1	Lifetime Bipolar Disorder comorbidity and related clinical characteristics in
2	patients with primary Obsessive Compulsive Disorder: a report from the
3	International College of Obsessive-Compulsive Spectrum Disorders (ICOCS)
4	Bernardo Dell'Osso ^{1,2,3,*} , Matteo Vismara ¹ , Beatrice Benatti ¹ , Giovanna Cirnigliaro ¹ , Benedetta
5	Grancini ¹ , Naomi A Fineberg ⁴ , Michael Van Ameringen ⁵ , Eric Hollander ⁶ , Dan J. Stein ⁷ , Josè M.
6	Menchon ⁸ , Carolyn I. Rodriguez ⁹ , Humberto Nicolini ¹⁰ , Nuria Lanzagorta ¹¹ , Stefano Pallanti ¹² ,
7	Giacomo Grassi ¹² , Christine Lochner ¹³ , Donatella Marazziti ¹⁴ , Georgi Hranov ¹⁵ , Oguz
8	Karamustafalioglu ¹⁶ , Luchezar Hranov ¹⁵ , Joseph Zohar ¹⁷ .
9	¹ University of Milan, Department of Mental Health, Department of Biomedical and Clinical Sciences Luigi Sacco, Milan, Italy
11 12 13	 ² Department of Psychiatry and Behavioral Sciences, Bipolar Disorders Clinic, Stanford University, CA, USA. ³ "Aldo Ravelli" Center for Neurotechnology and Brain Therapeutic, University of Milan, Milan, Italy. ⁴ Mental Health Unit, Hertfordshire Partnership Foundation Trust, Queen Elizabeth II Hospital, Welwyn Garden City, UK
15 16 17	⁵ Department of Psychiatry and Behavioural Neurosciences, McMaster University, MacAnxiety Research Center Hamilton, Canada. ⁶ Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine and Montefiore Medical
18 19	Center, New York, USA. ⁷ MRC Unit on Anxiety and Stress Disorders, Department of Psychiatry and Mental Health, University of Cape Town,
20 21	Cape Town, South Africa. ⁸ Department of Psychiatry, Bellvitge University Hospital-IDIBELL, University of Barcelona, Cibersam, Barcelona, Spacin
23 24 25 26	 ⁹ Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA. ¹⁰ Laboratorio de Genómica de Enfermedades Psiquiátricas y Neurodegenerativas, Instituto Nacional de Medicina Genómica, Ciudad de México, Mexico. ¹¹ Grupo Médico Carracci, Ciudad de México, México.
27 28 29	 ¹² Department of Psychiatry, University of Florence, and Institute of Neurosciences, Florence, Italy. ¹³ MRC Unit on Anxiety & Stress Disorders, Department of Psychiatry, University of Stellenbosch, Stellenbosch, South Africa
30 31 32 33 34	 ¹⁴ Dipartimento di Medicina Clinica e Sperimentale, Sezione di Psichiatria, Università di Pisa, Pisa, Italy. ¹⁵ University Multiprofile Hospital for Active Treatment in Neurology and Psychiatry Sveti Naum, Sofia, Bulgaria. ¹⁶ Department of Psychiatry, Sisli Eftal Teaching and Research Hospital, Istanbul, Turkey. ¹⁷ Department of Psychiatry, Chaim Sheba Medical Center, Tel Hashomer, Israel.
35 36	*Corresponding Author: Prof. Bernardo Dell'Osso,
37 38 39	Department of Psychiatry, Department of Biomedical and Clinical Sciences "Luigi Sacco", Director Psychiatry Unit 2, ASST Sacco-Fatebenefratelli, Via G.B. Grassi, 74, 20157, Milan, Italy, Phone +390239042904, email: <u>bernardo.dellosso@unimi.it</u>
40 41 42 43 44 45 46 47	Words count: Manuscript: 2467 Abstract: 204 References: 34 Tables:1 Figures:1

48 <u>Abstract</u>

Introduction: Bipolar Disorder (BD) and Obsessive Compulsive Disorder (OCD) are prevalent, comorbid and disabling conditions, often characterized by early onset and chronic course. When comorbid, OCD and BD can determine a more pernicious course of illness, posing therapeutic challenges for clinicians. Available reports on prevalence and clinical characteristics of comorbidity between BD and OCD showed mixed results, likely depending on the primary diagnosis of analyzed samples.

55 **Methods:** We assessed prevalence and clinical characteristics of BD comorbidity in a large 56 International sample of patients with primary OCD (n=401), through the International College of 57 Obsessive Compulsive Spectrum Disorders (ICOCS) snapshot database, by comparing OCD 58 subjects with vs without BD comorbidity.

59 Results: Amongst primary OCD patients, 6.2% showed comorbidity with BD. OCD patients with 60 vs without BD comorbidity more frequently had a previous hospitalization (p<.001) and current 61 augmentation therapies (p<.001). They also showed greater severity of OCD (p<.001), as measured 62 by the Y-BOCS.

Conclusion: These findings from a large International sample indicate that approximately 1 out of 16 patients with primary OCD may additionally have BD comorbidity along with other specific clinical characteristics, including more frequent previous hospitalizations, more complex therapeutic regimens and a greater severity of OCD. Prospective international studies are needed to confirm our findings.

68 Keywords: Bipolar Disorder, Obsessive Compulsive Disorder, comorbidity, prevalence.

69 Introduction

Obsessive Compulsive Disorder (OCD) and Bipolar Disorder (BD) are prevalent and chronic conditions, frequently comorbid, difficult-to-treat and highly disabling ^{1,2}. Of note, both conditions have been separated into autonomous chapters by the DSM-5, respectively from anxiety disorders and depressive disorders, with other spectrum conditions included within the new chapters ³.

While comorbidity in BD represents the rule rather than the exception, OCD seems to show lower -74 yet appreciable - rates of comorbidity, while mutual comorbidity (OCD+BD) prevalence was found 75 to differ according to patients' primary diagnosis ⁴. In a recent systematic review, patients with a 76 primary OCD diagnosis showed rates of BD comorbidity ranging from 6 to 10%, while patients 77 with primary BD were found to have comorbid OCD in 11 to 21% of the cases ⁴. However, given 78 the traditionally early onset of both OCD and BDs, it is often difficult to assess which condition 79 appeared first, family history being helpful - when positive - to help unraveling primary diagnosis 80 81 along with subsequent longitudinal evaluations.

Indeed, the presence of comorbidity between OCD and BD can determine a different course of 82 illness, according to the primary diagnosis. For instance, in case of primary BD, OCD comorbidity 83 was found to be associated with a more episodic course of OC symptoms, characterized by 84 85 symptoms' worsening during depression, symptoms' improvement during mania/hypomania, and a higher mean number of depressive episodes ^{4,5}. On the other hand, in patients with primary OCD, 86 the prescription of high doses of serotonergic antidepressants could induce mood elevation 87 episodes, confounding in both cases situations of real vs spurious comorbidity ⁴⁻⁶. Comorbidity 88 rates, moreover, may vary according to local (e.g., when detected in general psychiatric services vs 89 tertiary clinics), clinical (severity of illness) and cultural variables (e.g., attitudes including stigma, 90 secretiveness, access to treatment) 2 . 91

92 In the available literature, different studies addressed this topic, trying to better characterize this 93 phenomenon and mutual influence of these disorders. Indeed, when primary BD is comorbid with 94 OCD, the overall clinical condition may determine a more severe form of illness. In this respect, 95 comorbid patients have been differently associated with relevant disease-related variables, like an 96 earlier age at onset ^{7,8}, higher frequency of residual symptoms ⁹, poorer functioning and poorer 97 quality of life in different domains (i.e., lower GAF scale score ¹⁰, lower rate of employment in BDI 98 patients ¹¹), a higher rate of suicidal behavior ^{8,12,13}. Moreover, additional comorbidity seemed to be 99 higher in the comorbid group especially with anxiety disorders ^{7,9,11}, alcohol ¹² and substance abuse 100 ¹⁴, and with impulse control, eating, and tic disorders in BD female patients ⁹.

Other studies specifically assessed the clinical characteristics of primary OCD patients with vs without BD comorbidity, reporting that comorbid patients present a worse clinical prognosis compared to non-comorbid patients, being associated with a higher suicidal risk ¹⁵, more frequent hospitalizations ^{16,17}, more severe obsessive-compulsive symptoms according to Yale-Brown Obsessive Compulsive Scale (YBOCS) score ¹⁷, and a poorer response to treatments in a youth OCD sample ¹⁸. Moreover, an additional comorbid disease has been reported more frequently in these patients, in particular with alcohol ¹⁹ and substance abuse ¹⁷, and anxiety disorders ^{17,19}.

In light of the above, the aim of the present study was to assess rates and clinical correlates of BD 108 comorbidity in a large, international sample of primary OCD patients, recruited in centers affiliated 109 with the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS). In 110 particular, we hypothesized that BD comorbidity rates in the ICOCS sample could parallel 111 112 previously reported rates in available studies of primary OCD patients, although the geographical diversity of the sample might also show distinct peculiarities in terms of epidemiology and clinical 113 features. Moreover, based on the existing literature, we hypothesized that BD comorbid vs non 114 comorbid OCD patients could show a higher burden of the disease, presenting specific clinical 115 characteristics associated with a less favorable outcome like higher severity and related 116 hospitalizations, a more frequent suicidal behavior, more complex therapeutic regimens, and a 117 higher impact on social adaptation. 118

- 119
- 120 Methods

Among the whole ICOCS sample of 504 OCD outpatients, we selected and analyzed individuals 121 having available information on bipolar comorbidity. The resulting sample of the present analysis 122 consisted of 401 outpatients of either gender and any age, attending different OCD clinics 123 worldwide, participating in the ICOCS network. Diagnoses were obtained using the Structured 124 Clinical Interview for DSM-IV-TR Axis I disorders (SCID I)²⁰. After obtaining patients' written 125 informed consent and approval from local Ethic Committees/Institutional Review Boards for using 126 patients' information for research purposes, socio-demographic and clinical variables were 127 collected and included in a common web database. Additional details about sample assessment have 128 been published elsewhere ²¹. Suicidal behavior was assessed with Mini-International 129 Neuropsychiatric Interview²². 130

In a previous ICOCS publication on comorbidity with OC-related and other psychiatric conditions in a slightly different sample (due to additional patients being recruited and the exclusion of other patients with missing data and incomplete information), BD comorbidity had not been evaluated, being set aside for separate subsequent analysis and publication ¹.

For the purpose of the present study, patients were categorized into two subgroups based on the presence (OCD-wBD) or absence (OCD-w/oBD) of comorbidity with BD. The two subgroups were compared with respect to a series of socio-demographic and clinical variables specified in Table 1. Statistical analyses were performed with Pearson's chi-squared test for categorical variables and *t*test for continuous ones. For all the analyses, the level of statistical significance was set at .05.

140

141 <u>Results</u>

Within the overall sample, 6.2% (n=32) of OCD patients had comorbidity with BD. Sociodemographic and clinical variables of the two subgroups of OCD patients with vs without BD comorbidity are reported in Table 1.

Figure 1 shows socio-demographic and clinical variables that were found to differ between the twosubgroups. OCD patients with versus without BD comorbidity showed a higher rate of previous

psychiatric hospitalization (48.2% vs 20.6%, p<.001) and a higher prevalence of augmentation therapies vs monotherapies (77.3% vs 48.5%, p<.001), being augmentation therapies those compounds used as add-on for treatment resistant OCD patients. More in detail, on both OCD subgroups, the most frequently prescribed augmentation therapies were antipsychotics (OCD-wBD 66.7% and OCD-w/oBD 34.6%), being risperidone the most represented (OCD-wBD 42.2% and OCD-w/oBD 75%); given a high rate of missing data for these specific variables, both analyses did not reach a statistically significant threshold.

Additionally, significantly higher severity of OCD emerged in OCD patients with vs without BD comorbidity, as measured through the YBOCS 23 total scores (25.7 vs 22.5, p<.001), with no statistically significant differences in obsession (12.5 vs 11.5) and compulsion (12.1 vs 10.9) subscales.

While differences in terms of suicide attempts between the two groups were not observed, current suicide risk showed as twice the rate in OCD patients with vs without BD comorbidity (31.3% vs 14.6%), without reaching the statistically significant threshold. Lastly, OCD patients with vs without BD comorbidity were more frequently found to live alone (25% vs 13.8%), to be divorced (10.3% vs 5.9%), and to be unemployed (15.6% vs 8.7%), although not a statistically significant level.

164

165 **Discussion**

In this ICOCS report, we focused on prevalence and clinical correlates of BD comorbidity in primary OCD patients. Our observed lifetime prevalence of BD comorbidity (6.2%) can be positioned at the lower range in relation to the available studies in the field ⁴. This is likely due to the composition of the ICOCS sample, constituted by primary OCD patients attending tertiary OCD clinics worldwide, and to the fact that patients with a comorbid BD diagnosis are more frequently referred to community psychiatric centers or BD specialized centers. Additionally, this result might derive from the limited overall comorbidity rate (35%) characterizing our sample. BD comorbidity, therefore, appears to be less frequent in primary OCD patients than is OCD comorbidity in primary BD patients. In this respect, previous International reports showed a higher rate of other comorbid DSM-IV-TR Axis I disorders, compared to BD, with major depressive disorder and anxiety disorders being the most common comorbid conditions in primary OCD patients ^{1,24}.

The higher rate of previous hospitalization in the comorbid cases seems to be consistent with previous reports ^{4,17,19,25,26} and may likely be determined by the co-occurrence of BD episodes, causing more frequent admission to hospital (following severe manic or depressive episodes), even though it may also be related to OCD worsening due to a higher severity of OCD in comorbid patients (as suggested by the greater severity of illness confirmed by the Y-BOCS in these individuals).

The more complex psychopharmacological regimen observed in OCD with vs without BD 183 comorbidity, reflecting a higher rate of augmentation treatments vs monotherapies in the former 184 185 group, may also be interpreted as a characteristic of greater severity of OCD and overall illness, making it necessary to frequently add an antipsychotic to the serotonergic reuptake inhibitor (SRI), 186 due to the severe nature of OC symptoms and in order to prevent manic switches ²⁷. The same result 187 was reported in a study with young OCD subjects, where comorbid OCD+BD patients showed a 188 more frequently poly-therapy compared to a SRI only therapy, with second generation 189 antipsychotics, including risperidone, most prevalently used in the comorbid group ²⁸. Literature 190 data support Risperidone efficacy as augmentative therapy over SRI alone in OCD resistant patients 191 ^{29,30} particularly in those patients with a history of mood instability ³¹, emphasizing Risperidone 192 potential pharmacological effect on mood stabilization. Nonetheless, OCD comorbid patients could 193 have received more frequently augmentation therapies just for the occurrence of two diagnoses, 194 195 each one requiring a different therapeutic regimen. Of note, no significant differences emerged with respect to cognitive behavioral therapy or other psychotherapeutic treatments. 196

Arguably, another clinically relevant finding was the greater OCD severity in patients with vs
without BD comorbidity. Previous analyses showed mixed results in this respect ^{17,32}. As the Y-

BOCS focuses exclusively on obsessions and compulsions, it is not likely that the higher scores 199 would have been confounded by the presence of comorbid BD symptomatology per se. In fact, 200 while obsessions might possibly determine higher scores due to concomitant depressive ruminations 201 (though the two groups did not differ on depression scores) or flights of ideas, compulsions are 202 relatively pathognomonic for OCD and OC related disorders. In our analysis, both the obsessive and 203 the compulsive subscale scores, as well as the total score, were higher in the comorbid group, thus 204 205 indicating a more severe OCD phenotype. Nonetheless, it must be borne in mind that OCD symptomatology is strongly influenced by mood phases ^{4,5}, and consequently the latter might have 206 determined an impact on YBOCS scores assessed in the present sample. 207

208 Lastly, even though other statistically significant differences between OCD patients with vs without comorbid BD were not found, it is noteworthy to mention that current suicidal risk was almost 209 twice as high in comorbid subjects. OCD is per se associated with a higher suicidal ideation and 210 lifetime suicide attempts compared to the general population ^{33,34} and the comorbidity with BD 211 might increase this phenomenon. Nonetheless, in our sample, the rates of previous suicide attempt 212 were similar between the two subgroups, differing from a previous report showing a higher rate in 213 comorbid OCD patients ¹⁵ and encouraging additional investigation on suicidal behaviors and risk 214 in these patients. However, in this study, it needs to be noted that OCD patients without BD 215 216 comorbidity could have a range of other comorbid disorders contributing to higher suicide attempt 217 rates.

Finally, focusing on a sociodemographic perspective, despite not reaching the statistically significant threshold, a divorced status, living alone, and being unemployed were observed at rates twice as higher in OCD patients with vs without comorbid BD. These findings also deserve further investigation, as they may converge in delineating a more disadvantaged sociodemographic condition of OCD patients when comorbid BD is present.

The findings reported in the present study should be interpreted in light of some limitations. First, our study did not characterize BD phases at the assessment nor other issues related to BD polarity

(i.e., polarity at onset or prevalent polarity) and subtype. These variables could have made our 225 226 results easier to interpret, likely having a major impact on several clinical characteristics, including number of hospitalizations, pharmacological treatments, and YBOCS score. Additionally, OCD 227 phenotype was not assessed in the total sample nor in the two subgroups and sample collection 228 (mainly tertiary centers specialized in OCD) might have affected the results and influence their 229 generalizations. Lastly, given the International nature of the study, specific variables were recorded 230 only in a limited number of centers and consequently not analyzed due to the presence of missing 231 data that did not allowed us to compare and contrast all variables. At the same time, the 232 international sample assessed in the present study can be considered one of the strengths of this 233 234 report.

In conclusion, our results indicate that when OCD was comorbid with BD (6.2% of the cases), patients were found to show an overall higher severity of illness, as documented by a higher rate of hospitalization, a more complex pharmacological regimen, as well as a higher Y-BOCS score. Further studies are needed to verify the impact of BD comorbidity on OCD and to clarify the longitudinal relationship between these two disorders and their respective evolution.

240

241 <u>Conflicts of interest:</u>

Bernardo Dell'Osso reports: Angelini, speaker's bureau, speaker's fee; Lundbeck, speaker's bureau,
speaker's fee; Neuraxpharm, speaker's bureau, speaker's fee, outside the submitted work.

N. Fineberg reports: personal fees from Otsuka, personal fees from Lundbeck, nonfinancial support 244 from Janssen, grants and nonfinancial support from the ECNP, personal fees and nonfinancial 245 support from BAP, nonfinancial support from the World Health Organization, personal fees and 246 nonfinancial support from RANZCP, grants and nonfinancial support from Shire, grants from the 247 National Institute of Health Research, personal fees and nonfinancial support from the College of 248 Mental Health Pharmacists, nonfinancial support from the International Society of Behavioural 249 250 Addiction, nonfinancial support from the Royal College of Psychiatrists, nonfinancial support from the International College of Obsessive-Compulsive Spectrum Disorders, nonfinancial support from 251 Novartis, grants and nonfinancial support from Servier, personal fees from Bristol-Myers Squibb, 252 253 grants from MRC, grants from Wellcome, personal fees from Taylor and Francis, and personal fees from Oxford University Press, outside the submitted work. 254

E. Hollander reports: grants from Brainsway, grants from Roche, grants from Curemark, grants from Takeda, personal fees from Shire, and personal fees from Sunovion, outside the submitted work. D.J. Stein reports personal fees from Lundbeck, personal fees from Novartis, personal fees from the AMBRF, grants from the NRGF, grants from Servier, grants from Biocodex, grants from MRC, personal fees from CIPLA Inc., and personal fees from SUN, outside the submitted work.

M. Vismara, B. Benatti, G. Cirnigliaro, B. Grancini, M. Van Ameringen, J.M. Menchon, C.I.
Rodriguez, H. Nicolini, N. Lanzagorta, S. Pallanti, G. Grassi, C. Lochner, D. Marazziti, G. Hranov,
O. Karamustafalioglu, L. Hranov, J. Zohar have no conflict of interest with the content of the
present article.

264

265 <u>References</u>

- 266
- 267 1. Lochner C, Fineberg NA, Zohar J, et al. Comorbidity in obsessive–compulsive disorder
- 268 (OCD): A report from the International College of Obsessive–Compulsive Spectrum
- 269 Disorders (ICOCS). *Compr Psychiatry*. 2014;55(7):1513-1519.
- 270 doi:10.1016/j.comppsych.2014.05.020
- 271 2. Amerio A, Stubbs B, Odone A, Tonna M, Marchesi C, Ghaemi SN. The prevalence and
- 272 predictors of comorbid bipolar disorder and obsessive–compulsive disorder: A systematic
- 273 review and meta-analysis. J Affect Disord. 2015;186:99-109. doi:10.1016/j.jad.2015.06.005
- 274 3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*
- 275 (5th Ed.). Arlington, VA: American Psychiatric Publishing; 2013.
- Amerio A, Odone A, Liapis CC, Ghaemi SN. Diagnostic validity of comorbid bipolar
 disorder and obsessive-compulsive disorder: a systematic review. *Acta Psychiatr Scand*.

278 2014;129(5):343-358. doi:10.1111/acps.12250

- 279 5. Mucci F, Toni C, Favaretto E, Vannucchi G, Marazziti D, Perugi G. Obsessive-compulsive
- 280 disorder with comorbid bipolar disorders: clinical features and treatment implications. *Curr*

281 *Med Chem.* November 2017. doi:10.2174/0929867324666171108145127

- Amerio A, Tonna M, Odone A, Stubbs B, Ghaemi SN. Course of illness in comorbid bipolar
 disorder and obsessive–compulsive disorder patients. *Asian J Psychiatr*. 2016;20:12-14.
- doi:10.1016/j.ajp.2016.01.009
- Jeon S, Baek JH, Yang SY, et al. Exploration of comorbid obsessive-compulsive disorder in
 patients with bipolar disorder: The clinic-based prevalence rate, symptoms nature and clinical
 correlates. *J Affect Disord*. 2018;225:227-233. doi:10.1016/j.jad.2017.08.012
- 8. Ozdemiroglu F, Sevincok L, Sen G, et al. Comorbid obsessive-compulsive disorder with
- bipolar disorder: A distinct form. *Psychiatry Res.* 2015;230(3):800-805.
- doi:10.1016/j.psychres.2015.11.002

- 9. Issler CK, Monkul ES, Amaral JA de MS, et al. Bipolar disorder and comorbid obsessive-
- compulsive disorder is associated with higher rates of anxiety and impulse control disorders.
 Acta Neuropsychiatr. 2010;22(2):81-86. doi:10.1111/j.1601-5215.2010.00457.x
- Joshi G, Wozniak J, Petty C, et al. Clinical characteristics of comorbid obsessive-compulsive
 disorder and bipolar disorder in children and adolescents. *Bipolar Disord*. 2010;12(2):185-
- 296 195. doi:10.1111/j.1399-5618.2010.00795.x
- 297 11. Shashidhara M, Sushma BR, Viswanath B, Math SB, Janardhan Reddy Y. Comorbid
 298 obsessive compulsive disorder in patients with bipolar-I disorder. *J Affect Disord*.
- 299 2015;174:367-371. doi:10.1016/j.jad.2014.12.019
- 300 12. Magalhães PVS, Kapczinski NS, Kapczinski F. Correlates and impact of obsessive-
- 301 compulsive comorbidity in bipolar disorder. *Compr Psychiatry*. 2010;51(4):353-356.
- doi:10.1016/j.comppsych.2009.11.001
- Krüger S, Bräunig P, Cooke RG. Comorbidity of obsessive-compulsive disorder in recovered
 inpatients with bipolar disorder. *Bipolar Disord*. 2000;2(1):71-74.
- Angst J, Gamma A, Endrass J, et al. Obsessive-compulsive syndromes and disorders. *Eur Arch Psychiatry Clin Neurosci*. 2005;255(1):65-71. doi:10.1007/s00406-005-0576-8
- 307 15. Saraf G, Paul I, Viswanath B, Narayanaswamy JC, Math SB, Reddy YCJ. Bipolar disorder
- 308 comorbidity in patients with a primary diagnosis of OCD. *Int J Psychiatry Clin Pract*.
- 309 2017;21(1):70-74. doi:10.1080/13651501.2016.1233344
- Mahasuar R, Janardhan Reddy YC, Math SB. Obsessive-compulsive disorder with and
 without bipolar disorder. *Psychiatry Clin Neurosci*. 2011;65(5):423-433. doi:10.1111/j.14401819.2011.02247.x
- 313 17. Timpano KR, Rubenstein LM, Murphy DL. Phenomenological features and clinical impact
- of affective disorders in OCD: a focus on the bipolar disorder and OCD connection. *Depress*
- 315 *Anxiety*. 2012;29(3):226-233. doi:10.1002/da.20908
- 18. Masi G, Berloffa S, Mucci M, et al. A NATURALISTIC EXPLORATORY STUDY OF

- 317 OBSESSIVE-COMPULSIVE BIPOLAR COMORBIDITY IN YOUTH. J Affect Disord.
- 318 2018;231:21-26. doi:10.1016/j.jad.2018.01.020
- Perugi G, Toni C, Frare F, Travierso MC, Hantouche E, Akiskal HS. Obsessive-compulsive bipolar comorbidity: a systematic exploration of clinical features and treatment outcome. *J Clin Psychiatry*. 2002;63(12):1129-1134.
- First M, Spitzer R, Gibbon M, Williams J. *Structured Clinical Interview for DSM–IV–TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P).* New York: Biometrics
 Research, New York State Psychiatric Institute; 2002.
- 325 21. Dell'Osso B, Benatti B, Buoli M, et al. The influence of age at onset and duration of illness
 326 on long-term outcome in patients with obsessive-compulsive disorder: a report from the
- 327 International College of Obsessive Compulsive Spectrum Disorders (ICOCS). *Eur*

328 *Neuropsychopharmacol.* 2013;23(8):865-871. doi:10.1016/j.euroneuro.2013.05.004

- 329 22. Sheehan D V, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric
- 330 Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric
- interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59 Suppl 20:22-33;quiz 34-57.
- 332 23. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive
- Scale. I. Development, use, and reliability. *Arch Gen Psychiatry*. 1989;46(11):1006-1011.
- Brakoulias V, Starcevic V, Belloch A, et al. Comorbidity, age of onset and suicidality in
 obsessive-compulsive disorder (OCD): An international collaboration. *Compr Psychiatry*.
 2017;76:79-86. doi:10.1016/j.comppsych.2017.04.002
- 337 25. Kazhungil F, Mohandas E. Management of obsessive-compulsive disorder comorbid with
 bipolar disorder. *Indian J Psychiatry*. 2016;58(3):259. doi:10.4103/0019-5545.192001
- 339 26. Kazhungil F, Cholakottil A, Kattukulathil S, Kottelassal A, Vazhakalayil R. Clinical and
- 340 familial profile of bipolar disorder with and without obsessive-compulsive disorder: an
- 341 Indian study. Trends psychiatry Psychother. 2017;39(4):270-275. doi:10.1590/2237-6089-
- 342 2017-0061

- Koran LM, Hanna GL, Hollander E, Nestadt G, Simpson HB, American Psychiatric
 Association. Practice guideline for the treatment of patients with obsessive-compulsive
 disorder. *Am J Psychiatry*. 2007;164(7 Suppl):5-53.
- 346 28. Masi G, Millepiedi S, Perugi G, et al. Pharmacotherapy in paediatric obsessive-compulsive
 347 disorder: a naturalistic, retrospective study. *CNS Drugs*. 2009;23(3):241-252.
- doi:10.2165/00023210-200923030-00005
- Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF. A
 systematic review: antipsychotic augmentation with treatment refractory obsessive-
- 351 compulsive disorder. *Mol Psychiatry*. 2006;11(7):622-632. doi:10.1038/sj.mp.4001823
- 352 30. Dold M, Aigner M, Lanzenberger R, Kasper S. Antipsychotic Augmentation of Serotonin
- 353 Reuptake Inhibitors in Treatment-Resistant Obsessive-Compulsive Disorder: An Update

354 Meta-Analysis of Double-Blind, Randomized, Placebo-Controlled Trials. Int J

355 *Neuropsychopharmacol.* 2015;18(9):pyv047. doi:10.1093/ijnp/pyv047

- 356 31. Pfanner C, Marazziti D, Dell'Osso L, et al. Risperidone augmentation in refractory
 357 obsessive-compulsive disorder: an open-label study. *Int Clin Psychopharmacol.*
- 358 2000;15(5):297-301.
- 359 32. Zutshi A, Reddy YCJ, Thennarasu K, Chandrashekhar CR. Comorbidity of anxiety disorders
 360 in patients with remitted bipolar disorder. *Eur Arch Psychiatry Clin Neurosci*.
- 361 2006;256(7):428-436. doi:10.1007/s00406-006-0658-2
- 362 33. Dell'Osso B, Benatti B, Arici C, et al. Prevalence of suicide attempt and clinical
- 363 characteristics of suicide attempters with obsessive-compulsive disorder: a report from the
- 364 International College of Obsessive-Compulsive Spectrum Disorders (ICOCS). CNS Spectr.
- 365 2018;23(01):59-66. doi:10.1017/S1092852917000177
- 366 34. Albert U, De Ronchi D, Maina G, Pompili M. Suicide risk in Obsessive-Compulsive
- 367 Disorder and exploration of risk factors: a systematic review. *Curr Neuropharmacol*.
- 368 2018;16. doi:10.2174/1570159X16666180620155941