	Reference 2.18 (0.93 – 5.09)
Smoking counseling received anytime one year prior to index date No Yes	Reference **0.60 (0.45 – 0.80)***	Reference **0.67 (0.49 – 0.92)***	Reference 0.87 (0.48 – 1.60)	Reference 0.90 (0.44 – 1.84)	Reference **0.69 (0.54 – 0.87)***	Reference 0.72 (0.47 – 1.10)

Had the 2nd cessation exposure during week 16 – 1 year No Yes	n/a	n/a	Reference **0.31 (0.17 – 0.59)***	Reference **0.26 (0.13 – 0.55)***	Reference 1.23 (0.95 – 1.59)	Reference 0.77 (0.48 – 1.25)
Abstinence at week 12 No Yes	n/a	n/a	n/a	n/a	Reference **47.38 (32.09 – 69.94)***	Reference **56.49 (36.48 –87.49)***
OR: Odds Ratio; 95% CI: 95% Confidence Interval; * **p≤0.05.**						

3.5. Logistic regression for model 1b

In this analysis, we were only looking at schizophrenic patients who were prescribed Varenicline and NRT since the sample size was low for those who were prescribed Bupropion or combination that reached sustained abstinence at year 1. Patients who had a 2nd exposure were less likely to quit compared to those without the 2nd exposure (OR=0.26, 95% CI=0.13 – 0.55).

3.6. Logistic regression model for model 2

We were able to make comparisons between all medication groups because we had more patients who quit smoking at year 1 as this is for all cohorts and not specifically among those who quit at week 12. Those who quit at week 12 were also more likely to quit at one year (OR=56.49, 95% CI=36.48 – 87.49).

For all three models, no interactions were found between the cessation medications and other independent variables using chunck test.

4. Discussion

Our objective was to describe abstinence with different cessation medications among schizophrenic patients. Abstinence rate was 18.02% at week 12 and 17.20% at year 1. Among those who quit at 12th week, about 75.22% of the quitting effect sustained at 1 year.

The majority of our cohort (97.61%) had did not have any antipsychotics in injection forms one year prior to index date. This may indicate some reluctance to prescribe cessation products to patients requiring treatment with antipsychotic injections. A potential reason could be the possible beneficial effect of tobacco, which could be used to alleviate some of the symptoms in schizophrenia and reduce the side-effects of antipsychotic medications [6]. Or it could be that smoking seems to be a small problem in comparison to the unpredictable schizophrenic symptoms and not the primary focus of healthcare providers. However, further studies are needed to make any conclusions.

Among the cohort were prescribed cessation medications, almost half were whites (45.40%), followed by other races (38.96%), and blacks (15.64%). Compared to all other races, quitting rates were the lowest for blacks and, similarly, quitting odds were significantly lower in the first logistic regression model (model 1a). Previous studies have reported racial inequalities in prescribing as well as racial differences in successful quitting. Barriers to receipt of treatment could be due to lack of health-insurance coverage or geographic location. Another possible reason could be that blacks were less likely to receive healthcare providers' advices to quit [23,24]. However, previous trials targeted to minority smokers like blacks have demonstrated the efficacy of a variety of smoking cessation treatments [23].

Medicaid enrollees are reported to have nearly twice the smoking rates of the general population [25] and schizophrenic patients are usually with lower social-economic statuses. In our study, we found 53.62% of the cessation medications were prescribed to smokers with Medicare/Medicaid. Abstinence rates were higher for those who were insured under the governmental health insurance in both short (18.78% vs. 16.46%) and long term (79.69% vs. 72.41% for continuous

abstinence and 19.32% vs. 14.57% at year 1). This could be related to the coverage of tobacco cessation in Medicaid program, which was a part of all states' plans by 2002 [26].

Of the 3,976 patients, only 40% of them received smoking counseling. Patients see physicians as valuable and credible sources of health information, and patients generally adhere to physician advice [27]. With the low level of counseling documented in this study, there is a need to evaluate the potential reasons and improve these rates for future research.

Among all the medications, NRT was the most commonly prescribed (65.14%). This could be because NRT products are easily accessible. Prescriptions for Bupropion (Zyban®) (2.24%) were even lower than the most recent approved Varenicline (29.28%). In our cohort of schizophrenic patients, depression is a common comorbid conditions. One would expect physicians to prescribe Bupropion more as it could be used both for treating depression and reducing smoking cravings. Additionally, a Cochrane review by Tsoi et al. in 2013, found that buproprion helps patients with with schizophrenia to quit or to reduce smoking[28]. The low prescription percentage we observed here could be under estimated due to insurance coverage. Insurance companies are more likely to cover depression medications compared to cessation medications, therefore, Zyban® is less likely to be covered but the same ingredients Wellbutrin® is usually covered. When physicians want to prescribe Bupropion to their patients, they might rather prescribe Wellbutrin® but not Zyban® for lower out of pockets expenses for patients. It is important to note here that recent literature of smoking cessation agents in patients with schizophrenia concluded that the safety of varenicline for smoking cessation in this group of patients is still unclear[28,29].

We found the overall quitting for the short term was 18.02%. This quitting rate was not low indicated it is possible for schizophrenic patients to stop smoking. An interesting finding was that those who were prescribed more than one medication within 3-month treatment window had the lowest quitting rate. This result was also similar in the logistic regression model (OR=0.38, 95% CI=0.15 – 1.00). This indicates that if an individual was not successful in quitting smoking with the product provided to him, it is very likely that adding on more medications or switching to other treatment alternatives will not help.

Among the 235 quitters at 12th week, 75.22% of them were still not smoking at year 1. The percentage was high which indicates that if schizophrenic smokers could make it through week 12, chances are high that they would not go back to the smoking behavior. This finding, however, was based on those who got prescribed Varenicline or NRT. Bupropion or combination group were not included in further analysis because the small sample size precludes us from making generalizable conclusions.

Findings also demonstrate that regardless of quitting at the 12th week, overall abstinence at one year was 17.20%. RCTs for this minority population usually were conducted in a short term timeline so none tracked patients' smoking status up to year 1. Comparing our results with that in the general population, quitting rates were lower among schizophrenic patients for all medications [30-33]. This is expected as our population was specifically among smokers with psychiatric illnesses.

Our results showed that patients who received smoking counseling were less likely to quit compared to those who did not receive the counseling message. This finding was similar in multiple logistic regression for model 1a (OR=0.67, 95% CI=0.49 – 0.92). It was not expected because there is strong evidence that cessation interventions with both pharmacological and behavioral intervention are more effective than any intervention alone [34]. One possible explanation could be that patients who received the counseling were also more addicted to nicotine; therefore, quitting for them was a bigger challenge. Schizophrenic patients, however, may need more tailored approaches for counseling and that should be evaluated in future studies to achieve a successful cessation outcome.

In our first logistic regression model, patients at the West region of U.S. were more likely to quit (OR=2.18, CI=1.39 – 3.41). This may be a result of the different law restrictions regarding smoking across the nation. According to a previous study, California and Utah are the top two supportive states toward smoke-free laws [35]. Most indoor California workplaces, clubs/bars and gaming rooms were mandated to be smoke-free. Fewer people will smoke in a society where smoking is not viewed as an acceptable activity.

In our model 1a, we found that as one year increase in age, chances of successful short term quitting increases by 2% (OR=1.02, 95% CI=1.01 – 1.03). Our finding is consistent with the study conducted by Lee et al. among general population [36]. This seems reasonable since older smokers have more medical conditions and they tend to be more concerned about their health. They understand the harmful effects of smoking and may be more serious about quitting.

Among those who quit at week 12, if there was a second exposure week 16 - 1 year, then they were less likely to quit at year 1 (OR=0.26, 95% CI=0.13 – 0.55). This was the only predictor we found in model 1b. There are two possibilities for patients to receive cessation medications during this period; either the medication was used as a treatment for preventing smoking relapse, or it was used because patients went back to their previous smoking behavior. Cessation medication used for preventing smoking relapse is not uncommon as previous articles have provided some examples [37,38]. If the second exposure were used for smoking prevention, then our results contradicted with their findings. This could be due to adherence issues: schizophrenic patients usually are on multiple medications and they might not adhere to cessation medication regimen that is required taking for a longer term [39]. Without taking the medication on a regular basis, treatment for preventing smoking relapse will come to a failure. It's also possible that the second medication was because they relapsed to the original smoking behavior. In our model 2, we found a strong and only predictor - those who did not smoke at week 12 were more likely to be abstinent at year 1 (OR=56.49, 95% CI=36.48 – 87.49). Combing these two points, chances of sustained quitting may be low for those without a firm determination to quit, and if schizophrenic smokers could make it through week 12, it's highly likely that they would not go back to the smoking behavior.

There are several limitations in this study. Limitations related to the use of EMR data include: (1) we could not track if patients picked up the medication at a pharmacy. Medication data were identified by physician orders, which did not guarantee patients actually filled the prescription. (2) We are not certain how compliant the patients were. Unlike chronic medications, cessation products are for a short term use, so compliance should not be a significant problem [39]. (3) Some important variables were with missing information, for example, the stop dates of medications and smoking status was not recorded regularly. With missing values, it is difficult to generalize our findings. Furthermore, some possible confounders like education level and nicotine addiction level (or how many cigarettes they smoke per day) were not recorded in GE data.

Schizophrenia diagnosis was based on ICD-9-CM codes. However, the study extended from 1995 – 2011, and the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) was published during the study (in 2000). More so, DSM-5 has since been published in 2013, which affects the criteria for identification of schizophrenia and schizophrenic disorder in clinical practice. We tried to infer nicotine addiction level from the NRT dosages and assumed that patients receiving Bupropion or Varenicline had high addiction levels as they did not go for easily accessible NRT. However, this approach may not align with the standard, but was used to provide some level of control in the absence of Fagerstrom Test of Nicotine Dependence (FTND) which, when available, is utilized as the standard. The addiction level was not a significant predictor of smoking cessation in our models. The study has made assumptions about degree of mental health control which may not always stand true in clinical practice.

Given the limitations above, the population distribution in GE has been compared to nationally representative data and provide accurate estimates of diagnosis in ambulatory visits in the US[40]. It is also rich in clinical information including vital signs, laboratory results, medications/prescriptions, and diagnoses. With proper smoking status and smoking cessation medications (including NRT OTCs), it was considered an appropriate database for our research questions.

5. Conclusions

This was the first retrospective study to examine smoking abstinence among schizophrenic smokers. Abstinence rate was 18.02% at week 12 and 17.20% at year 1. Among those who quit at 12th week, about 75.22% sustained at 1 year. We didn't find any statistical differences in quitting between medications. However, those who were on more than one medication had slightly lower chances of quitting with the effect almost reached the significance level. Other predictors included being older, white, whose residential area was in the west part of U.S., and without smoking counseling. Patients who reported not smoking at week 12 and who did not receive cessation medications during week 16 to year 1 were more likely to be abstinent from smoking at year 1. Predictors identified in this study should be considered when designing interventions as this minority population may need more tailored approaches to achieve a successful cessation outcome.

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