Severity of Tardive Dyskinesia and Negative Symptoms are Associated with Poor Quality of Life in Schizophrenia Patients

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ABSTRACT

Objective: **Aim of this study is to determine the association between tardive dyskinesia (TD) and quality of life (QOL).**

Methods: **Seventy-one stable schizophrenia patients with TD attending psychiatric clinic at Hospital Raja Perempuan Zainab II (HRPZ II) or Hospital Universiti Sains Malaysia (HUSM) between January to November 2011 were assessed by a single rater. TD, QOL and psychopathology were assessed using Abnormal Involuntary Movement Scale (AIMS), Quality of Life Scale (QLS) and Positive and Negative Symptom Scale (PANSS) respectively. The main outcome in this study was QLS total score. Descriptive analysis, simple linear regression and multiple linear regressions were appropriately used in data analysis.**

Results: **Majority of subjects were unemployed (73.2%), single (63.4%), Malay (98.6%) male (70.4%), and on typical antipsychotics before onset of TD (95.8%). The mean duration of illness and mean duration on treatment were 22 (SD 9.9) and 21.8 (SD 10.1) respectively. Mild, moderate and severe TD was experienced by 54.9, 32.4 and 12.7 % of subjects in that order. The mean QLS total score was 52.11 (SD 26.7) with the majority of subjects (76.1%) scored lower than mid score indicating low level of QOL. Employment status, marital status, PANSS negative symptoms and severity of TD were negatively associated with QOL.**

Conclusions: **These findings convey important message to the health care providers to recognize QOL was significantly and negatively associated with severity of TD and negative symptoms. Further, low QOL was also associated with the subjects being single, unemployed or partially employed.**

KEY WORDS

tardive dyskinesia, schizophrenia, quality of life, QLS

INTRODUCTION

Antipsychotics are an important component of schizophrenia treatment. However, prolonged use of antipsychotics is associated with the occurrence of extrapyramidal side effects (EPS) such as parkinsonism, dystonia, akathisia, and tardive dyskinesia (TD) represents one of the most serious complications of treatment with antipsychotics. TD is characterized by involuntary movements, typically of the mouth, lips, and tongue, but may involve any muscle in the body. The longer the patients take antipsychotics, the more likely they are to experience TD. About 10-20% of patients who are treated for more than one year have TD and about 15-20% of long-term hospital patients have TD (Sadock and Sadock, 2003). The physical disabilities due to TD can affect patient's Quality Of Life (QOL).

QOL is now recognized as an important health outcome measure. QOL is generally thought to include life satisfaction, social functioning, daily living activities, and physical health, and it has been recognized as an important indicator of how well patients with schizophrenia can function. To date, there is only a few studies examined the association between TD and reduced QOL. A study involving 60 patients examined the influence of socio-demographic, clinical and treatment factors on QOL of patients with schizophrenia[1)]. That study found that TD was associated with a poorer QOL. However, given the relatively small sample of patients with TD (n = 15) in that study, the conclusions must be interpreted with caution. Another study comparing the QOL of schizophrenia patients treated with clozapine or first generation antipsychotics found that lack of EPS predicted QOL[2)]. Data from clozapine-haloperidol study for patients with treatment resistant schizophrenia showed a small but progressive decline in QOL with more severe TD[3)]. Another study comparing olanzapine and haloperidol for patients with non-treatment resistant schizophrenia also showed significantly lower QOL scores with TD[4)].

Hence, this study aims to determine the QOL of schizophrenia patients with TD using a newly developed and validated Malays version quality of life score (QSL)[5)]. This study also aims to find an association between TD and patients' socio-demographic and clinical variables.

METHODOLOGY

Study sample

The study protocol was approved by the Research and Ethics Committee, School of Medical Science, Universiti Sains Malaysia and Ministry of Health. A written consent was obtained from the patient before the researcher administered the questionnaires. The subjects were 71 clinically stable, aged 18 to 65, schizophrenia outpatients with TD conveniently recruited from HUSM or HRPZ II during the study period January to November 2011. All the patients were cooperative and understand the Malay language. Patients with mental

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Table 1. Socio-demographic characteristics of the subjects (n = 71)

	Frequency (%)	Median (IQR)
Age (year)		49 (20)
18- 35	12(16.9)	
36-45	17 (23.9)	
46-55	18 (25.4)	
56- 65	24 (33.8)	
Gender		
Male	50 (70.4)	
Female	21 (29.6)	
Race		
Malay	70 (98.6)	
Chinese	1 (1.4)	
Educational level		
Never schooling	2 (2.8)	
Primary	26 (36.6)	
Secondary	40 (56.3)	
Tertiary	3 (4.2)	
Marital status		
Single	45 (63.4)	
Married	9 (12.7)	
Divorced/widow	17 (23.9)	
Employment status		
Unemployed	52 (73.2)	
Full time Employment	12 (16.9)	
Part time Employment	7 (9.9)	
Household income		
Less than RM 500	23 (32.4)	
RM 501-RM 1,000	28 (39.4)	
RM 1,001-RM 2,000	14 (19.7)	
More than RM 2,000	6 (8.5)	
Living arrangement		
Alone	8 (11.3)	
With family	61 (85.9)	
With friend/maid	2 (2.8)	

Table 2. Clinical characteristics of the subjects (n = 71)

	Frequency (%)	Median (IQR)	Mean (SD)
Age at first treatment (year)			24.8 (5.9)
Overall duration of treatment (year)			21.8 (10.1)
Duration on same medication prior onset of TD (year)			8.2 (5.7)
Duration on current medication after onset of TD (year)			1.7 (1.4)
Overall duration of illness (year)			22 (9.9)
Duration of outpatient treatment after last hospitalization (year)		3 (5.4)	
Less than 6 months	20 (28.2)		
7 months to 1 year	9 (12.7)		
1 to 3 years	10 (14.1)		
More than 3 years	32 (45.1)		
Number of hospitalization		7 (9)	
Type of pharmacotherapy before onset of TD			
Typical antipsychotic	68 (95.8)		
Atypical antipsychotic	3 (4.2)		
Type of pharmacotherapy after onset of TD			
Typical antipsychotic	30 (42.3)		
Atypical antipsychotic	40 (56.3)		
Both type	1 (1.4)		
Psychiatric symptoms severity			
PANSS total score			49.8 (13.5)
PANSS positive			10.2 (3.2)
PANSS negative			15.0 (5.6)
PANSS general psychopathology			24.6 (6.0)
Severity of TD (AIMS score)			8.6 (4.8)
Mild	40 (56.3)		
Moderate	22 (31)		
Severe	9 (12.7)		
QLS score (total)			52.11
Below midpoint	54 (76.1)		(26.7)

retardation or substance abuse were excluded from the study.

Assessments

The socio-demographic and clinical variables questionnaires comprised of participants' age, gender, ethnicity, marital status, employment status, educational level, family income, living arrangement, age at first treatment, number of hospitalization, duration of outpatient treatment after last hospitalization, overall duration of illness, type of antipsychotic prior to onset of abnormal movement and current antipsychotic, duration on previous and current antipsychotic and overall duration on treatment were administered to the patients.

Patients' qualities of life were assessed using the Quality of Life Scale (QLS) Malay version[5]. QLS is a semi-structured interview in which a trained clinician rates the patient's quality of life on the basis of the patient's self-report and the clinician's professional judgment about the patient's functioning and life circumstances[6]. Each of the scale's 21 items is rated from 0 to 6, and the scale provides descriptive anchors for every other point. High scores (scores of 5 or 6) for a particular item reflects normal or unimpaired functioning compared to local norms.

Abnormal Involuntary Movement Scale (AIMS) was used to establish the presence and severity of involuntary movements in patients with schizophrenia[7]. AIMS consists of rating the severity of movement in three main anatomic areas (facial/oral, extremities, and trunk), based on a five-point scale (0 = none, 4 = severe). The scale provides a total score (items 1 through 7) or item 8 can be used in isolation as an indication of overall severity of symptoms.

Patients' psychopathology was scored using the Positive and Negative Symptom Severity of Schizophrenia (PANSS) based upon information relating to the past week[8]. There are 7 items for PANSS positive syndrome and PANSS negative syndrome. For PANSS general psychopathology, there are 16 items. In the study analysis, total score for all three subscales were calculated. Then, the total score for each subscale was also calculated. Finally, the case record was reviewed by researcher to acquire detail information regarding current type of pharmacotherapy, either monotherapy with typical antipsychotic or atypical antipsychotic or polytherapy with combination of atypical, typical or depot antipsychotic.

Statistical Analysis

Data entry and statistical analysis were conducted using Predictive Analytics Software (PASW) Statistics version 18.0.

Table 3. Simple linear regression analysis of socio-demographic and clinical factors with level of quality of life

Variable	Simple Linear Regression[a]		
	b[b] (95% CI)	t stat	P-value
Age (year)	0.41 (-0.17,0.98)	1.42	0.16
Gender	-6.67 (-20.52,7.18)	-0.96	0.34
Education			
Never schooling vs. Tertiary	-45.17 (-93.31,1.98)	-1.91	0.060
Primary vs. Tertiary	-42.78 (-74.27,-11.29)	-2.71	0.008[c]
Secondary vs. Tertiary	-38.37 (-69.28, -7.45)	-2.48	0.016[c]
Marital Status			
Single vs. Married	39.42 (-56.67,-22.18)	-4.56	< 0.001[c]
Divorced/widow vs. Married	-29.75 (-49.22,-10.28)	-3.05	0.003[c]
Employment Status			
Part time vs. full time	-37.75 (-51.40,-24.11)	-5.52	< 0.001[c]
Unemployed vs. full time	-59.96 (-69.15,-50.77)	-13.02	< 0.001[c]
Household Income			
< RM 500 vs. > RM 2,000	-46.04 (-67.71,-24.38)	-4.24	< 0.001[c]
RM 501-1,000 vs. > RM 2,000	-24.39 (-45.65,-3.13)	-2.29	0.025[c]
RM 1,001-2,000 vs. > RM 2,000	-27.14 (-50.20,-4.08)	-2.35	0.022[c]
Living arrangement			
With family vs. Alone	-21.84 (-41.02,-2.67)	-2.27	0.026[c]
With friend/maid vs. Alone	13.50 (-26.81,53.81)	0.668	0.506
Age at first treatment	1.01 (-0.05,2.06)	-1.90	0.061
Overall duration of treatment (year)	0.13 (-0.50,0.76)	0.42	0.678
Duration on same medication prior to onset of TD (year)	0.58 (-0.53,1.68)	1.04	0.302
Duration on current medication after onset of TD (year)	3.47 (-1.02,7.96)	1.54	0.128
Overall duration of illness (year)	0.12 (-0.52,0.77)	0.39	0.699
Duration of out-patient treatment after last hospitalization (year)	2.20 (1.10,3.30)	3.99	< 0.001[c]
Number of hospitalization	-1.74 (-2.69,-0.78)	-3.63	0.001[c]
Type of pharmacotherapy before onset of TD	-16.82(-17.87,12.26)	-0.37	0.71
Type of pharmacotherapy after onset of TD			
Atypical vs. Typical antipsychotic	-23.08 (-34.84,-11.33)	-3.92	< 0.001[c]
Both type vs. Typical antipsychotic	-29.53 (-79.02,19.95)	-1.19	0.238
Psychiatric symptoms severity			
PANSS positive	-5.71 (-7.16,-4.25)	-7.83	< 0.001[c]
PANSS negative	-3.67 (-4.40,-2.93)	-9.94	< 0.001[c]
PANSS general psychopathology	-3.24 (-3.97,-2.51)	-8.88	< 0.001[c]
Severity of TD			
AIMS total score	-2.62 (-3.79,-1.45)	-4.48	< 0.001[c]

[a]SLR (outcome as QLS total score);

[b]Crude regression coefficient;

[c]P-value level of significant < 0.05

Table 4. Adjusted factors related to the level of quality of life among schizophrenia patient with TD

Variable	Multiple Linear Regression		
	B[a] (95% CI)	t stat	P-value
Employment Status			
Part time vs. full time	29.88 (-37.90,-21.86)	-7.45	< 0.001[b]
Unemployed vs. full time	40.79 (-46.89,-34.69)	-13.37	< 0.001[b]
Marital status			
Single vs. married	-5.30 (-9.65,-0.95)	-2.44	0.018[b]
Psychiatric symptoms severity			
PANSS negative	-1.66 (-2.01,-1.22)	-7.55	< 0.001[b]
Severity of TD			
(AIMS total score)	-0.79 (-1.25,-0.34)	-3.49	0.001[b]

[a]Adjusted regression coefficient;

[b]P-value level of significant < 0.05

Table 5. Comparing QLS total score between the three levels of severity of TD by One-way ANOVA

Severity of TD	Mean (SD)	F-statistic (df)	P-value
Mild	62.15 (27.79)		
Moderate	43.68 (20.10)	9.37 (2)	< 0.001
Severe	28.11 (7.87)		

Continuous variables were expressed as mean and standard deviation. Median and inter-quartile range were used when they were not normally distributed. Categorical variables were expressed as frequencies and percentage. Simple and multiple linear regression analysis were used to explore the association between socio demographic and clinical factors with the level of quality of life. Then, ANOVA and post hoc test were used to compare the mean differences between QLS total score (level of QOL) and three levels of the severity of TD.

RESULTS

A total of 79 patients fulfilled the inclusion and exclusion criteria and invited to participate in the study from January to November 2011. However, 8 patients refused to participate because they were in a hurry. Thus, a total of 71 schizophrenia patients with neuroleptic-induced TD participated in this study. The socio-demographic and clinical characteristics of the study participants are summarised in table 1 and table 2 respectively. Majority of subjects were unemployed, single, Malay, males, educated up to secondary level and living with the family with household income less than RM 1,000.

Most subjects experienced mild TD, had been on out-patient treatment for more than 3 years, received typical before and atypical antipsychotics after the onset of TD as summarized in table 2. However, majority of subjects (76.1%) scored below the midpoint reflecting overall poor quality of life among study participants.

Each of the independent socio-demographic and clinical variables were analyzed using simple linear regression analysis (SLR) to determine any association between socio-demographic and clinical variables, with the level of quality of life measured by QLS. Race was not included in the analysis since only 1 out of 71 patients was Chinese and the other 70 patients were Malays. The results are shown in tables 3.

The data was further analysed using multiple linear regression analysis (MLR) to control for confounding effects among the clinical and statistical significant variables and to determine the significant associated factors for quality of life. The variables that were found to be significant by SLR were entered into the MLR. Variables selection to establish the preliminary main effect model was done using backward linear regression (LR) and forward LR method (p value for removal is 0.10 and p value for entering is 0.05). The preliminary main effect model was chosen from backward method and checked for multi collinearity. There was no multi collinearity among the variables as evidence by low VIF value (1.19-2.52), small standard error (compared to each b value) and narrow confidence interval.

The preliminary final model was established and checked further for assumptions. The model was checked for overall linearity and equal variance by scatter plot of residuals versus predicted mean value. The linearity of each numerical independent; namely PANSS

negative and AIMS total score variable were checked with scatter plot of residuals versus each independent variables mentioned. The histogram of the residuals was normally distributed. The model met all the assumptions. The R^2 value is 91%, thus the model could accurately discriminate 91% of the cases. Finally, the final model was established, and Table 4 showed that employment status, marital status (single vs. married), PANSS negative symptoms and AIMS score for TD are negatively associated with quality of life. In this study, for every 1 unit increased of AIMS score, the QLS score will decrease by 0.79 (-1.25,-0.34) units. For every 1 unit increase of PANSS negative symptoms score, the QLS score will decrease by 1.66 (-2.10, -1.22).

One-way ANOVA (table 5) followed by post hoc tests were used to compare the QLS total score between the three levels of severity of TD. There were significant differences in QLS total score between the three levels of severity of TD where severe TD had low QLS total score. There were significant differences in QLS total score between mild vs. Moderate (mean 18.47, CI 3.26-33.67) and mild vs. severe TD (mean 18.47, CI 3.26, 33.67)

DISCUSSION

This study revealed that 12.7% of the patients with schizophrenia had severe TD and this finding was higher than previously reported findings. The percentage of schizophrenia patients with severe TD was earlier reported to be 5.4%[9] and 3.5%[10]. The inconsistency could be explained by the differences in participants' characteristics. In earlier study, out of 210 patients screened 37 (17.6%) had TD with only 2 (5.4%) patients had severe TD[9]. However, only 30 (81.1%) of patients with TD and 144 (83.2%) of patients without TD were currently receiving neuroleptics. Discontinuation of antipsychotic treatment could have contributed to resolution of TD in some of the patients.

In another study, 647 Japanese inpatients (361 men and 286 women) with a mean age of 49.8 years, receiving a mean dose of antipsychotic drugs of 276.8 mg of chlorpromazine equivalent were assessed for TD[10]. The overall prevalence of TD was 22.3%. Mild TD was found in 67.4% of TD patients, moderate TD in 29.2%, and severe TD in 3.5%. Low percentage of patients with severe TD in that study was likely due to the use of low dose of antipsychotic in the study population. It is well established that the dose of antipsychotic drug play a role in development of TD and reducing the dose of antipsychotic is one of the effective interventions to treat TD[11]. All the patients in this study were on antipsychotic treatment and they were on normal dose for a long period of time. This may explain the high percentage of severe TD as increased length of antipsychotic exposure contributed to TD[12].

Majority (76.1%) of the patients in this study scored below the midpoint of QLS total score reflecting poor overall quality of life. This finding was consistent with previous findings where patients with schizophrenia have poor quality of life and TD was one of the contributing factors for their poor quality of life[13,14]. In this study, multiple linear regression analysis was carried out to identify factors associated with quality of life among schizophrenia patients with TD. After controlling for potential confounders, employment status, marital status (single vs. married), PANSS negative symptoms and AIMS total score variables were negatively associated with QLS total score.

Despite the fact that majority of the patients received secondary education and suffered only mild psychotic symptoms, majority (75%) of them were unemployed. Employment allows more social interactions which can increase quality of life. Previous studies also reported similar findings as employed patients had significantly higher quality of life in terms of physical health, social relations, support and global QOL score[15-17]. Recent EGOFORS (Employment and its relationship with functionality and quality of life in patients with schizophrenia) study reported that those who work/study had lower symptoms, better functioning and higher levels of QOL[18]. A study in China reported that employment status and income significantly contributed to some of the QOL domains[16]. Another study reported that total monthly income had significant positive correlation with social relationship domain and total QOL[19].

Our patients with higher PANSS negative symptoms scores were more likely to have poor quality of life. This finding was in agreement with previous studies[20-22]. A study involving 50 out-patients using PANSS and WHO-QOL BREF found that negative subscale had significant negative correlation with physical and psychological domains and total QOL[19]. Another recent study found that severity of negative symptoms was found to be related to employment status and those who were unemployed had poor QOL[18]. In contrast, a cross-sectional study of 206 stable out-patients with schizophrenia in similar setting found the only significant associated factors for subjective QOL were general psychopathology and depressive symptoms. The socio-demographic variables, level of function and other clinical features were not significantly associated with subjective QOL[23].

This study revealed that severity of TD was negatively associated with quality of life. When comparing QLS total score and the three level of severity of TD, there was significant difference in the mean QLS score between mild and severe TD. There is only one previous study (involving 60 patients with only 15 patients had TD) examined the association between TD and quality of life. That study found modestly lower quality of life in patient with TD[1]. However, the sample of that study was too small to allow generalization to other study population. A recent study on the association of treatment-emergent adverse events with health-related quality of life involving 16091 patients found that TD has negative association with health-related quality of life[14].

There were a few limitations in this study. First, the sample size was small and the samples were conveniently selected from schizophrenia out-patient thereby limiting the generalization. Similar study needs to be replicated at different centres. In conclusion, schizophrenia patients with TD had low overall quality of life and there were significant negative associations between quality of life and severity of TD, negative symptoms as well as subjects being single, unemployed of partially employed. These findings convey important message to the health care providers to recognize and treat TD as early as possible in order to improve their patients' quality of life.

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