A Study of Oxytocin Levels in a Sample of Bipolar Affective Disorder

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Abstract

Background: Bipolar disorder is characterized by mood swings with both manic and depressive symptoms. Social cognitive abnormalities have recently been recognized as a core feature of mood disorders which persist during remission. The neuropeptide oxytocin may be a trait marker of bipolar disorder and it's dysregulation might be involved in the pathophysiology of bipolar disorder.

Aim of the study: To compare oxytocin levels between cases of bipolar disorders and control group and to search for a correlation between oxytocin levels and various clinical parameters.

Methods: Forty five (45) bipolar patients and thirty (30) healthy controls with matching age and sex were examined. SCIDI was for confirmation of diagnosis of bipolar disorder. Further assessment using Beck depression inventory, Young mania scale were also performed. Salivary Oxytocin hormone level was also measured. Results: Oxytocin showed higher significant levels in bipolar patients whether in depression, mania or in remission when compared to controls ($p<0.001$, <0.001, <0.001, $=0.002$ respectively).Where manic cases showed significantly higher level of Oxytocin when compared to depressive and remittent cases ($p=0.015$, 0.007 respectively). Only higher Oxytocin levels was suggested to be a predictor for bipolar disorder or mania development and lower levels of Oxytocin might predict remission but doesn't predict the severity of the disorder.

Conclusion: Higher Oxytocin levels was suggested to be a predictor for bipolar disorder or mania development and lower levels of Oxytocin might predict remission but doesn't predict the severity of the disorder.

Key words: Oxytocin, bipolar disorder, affective disorder, biomarker, Beck depression, Young mania.

Introduction:

Bipolar disorder (BD) is a major health concern, characterized by mood episodes; namely periods of elevated or irritable mood, referred to as mania, periods of depression, and mixed manic and depressed states **(American Psychiatric Association, 2013).**

The one year prevalence of bipolar disorder in Egypt was 2.7 % according to the national survey for mental health in Egypt (2017) **(Odejimi et al., 2020).**

The neuropeptide oxytocin has attracted great attention of the general public, basic neuroscience researchers, psychologists, and psychiatrists due to its profound pro-social, anxiolytic, and "anti-

stress" behavioral and physiological effects, and its potential application for treatment of mental disorders associated with altered socio-emotional competence. During the last decade, substantial progress has been achieved in understanding the complex neurobiology of the oxytocin system **(Grinevich & Neumann, 2021).**

By definition, Bipolar disorder patients would ideally be free from inter-episode disturbance. However, reduced performance in neuropsychological tests is reported in euthymic patients with bipolar disorder **(Kato, 2019).**

Social cognitive abnormalities have recently been recognized as a core feature of mood disorders and it correlates with illness load (i.e., illness duration and symptom severity) supporting the need for early intervention **(Billeke and Aboitiz, 2013).** It is also associated with lower social functioning, higher disability, and poor prognosis. As these deficits are known to persist in the remitted state, patients may still have poor social adjustment due to impairments in social cognition even during symptomatic remission from affective or psychotic episodes **(Mercedes Perez-Rodriguez et al., 2015).**

Despite the clinical significance of social cognitive impairment, pharmacological treatment for this core illness feature is not currently available. Several lines of evidence suggest that the neuropeptide oxytocin may be a potential treatment for social cognitive deficits across diagnoses **(Gumley et al., 2014).** Many studies review the evidence for social cognitive abnormalities in mood and psychotic disorders as well as the clinical trials of intranasal oxytocin administration across diagnoses and evaluate the evidence for improvement of social cognition across disorders **(Cusi et al., 2013).**

Due to the novality of the role of Oxytocin in bipolar disorder, thus the present research was conducted to evaluate levels of Oxytocin in bipolar patients and to compare it with normal healthy controls; Moreover this study aims to find whether Oxytocin could serve as a biomarker for bipolar disorder.

Patients and Methods:

This is a comparative cross sectional study, conducted on forty five (45) bipolar patients which are divided equally to depressive, manic patients and also patients in remission and thirty (30) healthy controls with matching age, sex, residency, marital status and occupational state. Recruited patient were selected from two psychiatric hospitals in Benha (Benha University Hospial, Benha Mental Hospital).A SCIDI for confirmation of diagnosis of bipolar disorder; exclusion of comorbidities and for the exclusion of any psychiatric disorder in cases and control groups was used. Further assessment using Beck depression inventory, Young mania scale were also performed. In addition to a salivary Oxytocin sample from all participants. Study subjects were informed of the possibility of using the data obtained for academic purpose.

Both genders were included from age of 18 years and above, Patients on their psychotropic medications provided the dose has not been adjusted in the last week.

While excluding age less than 18 years old, Female participants: currently pregnant or lactating, or with menstrual irregularities, patients with comrbid medical disorders (seizures, major head trauma), major illnesses (Cancer, IHD, renal failure or liver cell failure), endocrinal diseases (hypopituitarism, hyperprolactinemia and thyroid disorders) and neurological disorders which may affect mood e.g. D.S and other comorbid psychiatric disorders e.g. schizophrenia, anxiety disorders and history of substance abuse. Patients receiving any hormonal therapy or females using hormonal contraceptives, and drugs which might affect mood or oxytocin levels e.g. corticosteroids.

Tools:

All participants (cases & control) were subjected to the following:

1) Psychometric test measuring psychiatric disorders (Structured Clinical Interview for DSM Disorders) (SCIDI) for diagnosing the major Axis I DSM-IV disorders for all participants) **(First et al., 1995).**

The Arabic version of the SCID-I was used in this study **(El Missery et al., 2003)**

2) Beck Depression Inventory (BDI-II) for assessment of depression (**Beck et al., 1996)** for only depressive patients or cases in remission..

The Arabic version of the BDI-II used in this study was translated and validated by ***(*Abdel-Khalik, 2002).**

3) Young Mania Rating Scale (YMRS) **(Young et al., 1978)** for only manic patients or cases in remission. The Arabic version of the YMRS used in this study was translated and validated by **(Abdel-Hamid et al; 2018).**
4) ***Biological investigations*: salivary Oxytocin level measurement.**

Ethical consideration:

A consent was obtained from the patients and care givers, including data about the aim of the work, study design ,site of the study , tool used in it. It was explained to both groups that they can withdraw from the study at any time without any consequences and it will not affect the type of care they are receiving from the facility. It was also assured to all participants regarding the confidentiality of results.

Statistical analysis:

The collected data was revised, coded and tabulated using Statistical package for Social Science **(IBM , 2011).** Shapiro test, Mean Standard deviation (± SD), Student T Test, Mann Whitney Test (U test), The Kruskal-Wallis test, Chi-Square test, Fisher's exact test, Correlation analysis: and Regression analysis was used. All reported p values were two-tailed and $p < 0.05$ was considered to be significant **(Greenberg et al., 1996; Khothari, 2004; Fischer et al., 2003).**

Results:

Table (1): Comparison of sociodemographic data among studied bipolar cases& controls:

			Control n=30		Bipolar n=45		*p*
Age	**Age (years)**	**Mean ±SD**	31.6	10.2	33.0	12.1	0.634
	<30	**N, %**	15	50.0%	25	55.6%	0.730
	30-50	**N, %**	13	43.3%	15	33.3%	
	>50	**N, %**	2	6.7%	5	11.1%	
Gender	**Males**	**N, %**	11	36.7%	19	42.2%	0.630
	Females	**N, %**	19	63.3%	26	57.8%	
Marital status	**Single**	**N, %**	14	46.7%	17	37.8%	0.601
	Married	**N, %**	16	53.3%	25	55.6%	
	Separated	**N, %**	0	0%	2	4.4%	
	Widow	**N, %**	0	0%	1	2.2%	
Occupation	**Higher performance**	**N, %**	7	23.3%	8	17.8%	0.666
	House wife	**N, %**	5	16.7%	9	20.0%	
	Student	**N, %**	4	13.3%	10	22.2%	
	worker	**N, %**	5	16.7%	4	8.9%	
	Clerk	**N, %**	3	10.0%	8	17.8%	
	Unemployed	**N, %**	6	20.0%	5	11.1%	
	Retired	**N, %**	0	0.0%	1	2.2%	
Residence	**Rural**	**N, %**	21	70.0%	27	60.0%	0.377
	Urban	**N, %**	9	30.0%	18	40.0%	
Smoking		**N, %**	2	6.7%	12	26.7%	**0.029***

Table (2): Comparison of occupation among studied bipolar cases& controls:

		Control N=30	Bipolar N=45				*Pct*	*pcd*	*pcm*	*pcr*	*pdm*	*pdr*	*pmr*
			Total n=45	depressive N=15	manic N=15	remission N=15							
Higher performance	**N**	7	8	2	4	2	0.666	0.063	0.276	0.727	**0.001****	0.170	0.380
	%	23.3%	17.8%	13.3%	26.7%	13.3%							
House wife	**N**	5	9	6	0	3							
	%	16.7%	20.0%	40%	0%	20.0%							
Student	**N**	4	10	6	2	2							
	%	13.3%	22.2%	40.0%	13.3%	13.3%							
Worker	**N**	5	4	0	3	1							
	%	16.7%	8.9%	0%	20.0%	6.7%							
Clerk	**N**	3	8	0	5	3							
	%	10.0%	17.8%	0%	33.3%	20.0%							
Unemployed	**N**	6	5	1	1	3							
	%	20.0%	11.1%	6.7%	6.7%	20.0%							
Retired	**N**	0	1	0	0	1							
	%	0%	2.2%	0.0%	0.0%	6.7%							

Table (3): Comparison of oxytocin level among bipolar studied cases & controls:

		Control N=30	Bipolar N=45			
			Total n=45	depressive N=15	manic N=15	remission N=15
Oxytocin	**median**	85.4	139.1	126.9	188.5	135.3
	minimum	30	52.8	110	99.2	52.8
	maximum	116.5	281.6	183.4	281.6	196.8
	p values	-	***pct*<0.001*****	***pcd*<0.001*****	***pcm*<0.001*****	***pcr*=0.002****
		-	-	***pdm*=0.015***	***pmr*=0.007****	*pdr*=0.443

Table (4): Regression analysis for prediction of bipolar disorder susceptibility:

	Univariable			Multivariable		
	p	**OR**	**95% CI**	***p***	**OR**	**95% CI**
Age	0.920	0.999	(0.972-1.026)			
Gender	0.998	1.000	(0.518-1.931)			
Married	0.653	1.163	(0.603-2.244)			
Urban	0.584	1.207	(0.615-2.369)			
Higher education	0.704	0.759	(0.184-3.139)			
Smoking	**0.022***	2.970	(1.169-7.546)	0.447	1.626	(0.465-5.688)
Oxytocin	**0.007****	1.073	(1.02-1.129)	**0.008****	1.074	(1.019-1.132)

Table (5): Regression analysis for prediction of bipolar remission in studied group:

	Univariable			Multivariable		
	p	**OR**	**95% CI**	***p***	**OR**	**95% CI**
Age (numerical)	0.218	1.019	(0.989-1.049)			
Gender (female versus male)	0.288	0.660	(0.306-1.421)			
Married versus single	0.963	1.019	(0.462-2.249)			
Urban versus rural	0.520	1.288	(0.596-2.782)			
Higher education versus lower education	0.381	1.276	(0.376-2.487)			
Smoking	0.471	0.722	(0.298-1.752)			

Duration	0.946	0.998	(0.955-1.043)			
number of attacks	0.466	0.980	(0.927-1.035)			
Severity scales	**0.025***	0.990	(0.979-0.998)	**<0.001*****	0.989	(0.988-0.991)
Hospitalization	0.496	0.634	(0.17-2.359)			
Family history	0.158	0.462	(0.208-1.025)			
Suicide	**0.006****	0.319	(0.142-0.716)	0.279	0.972	(0.914-1.094)
ECT	1.000	1.000	(0.388-2.578)			
Mood stabilizers	0.364	0.605	(0.205-1.789)			
atypical antipsychotics	0.121	1.953	(0.838-4.553)			
LAP	0.239	0.481	(0.142-1.628)			
Oxytocin	**0.043***	0.990	(0.981-0.998)	**0.041***	0.824	(0.728-0.965)

Significant; < 0.05, * High significant; < 0.01, ***** Very high significant< 0.001.Pct, comparison between total bipolar and control

Pcd, comparison between depression and control
Pcm, comparison between mania and control
Pcr, comparison between remission and control
Pdm, comparison between depression and mania.
Pdr, comparison between depression and remission.
Pmr, comparison between mania and remission

Table (1) shows 42.2% of the sample was males while 57.8 % were females, with mean age was 33 ranging from 18 -65years. Among all studied cases, 37.5% were singles, 55.6% were married, 4.4% were separated and 2.2% were widows, regarding occupations, 17.8% had higher performance, 20 were housewives, 22.2% were students, 8.9% were workers, 17.8% were clerks, 11.1% were unemployed, 2.2% were retired, as regard residence, 60% resided in rural areas, 40% resided at urban areas. No significant differences were found between studied cases and controls regarding age, sex, marital status and residence ($p>0.05$ for each). Higher frequency of smoking was significantly high in bipolar patients when compared to control group ($p=0.029$).

Table (2) shows that occupations differed significantly between mania and depression ($p=0.001$), the highest frequency of those having depression were house wives and students, while the highest frequency in manic patients were clerks, higher performance and workers. Otherwise, no significant differences were found regarding occupations between studied groups.

From table (3) it was deducted that all Oxytocin values in the current study were within normal range. However, total, depressive, manic and remittent cases showed significantly higher level of oxytocin when compared to control groups ($p<0.001$, <0.001, <0.001, $=0.002$ respectively). Although manic cases showed significantly higher levels of Oxytocin when compared to depressive and remittent cases ($p=0.015$, 0.007 respectively) but levels of Oxytocin did not differ significantly between depression and remission (Table 3).

In table (4) logistic regression analysis was conducted for prediction of bipolar disorder susceptibility using age, gender, marital status, residence, education, smoking, and oxytocin level as confounders. Smoking and high oxytocin were associated with risk of bipolar disorder occurrence in Univariable analysis. However, in multivariable analysis, only higher oxytocin was suggested to be an independent risk predictor for bipolar disorder development.

In table (5) logistic regression analysis was conducted for prediction of remission of bipolar disease using age, gender, marital status, residence, education, smoking, attacks, baseline severity, hospitalization, Family history, suicidal thoughts, ECT, treatment modalities and oxytocin level as confounders. Lower baseline severity scales, frequency of suicidal thoughts, lower oxytocin levels were associated with prediction of remission in univariable analysis. However, in multivariable analysis, only lower baseline severity scale, lower oxytocin levels were suggested to be independent favorable predictors for remission of bipolar disease .

Discussion:

Bipolar affective disorder is a chronic and complex disorder of mood that is characterized by a combination of manic, hypomanic and depressive episodes, with substantial subsyndromal social cognitive impairment that commonly presents between major mood episodes **(Haggarty et al., 2021).**

The neuropeptide Oxytocin has attracted great attention of the basic neuroscience researchers, psychologists, and psychiatrists due to its profound pro-social, anxiolytic, and "anti-stress" behavioral and physiological effects, and its potential application for treatment of mental disorders associated with altered socio-emotional competence **(Grinevich & Neumann, 2021).**

A range of studies have shown correlations between basal Oxytocin levels and the strength of social and bonding behaviors in both healthy individuals and in those suffering from psychiatric disorders (**Striepens et al., 2011**). Clinical reports suggest Oxytocin to be a promising drug for psychiatric disorders such as anxiety disorders, schizophrenia, and autism. OXT may also have therapeutic potential in the treatment of bipolar affective disorders (**Matsuzaki et al., 2011**).

So this study was aimed to investigate whether there is a reliable relation which could serve as biomarker between patients and healthy controls by finding out the level of oxytocin in cases of bipolar disorder, in depressive episodes, manic episodes and also during remission. In addition to compare Oxytocin levels between cases of bipolar disorders and control group and to find out the correlation between Oxytocin levels and different sociodemographic factors and clinical data of bipolar patients.

As regard smoking, bipolar cases had a significantly higher proportion of smokers when compared to the control group (p=0.029) this was similar to **Vermeulen et al., (2021) who** found that smoking initiation and lifetime smoking are likely to be a causal risk factor for developing bipolar disorder. Another study also found important clinical correlates of tobacco smoking in BD subjects **(Medeiros et al., 2018) and t**his may be explained out of impulsivity which is a core feature of bipolarity even in females. Also most of the studied control group was females from rural or small towns were it is not common for females to smoke or a trial to reduce side effects of treatment.

Regarding occupation, this study revealed that (44.5%) of the cases were employed, ***Ekinci et al.,(2011)*** had a different finding as (81.3%) of their study cases were employed which may be explained by higher employment rate among mentally ill patients in developed countries. Occupations also differed significantly between mania and depression (p=0.001), the highest frequency of those having depression were housewives and students, while the highest frequency of those having mania were clerks, higher performance and workers. Otherwise, no significant differences were found regarding occupations between the studied groups. This is in agreement with **Xiang et al. (2013)** in his research on a Chinese population. The slight increase of female housewife ratio which may be a consequence of the social and occupational deterioration

associated with the disease itself and It is also culturally accepted for the females to show slight impairment of functional outcomes especially in rural areas and usually they don't seek psychiatric help for fear of stigma of mental illness moreover, students were prevalent as most of the studied group were younger age.

All Oxytocin values in the current study were within normal range. However, Oxytocin levels showed higher significant levels when comparing bipolar patients whether in depression, mania or in remission to control group ($p<0.001$, <0.001, <0.001, $=0.002$ respectively). Manic cases showed significantly higher levels of oxytocin when compared to depressive and remittent cases ($p=0.015$, 0.007 respectively). Strikingly levels of Oxytocin did not differ significantly between depression and remission. This is in line with **Lien et al., (2016)** study which found that Oxytocin levels of the BP patients (42.0 ± 23.7) was significantly higher than those of controls (28.4 ± 14.0, $p < 0.01$). **Turan et al. (2013)** also stated that serum Oxytocin was significantly higher in patients with manic attacks of bipolar disorder and lower in those with depressive attacks in comparison with control. **Daban et al. (2007)** provided evidence of the association between oxytocin and affective disorders as Oxytocin levels were significantly higher during manic attacks. **Eser et al., (2013),** revealed elevated serum oxytocin in both manic and depressed patients of bipolar disorders with no significant difference between both groups. This was also confirmed by **Yuen et al. (2014)** when comparing bipolar patients to controls in which P value =0.0093, 0.015 respectively. Another Egyptian study assumed that significant difference between manic patients and control according to serum oxytocin level with p-value <0.111 being higher in cases with manic symptoms **(Bayomy et al., 2016).**

From the previous researches it may be hypothesized that Oxytocin may be a biomarker of BP in either manic or depressive episodes.

In contrast, these studies weren't in agreement with **Ozsoy et al. (2009)** as serum Oxytocin levels were decreased in the patients compared with those in the controls. **Bao et al., (2008)** also found decreased plasma oxytocin levels in patients especially during depressive episodes

However, early studies speculated no difference between the CSF oxytocin levels of patients and those of the control groups **(Marazziti and Catena Dell'osso, 2008).**

With the information in the literature and the findings from this study (namely that oxytocin levels increase during manic episode) are evaluated together, it is likely that increased dopamine as well as oxytocin may play a role in the occurrence of euphoria, distractibility, excessive involvement in pleasurable activities that have a high potential for painful consequences, hypersexuality, socially incompatible behavior and cognitive dysfunction which are seen during manic episodes in bipolar disorder.

When gender was studied in relation to OXT as one of the most important sociodemographic data, it revealed a – non statistically significant association which is similar to **Omar et al., (2018) who found** no sex nor age-related differences in oxytocin levels.

Contrary, previous studies have shown that depressed females have a lower mean oxytocin concentration **(Ozsoy et al., 2009)**. Moreover; an elevated plasma oxytocin level was noted during relationship distress in women. These different results may be contributed to by the greater variability in pulsatile oxytocin release in depressed females **(Yuen et al., 2014).**

This may be explained by the hypothesis that females may be more sensitive to the effect of stress on Oxytocin and the variation in the females may be gender-specific features such as number of births and lactation history. However, due to the small numbers of male patients and controls, it would be unwise to draw a conclusion from the result. Nevertheless, this finding may indicate that alterations in oxytocin levels in depression vary between the sexes.

A logistic regression conducted analysis for prediction of bipolar disorder susceptibility whether mania, depression or remission. Smoking and high Oxytocin levels were associated with risk of bipolar disorder generally or manic episodes occurrence not depression in univariable analysis. However, in multivariable analysis, only higher Oxytocin was suggested to be an independent risk predictor for bipolar disease whether mania, depression or remission.

This agreed with **Vermeulen et al., (2021) & Medeiros et al., (2018)** which found that smoking initiation and lifetime smoking are likely to be a causal risk factor for developing bipolar disorder. Given that smoking is a modifiable risk factor, these findings further support investment into smoking prevention and treatment in order to reduce mental health problems in future generations.

When logistic regression analysis was conducted for prediction of remission of bipolar disease, it revealed that lower baseline severity scale, frequency of suicidal thoughts, lower Oxytocin levels were associated with prediction of remission in univariable analysis. However, in multivariable analysis, only lower baseline severity scale and lower Oxytocin levels were suggested to be independent favorable predictors for remission of bipolar disorder

Thus high levels of OXT is considered a predictor for susceptibility of bipolar disorder whether mania, depression or remission and lower levels were associated with prediction of remission but doesn't predict severity of the disorder.

This should be taken in consideration as it may act as a biomarker of bipolar disorder and trend toward a potential treatment may take a place to reduce prevalence of subsyndromal social cognitive impairment which has been negatively associated with, compliance with therapy including rehabilitation, functional outcome, resumption of social activities, quality of life and to reduce it's economic burden including hospitalization, rehabilitation, these direct and indirect costs are very high and should not be underestimated.

Conclusion:

In conclusion, this study revealed that Oxytocin levels showed higher significant levels when comparing bipolar patients whether in depression, mania or in remission to the control group ($p<0.001$, <0.001, <0.001, $=0.002$ respectively). Manic cases showed significantly higher levels of Oxytocin when compared to depressive and remittent cases ($p=0.015$, 0.007 respectively). Strikingly levels of Oxytocin did not differ significantly between depression and remission.

Smoking and high oxytocin were associated with risk of bipolar disorder or mania occurrence in Univariable analysis. However, in multivariable analysis, only higher oxytocin was suggested to be independent risk predictor for bipolar disease or mania development &lower levels might predict remission but not predict severity of the disease.

Limitations:

The studied groups were taken from two hospitals that represent only small social category. All the patients were on psychotropic medications thus it was not possible to prevent drug effect on OXT levels. We did not experimentally control female menstrual cyclicty in the study, as there is interaction of female reproductive hormones and Oxytocin. Only **s**alivary Oxytocin was measured, which wasn't enough as central & peripheral OXT can be independently regulated under certain conditions

Recommendation:

Taking into account, all the limitations of the study, Further studies with larger study groups are recommended to replicate, extend the current study findings and to achieve more adequate power to test the hypothesis and so that some insignificant correlations may prove to be significant. More participants, especially males, are necessary to bring greater clarity to gender effects on OXT biology in bipolar disorder. Assessing the relationship between concomitantantly collected salivary and CSF samples to more precisely determine the role of OXT biology in bipolar disorder. Further studies regarding the impact of the different treatment modalities on Oxytocin levels & it's outcome of bipolar disorder.

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Conflicts of interest:

There are no conflicts of interest.

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