Heliyon 5 (2019) e01745

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.heliyon.com

Analysis of risk factors and outcomes in psychiatric inpatients with tardive dyskinesia: A nationwide case-control study

Rikinkumar S. Patel [a,*], Zeeshan Mansuri [b], Amit Chopra [c]

[a] Department of Psychiatry, Griffin Memorial Hospital, 900 E Main St, Norman, OK 73071, USA
[b] Department of Psychiatry, Texas Tech University Health Science Center, 314 Secor St, Midland, TX 79701, USA
[c] Department of Psychiatry, Allegheny Health Network, 4 Allegheny Center 8th Floor, Pittsburgh, PA 15212, USA

ARTICLE INFO

Keyword:
Psychiatry

ABSTRACT

Objective: To analyze comorbidities and outcomes in patients with tardive dyskinesia (TD) during psychiatric inpatient management.
Methods: We conducted a case-control study using the Nationwide Inpatient Sample. It included 77,022 adult inpatient admissions for mood disorders and schizophrenia. Cases had a secondary diagnosis of TD, and controls without TD were matched for age. Multivariable logistic regression was used to generate odds ratio (OR).
Results: Majority of TD patients were older age adults (50–64 years; 40%), and were in nearly equal proportions of men and women. African Americans had two-fold higher odds of TD. TD patients had a higher likelihood for cardio-metabolic comorbidities-obesity (OR 1.61, 95% CI 1.481–1.756), hypertension (OR 1.78, 95% CI 1.635–1.930) and diabetes (OR 1.54, 95% CI 1.414–1.680) compared to controls. They also had 1.5-fold increased risk of comorbid drug abuse. Patients with schizophrenia and bipolar disorder (depressive) had four-fold higher odds of TD. TD patients had about six-fold higher odds of severe morbidity. They had a higher likelihood of extended hospitalization stay by 6.36 days (95% CI 6.174–6.550) and higher cost by $20,415 (95% CI 19537–21293) compared to controls.
Conclusion: Psychiatric inpatients with TD have greater severity of illness, and those with schizophrenia and bipolar disorders are at highest risk. Presence of TD portends poor hospital outcomes and need for higher acute inpatient care.

1. Introduction

Tardive Dyskinesia (TD) is characterized by involuntary movements, most commonly of orofacial muscles, but also involving muscles of the extremities, trunk and hip (Correll et al., 2017). Faurbye introduced the term "Tardive Dyskinesia" in 1964 (Wolf et al., 1993) and noted TD to be more severe and problematic in the United States due to the liberal indications for antipsychotic use, prescribing higher doses of drugs and having a limited choice of antipsychotics (Wolf et al., 1993). Tardive dyskinesia (TD) is a severe condition that can affect approximately one out of four patients (25%) receiving dopamine receptor blocking agents (DRBAs), specifically first and second-generation antipsychotics (Carbon et al., 2017). According to a study, the prevalence of TD is 32% with typical antipsychotics and 13% with atypical antipsychotics (D'Abreu et al., 2018). The incidence of antipsychotic-induced TD is about 3–5% in young adults as compared to 30% in the middle-aged and elderly after one year of antipsychotic treatment (Kane et al., 1985; Waln and Jankovic, 2013). In elderly patients, those receiving DRBA treatment for three months have been noted to have a 29% prevalence of TD as compared to 26–67% of those receiving long-term treatment for six months (Brasic, 2018).

Chronic antipsychotic-induced dopamine blockade causes an up-regulation and supersensitivity of dopamine receptors resulting in an increase in dopamine neurotransmission in the basal ganglia (Hanna and Jankovic, 2010). Even after completely stopping the DRBA, TD may persist for years in the patient. In some patients' TD remits entirely even while on DRBAs and in a few patients after stopping the offending agent (Waln and Jankovic, 2013). About 33% of patients experienced remission of their TD after two years of discontinuing/stopping DRBA (Waln and Jankovic, 2013). Some studies have concluded that longer duration of exposure to DRBAs before discontinuation decreases the chances of remission of TD (Waln and Jankovic, 2013). TD has also been related to

* Corresponding author.
E-mail address: dr.rknpatel@gmail.com (R.S. Patel).

https://doi.org/10.1016/j.heliyon.2019.e01745
Received 8 February 2019; Received in revised form 11 April 2019; Accepted 13 May 2019

poor quality of life (Browne et al., 1996) as well as considered as a risk factor concerning mortality (Ballesteros et al., 2000) in patients with psychiatric illness.

Prior studies on TD have been conducted to assess its prevalence (Arisco and Holden, 1989; Chiu et al., 1992; Chiu et al., 1993; Gatere et al., 2002; Woerner et al., 1991), risk factors associated with TD severity (Hansen et al., 1992; Wade et al., 1993; Yassa et al., 1992), and association of TD with different antipsychotics (Chan et al., 2018; Li et al., 2009; Mentzel et al., 2017; Ryu et al., 2015; van Harten et al., 1998). The objective of this study is to analyze the risk factors associated with TD in psychiatric inpatients and assess the differences in hospitalization outcomes regarding the length of stay (LOS) and cost, morbidity and disposition between psychiatric inpatients with versus without TD.

2. Methods

2.1. Data source

We conducted a case-control study, using the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) database, sponsored by the Agency for Healthcare Research and Quality (AHRQ) (" HCUP NIS Database Documentation," 2018). NIS is the largest database of inpatient stays in the United States and is known to be a valid and reliable data source for epidemiological estimates that involve inpatient care. We used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to identify admission with mood disorders, schizophrenia, and other psychotic disorders as the primary diagnosis (DX1).

2.2. Inclusion criteria

We analysed the NIS database (" HCUP NIS Database Documentation, " 2018) from January 2010 to December 2014 to identify cases– patients (age 18–70 years) with a primary ICD-9-CM diagnosis code for bipolar disorder, manic type (293.83, 296.00–296.06, 296.10–296.16, 296.40–296.46, 296.60–296.66 or 296.7), bipolar disorder, depressive type (296.50–296.56 or 296.82), bipolar disorder NOS (296.80, 296.89 or 296.7), major depressive disorder (296.20–296.26 or 296.30–296.36), depressive disorder NOS (296.82, 300.4 or 311), mood disorder NOS (293.83, 296.90 or 296.99) or schizophrenia and other psychotic disorders (293.81, 293.82, 295.00–295.05, 295.10–295.15, 295.20–295.25, 295.30–295.35, 295.40–295.45, 295.50–295.55, 295.60–295.65, 295.70–295.75, 295.80–295.85, 295.90–295.95, 297.0–297.3, 297.8–298.4, 298.8 or 298.9) and secondary diagnosis for tardive dyskinesia (TD). We identified patients with TD using the ICD-9-CM diagnosis codes 333.85 (TD); 333.82 (oral-facial dyskinesia); 333.99, 781.0 (akathisia); 333.71 (athetosis); 307.3 (stereotypy); 307.20, 351.8 (facial tics); 333.81 (blepharospasm). Controls included the patients with a primary diagnosis of mood disorders or schizophrenia and other psychotic disorders as mentioned in the inclusion criteria for cases, and without a secondary diagnosis of TD. We performed a retrospective analysis to derive a control cohort that was matched with the cases on age.

2.3. Variables

Demographic variables examined in this study included age, gender, race, health insurance and median household income (" NIS Description of Data Elements. Healthcare Cost and Utilization Project (HCUP).," 2017). Comorbidities are considered coexisting conditions to primary psychiatric diagnoses under this study (" NIS Description of Data Elements. Healthcare Cost and Utilization Project (HCUP).," 2017). AHRQ comorbidity software of the HCUP was applied to identify comorbidities in the patient records using ICD-9-CM codes– diabetes (249.00–249.31, 250.00–250.33 or 648.00–648.04), hypertension (401.1, 401.9, 642.00–642.04, 401.0, 402.00–405.99, 437.2, 642.10–642.24 or 642.70–642.94), obesity (278.0, 278.00, 278.01, 278.03, 649.10–649.14, 793.91, V85.30-V85.39, V85.41-V85.45 or V85.54), tobacco use (305.1 or 989.84), alcohol abuse (291.0–291.3, 291.5, 291.8, 291.81, 291.82, 291.89, 291.9 or 303.00–303.93, 305.00–305.03) and drug abuse (292.0, 292.82–292.89, 292.9, 304.00–304.93, 305.20–305.93, 648.30–648.34).

To compare the differences in psychiatric hospitalization outcomes of patients with and without TD, the outcome variables of interest included the severity of illness that measures the loss of body functions, LOS, total charges, and disposition of patient. The All Patient Refined DRGs (APR-DRGs) and 3M Health Information Systems software were used to measure the severity of illness subclass (" NIS Description of Data Elements. Healthcare Cost and Utilization Project (HCUP).," 2017). In the NIS, we defined the LOS as the number of nights the patient was hospitalized for a particular primary diagnosis (DX1) (" NIS Description of Data Elements. Healthcare Cost and Utilization Project (HCUP).," 2017). Total charges does not include professional fees and non-covered charges. If the source provided total charges with professional fees, then these fees were removed from the charges during data processing ("NIS Description of Data Elements. Healthcare Cost and Utilization Project (HCUP).," 2017).

2.4. Statistical analysis

All statistical analyses was done on SPSS version 23 (IBM Corp. Armonk, NY). Discharge weight (DISCWT) variable in the NIS were applied during the analysis to obtain nationally representative inpatient data. In these analyses, the Pearson Chi-squared test was used for categorical data to compare characteristics of patients with TD versus without TD. The mean LOS and cost differences between both groups was analyzed using a univariate general linear model. A multivariable logistic regression model was used to evaluate TD for several demographic variables, comorbidities and hospital outcomes with patients without TD as the reference category. Separate models were run for each outcome. We applied discharge weights in all regression models and adjusted for age, gender, race, income, and comorbidities. We also examined the effect of TD on the LOS and total charges of inpatient care for patients with mood disorders and schizophrenia. General linear multiple regression analysis was used to estimate the association of TD with the LOS and total charges, with control for demographic variables and disease morbidity. Due to the large sample size and multiple comparisons of data, statistical significance was set a priori at $<.001$ for all analyses.

2.5. Ethical approval

Our database did not contain patients' personally identifiable information. KEYID variable in the NIS was used to conceal patient identity and prevent identification of patient health information. Also, the diagnostic information in the NIS are identified using the ICD-9-CM codes. Therefore, analysis on a de-identified NIS data does not require Institution Review Board (IRB) approval.

3. Results

3.1. Sample characteristics

Our study included 77,022 inpatient admissions for mood disorders, schizophrenia and other psychotic disorders, and 38,382 patients with a secondary diagnosis of TD. The mean age of the study population was 47.2 years (±14.13) and the study sample comprised of patients in following age groups: 18–30 (16.9%), 31–40 (14.3%), 41–50 (21.1%), 51–60 age (28.0%) and 61–70 (19.7%). There were 50.6% females, and regarding racial distribution, the majority were Caucasian (74.7%) followed by African American (12.9%) and Hispanic (7.9%).

About 40.9% patients in the study had schizophrenia and other psychotic disorders (N = 31468) followed by major depressive disorder (N = 18141, 23.6%), mood disorder NOS (N = 6328, 8.2%), bipolar

disorder–manic type (N = 6210, 8.1%), bipolar disorder NOS (N = 5323, 6.9%), bipolar disorder–depressive type (N = 5175, 6.7%), and depressive disorder NOS (N = 4376, 5.7%) as the primary psychiatric diagnosis for admission.

3.2. Demographic predictors of TD

Majority of the patients with TD were aged 35–49 years (26.5%) and 50–64 years (40%). So, advanced age is a risk factor for increased rates of TD. No significant gender difference for higher odds of TD was seen (OR = 1.033; 95% CI 1.012–1.053; P = .002). A higher proportion of African Americans were noted in the TD group as compared to the non-TD group (17.7% vs. 8.7%). They had two-fold higher odds of TD (OR = 1.812; 95% CI 1.737–1.890; P < .001). Majority of the patients with TD were covered by Medicare (45.1%), followed by Medicaid (25.4%) and private health insurance (20%). More than 60% of the patients with TD were from low-income families (household income $<50^{th}$ percentile). The demographic differences between patients with and without TD are shown in Table 1.

3.3. Comorbidity-related risk factors of TD

Regression model controlled age, gender, race and median household income was used to evaluate the odds ratio (OR) in patients with TD. These patients had a higher risk of cardio-metabolic comorbidities including diabetes (OR = 1.542), hypertension (OR = 1.776) and obesity (OR = 1.613) as shown in Table 2. Patients with TD had higher odds of concurrent tobacco abuse (OR = 1.967) and drug abuse (OR = 1.507) compared to those without TD.

3.4. Clinical characteristics and hospital outcomes

Patients with diagnosis of schizophrenia and other psychotic disorders had approximately five-fold higher odds of TD (OR = 4.643, 95% CI 4.271–5.047, P < .001) followed by those with bipolar disorder–depressive type (OR = 4.171, 95% CI 3.772–4.613, P < .001) and bipolar disorder–manic type (OR = 3.712, 95% CI 3.368–4.092, P < .001). Majority of the patients admitted to the hospital for the psychiatric illness had a moderate loss of function. Although, patients with TD have a roughly six-folds higher odds of severe disability due to a major loss of function compared to those patients without TD (OR = 5.755, 95% CI 5.207–6.361, P < .001). The mean LOS per admission was 12.8 days (95% CI 12.696–12.991) in patients with TD which was higher compared to patients without TD (9.7 days; 95% CI 9.596–9.891). The mean total charges per admission was $35,598 (95% CI 34897–36299) in patients with TD which was much higher than patients without TD ($22784; 95% CI 22087–23481). Patients with TD had higher odds of longer hospitalization of more than seven days (median LOS of the study population) (OR = 3.502, 95% CI 3.224–3.804, P < .001) and higher hospitalization total charges of above the median $16,085 (OR = 3.756, 95% CI 3.457–4.081, P < .001) compared to the patients without TD.

A lesser number of patients with TD (79.4%) were discharged routinely to their home as compared to 84.9% of the patients without TD. Patients with TD had highest likelihood of disposition to skilled nursing facility (SNF)/intermediate nursing facility (INF) (OR = 5.358, 95% CI 4.865–5.901, P < .001) and short-term hospital (OR = 3.294, 95% CI 2.924–3.710, P < .001). The distribution of hospital outcomes is shown in Table 3.

Based on a multiple linear regression model, co-diagnosis of TD was an independent risk factor for extended hospitalization and was associated with a 6.36-day increase in LOS and an increase of $20,415 in total charges during hospitalization. Other factors associated with higher hospital charges included older patient age (>50 years), females, Caucasian race, and severe morbidity. Table 4 summarizes the predictors of LOS and cost of hospitalization in psychiatric inpatients.

Table 1
Demographic distribution.

Characteristic	TD (-) N = 38640		TD (+) N = 38382		Pearson χ^2 Test	
	N	%	N	%	χ^2 statistic	P value
Age						
18–34 years	8910	23.1	8845	23.0	.039	.998
35–49 years	10250	26.5	10167	26.5		
50–64 years	15425	39.9	15348	40.0		
≥65 years	4055	10.5	4022	10.5		
Gender						
Male	18735	48.5	19344	50.4	28.601	<.001
Female	19905	51.5	19027	49.6		
Race						
Caucasian	30260	79.4	23597	69.4	1649.648	<.001
African American	3315	8.7	6006	17.7		
Hispanic	3270	8.6	2413	7.1		
Other	1270	3.3	1968	5.8		
Health insurance						
Medicare	15225	39.5	17272	45.1	466.033	<.001
Medicaid	10650	27.6	9715	25.4		
Private	9630	25.0	7669	20.0		
Self-pay	1355	3.5	1829	4.8		
Other	1720	4.5	1811	4.7		
Median household income						
$0–25^{th}$ Percentile	7825	20.8	12642	34.2	3468.591	<.001
$26^{th} – 50^{th}$ Percentile	7450	19.8	10151	27.4		
$51^{st} – 75^{th}$ Percentile	11065	29.3	7731	20.9		
$76^{th} – 100^{th}$ Percentile	11370	30.2	6487	17.5		

Difference between groups measured by Pearson's Chi-squared Test. Significant P values ≤.0001 at 95% Confidence Interval. Components may not add up to the rounded sum due to weighting and rounding or missing data. TD: Tardive Dyskinesia.

4. Discussion

Our study of psychiatric inpatients with TD reveals the demographic and medical risk factors associated with TD and the impact of TD on the psychiatric hospitalization and related outcomes. Previous studies conducted to evaluate the relationship of TD with age have revealed strong predisposition of TD in elder patients above 60 years (Miller et al., 2005; Smith and Baldessarini, 1980). Owing to the increased vulnerability of TD, careful use of neuroleptics is warranted in the elderly population (Jeste et al., 1995). In our study, almost half of the patients with TD were middle-aged adults (40–60 years), and there was an age-related increase in the prevalence of TD in the inpatient study population. Our findings support the previous evidence that advanced age is a risk factor for the development of TD (Go et al., 2009). Our study did not find a significant gender difference in psychiatric inpatients with TD. On the contrary, a literature review on 76 selected studies on the prevalence of TD conducted by Yassa R et al. found that there was an increased preponderance and intensity of TD in women (26.6%) than in men (21.6%) (Yassa and Jeste, 1992). This review (Yassa and Jeste, 1992) comprised of studies from four continents including North America, Africa, Asia, and Europe, whereas our study sample comprises of inpatients in the United States only and the increasing use of antipsychotics in the last few decades especially in those with mood disorders may account for lack of gender difference.

The prevalence of TD was highest among Caucasian, yet African Americans had two-fold higher odds of TD compared to not having TD which supports prior findings. African Americans tend to develop TD after minimal exposure to antipsychotics for a short duration compared to other races (Go et al., 2009). Our results yielded an interesting linear relationship of TD with the income as increasing household income had a decreasing trend in the prevalence of TD and vice versa. In addition to age, gender, and race, other factors such as longer duration of illness and gene polymorphisms involving antipsychotic metabolism and dopamine functioning are some of the unmodifiable and illness related risk factors

Table 2
Association of comorbidities in patients with tardive dyskinesia.

Comorbidity	TD (-)		TD (+)		P	Logistic regression		
	N	%	N	%		OR	95% CI	P value
Diabetes	5405	14.0	5445	14.2	.429	1.542	1.414–1.680	<.001
Hypertension	13080	33.9	13867	36.1	<.001	1.776	1.635–1.930	<.001
Obesity	3830	9.9	3800	9.9	.957	1.613	1.481–1.756	<.001
Tobacco use	6775	17.5	8525	22.2	<.001	1.967	1.843–2.099	<.001
Alcohol abuse	10920	28.3	6457	16.8	<.001	1.030	.954–1.111	.450
Drug abuse	12700	32.9	9581	25.0	<.001	1.507	1.403–1.619	<.001

Differences between groups conducted by Pearson's Chi-squared Test. Significant P values ≤.0001 at 95% Confidence Interval. Components may not add up to the rounded sum due to weighting and rounding or missing data.
Odds Ratio generated by multinomial logistic regression model were adjusted for age, gender, race and median-household income. Reference category for this model was patients without TD (-). TD: Tardive Dyskinesia; OR: Odds Ratio; CI: Confidence Interval.

Table 3
Primary psychiatric diagnosis, illness severity and hospital outcomes.

Characteristic	TD (-)		TD (+)		Pearson χ^2 Test	
	N	%	N	%	χ^2 statistic	P value
Primary psychiatric diagnosis						
Bipolar disorder, manic type	2760	7.1	3450	9.0	7627.834	<.001
Bipolar disorder, depressive type	2185	5.7	2990	7.8		
Bipolar disorder, NOS	2940	7.6	2383	6.2		
MDD	11605	30.0	6536	17.0		
Depressive disorder NOS	3050	7.9	1326	3.5		
Mood disorder NOS	5115	13.2	1213	3.2		
Schizophrenia & other psychotic disorders	10985	28.4	20483	53.4		
Severity of illness						
Minor loss of function	14145	36.6	7030	18.3	3250.218	<.001
Moderate loss of function	21535	55.7	27174	70.8		
Major loss of function	2960	7.7	4177	10.9		
Hospital LOS and cost						
>7 days (median)	15980	41.4	20048	52.2	914.985	<.001
> $16085 (median)	16895	43.7	21369	55.7	1100.003	<.001
Disposition of patient						
Routine	32700	84.9	30440	79.4	470.071	<.001
Short-term hospital	1170	3.0	1324	3.5		
SNF/INF	2900	7.5	5526	14.4		
Home healthcare	1280	3.3	716	1.9		
AMA	445	1.2	315	.8		

Differences between groups conducted by Pearson's Chi-squared Test. Significant P values ≤.0001 at 95% Confidence Interval. Components may not add up to the rounded sum due to weighting and rounding or missing data. TD: Tardive Dyskinesia; MDD: Major Depressive Disorder; NOS: not otherwise specified; LOS: length of stay; SNF: skilled nursing facility; INF: intermediate nursing facility; AMA: against medical advice.

Table 4
Predictors of LOS and cost for adult psychiatric inpatients.

Predictor	LOS (days)	95% CI	Cost ($)	95% CI
Tardive Dyskinesia	6.36	6.174–6.550	20415	19537–21293
Age >50 years	4.13	3.921–4.335	10262	9296–11227
Female	2.92	2.723–3.124	6378	5442–7314
Caucasian	3.81	3.622–4.001	8518	7635–9401
Severe Morbidity	6.87	6.504–7.244	19695	17966–21424

Significant P values ≤.0001 at 95% Confidence Interval (CI). The estimated increase in length of hospital stay and cost was generated by linear regression model. LOS: length of stay.

associated with TD (Solmi et al., 2018; Tenback and van Harten, 2011; Waln and Jankovic, 2013). These factors were not analyzed in our study due to the nature of available data and the scope of our study.

Prior studies have concluded that diabetes mellitus, cigarette smoking, alcohol, and drug abuse are some of the modifiable risk factors associated with the higher risk of development of TD (Solmi et al., 2018; Tenback and van Harten, 2011; Waln and Jankovic, 2013). In our study, patients with TD had two-fold higher odds of comorbid hypertension, and this may be due to antipsychotic-related metabolic dysfunction in psychiatric inpatients. Two prospective studies on diabetic and non-diabetic participants on chlorpromazine state that an increased prevalence and severity of TD was seen with diabetes (Ganzini et al., 1992; Ganzini et al., 1991). Our study results suggest that patients with TD were at 1.5 times higher odds of having diabetes as compared to the other psychiatric inpatients without TD. The N-Methyl-D-Aspartate system can be possibly implicated in the association of TD and drug abuse (Bailey et al., 1997). Alcohol abuse was associated with severe orofacial dyskinesia and acts as an added risk factor for the development of TD as per past survey (Duke et al., 1994; Wolf et al., 1987). In our study, TD patients had 1.5-fold higher risk of co-existing drug abuse, but the odds for comorbid alcohol abuse was lower in TD patients as the prevalence of alcohol abuse was much lower (16.8%) than that seen in patients without TD (28.3%).

Schizophrenia patients may develop TD eventually in the advancement of the disease irrespective of the use of antipsychotics (Waln and Jankovic, 2013; Wolf et al., 1987). Based on the age and duration of illness, patients with schizophrenia and on antipsychotics have a 4%–40% chance of developing TD (Waln and Jankovic, 2013). In our study, patients with a primary diagnosis of schizophrenia and other psychotic disorders had five-fold higher odds of TD, and the regression model was controlled for demographic characteristics and comorbidities. Waddington JL et al. (Waddington and Youssef, 1988) reported that long-term exposure to antipsychotics leads to chronic, deteriorating, psychiatric illness and also leads to the occurrence of movement disorder. Patients with TD constitute a physically deprived group due to broader disease syndrome including cardiovascular disorders and morbidity (Youssef and Waddington, 1987). Our study supports this fact as patients with TD had about six-folds higher odds of severe disability due to major loss of function compared to patients without TD. It must be noted that we are not able to comment on the duration of psychotic illness and exposure to antipsychotic medications due to the limitations of the NIS dataset used in our study.

A study conducted by Browne et al. (1996) in a rehabilitation center concluded that presence of TD was associated with a poorer quality of life which was related to psychiatric symptom severity, illness duration and increased the length of previous hospitalization (Browne et al., 1996). Our study results suggest that patients with TD had roughly four-fold likelihood of extended hospitalization and higher hospitalization total charges compared to patients without TD. Even past studies support this fact as TD patients had more extended hospitalization due to severe morbidity (Browne et al., 1996; Wolf et al., 1987). In multiple linear regression model of our study, inpatients with TD had about 6.36-day increase in LOS and an increase of $20,415 in total charges per hospital admission. As patients with TD had severe morbidity or disability

(Browne et al., 1996; Waddington and Youssef, 1988; Youssef and Waddington, 1987), they had higher odds of adverse disposition (SNF/INF and short-term hospital) compared to patients without TD.

Our study has some limitations. The NIS is an administrative database and lacks the patient level data needed to make accurate clinical associations. Further, such retrospective studies are always subject to selection bias, which might be highlighted by the moderate sensitivity of diagnostic codes for TD and primary psychiatric diagnoses. Another limitation was the lack of information on the type of antipsychotics administered during hospitalization, total cumulative amount of antipsychotics, past medication history and the duration of psychiatric illnesses. Therefore, this study does not provide an association of comorbidities and hospital outcomes about first versus second-generation antipsychotics. Due to the cross-sectional design of this study we were not able to address longitudinal treatment process including switching to another class of antipsychotics which may affect the propensity to develop TD. Severity of the condition that is mentioned in this study is based APR-DRGs variable in the NIS, and we were not able assess the clinical severity of TD based on clinical scales. We were not able to account for re-hospitalizations, given the nature of the database, although they add to the total inpatient burden. Despite these potential limitations, the NIS database (" HCUP NIS Database Documentation," 2018) provides a unique population-based perspective on disease associations with systematic and temporal factors and provides a rationale for further in-depth studies. The biggest strength of our study lies in the national representation of the dataset, with a uniform collection of data, through ICD-9-CM codes over five years. This is the first study, to our knowledge, to report the association of various comorbidities and risk of adverse hospital outcomes in psychiatric inpatients with TD. Using the NIS, we were able to obtain a large sample size as we included 77,022 patients admitted for primary psychiatric diagnoses. This dataset is subject to minimal reporting bias, and all information is coded independently of the individual practitioner, making it a more reliable source.

In the inpatient settings, TD was highly associated with advancing age, lower socioeconomic status and African-American. Psychiatric inpatients with TD have greater severity of illness, and those with schizophrenia and bipolar disorders are at the highest risk of TD. Presence of TD portends poor hospital outcomes including increased LOS and total charges during hospitalization and more indigent post-management disposition. More systematic research is warranted to implement clinical strategies to both prevent TD and optimize inpatient outcomes in psychiatric patients with TD.

Declarations

Author contribution statement

Rikinkumar Patel: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Zeeshan Mansuri: Contributed reagents, materials, analysis tools or data.

Amit Chopra: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

Arisco, J.P., Holden, L.D., 1989. Prevalence of tardive dyskinesia in private psychiatric inpatients. Tex. Med. 85 (1), 25–28.

Bailey, L.G., Maxwell, S., Brandabur, M.M., 1997. Substance abuse as a risk factor for tardive dyskinesia: a retrospective analysis of 1,027 patients. Psychopharmacol. Bull. 33 (1), 177–181.

Ballesteros, J., Gonzalez-Pinto, A., Bulbena, A., 2000. Tardive dyskinesia associated with higher mortality in psychiatric patients: results of a meta-analysis of seven independent studies. J. Clin. Psychopharmacol. 20 (2), 188–194.

Brasic, J.R., 2018. Tardive Dyskinesia. Retrieved from. https://emedicine.medscape.com/article/1151826-overview.

Browne, S., Roe, M., Lane, A., Gervin, M., Morris, M., Kinsella, A., Callaghan, E.O., 1996. Quality of life in schizophrenia: relationship to sociodemographic factors, symptomatology and tardive dyskinesia. Acta Psychiatr. Scand. 94 (2), 118–124.

Carbon, M., Hsieh, C.H., Kane, J.M., Correll, C.U., 2017. Tardive dyskinesia prevalence in the period of second-generation antipsychotic use: a meta-analysis. J. Clin. Psychiatry 78 (3), e264–e278.

Chan, C.H., Chan, H.Y., Chen, Y.C., 2018. Switching antipsychotic treatment to aripiprazole in psychotic patients with neuroleptic-induced tardive dyskinesia: a 24-week follow-up study. Int. Clin. Psychopharmacol. 33 (3), 155–162.

Chiu, H., Shum, P., Lau, J., Lam, L., Lee, S., 1992. Prevalence of tardive dyskinesia, tardive dystonia, and respiratory dyskinesia among Chinese psychiatric patients in Hong Kong. Am. J. Psychiatry 149 (8), 1081–1085.

Chiu, H.F., Wing, Y.K., Kwong, P.K., Leung, C.M., Lam, L.C., 1993. Prevalence of tardive dyskinesia in samples of elderly people in Hong Kong. Acta Psychiatr. Scand. 87 (4), 266–268.

Correll, C.U., Kane, J.M., Citrome, L.L., 2017. Epidemiology, prevention, and assessment of tardive dyskinesia and advances in treatment. J. Clin. Psychiatry 78 (8), 1136–1147.

D'Abreu, A., Akbar, U., Friedman, J.H., 2018. Tardive dyskinesia: epidemiology. J. Neurol. Sci. 389, 17–20.

Duke, P.J., Pantelis, C., Barnes, T.R., 1994. South Westminster schizophrenia survey. Alcohol use and its relationship to symptoms, tardive dyskinesia and illness onset. Br. J. Psychiatry 164 (5), 630–636.

Ganzini, L., Casey, D.E., Hoffman, W.F., Heintz, R.T., 1992. Tardive dyskinesia and diabetes mellitus. Psychopharmacol. Bull. 28 (3), 281–286.

Ganzini, L., Heintz, R.T., Hoffman, W.F., Casey, D.E., 1991. The prevalence of tardive dyskinesia in neuroleptic-treated diabetics. A controlled study. Arch. Gen. Psychiatr. 48 (3), 259–263.

Gatere, N., Othieno, C.J., Kathuku, D.M., 2002. Prevalence of tardive dyskinesia among psychiatric in-patients at Mathari Hospital, Nairobi. East Afr. Med. J. 79 (10), 547–549.

Go, C.L., Rosales, R.L., Caraos, R.J., Fernandez, H.H., 2009. The current prevalence and factors associated with tardive dyskinesia among Filipino schizophrenic patients. Park. Relat. Disord. 15 (9), 655–659.

Hanna, P.A., Jankovic, J., 2010. Basal ganglia and movement disorders. In: Neurology Secrets, fifth ed. Elsevier Inc, pp. 168–203.

Hansen, T.E., Brown, W.L., Weigel, R.M., Casey, D.E., 1992. Underrecognition of tardive dyskinesia and drug-induced parkinsonism by psychiatric residents. Gen. Hosp. Psychiatry 14 (5), 340–344.

HCUP NIS Database Documentation, 2018. In: H. C. a. U. P. (HCUP). Agency for Healthcare Research and Quality, Rockville, MD.

Jeste, D.V., Caligiuri, M.P., Paulsen, J.S., Heaton, R.K., Lacro, J.P., Harris, M.J., et al., 1995. Risk of tardive dyskinesia in older patients. A prospective longitudinal study of 266 outpatients. Arch. Gen. Psychiatr. 52 (9), 756–765.

Kane, J.M., Woerner, M., Lieberman, J., 1985. Tardive dyskinesia: prevalence, incidence, and risk factors. Psychopharmacol. Suppl. 2, 72–78.

Li, C.R., Chung, Y.C., Park, T.W., Yang, J.C., Kim, K.W., Lee, K.H., Hwang, I.K., 2009. Clozapine-induced tardive dyskinesia in schizophrenic patients taking clozapine as a first-line antipsychotic drug. World J. Biol. Psychiatr. 10 (4 Pt 3), 919–924.

Mentzel, C.L., Bakker, P.R., van Os, J., Drukker, M., Matroos, G.E., Hoek, H.W., et al., 2017. Effect of antipsychotic type and dose changes on tardive dyskinesia and parkinsonism severity in patients with a serious mental illness: the curacao extrapyramidal syndromes study XII. J. Clin. Psychiatry 78 (3), e279–e285.

Miller, D.D., McEvoy, J.P., Davis, S.M., Caroff, S.N., Saltz, B.L., Chakos, M.H., et al., 2005. Clinical correlates of tardive dyskinesia in schizophrenia: baseline data from the CATIE schizophrenia trial. Schizophr. Res. 80 (1), 33–43.

NIS Description of Data Elements. Healthcare Cost and Utilization Project (HCUP), 2017. Retrieved from. https://www.hcup-us.ahrq.gov/db/nation/nis/nisdde.jsp. (Accessed 20 August 2018).

Ryu, S., Yoo, J.H., Kim, J.H., Choi, J.S., Baek, J.H., Ha, K., et al., 2015. Tardive dyskinesia and tardive dystonia with second-generation antipsychotics in non-elderly schizophrenic patients unexposed to first-generation antipsychotics: a cross-sectional and retrospective study. J. Clin. Psychopharmacol. 35 (1), 13–21.

Smith, J.M., Baldessarini, R.J., 1980. Changes in prevalence, severity, and recovery in tardive dyskinesia with age. Arch. Gen. Psychiatr. 37 (12), 1368–1373.

Solmi, M., Pigato, G., Kane, J.M., Correll, C.U., 2018. Clinical risk factors for the development of tardive dyskinesia. J. Neurol. Sci. 389, 21–27.
Tenback, D.E., van Harten, P.N., 2011. Epidemiology and risk factors for (tardive) dyskinesia. Int. Rev. Neurobiol. 98, 211–230.
van Harten, P.N., Hoek, H.W., Matroos, G.E., Koeter, M., Kahn, R.S., 1998. Intermittent neuroleptic treatment and risk for tardive dyskinesia: curacao Extrapyramidal Syndromes Study III. Am. J. Psychiatry 155 (4), 565–567.
Waddington, J.L., Youssef, H.A., 1988. The expression of schizophrenia, affective disorder and vulnerability to tardive dyskinesia in an extensive pedigree. Br. J. Psychiatry 153, 376–381.
Wade, J.B., Hart, R.P., Dougherty, L.M., 1993. Factors related to the severity of tardive dyskinesia. Brain Cogn. 23 (1), 71–80.
Waln, O., Jankovic, J., 2013. An update on tardive dyskinesia: from phenomenology to treatment. Tremor Other Hyperkinet Mov (N Y) 3.
Woerner, M.G., Kane, J.M., Lieberman, J.A., Alvir, J., Bergmann, K.J., Borenstein, M., et al., 1991. The prevalence of tardive dyskinesia. J. Clin. Psychopharmacol. 11 (1), 34–42.
Wolf, M.A., Yassa, R., Llorca, P.M., 1993. [Neuroleptic-induced movement disorders: historical perspectives]. Encephale 19 (6), 657–661.
Wolf, M.E., DeWolfe, A.S., Mosnaim, A.D., 1987. Risk factors for tardive dyskinesia according to primary psychiatric diagnosis. Hillside J. Clin. Psychiatry 9 (1), 3–11.
Yassa, R., Jeste, D.V., 1992. Gender differences in tardive dyskinesia: a critical review of the literature. Schizophr. Bull. 18 (4), 701–715.
Yassa, R., Nastase, C., Dupont, D., Thibeau, M., 1992. Tardive dyskinesia in elderly psychiatric patients: a 5-year study. Am. J. Psychiatry 149 (9), 1206–1211.
Youssef, H.A., Waddington, J.L., 1987. Morbidity and mortality in tardive dyskinesia: associations in chronic schizophrenia. Acta Psychiatr. Scand. 75 (1), 74–77.