# CO-MORBIDITY BETWEEN MAJOR DEPRESSION AND SCHIZOPHRENIA: PREVALENCE AND CLINICAL CHARACTERISTICS

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## SUMMARY

**Backround:** *The aim of this study was to explore the co-morbidity between Major Depressive Disorder (MDD) and Schizophrenia (SZ) among a large number of patients describing their clinical characteristics and rate of prevalence.*

**Subjects and methods:** *A cohort-study was carried out on 396 patients affected by MDD and SZ who consecutively attended the Department of Psychiatry, Rumeilah Hospital in Qatar. We employed the World Health Organization - Composite International Diagnostic Interview (WHO-CIDI) and the Structured Clinical Interview for DSM-5 (SCID-5) for diagnoses. Patients were also grouped in MDD patients with and without co-morbid SZ (MDD vs MDD/SZ) for comparisons.*

**Results:** *A total of 396 subjects were interviewed. MDD patients with comorbid SZ (146(36.8%)) were 42.69±14.33 years old whereas MDD without SZ patients (250 (63.2%)) aged 41.59±13.59. Statistically significant differences between MDD with SZ patients and MDD without SZ patients were: higher BMI (Body Mass Index) (p=0.025), lower family income (p=0.004), higher rate of cigarette smoking (p<0.001), and higher level of consanguinity (p=0.023). Also, statistically significant differences were found in General Health Score (p=0.017), Clinical Global Impression-BD Score (p=0.042), duration of illnesses (p=0.003), and Global Assessment of Functioning (p=0.012). Rates of anxiety dimensions (e.g.: general anxiety, agoraphobia, somatisation, etc.), mood dimensions (e.g.: major depression, mania, oppositional defiant behaviour, Bipolar disorder), Attention Deficit Hyperactivity Disorder, psychotic and personality dimensions were higher among MDD with SZ patients than MDD without SZ.*

**Conclusion:** *This study confirms that MDD with SZ is a common comorbidity especially among patients reporting higher level of consanguinity. MDD/SZ comorbidity presents unfavourable clinical characteristics and higher levels of morbidity at rating scales.*

**Key words:** *schizophrenia - major depressive disorder - co-morbidity - consanguinity*

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## INTRODUCTION

Patients reporting comorbidity between Major Depressive Disorder (MDD) and Schizophrenia (SZ) may represent a specific diagnostic category requiring specific treatments (Moller 2008, Bartels & Drake 1988). Also, detecting MDD symptoms among patients with Schizophrenia or psychotic symptoms among MDD patients may be especially important in order to consider appropriate treatments beyond mood and psychotic symptoms (Knights & Hirsch 1981). The prevalence of negative symptoms and the prevalence of Depression in Schizophrenia may vary depending on the way these symptoms are clinically considered and recognised. A recent survey reports that clinicians prescribe antidepressants to 30% of inpatients and 43% of outpatients with co-morbid schizophrenia and depression at all ages (Kasckow & Zisook 2008). Same authors report

that prevalence of such comorbidity may vary and ranges from 20 to 70 % and, in their own study, ranges from 6 to 75% (Häfner et al. 2002). Moreover, depressive symptoms are often recognized as the earliest and most frequent signs of impending schizophrenia (Häfner et al. 2002, An der Heiden et al. 2005, Addington et al. 1998, Koreen et al.1993, Chemerinski et al. 2008).

Depressive symptoms are also associated with higher impairment in social and vocational functioning, poor quality of life and an increased risk of relapse (Tollefson & Andersen 1999), contributing to the alarmingly high rates of suicide in patients with schizophrenia (Moller 2008, Muller et al. 2001). It is of note that depressive mood as well as loss of self-confidence, feelings of guilt and suicidal thoughts are prevalent symptoms in patients admitted for the first time for the exacerbation of their psychosis (An der Heiden et al. 2005, Jin et al. 2001). However, despite the clinical

interest on depression among schizophrenia patients, research studies explicitly examining depressive symptoms and their association with other psychopathological and clinical characteristics in psychotic patients are scarce (Jin et al. 2001, Conley et al. 2007). In addition, previous studies vary considerably in terms of their methodology of assessment, interval of observation or patients selection (Siris 2000) with some limitations on the generalizability of the results. The evaluation and diagnosis of depression in schizophrenia patients is furthermore complicated by the fact that some depressive symptoms such as sleep disturbances, lack in concentration, etc., can affect help-seeking and clinical ratings (Spellmann et al. 2017, Bener et al. 2011, 2012a,b, 2015, 2016a, Ghuloum et al. 2014). In addition, consanguinity has been shown to be clearly associated with an increased risk of genetically complex disorders (Bener et al. 2012a,b, 2016b, Ghuloum et al. 2014, Bittles 2013).

The aim of this study was to describe the co-morbidity between Major Depressive Disorder (MDD) and Schizophrenia (SZ) and compare clinical characteristics of MDD patients *with* versus *without* co-morbid SZ and to contribute to the understanding of the role of depressive symptoms in Schizophrenia patients as well as psychotic symptoms in MDD.

## SUBJECTS AND METHODS

This is a cohort-study including patients from Qatar with age ranging 18- 65 years old and interviewed from March 2011 to June 2014, who consecutively attended the Department of Psychiatry at Rumeilah Hospital. All psychiatric diagnoses met the ICD-10 (International Classification of Diseases) criteria and were based on the Arabic World Mental Health - Composite International Diagnostic Interview (WMH-CIDI version 3.0; Kessler et al. 2004a, Kessler et al. 2004b). Paper and Pencil Personal Interview (PAPI) - version 6 has been employed to bridge the data into the BLAISE software (a computer-assisted interviewing) (Bener et al. 2012a,b, 2016b, Ghuloum et al. 2014, Bittles 2013, Kessler et al. 2004 a,b).

600 Qatari patients affected by Major Depression and Schizophrenia were approached; 396 (73.3%) agreed to be assessed and were interviewed using the Arabic World Mental Health - Composite International Diagnostic Interview (WMH-CIDI version 3.0) validated by the Institute for Development, Research, Advocacy and Applied Care (IDRAAC) centre in Lebanon (Kessler et al. 2004a,b). 204 subjects did not agree to be interviewed showing no personal interest in the current study. Additionally, we employed the rating scale by American Psychiatric Association (2015), structured clinical interview for DSM-5 (SCID-5). The WMH-CIDI instrument in Arabic language was administered by well trained interviewers under supervision of the co-investigators (EED *and* MTAS). After the

diagnostic assessment, all patients were rated employing the following instruments:

- Hamilton Depression Rating Scale and (HAM-D) (Hamilton 1967);
- Young Mania Rating Scale (YMRS) (Young et al. 2000);
- Beck Depression Inventory (BDI) (Beck et al. 1988) - Depression was considered to be present if BDI score was greater than 10.

Socio-demographics, medical and family history were collected using a validated self-administered questionnaire with the help of clinicians and trained nurses. A good inter-rater reliability, test-retest reliability and validity for almost all diagnostic categories have been tested for the CIDI. Cronbach's alpha was 0.89 and 0.90 upon test and retest, respectively, which proved good internal consistency. The mean kappa value was 0.87, indicating a high level of reproducibility.

Institutional Review Board approval has been obtained from Weill Cornell Medical College and Hamad Medical Corporation for conducting this research in Qatar.

### Statistical Analysis

Data were entered and analyzed with the Statistical Packages for Social Sciences [SPSS], Window version No.22. Frequency distributions, one and two-way tabulations were obtained. Student-t test was used to ascertain the significance of differences between mean values of two continuous variables and confirmed by non-parametric Mann-Whitney test. Chi-square analysis was performed to test for differences in proportions of categorical variables between two or more groups. In 2x2 tables, the Fisher's exact test (two-tailed) replaced the chi-square test if the assumptions underlying chi-square violated, namely in case of small sample size and where the expected frequency is less than 5 in any of the cells. Findings are considered statistically significant with a two-tailed value less than 0.01, to compensate for multiple comparisons.

## RESULTS

396 subjects (over 600) were recruited for the study and interviewed. 141 / 396 (35.6%) reported co-morbid MDD/SZ.

MDD *with* SZ were 42.69±14.33 years old whereas MDD patients *without* SZ aged 41.59±13.59. Socio-demographics of MDD patients *with* Schizophrenia *vs* MDD *without* SZ are shown in Table 1.

Statistically significant differences between patients affected by MDD *with* SZ and MDD *without* SZ were: higher BMI (Body Mass Index) (p=0.025), lower family income (p=0.004), higher rate of cigarette smoking (p<0.001), and higher level of consanguinity (p=0.023). The rate of consanguinity among MDD *with* SZ patients was 31.9% (95% CI=29.0-34.6).

**Table 1.** Socio-demographic characteristics of Major Depressive Disorder with/without Schizophrenia (N=396) patients

| Variables | MDD with Schizophrenia n=141; (%) | MDD without Schizophrenia n=255; (%) | *p*-value |
|---|---|---|---|
| Age groups | | | 0.905 |
| <34years | 44 (31.2) | 79 (31.0) | |
| 35-49 year | 52 (36.9) | 101 (39.6) | |
| 50-64 years | 27 (19.1) | 48 (18.8) | |
| >65 years | 18 (12.8) | 27 (10.6) | |
| Gender | | | 0.131 |
| Males | 52 (26.9) | 114 (44.7) | |
| Females | 89 (63.1) | 141 (55.3) | |
| BMI Group | | | 0.025 |
| Normal (<25 kg/m$^2$) | 37 (26.2) | 96 (37.6) | |
| Overweight (26-39) | 53 (37.6) | 95 (37.3) | |
| Obese (30+) | 51 (36.2) | 64 (25.1) | |
| Marital Status | | | 0.241 |
| Single | 24 (17.0) | 56 (22.0) | |
| Married | 117 (83.0) | 199 (78.0) | |
| Education Level | | | 0.281 |
| Primary | 19 (13.5 | 48 (18.8) | |
| Intermediate | 37 (26.2) | 48 (18.8) | |
| Secondary | 46 (32.6) | 89 (345.9) | |
| University | 39 (27.7) | 70 (27.5) | |
| Occupation | | | 0.554 |
| Housewife | 20 (14.2) | 50 (19.6) | |
| Sedentary/Professional | 48 (34.0) | 93 (36.54) | |
| Manual | 41 (29.1) | 66 (25.9) | |
| Business man | 12 (8.5) | 18 (7.1) | |
| Army/police | 20 (14.2) | 28 (11.0) | |
| Household income/month | | | 0.004 |
| <$3,000 | 37 (26.2) | 99 (38.8) | |
| $3,000-$5,000 | 60 (42.6) | 69 (27.1) | |
| >$5,000 | 44 (31.2) | 87 (34.1) | |
| Cigarette smoking | | | <0.001 |
| Never | 105 (74.5) | 233 (91.4) | |
| Current | 21 (14.8) | 16 (6.3) | |
| Past | 15 (10.6) | 6 (2.4) | |
| Consanguinity | | | 0.023 |
| Yes | 45 (31.9) | 55 (21.6) | |
| No | 96 (68.1) | 200 (78.4) | |

MDD: Major Depression Disorder; SZ: Schizophrenia

Table 2 shows the prevalence and clinical characteristics of MDD *with* and *without* SZ. Significant differences were found in General Health Score (p=0.017), Clinical Global Impression-BD Score (p=0.042), duration of illnesses (p=0.003), and Global Assessment of Functioning (p=0.012), as shown. Rates of anxiety dimensions (e.g.: general anxiety, agoraphobia, somatisation, etc.), mood dimensions (major depression, mania, oppositional defiant behaviour, Bipolar disorder), Attention Deficit Hyperactivity Disorder, psychotic and personality dimensions were higher among MDD *with* SZ patients than MDD *without* SZ.

Figure 1 illustrates the Venn Diagram showing the overlapping prevalence of MDD with/without SZ and consanguinity/family history.

## DISCUSSION

The aim of the current study was to explore the prevalence of comorbidity between MDD and SZ and compare clinical features of MDD patients *with* and *without* SZ. Co-morbidity between MDD and SZ is relatively common (Bartels & Drake 1988, Kasckow & Zisook 2008, An der Heiden et al. 2016, Bener et al. 2018).

**Table 2.** Clinical characteristics of Major Depressive Disorder with/without Schizophrenia (N=396) patients

| Clinical Characteristics | MDD with Schizophrenia n=141 Mean ± SD | MDD without Schizophrenia n=255 Mean ± SD | *p*-value |
|---|---|---|---|
| Age at onset of illness | 42.10±12.80 | 41.75±12.40 | 0.795 |
| Duration of illness( years) | 9.34±3.31 | 10.47±3.84 | 0.003 |
| No. of visits/ Hospitalizations | 3.00±1.58 | 2.75±1.62 | 0.419 |
| General Health Questionnaire Score | 15.00±7.32 | 16.20±6.63 | 0.017 |
| Hamilton Depression rating Score | 3.64±0.56 | 3.70±0.51 | 0.061 |
| Young Mania Rating scale-YMRS Score. | 34.23±5.26 | 34.75±5.48 | 0.443 |
| Clinical Global impression Score | 4.80±0.76 | 4.30±0.60 | 0.042 |
| Global Assessment of Functioning | 38.04±6.36 | 36.65±5.52 | 0.010 |
| Anxiety Dimensions at DSM-5 (SCID-5)[*] | n (%) | n (%) | p-value |
| Generalized Anxiety Disorders | 35 (24.8) | 33 (12.9) | 0.003 |
| Panic Disorder | 28 (19.9) | 24 (8.4) | 0.005 |
| Agoraphobia without panic | 25 (17.7) | 23 (9.10) | 0.011 |
| Specific Phobia | 10 (7.1) | 19 (7.5) | 0.8966 |
| Social Phobia | 22 (15.6) | 31 (12.2) | 0.335 |
| Post Traumatic stress Disorder | 21 (14.9) | 32 (12.5) | 0.512 |
| Separation Anxiety Disorders | 35 (24.8) | 27 (10.6) | 0.001 |
| Somatization disorder | 29 (20.6) | 23 (9.10) | 0.001 |
| Any Anxiety Disorders | 39 (26.7) | 24 (12.6) | 0.002 |
| Mood Dimensions at DSM-5 (SCID-5)[*] | | | |
| Major Depression Disorders | 32 (22.7) | 26 (10.2) | 0.001 |
| Dysthymia | 26 (18.4) | 29 (11.4) | 0.050 |
| Mania | 34 (24.1) | 30 (10.2) | 0.001 |
| Bipolar Disorder | 22 (15.6) | 19 (6.5) | 0.003 |
| Any Mood Disorders | 41 (29.0) | 44 (17.3) | 0.030 |
| Oppositional Defiant Disorder | 21 (14.9) | 33 (11.2) | 0.560 |
| Attention Deficit Hyperactivity (ADHD) | 34 (24.1) | 39 (15.3) | 0.030 |
| Psychotic dimensions at DSM-5 (SCID-5)[*] | 28 (19.9) | 29 (11.4) | 0.025 |
| Personality traits dimension at DSM-5 (SCID-5)[*] | 26 (18.4) | 26 (10.2) | 0.020 |

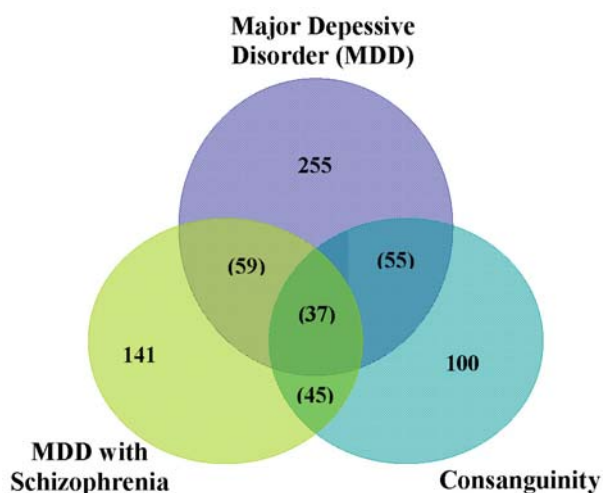 * American Psychiatric Association. (2015). Structured Clinical Interview for DSM-5 (SCID-5)



**Figure 1.** Venn Diagram showing the overlapping Prevalence of Major Depressive Disorder with/without Schizophrenia and consanguinity (N=396)

In our study the rate of co-morbidity was 35.60% which appears consistent with previous studies reporting 30% of inpatients and 43% of outpatients with schizophrenia and depression at all ages (Bartels & Drake 1988).

As suggested by Schennach et al. (2015), depressive symptoms may be considered as a distinct psycho-pathological domain in patients suffering from schizophrenia and our study seems to confirm this evidence since comorbidity between MDD and SZ reported specific different clinical characteristics (as shown). Moreover, a recent study investigated the application and comparison of common remission and recovery criteria between patients with schizophrenia and major depressive disorder reporting that functional remission and recovery rates were significantly lower in schizophrenia than in depressive patients at the one-year follow-up (Spellmann et al. 2017).

Although the co-occurrence of SZ and MDD is a common and challenging co-morbid condition, the relationship between SZ and MDD has remained unclear (Bener et al. 2018). Even if this condition is under-recognized in clinical practice, it may significantly change the illness presentation and its outcome as shown by the clinical differences reported in our study.

In addition it appears that in general, consanguinity increases the risk of mental illness. Bener and colleagues (2016a,b) found that subjects from consanguineous parents report a significantly higher risk to develop a

mental disorders. Bener et al. (2015, 2016b, 2018) have reported that rates of major depression, bipolar disorder were significantly higher in consanguineous marriages than in non-consanguineous ones as well as having an impact on the onset of symptoms. This study confirms a higher level of consanguinity among patients reporting MDD and SZ comorbidity.

## CONCLUSIONS

In conclusion, this study has shown that MDD-SZ is a common clinical co-morbidity, largely under-recognized in clinical practice, which may significantly change the illness presentation and outcome. Also, prevalence of MDD with SZ was higher among patients reporting a degree of consanguinity.

### Contribution of individual authors:

Abdulbari Bener designed and supervised the study and was involved in data collection, statistical analysis, the writing of the paper.

Elnour E. Dafeeah & Mohammed T. Abou-Saleh were involved in data collection, interpretation of data and writing manuscript.

Dinesh Bhugra & Antonio Ventriglio were involved in the interpretation of data and in writing the manuscript.

All authors approved the final version.

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