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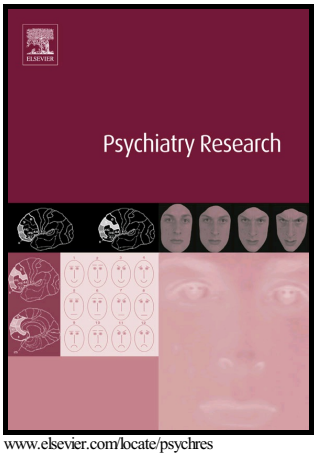

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Major Depressive Disorder and Depressive Symptoms in Intermittent Explosive Disorder

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Abstract

It is estimated that between 1.7 and 2.6 million people had intermittent explosive disorder (IED) during their life in the United States alone. Co-occurring psychiatric disorders are very common in IED, being major depressive disorder arguably the most common. The objective of this study was to examine the clinical correlates of IED and depressive manifestations in 74 treatment-seeking subjects. After controlling for confounders, there were associations between severity of depressive disorder/major depressive disorder and (a) higher assault scores, (b) more severe hostile behavior and (c) worse social adjustment. Proper management of depressive disorder/symptoms may be an important step for treatment.

Keywords: intermittent explosive disorder; major depressive disorder; clinical aspects

1. Introduction

It is estimated that between 1.7 and 2.6 million people had Intermittent Explosive Disorder (IED) during their life in the United States alone (Coccaro, 2012; U.S. and World Population Clock, 2017). IED is associated with marital, financial, work-related, marital and legal difficulties (American Psychiatric Association [APA], 2013; Kessler et al., 2006;). Psychiatric comorbidity is very common in this disorder. Approximately 82% of the subjects with IED will have one additional co-occurring psychiatric disorder during their lives, with major depressive disorder (MDD) being among the most common (APA, 2013; Kessler et al., 2006). MDD is approximately four times more common in IED than in the general population (Coccaro, 2012). Despite the high co-occurrence of IED and MDD, research on this comorbidity is still very limited.

There are some important shared features between IED and MDD. Both disorders: 1) may present with irritability, impulsiveness and aggressive behavior (APA, 2013; Fava et al., 2010; Judd et al., 2013; Kessler et al., 2006); 2) are highly impairing (APA, 2013; Ferrari et al., 2013; Greenberg et al., 2015; Kessler et al., 2006); and 3) demonstrate significant suicide rates (APA, 2013; Kessler et al., 2006; McCloskey et al., 2008). In this context, IED and MDD may clinically interact in significant ways. Nevertheless, to the best of our knowledge, there is no article specifically investigating this comorbidity.

The objective of the study was to examine the clinical correlates of IED as a function of comorbid MDD / depressive symptoms. There is currently some disagreement as to whether depressive symptoms are better investigated from a categorical or dimensional approach, but no definitive answer has been reached (Kramer et al., 2004). Thus, we decided to use both strategies (categorical and dimensional) in the current study. Our main hypotheses were that the co-

occurrence of MDD / depressive symptoms in IED would be associated with: a) more severe hostile behavior, especially externalizing hostile behavior such as assault and verbal hostility; b) higher levels of impulsiveness; c) worse social adjustment; and d) more suicide attempts. A better understanding of the relationship between IED with and without depressive manifestations may provide important clinical insight regarding proper treatment of IED.

2. Methods

2.1 Sample and Procedures

Our sample consisted of treatment-seeking subjects recruited at the Impulse Control Disorders Outpatient Unit at the University of São Paulo, Brazil. This research´s inclusion criteria were: a) age of 18 or more; b) diagnosis of IED according to the Diagnostic and Statistical Manual for Mental Disorders Version 5 (DSM-5); and c) at least 5 years of formal education.

The studied sample was enlisted between November, 2007 and September, 2013. We revaluated one hundred twenty-two subjects who sought treatment for maladaptive aggression. They were initially assessed for IED using an Impulse Control Disorder structured clinical interview modeled after the Structured Clinical Interview (SCID), which used DSM-IV criteria. The studied individuals had her aggressive behavior characterized including type of aggression (verbal, against property/animals, physical assault, others); frequency (per week/month/year); and negative consequences. After the initial screening, eighteen individuals were excluded from this research because their aggressive behavior was better explained by other mental disorders. They fulfilled criteria for IED exclusively during episodes of another disorder such as in bipolar disorder [n = 5] or MDD [n = 9]; or had aggressive outbursts associated with a pervasive behavioral pattern such as in borderline personality disorder [n = 4].

After the release of DSM-5, the data on aggressive behavior previously collected was retrospectively evaluated for the new diagnostic criteria. This procedure excluded additional thirty individuals due to inconclusive/missing data that hindered the evaluation for DSM-5 criteria. Our protocol also excluded individuals who: a) needed emergency care; b) had psychotic symptoms; and c) refused to provide informed consent.

2.2 Measures

This study collected the following demographics: age (in years), gender, ethnicity, marital status, occupational status and educational level (in years of formal education). Current psychiatric comorbidity and previous suicide attempts were assessed by the Mini International neuropsychiatric interview (Hergueta et al., 1998). Depressive Symptoms were evaluated using the Beck Depression Inventory [version I] (Beck et al., 1988). We examined hostile behavior with the Buss-Durkee Hostility Inventory (Buss and Durkee, 1957) while impulsiveness was assessed by the Barratt Impulsiveness Scale (Patton et al., 1995). Difficulties in social adjustment were evaluated using the Social Adjustment Scale – Self Report.

2.3 Statistics

We used two different approaches in the current study: categorical and dimensional.

In the categorical strategy, the sample was divided into two groups (with and without MDD). Continuous variables were analyzed with Student t-tests or Mann-Whitney U-tests for variables with, respectively, parametric and non-parametric distribution. We used chi-square tests or Fisher´s exact tests for categorical variables. The latter was used when there were cells with five or fewer participants.

With respect to the dimensional approach, we studied the association between depressive symptoms (measured by the BDI) and demographic/clinical variables. We studied the

relationship between two continuous variables using correlation coefficients (Pearson's or Spearman's). We compared BDI scores with categorical demographic/clinical variables with Student t-tests, which were chosen due to the parametric distributions of BDI scores.

In order minimize confounders our study controlled for the demographics that were statistically significant (i.e age in the categorical comparison; and gender and ethnicity in the dimensional analysis), current prevalence of any anxiety disorder, and current prevalence of alcohol and/or substance disorder. We used multiple linear regressions, a common strategy to control for multiple confounders (Pourhoseingholi et al., 2012). This approach has been used in several studies in mental health (see Ibáñez et al., 2001; Wilens et al., 2002; Medeiros et al., 2017).

2.4 Ethics

The Ethics Committee of the Clinics Hospital of the University of São Paulo, Brazil approved the current research. We collected written informed consent from all participants.

3. Results

The studied sample showed a current MDD prevalence of 32.4% (n = 24). The mean and median BDI scores were, respectively, 19.4 (±9.9) and 19.5. These ratings correspond to the severe depression range (Hamilton, 1960).

With respect to the categorical approach, subjects with MDD were younger than those without MDD. Moreover, depressed participants had higher assault and total scores when compared to individuals without MDD. Subjects who fulfilled criteria for MDD also demonstrated more difficulties in social adjustment.

In terms of the dimensional analysis, females and non-Caucasians showed more elevated depressive symptoms. Additionally, we observed positive correlations between severity of

depressive symptoms and: 1) assault scores; 2) resentment scores; 3) suspicion scores; and 4) total BDHI scores. Depressive symptoms also showed positive correlations with motor impulsiveness and problems in social adjustment.

All the clinical results described above kept their statistical significance after controlling for demographics, alcohol/substance use disorder and anxiety disorders (see Table 1).

4. Discussion

The current study investigated clinical associations between IED and MDD/depressive symptoms. This research has several strengths as, for example, 1) being the first investigation on a highly common comorbidity; 2) the utilization of categorical and dimensional approaches to depressive manifestations (consistent findings in both approaches may significantly reduce the likelihood of a Type-I error); and 3) a comprehensive statistical control for important confounders such as demographic differences, alcohol/substance use disorder and anxiety disorders. Our main findings were that depressive manifestations were associated with higher assaults and hostility total scores, as well as more difficulties in social adjustment.

The high rates of comorbidity between IED and MDD may have several causal explanations. The cross-sectional design of our study does not allow us to infer causality. However, MDD may often develop secondary to IED (APA, 2013; Kessler et al., 2006). One possibility is that the feelings of regret and guilt over the aggressive episodes due to the negative consequences of the outburst (familial, social, work-related legal, financial) may facilitate the onset of MDD. This is consistent with the fact that subjects with MDD/depressive symptoms have more social difficulties. There is a need for longitudinal research that may better explain the chronological relationship between IED and MDD. Timely management of IED may prevent the secondary development of MDD and the worsening of depressive symptoms. Alternatively, it is

possible that there is a common biological vulnerability between the disorders. This may be reinforced by the serotoninergic abnormalities (APA, 2013; McCloskey et al., 2008) and frontal hypoactivation found in both disorders (Drevets, 2007, Coccaro, 2012).

Despite these strengths, this research should be interpreted in light of its limitations. First, our research used the general diagnostic criteria for MDD. Nonetheless, there are diverse subtypes of depression, which may interact differently with IED. Second, this study used a relatively small sample collected in one location. Third, the diagnosis of IED was initially made according to the DSM-IV; and the DSM-5 criteria were retrospectively applied. Finally, we investigated treatment-seeking subjects. Consequently, caution is needed when extrapolating our results to other groups. However, our results are clinically relevant since the site of recruitment represents a usual treatment setting.

Our study observed a high current prevalence of MDD (32.4%) in subjects with IED. The categorical and dimensional approaches to depressive symptoms found an association between these mood manifestations and a) a more severe hostile behavior (particularly assault to others), and b) difficulties in adjustment to the environment. Future research should better understand causal relationships and biological basis of this association such as neuroimaging, genetic vulnerability and biomarkers. Proper management of depressive disorder/symptoms appears to be an important part of the treatment to IED.

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Table 1 – Current Major Depressive Disorder (MDD) and Depressive Symptoms in Individuals with Explosive Intermittent Disorder Divided (n = 74).

Variables	*CATEGORICAL APPROACH*				*DIMENSIONAL APPROACH*		
	With MDD n = 27 Mean (SD)/ Median or % (n)	Without MDD n = 47 Mean (SD)/ Median or % (n)	*p* value [a]	*p* value contr. [b]	Depressive Symptoms (BDI) n = 74 Correlation Coefficient or Mean (SD) / Median	*p* value [c]	*p* value contr. [d]
➢ DEMOGRAPHICS							
Age (in years)	38.6 (±10.9) / 37.0	45.0 (±12.8) / 43.0	**0.023**	NA	Spearman's Cor. = .029	0.804	NA
Gender							
- Male	77.8 (21)	80.9 (38)	0.752	NA	17.6 (±9.0) / 18.0	**0.001**	NA
- Female	22.2 (6)	19.1 (9)			26.5 (±10.3) / 28.0		
Ethnicity							
- Caucasian	55.6 (15)	76.6 (36)	0.060	NA	17.6 (±9.0) / 18.0	**0.017**	NA
- Non-Caucasian	44.4 (12)	23.4 (11)			23.4 (±10.8) / 22.0		
Marital Status [N[e]=73]							
- With Partner	63.0 (17)	63.0 (29)	0.995	NA	20.5 (±8.8) / 19.5	0.282	NA
- Without Partner	37.0 (10)	37.0 (17)			17.8 (±11.5) /		

					20.0		
Occupational Status [N=73]							
- Working or Studying	69.2	76.6	0.492	NA	18.5 (±9.5)	0.306	NA
- Unemployed or Retired	(18)	(36)			/ 18.5		
	30.8	23.4			21.3		
	(8)	(11)			(±10.9) /		
					20.0		
Years of Formal Education	14.6	14.4	0.794	NA	Spearman'	0.538	NA
	(±3.5)	(±3.7) /			s Cor. = -		
	/ 15.0	15.0			.073		
➢ CLINICAL VARIABLES							
Hostile Behavior (BDHI) [N=73]			.				
- Verbal Hostility	10.6	9.7	**0.038**	0.270	Spearman'	0.431	0.926
	(±2.1)	(±2.0) /			s Cor. =		
	/ 11.0	10.0			.094		
- Assault	7.1	5.8	<	**0.004**	Spearman'	**0.025**	**0.036**
	(±1.1)	(±1.6) /	**0.001**		s Cor. =		
	/ 7.0	6.0			.262		
- Irritability	9.8	9.0	0.074	0.129	Spearman'	0.062	0.087
	(±1.1)	(±1.7) /			s Cor. =		
	/ 10.0	10.0			.219		
- Negativism	3.4	3.4	0.614	0.918	Spearman'	0.864	0.937
	(±1.7)	(±1.1) /			s Cor. =		
	/ 4.0	3.0			.020		
- Resentment	5.9	5.1	**0.040**	0.234	Spearman'	**0.005**	**0.039**
	(±1.9)	(±1.7) /			s Cor. =		
	/ 6.0	5.0			.326		
- Guilty	7.5	6.5	**0.028**	0.115	Spearman'	**0.009**	0.078
	(±1.4)	(±2.0) /			s Cor. =		
	/ 8.0	7.0			.305		
- Suspicion	7.4	6.3	**0.026**	0.126	Spearman'	<	**0.006**
	(±2.0)	(±2.0) /			s Cor. =	**0.001**	
	/ 7.0	7.0			.432		
- Indirect Hostility	6.9	6.1	**0.032**	0.051	Spearman'	0.809	0.378
	(±0.9)	(±1.4) /			s Cor. = -		
	/ 7.0	6.0			.029		
- TOTAL SCORE	58.6	51.9	**0.001**	**0.011**	Spearman'	**0.001**	**0.012**
	(±7.0)	(±7.9) /			s Cor. =		
	/ 60.0	53.0			.393		
Impulsivity (BIS)							
- Attentional	21.6	20.6	0.207	0.351	Pearson's	**0.033**	0.154
Impulsiveness	(±2.8)	(±3.4) /			Cor. =		
	/ 22.0	20.0			.249		

- Motor Impulsiveness	25.4 (±6.2) / 25.0	23.0 (±5.3) / 23.0	0.050	0.108	Spearman's Cor. = .374	**0.001**	**0.013**
- Lack of Planning Impulsiveness	28.8 (±6.1) / 30.0	26.3 (±5.3) / 26.0	0.059	0.199	Spearman's Cor. = .060	0.613	0.580
- Difficulties in Adjustment (SAS) [N=73]	2.5 (±0.5) / 2.5	2.3 (±0.5) / 2.2	**0.026**	**0.019**	Pearson's Cor. = .579	< **0.001**	< **0.001**
Any Previous Suicide Attempt							
- Yes	18.5 (5)	19.1 (9)	1.000 [f]	0.858	22.1 (±12.9) / 20.5	0.261	0.689
- No	81.5 (22)	80.9 (38)			18.8 (±9.1) / 19.5		

a) Statistical significance for the comparison between *subjects with MDD* and *individuals without MDD.*
b) Statistical significance for the association between *depressive symptoms (score at the BDI)* and *demographic/clinical variables.*
c) Statistical significance for the comparison between *subjects with MDD* and *individuals without MDD.* Controlled for age, current prevalence of alcohol/substance use disorder, and current prevalence anxiety disorder.
d) Statistical significance for the association between *depressive symptoms (score at the BDI)* and *demographic/clinical variables.* Controlled for gender, ethnicity, current prevalence of alcohol/substance use disorder, and current prevalence anxiety disorder.
e) N = number of participants evaluated in for the variable. If *N* is not displayed, the whole sample (n = 74) was assessed.
f) We conducted Fisher's exact test due to the existence of cells with 5 or less subjects.

SD = standard deviation; % = relative values; n = absolute values; *p* value = statistical significance; BDI = Beck Depression Inventory; bold = statistical significant (*p* value < 0.05); NA = Do not apply; Spearman's Cor. = Spearman's Correlation Coefficient; Pearson's Cor.= Pearson's Correlation Coefficient. BDHI = Buss-Durkee Hostility Inventory; BIS = Barratt Impulsiveness Scale; SAS = Social Adjustment Scale.

HIGHLIGHTS

- First paper specifically examining depressive manifestations on IED.
- We conducted a broad clinical assessment and a comprehensive statistical analysis.
- Association between depressive manifestations and worse aggressive symptoms.
- IED patients with depressive symptoms/disorder had poorer social adjustment.
- Depressive manifestations may be important on IED clinical presentation/treatment.