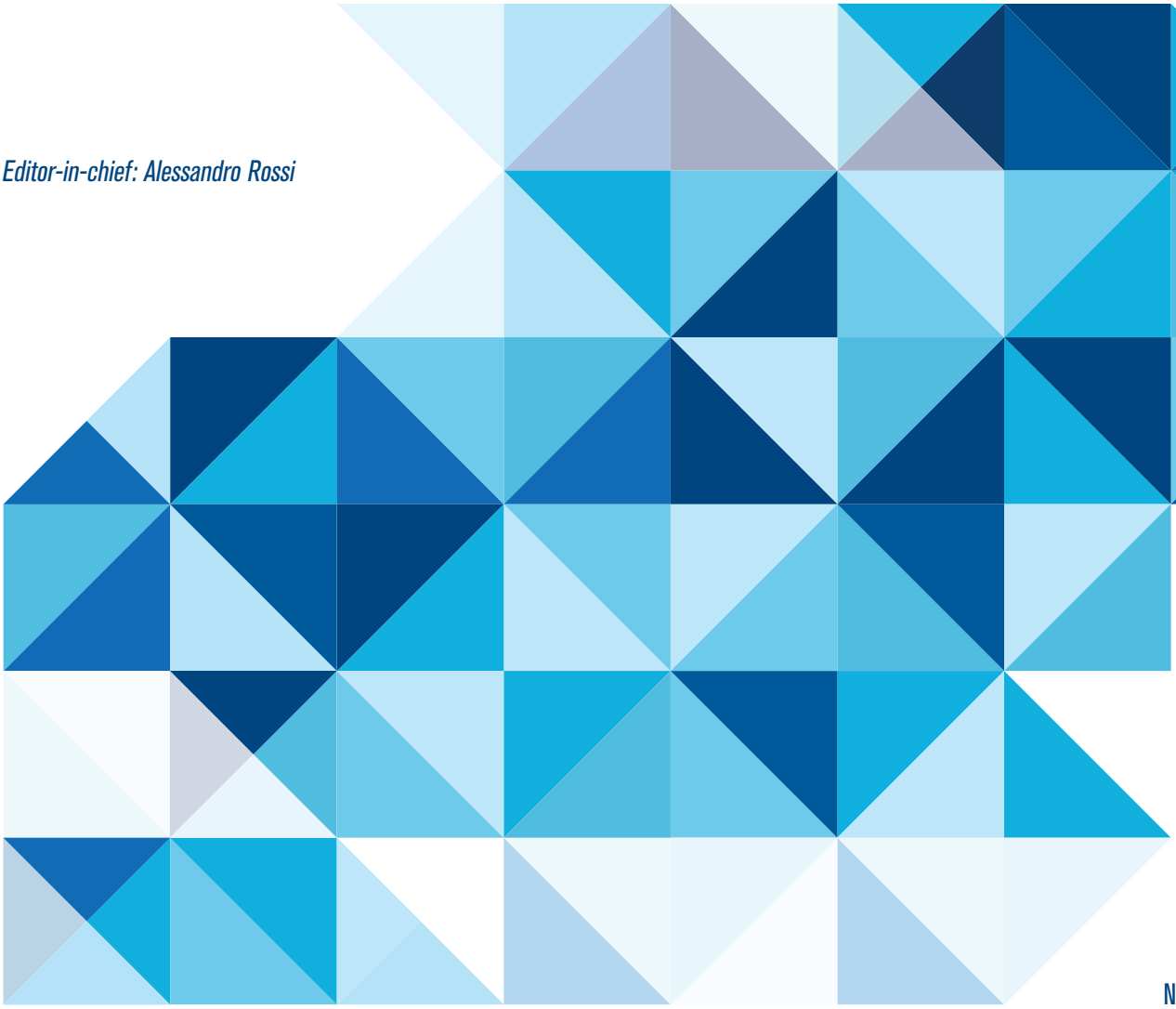
OFFICIAL JOURNAL OF THE ITALIAN SOCIETY OF PSYCHOPATHOLOGY

Journal of PSYCHOPATHOLOGY

Editor-in-chief: Alessandro Rossi



Special Issue
VOL. 24 - 2018
NUMBER 3

Cited in: EMBASE - Excerpta Medica Database • Index Copernicus • PsycINFO • SCOPUS • Google Scholar

Hot issues in clinical psychopathology

Guest Editor: Andrea Fiorillo

www.jpsychopathol.it

PACINI EDITORE MEDICINA

Periodico trimestrale POSTE ITALIANE SpA - Spedizione in Abbonamento Postale - D.L. 353/2003 conv.in L.27/02/2004 n°46 art.1, comma 1, DCB PISA - Aut. Trib. di Pisa n. 9 del 03/06/95 - September - ISSN 2284-0249 (Print) ISSN 2499-6904 (Online)

OFFICIAL JOURNAL OF THE ITALIAN SOCIETY OF PSYCHOPATHOLOGY

Journal of PSYCHOPATHOLOGY

Founders: Giovanni B. Cassano, Paolo Pancheri

Editorial Assistant: Francesca Pacitti, Roberto Brugnoli

Managing Editor: Patrizia Alma Pacini

Editing: Lucia Castelli, Pacini Editore Srl, Via Gherardesca 1, 56121 Pisa
Tel. 050 3130224 • Fax 050 3130300 • lcastelli@pacinieditore.it • journal@jpsychopathol.it

Scientific Secretariat: Valentina Barberi, Pacini Editore Srl, Via Gherardesca 1, 56121 Pisa
Tel. 050 3130376 • Fax 050 3130300 • vbarberi@pacinieditore.it • journal@jpsychopathol.it

Publisher: Pacini Editore Srl, Via Gherardesca 1, 56121 Pisa • www.pacinimedicina.it

VOL. 24 - 2018

NUMBER 3

Cited in:
EMBASE - Excerpta Medica Database ▪ Index Copernicus
PsycINFO ▪ SCOPUS ▪ Google Scholar

www.jpsychopathol.it

Contents

JOURNAL OF PSYCHOPATHOLOGY
2018;24:111-112

A. Fiorillo[1], B. Dell'Osso[2], G. Maina[3], A. Fagiolini[4]

[1] Department of Psychiatry, University of Campania "Luigi Vanvitelli", Naples, Italy; [2] University of Milan, Department of Mental Health, Fondazione IRCCS Ca' Granda Policlinico, Milan, Italy; Department of Psychiatry and Behavioral Sciences, Bipolar Disorders Clinic, Stanford University, CA, USA; "Aldo Ravelli" Center for Neurotechnology and Brain Therapeutic, University of Milan, Italy; [3] Rita Levi Montalcini Department of Neuroscience, University of Turin, Italy; [4] University of Siena, Department of Molecular and Developmental Medicine, Siena, Italy

The role of psychopathology in modern psychiatry

Psychiatry has been significantly influenced by the social, economic and scientific changes that have occurred within the last few years. These influences have evolved psychiatry into a modern medical specialty that is increasingly knowledgeable about the structure and function of the brain, mind (thoughts, feelings, and consciousness), behaviors and social relationships. Nonetheless, this knowledge has not uniformly spread and, in many institutions, psychiatric education and practice remain largely based on knowledge developed over the last century. Over a century ago, the target of psychiatry was madness, and psychiatrists were called "alienists" [1]. Along the years, the target has changed: for a number of years psychiatrists have been asked to treat mental disorders, and now the target has evolved to include the promotion of the mental health of the general population [2 3]. In fact, some traditional illnesses have seemingly disappeared from clinical observation (e.g., organic brain disorder or involutional depression which were listed among the DSM-III diagnoses), while new forms of mental health problems have become of frequent observation by psychiatrists.

Body image is becoming more and more important in Western cultures, since it represents the link between the inner and outer world. Many new mental disorders arise from the need "to appear in order to be someone" rather than on the need "to be someone". The pathological use of social media and the Internet, as well as the excessive importance attributed to body image (such as in orthorexia and vigorexia), are valid examples of this mismatch between being and appearing.

Excessive use of the Internet can have detrimental effects on mental health in vulnerable people, particularly younger persons. In fact, Internet Gaming Disorder has been recently included among the behavioral addictions in the ICD-11 [4], following the cases of the Japanese *hikikomori* and the high rates of hospital admissions in emergency units after hours spent gaming online. Several pathological behaviors occurring in young people, such as excessive cannabis use, contribute to the increased suicide rates in this population, highlighting the need to better characterize the psychopathological characteristics of modern adolescents. Suicide is also increased in clinical populations, such as patients diagnosed with Traumatic Brain Injury (TBI) or Obsessive-Compulsive Disorder (OCD), but this relationship has too often been neglected by clinicians and needs to be deepened.

It is now clear that modern psychiatrists should balance the classical knowledge with new findings coming from research and evidence-based medicine. For example, OCD has been moved in both the DSM-5 and the ICD-11 from the chapter of anxiety disorders to a new stand-alone chapter, which also includes trichotillomania, hoarding disorder, body dysmorphic disorder, and excoriation disorder [5]. This change is mainly due to a modern clinical and psychopathological characterization of OCD with relevant implications for clinical practice and treatment options. And yet, Post-Traumatic Stress Disorder (PTSD) and bipolar disorders have followed a similar course. Finally, research on schizophrenia is moving towards ultra-high risk and predictive models of psychoses [6]. Schizophrenia is now conceptualized as a complex disorder with multiple genetic, environmental and psychosocial risk factors. The

Correspondence

Andrea Fiorillo
Department of Psychiatry, University of Campania "Luigi Vanvitelli", Largo Madonna delle Grazie, 80138 Naples, Italy • E-mail: andrea.fiorillo@unicampania.it

polygenic risk score represents one good example of the complexity of schizophrenia.

In order to achieve effective integration of the ever growing wealth of knowledge in mental health practice it is essential to redefine the clinical foundations of psychiatry, and to reconsider and reinterpret "old" concepts and approaches that are still valid ("back to fundamentals"). Psychiatrists will have to show a courageous openness towards innovation and experimentation [7]. It is the time to update the training curricula by integrating the theoretical bases of psychiatry with recent evidence coming from scientific studies. In particular, from an educational perspective, it may be useful to identify a "common trunk" of knowledge and skills for all psychiatrists, and several different professional "ramifications" for differentiating skills and knowledge [8]. This will characterize the professionalism of psychiatrists of the future, as it happens for other branches of medicine. Among the elements constituting the common trunk of the psychiatrist's professionalism, psychopathology certainly plays a major role. Other elements of this common trunk are: 1) to care for the patient as a person. If the patient is not considered as a whole, with an attention on his/her life history, the clinical approach will fail, because patients will not trust psychiatrists who do not show a real interest toward them; 2) to differentiate mental health problems due to social difficulties from full-blown psychiatric syndromes. It is not the psychiatrist's task to intervene in cases of social distress, but psychiatrists' have the skills to recognize these situations and to propose psychological or social support; 3) to provide patients with evidence-based personalized treatments on the basis of the bio-psycho-social approach; 4) to organize and coordinate the community activities for promoting mental health.

The ramifications can include the application of the different psychotherapeutic techniques, the use of multiple diagnostic tools, the knowledge of the various rehabilitation methods, the specialization on specific population groups (e.g., adolescents or the elderly) or particular stressful conditions (e.g., the mental health of migrants or prisoners) or clinical situations (e.g., the pathologies due to excessive use of the new technologies or of the new drugs).

In this issue of the Journal, modern psychiatric psychopathological needs have been addressed in terms of clinical practice, training and research, bringing together epidemiological and clinical findings with psychopathological features of classical and new forms of mental disorders, in an integrated approach to psychiatry. We have read with the utmost interest the selected articles, which have been delivered by expert clinicians and researchers in their fields. We hope our readership will do the same.

References

1 Hunter R, MacAlpine R. *Three hundred years of psychiatry.* New York: Carlisle Press 1982.

2 Maj M. *From "madness" to "mental health problems": reflections on the evolving target of psychiatry.* World Psychiatry 2012;11:137-8.

3 Maj M. *Adherence to psychiatric treatments and the public image of psychiatry*. World Psychiatry 2013;12:185-6.

4 Rumpf HJ, Achab S, Billieux J, et al. *Including gaming disorder in the ICD-11: the need to do so from a clinical and public health perspective.* J Behav Addict 2018;16:1-6.

5 Marras A, Fineberg N, Pallanti S. *Obsessive compulsive and related disorders: comparing DSM-5 and ICD-11*. CNS Spectr 2016;21:324-33.

6 Mistry S, Harrison JR, Smith DJ, et al. *The use of polygenic risk scores to identify phenotypes associated with genetic risk of schizophrenia: systematic review*. Schizophr Res 2017;9 Nov: Doi:10.1016/j.schres.2017.10.037 [Epub ahead of print]

7 Maj M. *Prefazione*. In: Fiorillo A, Ed. *Lezioni di psichiatria per il nuovo millennio*. Roma: Il Pensiero Scientifico Editore 2010, pp. IX-XIII.

8 Fiorillo A, Maj M. *The role of psychiatry in modern medicine*. Int Rev Psychiatry 2018;30:169-75.

JOURNAL OF PSYCHOPATHOLOGY
2018;24:113-117

M. Poletti[1*], E. Gebhardt[2*], A. Raballo[3*], T. Sciarma[3], A. Tortorella[3]

[1] Department of Mental Health and Pathological Addiction, Reggio Emilia Public Health-Care Centre, Reggio Emilia, Italy; [2] Cmed Polyspecialistic Diagnostic and Therapeutic Centre, Rome, Italy; [3] Department of Medicine, Division of Psychiatry, Clinical Psychology and Rehabilitation, University of Perugia, Perugia, Italy

* These authors contributed equally to this manuscript

Schizophrenia polygenic risk score: zooming-in on early, non-psychotic developmental expressions of vulnerability

Summary

Polygenic Risk Scores (PRS) are proxy values generated combining multiple genetic markers into a single score indicative of specific lifetime risk for a disease. The PRS approach has been increasingly implemented in psychiatry, especially for the study of schizophrenia. Although the majority of studies on PRS focused on possible associations with overt clinical features in patients with already diagnosed schizophrenia spectrum disorders, an emerging trend involves early phenotypic expression of genetic risk for schizophrenia in the general population. This article offers an update on this emerging trend, focusing on how the genetic risk for schizophrenia is early expressed at an endophenotypic level, through a broad range of soft non-psychotic neurocognitive and behavioral manifestations. These features might be integrated with other prediction paradigms, such as familial-high-risk, neurodevelopmental and clinical staging models, to empower and refine early detection strategies.

Key words
Polygenic Risk • Schizophrenia • Phenotype • Neurodevelopment • Early detection

Introduction

Polygenic Risk Scores (PRS), i.e. proxy values generated combining multiple genetic markers into a single score indicative of specific lifetime risk for a disease [1,2], are becoming increasingly popular as research and translational tools in somatic medicine and in psychiatry [3,4]. Within psychiatry, PRS define cumulative risk profiles based on the identification of genetic variants related to psychiatric disorders, obtained through genome-wide association studies (GWAS). This approach has proven particularly promising in schizophrenia, although the etiopathogenetic complexity (and the multiple genotype-environment (GxE) interactions) involved in the development of its spectrum conditions remain largely unknown [5].

Most studies on schizophrenia-related PRS (s-PRS) mainly focused on testing and assessing possible associations between with overt (or emergent) clinical features in patients with already diagnosed schizophrenia spectrum disorders. In this perspective, a recent study [6] reported that s-PRS was associated with general psychopathology at the Positive and Negative Syndrome Scale (PANSS) and with anxiety at the Hamilton Anxiety Rating Scale rather than with positive or negative symptoms in a sample of patients with first-episode of psychosis. Other studies focused on the association between s-PRS and psychopathological liability in the adult general population; in fact, another recent study [7] reported that s-PRS was associated in youth (18-22 age range) with phenotypic expressions involving anxiety, depression, nicotine use, trauma and family history of psychological disorders.

Empirical evidence on the effects of s-PRS at different levels of analysis and in different populations (general vs. clinical) was recently reviewed [8],

Correspondence
Andrea Raballo
Department of Medicine, Division of Psychiatry, Clinical Psychology and Rehabilitation, University of Perugia, P.le L. Severi 1, 06132 Perugia, Italy • E-mail: andrea.raballo@unipg.it

and studies centered on s-PRS, published until March 2016 seem to converge on four main issues.

1. Pleiotropy between schizophrenia and other psychiatric disorders. Genetic risk for schizophrenia in the general population has a phenotypic effect at the psychopathological level not only related to schizophrenia spectrum disorder manifestations, but also to other non-schizophrenic manifestations, such as bipolar disorder, schizoaffective disorder and anxiety. Interestingly, s-PRS studies suggest possible relationships and overlaps between disorders [9]: for example, in bipolar disorder s-PRS is associated with mood-incongruent psychotic symptoms [10] and is inversely associated with lithium response [11].
2. Less common-variant genetic overlap between schizophrenia and cognition than with other psychopathology. Available studies found an inverse relationship between s-PRS and global measures of cognition [12-14]. No robust empirical data are available on the association between s-PRS and specific cognitive functions; interestingly, recent studies found effects of s-PRS on neural activations during specific cognitive tasks such as reward processing [15], working memory [16] and memory encoding [17]. Considering the inverse association between s-PRS and cognition, an apparent counterfactual finding that needs replication regards the lack of association between s-PRS and primary school achievement [18]; however, it could be hypothesized that the age of assessment could influence this possible relationship, therefore the effects of s-PRS on school achievement need to be evaluated along the academic course.
3. Small variance explained by currently available s-PRS for all phenotypes (presumably limited by the fact that PRS do not capture Copy Number Variants or rare Single Nucleotide Polymorphism contributions to variance).
4. Early phenotypic expression of genetic risk for schizophrenia in the general population through a broad range of soft (i.e. non-psychotic) neurocognitive and behavioral features during development. Vulnerability to schizophrenia spectrum conditions is manifested through a phenotypic cloud that incorporates cognitive-emotional, interpersonal and socio-functional features presumably more relevant for the emergence of negative symptoms and social impairments than for the onset of positive psychotic experiences [19-21].

The latter point represents the specific focus of this review, that expands conclusions of the cited review [8] including recent additional empirical findings that might be useful to complete the phenotypic puzzle and enrich our understanding of the dynamic mosaic of early developmental expressions related to s-PRS in the general population.

s-PRS and vulnerability (endo)phenotypes

In the last two years, several empirical contributions investigated phenotypic effects in infancy and childhood of s-PRS in the general population. Jansen and colleagues [22] indicated a selective association of s-PRS with higher internalizing scores at Child Behavior Checklist at all ages, as well as with higher externalizing scores at age 3 and 6. Moreover, looking at the syndromic subscales, s-PRS was positively associated with higher emotional reactivity at age 3, all internalizing subscales (emotional reactivity, anxiety/depression, somatic complaints, withdrawal) at age 6, and Thought Problems (a proxy score for psychosis-proneness and soft positive symptoms) at age 10.

Nivard et al. [23] reported a strong association of s-PRS with childhood (age 7 to 10) and adolescent (age 12 to 15) depression, a weaker association with Oppositional Defiant Disorder/Conduct Disorder (ODD/CD) at age 7, and a steeper increase in the association from childhood to adolescence for Attention Deficit/Hyperactivity Disorder and ODD/CD. Riglin et al. [24] reported an association of s-PRS with Performance IQ, speech intelligibility and fluency, and headstrong behavior at age 7-9, and with social difficulties and behavioural problems at age 4. In a subsequent study [25] of the same group, s-PRS was prospectively associated with broadly-defined emotional difficulties constantly from childhood (age 7) to mid-life adulthood (age 42) through six points of assessment, differently from depression-PRS that was associated with emotional difficulties only in the last assessment. Moreover, a higher s-PRS was associated with non - optimal overall infant neuromotor development between 2 and 5 months in a recent study by Serdarevic et al. [26].

Overall, despite contingent differences in experimental settings and designs, these recent empirical findings encourage an updated perspective on the neurodevelopmental antecedents of schizophrenia [19-21]. From a developmental perspective, phenotypic effects of s-PRS are not only early and substantial, but they are also detectable at a behavioral level from the perinatal period (age 2-5 months) [26] through infancy (age 3-4) [22 24], childhood (age 7-9 years) [25] and adulthood [7 27].

These findings on the phenotype cohere with preliminary findings on the endophenotypes, as suggested by the reported association between s-PRS and neurodevelopmental features. The effects of s-PRS on cortical gyrification calculated at structural neuroimaging have been investigated in two independent and healthy general populations [28]: a higher s-PRS was significantly associated with a lower local gyrification index in the

bilateral inferior parietal lobes, where case-control differences have been reported in previous studies on schizophrenia. Similar findings were reported also by Neils et al. [29], who compared subjects at high familial risk of schizophrenia who remained well, with those who developed sub-diagnostic symptoms, or who developed schizophrenia with healthy controls. Authors tested whether individuals at high familial risk of schizophrenia carried an increased burden of trait-associated alleles using s-PRS, as well as the extent to which s-PRS was associated with gyral folding in the frontal and temporal lobes. Authors found that individuals at high familial risk of schizophrenia who developed the disorder carried a significantly higher s-PRS compared to those at high-risk who developed sub-diagnostic symptoms or remained well and to healthy controls; furthermore, within the high-risk cohort, there was a significant and positive association between s-PRS and bilateral frontal gyrification. These findings that S-PRS impacts on early neurodevelopment to confer greater gyral folding as detected in young adulthood are in line with early phenotypic effects.

Finally, a recent report [30] showed an interaction between the environment and genetics. In fact, parental behaviours can influence offspring developmental outcomes, supporting the hypothesis that PRS predict variation in characteristics beyond the target trait, including characteristics that are considered to be environmental. For example, the offspring genetic risk for schizophrenia is positively associated with paternal age: children whose father is over 45 at their birth have on average a genetic risk score for schizophrenia over one quarter standard deviation higher than children whose father is under the age of 26 at their birth. This finding may have implications for schizophrenia, in which several early environmental risk factors may play a trigger role for the atypical neurodevelopment.

Discussion: translational implication of s-PRS for early detection

The s-PRS approach applied in child-adolescent cohorts from the general population may provide an innovative opportunity to understand how the presumed genetic predisposition to schizophrenia is manifested in developmental time, attempting to disentangle the respective contribution of genetic and environmental risk factors along neurodevelopmental stages. This may be particularly helpful in the childhood premorbid period, in which neurobiological (schizotaxic [31 32]) vulnerability expresses itself in a mixed bag of unspecific phenotypic features (e.g. motor, cognitive, behavioral and social impairments), that might be rather difficult to ponder in terms of potential for psychopathological progression and prognostic trajectory [20 21]. Therefore, fine-grained empirical findings based on s-PRS, detailing the age-dependent stream of vulnerability phenotypes could have significant translational implications for the early detection of psychotic risk.

The construct of clinical high-risk state for psychosis (CHR) [33] – broadly conceived as a mental state at imminent risk of progressing into frank psychosis – has progressively evolved to capture the clinically subthreshold phase of psychosis, indexing people presenting with putatively prodromal symptoms. Early intervention mental health services for CHR may play a key role in preventing or delaying psychosis [34 35], but only a small proportion of those who develop psychosis is followed since prodromal stages in such services [36]. Consequently, programs for the detection of a larger proportion of subjects at risk of psychosis should strive to intervene earlier in the longitudinal trajectory of psychosis development [37]. Although the CHR/prodromal state and the subsequent risk of conversion to psychosis might appear, from a clinical and behavioral viewpoint, as early symptomatic stages, they nonetheless plausibly represent rather advanced/late stages from a neurodevelopmental perspective [38 39]. According to the neurodevelopmental hypothesis of schizophrenia [39], as well as for the clinical staging model [40], psychosis conceivably represents the last long-term stages of an altered neurodevelopmental process. Such process, although usually manifested in late adolescence/early-adulthood, is often antedated from the early years of life, by subtle expressions of biological vulnerability. Therefore, the goal of an early detection of psychotic risk in the premorbid period should be based on these subtle expressions of biological vulnerabilities, rather than on hypothetical early direct expressions of psychotic risks, as psychotic experiences, that has a modest and relative unspecific predictive power in youth [41]. At the same time, this goal is hampered by the poor knowledge of those early phenotypic expressions of biological vulnerability that are more specific for a longitudinal psychotic risk: in this perspective, a developmental view, corroborated by s-PRS finding could further increase our understanding of specific age-dependent GxE interactive [5] effects across neurodevelopment on both domain-general (e.g. cognitive and motor deficits) and domain-specific features of premorbid and prodromal stages (e.g. anomalies of subjective experiences, attenuated positive and negative symptoms) of psychosis. For example, motor functioning appears an intriguing specific domain of expression of the biological vulnerability to psychosis, as supported by distinct empirical paradigms, including the s-PRS paradigm [26], familial high-risk studies [42 43], and longitudinal birth-cohort studies [44 45]. These studies globally show that motor manifestations: 1) emerge al-

ready in premorbid stages, in terms of later achievement of motor milestones and poor motor coordination (i.e., dyspraxia); 2) persist in prodromal stages in terms, for example, of neurological soft signs [46 47]; 3) become more pronounced in psychotic clinical stages of schizophrenia (including drug-naïve individuals), due to distinct pathophysiological mechanisms, in terms of catatonia, chorea, dystonia, bradykinesia, tics, and stereotypies [48]. Interestingly, impairments in basic neurophysiological mechanisms as corollary discharges [49] may have a pathogenetic role both for early motor impairment and its maintenance as well as for specific longitudinal liability to psychosis [50], in terms of potential triggers for anomalous self-experiences, representing trait-like non-psychotic anomalies of subjective experience that have been recursively corroborated as schizophrenia spectrum vulnerability phenotypes [51].

In conclusion, studies based on the s-PRS paradigm are in their infancy and appear to have currently a limited explanatory power, as exemplified by the small variance explained for all phenotypes; although findings of s-PRS studies may have significant clinical implications for the early detection paradigm if integrated with empirical findings derived from other empirical paradigms, such as familial-high risk studies and longitudinal birth cohort studies, investigating phenotypic manifestations along the neurodevelopmental trajectory/clinical staging of psychosis. In particular the PRS paradigm may corroborate the value of early non-psychotic vulnerability phenotypes, as they emerge along development, for an early detection of psychotic risk. This is particularly important for childhood and early-adolescence premorbid stages, in which the psychopathological trajectories towards positive psychotic symptoms (i.e. the current gold standard for clinical high-risk stratification [33]) are still inchoate. At the same time, if psychosis prediction should be progressively antedated from prodromal stages, typically occurring in adolescence/young adulthood, to childhood premorbid stages, this has implications for the organization and the allocation of resources of mental health services, usually strictly distinct in Childhood and Adolescence Mental Health Services (CAMHS) and Adult Mental Health Services (AMH) [52].

Conflict of Interest

The authors have no conflict of interests.

References

1 Wray NR, Goddard ME, Visscher PM. *Prediction of individual genetic risk to disease from genome-wide association studies*. Genome Res 2007;17:1520-8.

2 Dudbridge F. *Power and predictive accuracy of polygenic risk scores*. PLOS Genetics 2013;9.

3 Goldman D. *Polygenic risk scores in psychiatry*. Biol Psychiatry 2017;82:698-9.

4 Bogdan R, Baranger DAA, Agrawal A. *Polygenic risk scores in clinical psychology: bridging genomic risk to individual differences*. Annu Rev Clin Psychol 2018;14:119-57.

5 Iyegbe C, Campbell D, Butler A, et al. *The emerging molecular architecture of schizophrenia polygenic risk scores and the clinical implications for GxE research*. Soc Psychiatry Psychiatr Epidemiol 2014;49:169-82.

6 Sengupta SM, MacDonald K, Fathalli F, et al. *Polygenic risk score associated with specific symptom dimensions in first-episode psychosis*. Schizophr Res 2017;184:116-21.

7 Docherty AR, Moscati A, Dick D, et al. *Polygenic prediction of the phenome across ancestry in emerging adulthood*. Psychol Med 2018;48:1814-23.

8 Mistry S, Harrison JR, Smith DJ, et al. *The use of polygenic risk scores to identify phenotypes associated with genetic risk of schizophrenia: systematic review*. Schizophr Res 2017;9 Nov: Doi:10.1016/j.schres.2017.10.037. [Epub ahead of print]

9 Martin J, Taylor MJ, Lichtenstein P. *Assessing the evidence for shared genetic risks across psychiatric disorders and traits*. Psychol Med 2018;1759-74.

10 Allardyce J, Leonenko G, Hamshere M, et al. *Association between schizophrenia-related polygenic liability and level of mood-incongruent psychotic symptoms in bipolar disorder*. JAMA Psychiatry 2018;75:28-35.

11 International Consortium on Lithium Genetics, Amare AT, Schubert KO, Hou L, et al. *Association of polygenic score for schizophrenia and HLA antigen and inflammation genes with response to lithium in bipolar affective disorder: a genome-wide association study*. JAMA Psychiatry 2018;75:65-74.

12 McIntosh AM, Gow A, Luciano M, et al. *Polygenic risk for schizophrenia is associated with cognitive change between childhood and old age*. Biol Psychiatry 2013;73:938-43.

13 Hubbard L, Tansey KE, Rai D, et al. *Evidence of common genetic overlap between schizophrenia and cognition*. Schizophr Bull 2016;42:832-42.

14 Shafee R, Nanda P, Padmanabhan JL, et al. *Polygenic risk score for schizophrenia and measured domains of cognition in individuals with psychosis and controls*. Transl Psychiatry 2018;8:78.

15 Lancaster TM, Linden DE, Tansey KE, et al. *Polygenic risk of psychosis and ventral striatal activation during reward processing in healthy adolescents*. JAMA Psychiatry 2016;73:852-61.

16 Miller JA, Scult MA, Conley ED, et al. *Effects of polygenic risk scores on brain activity and performance during working memory subprocesses in healthy young adults*. Schizophr Bull 2018;44:844-53.

17 Chen Q, Ursini G, Romer AL, et al. *Schizophrenia polygenic risk score predicts mnemonic hippocampal activity*. Brain 2018;141:1218-28.

18 Sorensen HJ, Debost JC, Agerbo E, et al. *Polygenic risk scores, school achievement and risk for schizophrenia: a Danish population study*. Biol Psychiatry 2018; Doi: 10.1016/j.biopsych.2018.04.012. [Epub ahead of print]

19 Poletti M, Gebhardt E, Raballo A. *Schizophrenia polygenic risk score and psychotic risk detection*. Lancet Psychiatry 2017;4:188.

20 Poletti M, Raballo A. *Polygenic risk score and the (neuro)developmental ontogenesis of the schizophrenia spectrum vulnerability phenotypes*. Schizophr Res 2018;4 May; Doi: 10.1016/j.schres.2018.04.036. [Epub ahead of print]

21 Poletti M, Raballo A. *Editorial perspective: from schizophrenia polygenic risk score to vulnerability (endo-)phenotypes: translational pathways in child and adolescent mental health*. J Child Psychol Psychiatry 2018;59:822-5.

22 Jansen, PR, Polderman TJC, Bolhuis K, et al. *Polygenic risk score for schizophrenia and educational attainment are associated with behavioral problems in early childhood in the general population*. J Child Psychol Psychiatry 2018;59:39-47.

23 Nivard MG, Gage SH, Hottenga JJ, et al. *Genetic overlap between schizophrenia and developmental psychopathology: longitudinal and multivariate polygenic risk prediction of common psychiatric traits during development*. Schizophr Bull 2017;43:1197-207.

24 Riglin L, Collishaw S, Richards A, et al. *Risk alleles of schizophrenia and neurodevelopmental outcomes in childhood: a genome-wide association study*. Lancet Psychiatry 2017;4:57-62

25 Riglin L, Collishaw S, Ricchards A, et al. *The impact of schizophrenia and mood disorder risk alleles on emotional problems: investigating change from childhood to middle age*. Psychol Med 2017;Dec 14; Doi:10.1017/S0033291717003634. [Epub ahead of print]

26 Serdarevic F, Jansen PR, Ghassabian A, et al. *Association of genetic risk for schizophrenia and bipolar disorder with infant neuromotor development*. JAMA Psychiatry 2018;75:96-8.

27 van Os J, van der Steen Y, Islam MA, et al. *Evidence that polygenic risk for psychotic disorder is expressed in the domain of neurodevelopment, emotion regulation and attribution of salience*. Psychol Med 47:2421-37.

28 Liu B, Zhang X, Cui Y, et al. *Polygenic risk for schizophrenia influences cortical gyrification in 2 independent general populations*. Schizophr Bull 2017;43:673-80.

29 Neilson E, Bois C, Clarke TK, et al. *Polygenic risk for schizophrenia, transition and cortical gyrification: a high-risk study*. Psychol Med 2018;48:1532-9.

30 Krapohl E, Hannigan LJ, Pingault JB, et al. *Widespread covariation of early environmental exposures and trait-associated polygenic variation*. PNAS 2017;114:11727-32.

31 Meehl PE. *Schizotaxia, schizotipy, schizophrenia*. Am Psychol 1962;17:827-38.

32 Meehl PE. *Schizotaxia revisited*. Arch Gen Psychiatry 1989;46:935-44.

33 Fusar-Poli P, Borgwardt S, Bechdolf A, et al. *The psychosis high-risk state: a comprehensive state of the art review*. JAMA Psychiatry 2013;70:107-20.

34 Correll CU, Galling B, Pawar A, et al. *Comparison of early intervention services vs treatment as usual for early phase psychosis: a systematic review, meta-analysis and meta-regression.* JAMA Psychiatry 2018;75:555-65.

35 Devoe DJ, Farris MS, Townes P, et al. *Attenuated psychotic symptom interventions in youth at risk of psychosis: a systematic review and meta-analysis*. Early Interv Psychiatry 2018;May 11; Doi: 10.1111/eip.12677. [Epub ahead of print]

36 Ajnakina O, Morgan C, Gayer-Anderson C, et al. *Only a small proportion of patients with first episode psychosis come via prodromal service*. BMC Psychiatry 2017;17:308.

37 Liu CH, Keshavan MS, Tronick, MS, et al. *Perinatal risk and childhood premorbid indicators of later psychosis: next steps for early psychosocial interventions*. Schizophr Bull 2015;41:801-16.

38 Insel T. *Rethinking schizophrenia*. Nature 2010;468:187-93.

39 Rapoport JL, Giedd JN, Gogtay N. *Neurodevelopmental model of schizophrenia: update 2012*. Mol Psychiatry 2012;17;1228-38.

40 Mc Gorry PD, Hickie IB, Yung AR, et al. *Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions*. Aust N Z J Psychiatry 2006;40:616-22.

41 Zammit S, Kounali D, Cannon M, et al. *Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study*. Am J Psychiatry 2013;170:742-50.

42 Burton, BK, Thorup AE, Jepsen JR, et al. *Impairments of motor function among children with a familial high risk of schizophrenia or bipolar disorders at 7 years old in Denmark: an observational cohort study*. Lancet Psychiatry 2017;4:400-8.

43 Hameed MA, Lewis AJ. *Offspring of parents with schizophrenia: a systematic review of developmental features across childhood*. Harv Rev Psychiatry 2016;24:104-17.

44 Jones P, Rodgers B, Murray R, et al. *Child development risk factors for adult schizophrenia in the British 1946 birth cohort*. Lancet 1994;344:398-402.

45 Isohanni M, Jones PB, Moilanen K, et al. *Early developmental milestones in adult schizophrenia and other psychoses. A 31-year follow-up of the Northern Finland 1966 Birth Cohort*. Schizophr Res 2001;52:1-19.

46 Chan RCK, Cui HR, Chu MY, et al. *Neurological soft signs precede the onset of schizophrenia: a study of individuals with schizotypy, ultra-high-risk individuals and first-onset schizophrenia*. Eur Arch Psychiatry Clin Neurosci 2018;268:49-56.

47 Schiffman J. *Motor issues in the clinical high risk phase of psychosis*. Schizophr Bull 2017;43:937-8.

48 Peralta V, Cuesta MJ. *Motor abnormalities: from neurodevelopmental to neurodegenerative through "functional" (neuro) psychiatric disorders*. Schizophr Bull 2017;43:956-71.

49 Feinberg I. *Efference copy and corollary discharge: implications for thinking and its disorders*. Schizophr Bull 1978;4:636-40.

50 Poletti M, Gebhardt E, Raballo A. *Corollary discharge, self-agency and the neurodevelopment of the psychotic mind*. JAMA Psychiatry 2017;74:1169-70.

51 Raballo A, Sæbye D, Parnas, J. *Looking at the schizophrenia spectrum through the prism of self-disorders: an empirical study.* Schizophr Bull 2011;37:344-51.

52 Raballo A, Poletti M, Mc Gorry PD. *Architectures of changes: rethinking child and adolescence mental health*. Lancet Psychiatry 2017;4:655-7.

Original article

JOURNAL OF PSYCHOPATHOLOGY
2018;24:118-124

The Adult Autism Subthreshold Spectrum (AdAS) model: a neurodevelopmental approach to mental disorders

L. Dell'Osso[1], D. Muti[1], B. Carpita[1], I.M. Cremone[1], E. Bui[2], C. Gesi[1], C. Carmassi[1]

[1] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [2] Massachusetts General Hospital & Harvard Medical School, Boston, USA

Summary

A growing interest has been devoted to adult presentations of Autism Spectrum Disorders. This led to focus on comorbidity between ASD and other mental disorders, mainly (but not limited to) Borderline Personality Disorders, Post Traumatic Stress Disorders, Mood Disorders and Eating Disorders. The presence of any psychiatric comorbidity can mask ASD, in particular in subjects with no intellectual impairment. To address this psychopathological issue, studies adopting the AdAS questionnaire, an instrument with strong convergent validity with alternative dimensional measures of ASD and excellent internal consistency and test-retest reliability, able to detect subthreshold forms of ASD in adulthood, have been reviewed. Based on these evidences, the Subthreshold Autism Spectrum Model has been developed, which includes threshold-level manifestations but also mild/atypical symptoms of the disorder, gender-specific features, behavioral manifestations and personality traits associated with ASD. This model encompasses, although not coinciding with, the Broad Autism Phenotype. This is a subthreshold form of autism described in the context of the neurodevelopmental trajectory that – starting from autistic traits – might lead to the broad range of mental disorders. Therefore, the Adult Autism Spectrum can be considered a transnosographic dimension. This approach should help to detect individual features for certain autistic cognitive and behavioral patterns that may predispose to other mental disorders.

Key words

Autism Spectrum Disorder • DSM-5 • AdAS spectrum • Subthreshold autism spectrum

Introduction

Autism Spectrum Disorder (ASD) defines a group of early-onset neurodevelopmental conditions characterized by alterations in brain connectivity with cascading effects on neuropsychological functions. Core symptoms include difficulties in communication and repetitive, stereotyped behaviors [1].

While etiopathogenesis of ASD is still unknown [2], there is a good evidence for genetic correlates. In particular, specific genetic mutations can be identified in about 20% of ASD cases and twin studies estimate an heritability between 64-91%, suggesting the interaction between heritable and environmental factors [4]. These data confirm the seminal findings by Kanner and Asperger [5], which observed that both first and second degree relatives of children with "autistic disturbances of affective contacts" shared some features with their offspring, such as late speech, mild obsessiveness and lack of interest in human interactions. Furthermore, Asperger [6] found that parents of autistic-like children report characteristics of pedantry, aloofness, social withdrawal and eccentricity.

Considering the early onset of these disorders, few studies have been described the adult courses of ASD. In particular, the mild subtype is likely to be underestimated since for a long-time only autism with pervasive intel-

Correspondence

Liliana Dell'Osso
Department of Clinical and Experimental Medicine, University of Pisa,
via Roma 67, 56126 Pisa, Italy
• E-mail: liliana.dellosso@med.unipi.it

lectual and language disabilities as well with severe impairment in human interactions have been diagnosed [7]. However, the interest on the milder forms and adult courses of disorder, previously labeled as Asperger's Disorder, has recently increased, with a focus on the high rates of comorbidity between these conditions and anxiety, mood, psychotic, trauma and stress related disorders. Moreover, the DSM-5 it introduced the diagnosis of ASD [1 8] with different levels of impairment. This radical change reflects the choice to classify psychopathology on the basis of both observable behavior and neurobiological measures, linking symptomatic manifestations with brain functioning [1 7].

The aim of this paper is to introduce a novel psychopathological model - the Subthreshold Autism Spectrum Model - broadening and redefining the dimensional approach introduced by the DSM-5.

This model has been developed in the broader framework of an international Italy-USA research project (*Spectrum Project*), whose aim was to apply a *Spectrum Model* approach to mental disorders, giving relevance not only to proper criteria but also to subthreshold symptoms and signs, behavioral manifestations, atypical features, temperamental traits. This new approach has been proved to be quite accurate for understanding the clinical features, course and comorbidity of most mental disorders, and the continuity between general and clinical populations [9 10].

The AdAS questionnaire

The interest on a dimensional model for autism has considerably increased, since several authors highlighted the usefulness of such approach [11-13]. Therefore, several psychometric instruments aiming to assess autistic symptoms as continuous dimensions have been developed [14-16].

Manifestations of ASD may vary depending on different factors: severity of the autistic symptomatology, developmental level and age and this degree of intensity is reflected by the diagnostic category of Autism Spectrum Disorders [1].

According to DSM-5, some individuals with severe ASD may completely lack spoken communication, while others may show normal speech with impaired use of language for reciprocal communication. Core diagnostic features are usually more evident during the developmental age, since interventions and acquired compensatory strategies may disguise several difficulties during adulthood. These factors defined the classical form of autism as a "disorder of childhood", although these do not reflect the variety of clinical practice. For example, an adult patient with ASD may show fluent language during clinical interview, with subtle impairment in eye contact, prosody, body posture and face expressivity. Therefore, patients with low level of cognitive impairments, when living in an environment matching their interests and skills, can report low level of impairment and can be underdiagnosed and undertreated.

The ASD is usually recognized (and recognizable) during early childhood, although some individuals with ASD might seek clinical assistance only during adulthood with other diseases in comorbidity. In particular, this is frequently the case of patients with no language or intellectual impairment and high (or medium-high) levels of functioning. The prevalence of ASD is growing across all age groups, with a particular rise in the number of adult cases: this might be correlated to changes in diagnostic criteria as well as with greater awareness of autism [17 18].

Patients with ASD have a reduced coping ability to stressful life events and they are at higher risk to develop other psychiatric conditions, such as trauma and stress-related conditions besides mood, eating and anxiety disorders [19-26], but their relative good level of social and cognitive functioning can impact of help-seeking and diagnostic delay.

Comorbidity between ASD and other mental disorders has been described quite extensively, highlighting that other mental disorders in comorbidity in subjects with lower levels of cognitive impairments and mild symptoms [20 24-25 27-29] can hide ASD.

The need to careful evaluate the presence of autistic symptoms both in clinical samples and in the general population has often been stressed in literature since autistic traits may impact on the clinical presentation of other mental disorders and may be a risk factor for other disorders or towards suicidality [24 30].

Available instruments mostly assess ASD in a quantitative way, such as the Autism Spectrum Quotient (AQ) developed by Baron-Cohen [14-16]. "Restricted and repetitive interests and behaviors" have been recognized as a core feature of ASD [1], although this dimension has been poorly evaluated in the existing questionnaires. Moreover, available questionnaires have been tailored on male patients with ASD. As a result, the profile of female patients with ASD has disappeared from the current nosography and from the range of detection of most instruments [31-35].

In order to address such limitations, the Adult Autism Subthreshold Spectrum (AdAS Spectrum) [38], a 160-items questionnaire for adult subjects with normal (or above normal) intelligence without language impairment, has been developed. In line with the Spectrum-Project [8-10] approach to psychopathology, the AdAS Spectrum refers not only to the core manifestations of the disorder, but also to the attenuated and atypical symptoms, the personality traits, and the behavioral manifestations that may be associated with ASD but that may also be present in

subthreshold or partial forms. In developing the questionnaire, great attention was given to the female phenotypes of ASD as well as to the sensory reactivity area of symptoms. In the questionnaire, some gender-related manifestations have been included such as the tendency of female patients with ASD to mitigate social symptoms by imitation and by acting as someone socially successful. Another gender-related feature is the avoidance of social interactions and the preference in engaging in creative solitary activities, in spending time with pets, or enjoying fictional media. Moreover, female patients with ASD are usually able to recognize their own social difficulties, and consequently develop intense anxiety in social situations and avoidance behaviors, therefore, some social anxiety-like behavioral features have also been included in the questionnaire [36-37].

The questionnaire includes 160 items, grouped into seven domains allowing the evaluation of a wider spectrum of manifestations of autism. Items' responses are binary (yes/no) and domain scores correspond to the sum of positive answers. The "Childhood/adolescence" domain includes symptoms related to early developmental phases (such as, being very quiet or unable to speak at all, avoiding eating or playing with other children or being teased or bullied). The "verbal communication" domain covers features of the speaking behavior, the preference for media communication, difficulties in participating in a conversation. The "non-verbal communication" domain explores difficulties in eye-contact and in physical contact, the presence of anger outbursts. The "empathy" domain explores impairment in understanding and interpreting facial expressions, intentions or thoughts, but also the presence of intense attachment to pets or objects. The "inflexibility and adherence to routine" domain includes difficulty in understanding the subtle aspects of verbal communication, insistence on sameness and habits, unwillingness to eliminate useless objects, tendency to follow specific procedures. The "restricted interests and rumination" domain includes the tendency of talking about few preferred topics and being fascinated by numbers, the incapacity to be concise, and the tendency to waste time over details, to lose track of time and to take refuge in daydreaming. The "hyper/hypo-reactivity to sensory input" domain explores the tendency to over- or under-react to stimuli such as textures, smells, noises, temperature and pain.

The AdAS Spectrum questionnaire – although evaluating the presence of features belonging to ASD psychopathology – it has not been developed as a diagnostic instrument. It aims to assess the presence/absence of a broad variety of clinical manifestations associated with ASD or that can be present in individuals not fulfilling the diagnostic threshold. The duration, the clustering and the severity of criterion symptoms, mandatory to make a diagnosis according to the DSM-5, cannot be defined using the AdAS Spectrum questionnaire. However, this assessment tool allows to define, assess and evaluate, together with the typical aspects of ASD, a wider area of clinical and non-clinical manifestations, with a specific focus to some gender-specific elements [39].

In its validation study, the AdAS Spectrum questionnaire was administered to subjects endorsing at least one DSM-5 ASD symptom criterion, patients with Feeding and Eating Disorders (FED) and healthy controls. The AdAS Spectrum questionnaire has an excellent internal consistency, a good test–retest reliability, and a strong convergent validity. Although performing differently among the three groups, the questionnaire showed a good sensitivity in identifying subjects expressing either a full or a partial phenotype (i.e., only one symptom criterion) of ASD [39].

Toward the adult autism subthreshold spectrum: ASD, Borderline Personality Disorder and Post-Traumatic Stress Disorder

Several studies highlighted a certain degree of resemblances between ASD and Borderline Personality Disorder (BPD) [40]. Core symptoms of BPD do not seem to be closely related to those of ASD, being mainly characterized by impulsivity with a pattern of instability of interpersonal relationships, of self-image, and of affects. Stressful situations and difficulties in managing anger may elicit anticonservative behaviors, such as threat and self-injuring, suicidal thoughts and behaviors [1].

However, ASD and BPD might show a significant overlap when considering patients with ASD and lack of cognitive impairment. In fact, impairments in social functioning, miscommunications, incorrectly assumed intentions and emotionally outbursts, which are core features of ASD, are frequently observed in patients with BPD as well. On the other hand, the focus on emotive actions and the establishment of intense relationships and superficial friendships, typical features of BPD, might also be observed in ASD presentations. The similarities between the two disorders also involve neurocognitive functioning: neuropsychological studies targeting the recognition of facial emotions and prosody have found that both subjects with ASD and BPD show similar difficulties in Theory of Mind tasks and in understanding emotions [40-44].

The relationship between ASD and BPD addresses also the trauma and stress related psychopahtology. Subjects with ASD suffering from chronic exposure to traumatic events may develop a peculiar post-traumatic phenotype known as Complex PTSD (cPTSD), characterized by emotional liability, long-term instability in in-

terpersonal relationships, unstable self-perception and maladaptive behaviors, substance abuse and self-injuring [45]. Due to this peculiar clinical presentation, these subjects might be misdiagnosed as BPD patients [19 46].
In this framework, it is noteworthy that the prevalence rate of BPD in patients with ASD is 10.6% [47] while the prevalence rate of ASD in patients with BPD is about 15% [48]. Moreover, a recent study showed a positive correlation between autistic spectrum symptoms and suicidality among BPD patients [44]. Furthermore, not only full blown ASD, but also subthreshold autistic traits might enhance the overall suicidality, including both suicidal thoughts and attempts, in BPD subjects. Higher levels of autistic traits have been found in BPD subjects who report a history of abuse (physical or sexual) than in those without a history of trauma. Subjects with full-blown ASD are often bullied or suffer from violence and sexual abuse, and these experiences are also very frequently reported by BPD patients [49-51]. Subjects with subthreshold ASD may both face a higher risk of exposure to trauma and have an increased vulnerability to the effects of the trauma, resulting in higher rates of PTSD and BPD-like symptoms [52]. On the other hand, PTSD symptoms may include a feeling of detachment from others and a decreased interest in significant activities, which can be similar to autistic symptoms. The high level of autistic traits found among subjects with a history of physical/sexual abuse might be interpreted both as a risk factor for being target of certain behaviors and as a consequence of stress-related abuse [44].
It has been reported that patients with ASD may be often exposed to traumatic experiences and they may be likely to develop PTSD [53]. Moreover, a growing body of data shows that individuals moderate forms of ASD, often come to clinical attention when other mental disorders arise [30]. Takara et al. [24] recently found a prevalence rate of ASD of 16% among first-visit depressed adult patients, while Kato et al. reported a 7.3% rate of previously unrecognized ASD among suicide attempters hospitalized [30]. It has been showed that suicidal thoughts and behaviors seem to be common in young patients with ASD, and these are associated with the presence of depression and PTSD. It should be noted how individuals with ASD may represent a low-resilience group that could be prone to develop Trauma and Stress Related Disorders [53]. Moreover, it has been reported that following the exposure to a natural disaster, the ability to cope with stressors decline faster over time in ASD than in healthy control subjects [19].
To explore the relationship between PTSD and ASD in the framework of the AdAS Spectrum model, the Trauma and Loss Spectrum Questionnaire (TALS-RS) and AdAS Spectrum have been administered to a sample of 134 parents of children diagnosed with epileptic syndrome [54]. Higher PTSD rates were found in women compared to men, with a 10.4% of parents (mothers: 13.3%; fathers: 4.5%) presenting PTSD. Mothers reported higher scores of the TALS-SR compared to fathers in the reaction to loss or traumatic events domain. A significant correlation between the TALS-SR and the AdAS Spectrum domains was found in the subgroup of fathers [54]. Similar findings have been found by Cernvall et al. [55] in parents of children on cancer treatment, showing how avoidance behaviors and ruminations were positively correlated with PTSD and symptoms of depression. Ruminations represent a nuclear feature of PTSD, but they are a transversal symptom, present also in major depression, PTSD and ASD [7 24].

Eating Disorders: the issue of phenotypes

Several studies have been focused on the overlap between the clinical characteristics of ASD and Eating Disorders (ED) [1].
Since the early conceptualization proposed in the '80s by Gillberg, suggesting that Anorexia Nervosa (AN) should be conceptualized as an empathy disorder on the same spectrum of autism [56], research on the link between ASD and eating disorders has evolved.
More recently, many studies confirmed the overlap in behavioral and cognitive features between AN and ASD [57]. It has been noted that rigid attitudes and behaviors are typical features of AN, which can be seen as resembling the unusually narrow interests and repetitive behaviors in ASD. The main difference is that "insistence on sameness" in AN patients becomes mainly focused on food or weight. The overlap in cognitive features is quite extensive, as both ASD and AN show difficulties on advanced "Theory of Mind" tests, deficits in emotional intelligence, social anhedonia, poor performance on tests of set-shifting, and excellent skills on tests on attention to details [58]. The behavioral and cognitive similarities are confirmed on a neurobiological level, as both ASD and AN are correlated with atypical structure and functioning of the fusiform face area, superior temporal sulcus, amygdala, and in the orbitofrontal cortex, which are involved in social processing [59].
ED could share some traits of both ASD and Obsessive-Compulsive Disorder (OCD) in terms of obsession for proper nutrition, focus on weight loss, concern and rituals about food and food consumptions, rumination about eating [58]. These patients are at risk for social isolation due to their sense of moral superiority and their intolerance to others' food beliefs. These intrusive features and behaviors share some similarities with deficits in social-emotional reciprocity, restricted and repetitive patterns of behavior and interests, and inflexible adherence to routines, that are typical of patients with low levels of autistic spectrum disorder. On the other hand, in

subjects with ASD an higher rate of eating problems has been reported since childhood, and the most frequent pattern appear related to food selection. The tendency to be over-selective or have an aversion to specific textures, colors, smells, and temperatures and to show rigidity to specific foods is associated with an increased risk toward underweight condition [1 58].

Recently, it has been conducted a study with 138 ED patients and 160 healthy control participants (HCs) [60], assessed by the SCID-5, the Eating Disorders Inventory version 2 (EDI-2) and the AdAS Spectrum. ED patients showed significantly higher AdAS Spectrum total scores than HCs, confirming previous studies [56]. Moreovoer, ED patients showed higher scores on all AdAS Spectrum domains with the exception of "non verbal communication" and "hyper/hypo-reactivity to sensory input" with binge eating/purging subtype of AN (AN-BP) participants, and of "childhood/adolescence" domain for AN-BP and with binge eating disorder participants. Subjects with restrictive AN scored significantly higher than subjects with binge-eating behaviors on the AdAS Spectrum total score, and on the "Inflexibility and adherence to routine and Restricted interest/rumination" AdAS Spectrum domain scores. Significant correlations emerged between the Interpersonal distrust EDI-2 sub-scale and the "non verbal communication" and the "restricted interest and rumination" AdAS Spectrum domains; as well as between the Social insecurity EDI-2 sub-scale and the "Inflexibility and adherence to routine" and "restricted interest and rumination" domains.

These results suggest the presence of a continuum across ED diagnostic groups, featuring also different degrees of severity [60]. This discrete continuum confirms the strong psychopathological overlap between ED and ASD, corroborating the possible conceptualization of ED, and in particular of restrictive ED, as a part of the "female ASD phenotype".

The Subthreshold Autism Spectrum Model

Based on these data, the Adult Autism Subthreshold Spectrum Model has been developed. This is a comprehensive psychopathological theory including the full-blown symptoms, mild and atypical manifestations, behavioral traits, and personality features associated with the ASD diagnostic category. These traits can be risk factors for other mental disorders, being distributed across a continuum from normality to pathology and including also positive aspects of neuroatypicality [38], such as originality, creativity, divergent thinking [61]. ASD manifestations often overlap with other mental disorders leading the investigations on a possible link between the AdAS spectrum and the full-blown clinical manifestations of mental disorders.

This model might have a huge impact in clinical practice, as AdAS instruments might help both to early detection of high-risk subjects and to identify ASD in different clinical presentations [8].

However, the AdAS Spectrum questionnaire – and its Model – allows investigations about the relationships between autism spectrum and other mental disorders, leading to a better understanding of psychopathology.

The Subthreshold Autism Spectrum Model and AdAS questionnaire could be also employed for investigate the genetic basis of autism. In fact, the DSM-5 still separate what should be considered autism, and what should not [62 63] and the DSM-5 criteria for ASD disregards atypical manifestations and more subtle phenomena such as the broad autism phenotype or the subthreshold autism spectrum [6]. Although general population obviously do not generally meet ASD criteria, it should not be forgotten that it does share genetic underpinnings with the clinical population [64-67]. The AdAS Spectrum approach could allow to test a wider range of endophenotypes in order to better investigate the genetic basis of ASD [61].

The Subthreshold Autism Spectrum Model has the potential to overcome the descriptive artifice of comorbidity. Considering the shared genetic risk and overlapping clinical features of different mental disorders with ASD, it should be noted that a neurodevelopmental deviation may represent a common vulnerability factor for the majority of mental disorders. The severity and the specific morphological features of the neurodevelopmental damage would lead to different grades of neuroatypicality, resulting in different psychiatric disorders [2 8]. Such an hypothesis is consistent with the definition of psychiatric disorders as "globalopathies", involving not only some specific brain networks, but the whole-brain organization [68 69], on the basis of a pathological neurodevelopmental trajectory with different outcomes [8 70].

According to this model, the AdAS Spectrum questionnaire might allow to assess some broad dimensions, which could predispose subjects to develop different kinds of clinical presentations. In this framework, some features associated with autistic psychopathology (such as ruminative thinking, social withdrawal, rigidity, perfectionism, social phobia, anhedonia, lack of empathy) might be reconsidered as an autistic core shared by different kind of disorders, reflecting the high rates of comorbidity between ASD and other mental disorders [71 72]. The AdAS Spectrum Model can be considered a transnosographic dimension involved in different conditions. This should allow clinicians, by using the AdAS Spectrum assessment, to shed light on the physiopathology and clinical course, as well as on possible treatment response, of most mental disorders.

Conflict of Interest

The authors have no conflict of interests.

References

1 American Psychiatric Association. *Diagnostic and statistic manual of mental disorders, 5th Edition.* Arlington: APA Publishing 2013.

2 Billeci L, Calderoni S, Conti E, et al. *The broad autism (endo)phenotype: neurostructural and neurofunctional correlates in parents of individuals with autism spectrum disorders.* Front Neurosci 2016;10:1-15.

3 Jeste SS, Geschwind DH. *Disentangling the heterogeneity of autism spectrum disorder through genetic findings.* Nat Rev Neurol 2014;10:74-81.

4 Tick B, Bolton P, Happé F, et al. *Heritability of autism spectrum disorders: a meta-analysis of twin studies.* J Child Psychol Psychiatry 2010;57:585-95.

5 Kanner L. *Autistic disturbances of affective contacts.* Nervous Child 1943;2:217-50.

6 Asperger H. *Die autistischen psychopathen im kindersalter.* Arch Prychiatr Nervenkr 1944;117:76-136.

7 Dell'Osso L, Dalle Luche R, Gesi C, et al. *From Asperger's autistischen psychopathen to DSM-5 autism spectrum disorder and beyond: a subthreshold autism spectrum model.* Clin Prat & Mental Health 2016;12:120-31.

8 Dell'Osso L, Dalle Luche R, Maj M. *Adult autism spectrum as a transnosographic dimension.* CNS Spectrums 2016;21:131-3.

9 Frank E, Cassano GB, Shear MK, et al. *The spectrum model: a more coherent approach to the complexity of psychiatric symptomatology.* CNS Spectrums 1998;3:23-34.

10 Cassano GB, Dell'Osso L, Frank E, et al. *The bipolar spectrum: a clinical reality in search of diagnostic criteria and an assessment methodology.* Jour Aff Dis 1999;3:319-28.

11 Leboyer M, Belliver F, Nosten-Bertrand M, et al. *Psychiatric genetics: search for phenotypes,* Trends Neurosci 1998;21:102-5.

12 Losh M, Sullivan PF, Trembath D, et al. *Current developments in the genetics of autism: from phenome to genome.* J Neuropath Exp Neurol 2008;67:829-37.

13 Picardi A, Fagnani C, Medda E, et al. *Genetic and environmental influences underlying the relationship between autistic traits and temperament and character dimensions in adulthood.* Compr Psych 2015;58:178-88.

14 Baron-Cohen S, Wheelwright S, Skinner R, et al. *The Autism Spectrum Quotient (AQ): evidence from Asperger syndrome/high functioning autism, males, females, scientists and matematicians.* J Autism Dev Disord 2001;31:5-17.

15 Costantino JN. *The Social Responsiveness scale.* Los Angeles: Western Psychological Services 2002.

16 Dawson G, Estes A, Munson J, et al. *Quantitative assessment of autism symptom-related traits in probands and parents.* J Autism Dev Disord 2006;37:523-36.

17 Brugha TS, Mc Manus S, Bankart J, et al. *The proportion of true cases of autism is not changing.* Br Med J 2014;348:3774.

18 Christensen DL, Baio J, Braun KV, et al. *Prevalence and characteristics of autism spectrum disorder a mong children aged 8 years.* MMWR Surveill Summ 2016;65:1-23.

19 Dell'Osso L, Dalle Luche R, Carmassi C. *A new perspective in posttraumatic stress disorder: which role for unrecognized autism spectrum?* Emerg Ment Health 2015;17:436-8.

20 Dell'Osso L, Dalle Luche R, Cerliani C, et al. *Unexpected subthreshold autism spectrum in a 25-year old male stalker hospitalized for delusional disorder: a case report*. Compr Psychiatry 2015;61:10-4.

21 Simoncini M, Miniati M, Vanelli F, et al. *Lifetime autism spectrum features in a patient with a psychotic mixed episode who attempted suicide*. Case Rep Psychiatry 2014;2014:1-4.

22 Lugnegard T, Hallerback MU, Gillberg C. *Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome*. Res Dev Disabil 2011;32:1910-7.

23 Hofvander B, Delorme R, Chaste P, et al. *Psychiatric and psychosocial problems in adults with normal intelligence autism spectrum disorders*. BMC Psychiatry 2009;9:35.

24 Takara K, Kondo T. *Autism spectrum disorder among first-visit depressed adult patients: diagnostic clues from backgrounds and past history.* Gen Hosp Psychiatry 2014;36:737-42.

25 Mito H, Matsuura N, Mukai K, et al. *The impacts of elevated autism spectrum disorder traits on clinical and psychosocial features and long-term treatment outcome in adult patients with obsessive-compulsive disorder*. Compr Psychiatry 2014;55:1526-33.

26 Sierro G, Rossier J, Mohr C. *Validation of the French Autism Spectrum Quotient scale and its relationships with schizotypy and Eysenckian personality traits*. Compr Psychiatry 2016;68:147-55.

27 Yirmiya N, Shaked M. *Psychiatric disorders in parents of children with autism: a meta-analysis*. J Child Psychol Psychiatry 2005;46:69-83.

28 Jacobi C, Agras WS, Bryson S, et al. *Behavioral validation, precursors, and concomitants of picky eating in childhood*. J Am Acad Child Adolesc Psychiatry 2003;42:76-84.

29 Karjalainen L, Gillberg C, Rastam M, et al. *Eating disorders and eating pathology in young adult and adult patients with ESSENCE*. Compr Psychiatry 2016;66:79-86.

30 Kato K, Mikami K, Akama F, et al. *Clinical features of suicide attempts in adults with autism spectrum disorders*. Gen Hosp Psychiatry 2013;35:50-3.

31 Auyeung B, Taylor K, Hackett G, et al. *Foetal testosterone and autistic traits in 18 to 24-month-old children*. Mol Autism 2010;1:11.

32 Baron-Cohen S, Cassidy S, Auyeung B, et al. *Attenuation of typical sex differences in 800 adults with autism vs 3,900 controls*, PLoS One 2014;9:e102251.

33 Lai M-C, Baron-Cohen S, Buxbaum JD. *Understanding autism in the light of sex/gender*, Mol Autism 2015;6:24.

34 Lai M-C, Lombardo MV, Auyeung B, et al. *Sex/gender differences and autism: setting the scene for future research*. J Am Acad Child Adolesc Psychiatry 2015;54:11-24.

35 Lombardo MV, Ashwin E, Auyeung B, et al. *Fetal programming effects of testosterone on the reward system and behavioral approach tendencies in humans*. Biol Psychiatry 2012;72:839-47.

36 Attwood T. *The pattern of abilities and development for girls with Asperger's syndrome*. In: Attwood T, Grandin T, Eds. *Asperger's and girls*, Arlington, TX: Future Horizons Inc 2006.

37 Clark J. *Asperger's in pink: pearls of wisdom from inside the bubble of raising a child with Asperger's*. In: Attwood T, Grandin T, Eds. *Asperger's and girls*, Arlington, TX: Future Horizons Inc 2006.

38 Dell'Osso L, Gesi C, Massimetti E, et al. *Adult Autism Subthreshold Spectrum (AdAS Spectrum): validation of a questionnaire investigating subthreshold autism spectrum*, Compr Psychiatry 2017;73:61-83.

39 Rynkiewicz A, Schuller B, Marchi E, et al. *An investigation of the 'female camouflage effect' in autism using a computerized ADOS-2 and a test of sex/gender differences*. Mol Autism 2016;7:10.

40 Fitzgerald M. *Borderline personality disorder and Asperger syndrome*. Autism 2005;9:452.

41 Niedtfeld I, Defiebre N, Regenbogen C, et

al. *Facing the problem: impaired emotion recognition during multimodal social information processing in borderline personality disorder*. J Pers Disord 2017;31:273-88.

42 Minzenberg MJ, Poole JH, Vinogradov S. *Social-emotion recognition in borderline personality disorder*. Compr Psychiatry 2006;47:468-74.

43 Mitchell AE, Dickens GL, Picchioni MM. *Facial emotion processing in borderline personality disorder: a systematic review and meta-analysis*. Neuropsychol Rev 2014;24:166-84.

44 Dell'Osso L, Cremone IM, Carpita B, et al. *Correlates of autistic traits among patients with borderline personality disorder.* Compr Psych 2018;83:7-11.

45 Dell'Osso L, Carmassi C, Stratta P, et al. *Gender differences in the relationship between maladaptive behaviors and post-traumatic stress disorder. A study on 900 L'Aquila 2009 earthquake survivors*. Front Psychiatry 2013;3:1-7.

46 King R. *Complex Post-traumatic stress disorder: implications for individuals with autism spectrum disorders-part I*. J Dev Disabil 2010;16:91-100.

47 Rydén E, Bejerot S. *Autism spectrum disorders in an adult psychiatric population. A naturalistic cross-sectional controlled study*. Clin Neuropsychiatry 2008;5:13-21.

48 Losh M, Childress D, Lam K, et al. *Defining key features of the broad autism phenotype: a comparison across parents of multiple- and single-incidence autism families*. Am J Med Genet B Neuropsychiatr Genet 2008;147:424-33.

49 Ogata SN, Silk KR, Goodrich S, et al. *Childhood sexual and physical abuse in adult patients with borderline personality disorder.* Am J Psychiatry 1990;147:1008-13.

50 Herman JL, Perry JC, Van der Kolk BA. *Childhood trauma in borderline personality disorder*. Am J Psychiatry 1989;146:490-5.

51 Paris J, Zweig-Frank H, Guzder J. *Psychological risk factors for borderline personality disorder in female patients*. Compr Psychiatry 1994;35:301-5.

52 Carmassi C, Corsi M, Gesi C, et al. *Post-traumatic stress spectrum and adult autism subthreshold spectrum in parents of children with epilepsy: correlations and gender differences*. Eur Psychiatry 2017;41:S721-2.

53 Storch EA, Sulkowski ML, Nadeau J, et al. *The phenomenology and clinical correlates of suicidal thoughts and behaviors in youth with autism spectrum disorders*. J Aut Dev Dis 2013;43:2450-9.

54 Dell'Osso L, Corsi M, Gesi C, et al. *Adult autism subthreshold spectrum (AdAS Spectrum) in parents of pediatric patients with epilepsy: correlations with post-traumatic stress symptoms.* Compr Psych 2018;83:25-30.

55 Cernvall M, Skogseid E, Carlbring P, et al. *Experimental avoidance and rumination in parents of children on cancer treatment: relationships with posttraumatic stress symptoms and symptoms of depression*. J Clin Psychol Settings 2016;23:67-76.

56 Gillberg IC, Gillberg C, Rastam M, et al. *The cognitive profile of anorexia nervosa: a comparative study including a community-based sample*. Compr Psychiatry 1996;37:23-30.

57 Tchanturia K, Smith E, Weineck F, et al. *Exploring autistic traits in anorexia: a clinical study,* Mol Aut 2013;4:1-8.

58 Dell'Osso L, Abelli M, Carpita B, et al. *Historical evolution of the concept of anorexia nervosa and relationship with ortorexia nervosa, autism and obsessive compulsive spectrum.* Neur Dis Treat 2016;12:1651-60.

59 Zucker NL, Losh M, Bulik CM, et al. *Anorexia nervosa and autism spectrum disorders: guided investigation of social cognitive endophenotypes*. Psychol Bull 2007;133:976-1006.

60 Dell'Osso L, Carpita B, Gesi C, et al. *Subthreshold autism spectrum disorder in patients with eating disorders.* Compr Psych 2017;81:66-72.

61 Baron-Cohen S, Richer J, Bisarya D, et al. *The systemizing quotient: an investigation of adults with Asperger syndrome or high-funcioning autism, and normal sex differences.* Philos Trans R Soc Lond B Biol Sci 2003;358:361-74.

62 Happé F, *Criteria, categories, and continua: autism and related disorders in DSM-5,* J Am Acad Child Adolesc Psuchiatry 2011;50:540-2.

63 Nemeroff CB, Weinberger D, Rutter M. *DSM-5: a collection of psychiatrist view on the changes, controversies and future directions.* BMC Med 2003;11:202.

64 Le Couteur A, Bailey A, Goode S, et al. *A broader phenotype of autism: the clinical spectrum in twins*. J Child Psychol Psychiatry1996;37:785-801.

65 Smith CJ, Lang CM, Kryzak L, et al. *Familial associations of intense preoccupations, an empirical factor of the restricted, repetitive behaviors and interests domain of autism*. J Child Psychol Psychiatry 2009;50:982-90.

66 Constantino JN, Zhang Y, Frazier T, et al. *Sibling recurrence and the genetic epidemiology of autism*. Am J Psychiatry 2010;167:1349-56.

67 Ronald A, Hoekstra RA. *Autism spectrum disorders and autistic traits: a decade of new twin studies*. Am J Med Genet B Neuropsychiatr Genet 2011;156B:255-74.

68 Peled A, Geva AB. *Clinical Brain profiling: a neuroscientific approach for mental disorders.* Med Hypotheses 2014;83:450-64.

69 Peled A. *Brain "globalopathies" cause mental disorders.* Med Hypotheses 2013;6:1046-55.

70 White PD, Rickards H, Zeman AZ. *Time to end the distinction between mental and neurological illness.* BMJ 2012;344:e3454.

71 Dell'Osso L, Conversano C, Corsi M, et al. *Polysubstance and behavioral addictions in a patient with bipolar disorder: role of lifetime subthreshold autism spectrum.* Case Reports in Psychiatry. 2018;2018:1547975.

72 Dell'Osso L, Carmassi C, Musetti L, et al. *Lifetime mood symptoms and adult separation anxiety in patients with complicated grief and/or post-traumatic stress disorder: a preliminary study*. PSych Res 2012;198:436-40.

JOURNAL OF PSYCHOPATHOLOGY
2018;24:125-132

Original article

E. Marzola[1], N. Delsedime[1], S. Scipioni[1], S. Fassino[1], G. Abbate-Daga[1], B. Murray Stuart[2]

[1] Eating Disorders Center, Department of Neuroscience, University of Turin, Italy; [2] Department of Psychiatry, University of California, San Francisco, San Francisco, CA, USA

The association between personality and eating psychopathology in inpatients with anorexia nervosa

Summary

Objectives

Anorexia nervosa is a severe mental illness with modest treatment outcomes, and hospitalizations are frequently required. AN is robustly associated with a constellation of personality traits, including perfectionism, harm avoidance and anxiety. Psychopathological and personality aspects can influence treatment response and outcome in the hospital setting potentially favoring a greater individualization of treatments. This study aims to analyze inpatients with AN to ascertain as to whether personality traits can be associated with the improvement of eating psychopathology. We expected that more adaptive personality traits upon admission could correlate with the improvement of eating psychopathology upon hospital discharge.

Methods

One-hundred and thirteen inpatients with AN were consecutively enrolled and asked to complete the following assessment instruments: Temperament and Character Inventory (TCI), State Trait Anxiety Inventory (STAI), Beck Depression Inventory (BDI), Eating disorders inventory-2 (EDI-2), and the Eating Disorders Examination Questionnaire (EDE-Q). Clinical parameters including Body Mass Index (BMI) were assessed at admission as well.

Results

When compared between admission and discharge, patients significantly improved in BMI, state anxiety and depression. As regards eating psychopathology, patients did not significantly improve on the EDI-2 core subscales (i.e., drive for thinness, bulimia, body dissatisfaction), with the exception of the bulimia subscale; in contrast, the EDE-Q total score showed a significant improvement upon discharge. According to their improvement (Improved Drive For Thinness, I-DT) versus worsening (Worsened Drive for Thinness, W-DT) of the DT subscale upon hospital discharge, 46 patients were classified as W-DT while 67 patients as I-DT. Only cooperativeness on the TCI was found to significantly differ between groups.

Conclusions

Increasingly effective and individualized treatments are needed for AN sufferers. We confirmed that hospitalizations are overall effective in improving eating symptoms; furthermore, higher cooperativeness upon admission, a character dimension of personality, resulted as associated with the improvement of drive for thinness upon discharge. A deeper psychopathological characterization of patients with AN could be helpful in planning treatments for AN patients.

Key words

Temperament • Drive for thinness • Cooperativeness • Hospitalization • Treatment outcome

Correspondence

Giovanni Abbate-Daga
Department of Neuroscience, University of Turin, via Cherasco 15, 10126 Turin, Italy
• Tel. +39 011 6335196 • Fax +39 011 6335749
• E-mail: giovanni.abbatedaga@unito.it

Introduction

Anorexia nervosa (AN) is a severe psychiatric disorder [1] for which the precise etiology remains elusive. Moreover, AN features severe medical sequelae [2], and demonstrates the highest rates of mortality among any psychiatric illness [3], and high psychiatric comorbidity with other psychiatric conditions [4]. Importantly, AN is robustly associated with a particular

constellation of personality traits, which may provide clues to the elusive neurobiology of AN, since these traits are neurally encoded.

Personality has been strongly linked to the development and maintenance of AN [5], and personality traits ought to be taken into account as potentially impacting on outcome in AN. For example, neuroticism and perfectionism have been acknowledged as risk factors for eating disorders [6]. With more detail, temperament in AN is typically characterized by heightened anxiety, marked cognitive inflexibility, high harm avoidance [6-8] mirroring the alterations of the neural circuit functions found in AN [9]. Moreover, such characteristics tend to persist after recovery [6 10] and need to receive close attention when planning treatments. Treatment models focused on temperament [11] and personality [12] have been proposed, and personality traits also predict outcome in outpatient setting [13]. Also, cognitive-behavioral [14] and psychodynamic [15] treatments positively modulate personality traits as well. However, it remains unclear as to whether changes in personality traits favor the improvement of symptoms or vice versa. Still, personality traits can impact on treatment compliance [7], possibly influencing those feelings of refusal and anger typical of a subgroup of patients with eating disorders [16].

The thorough explication of personality traits among patients with AN offers much promise, in both developing precision treatments, and discerning who may benefit from specific treatments [11]. However, a key endeavor in expanding this body of evidence relates to the delineation of state- versus trait-level risk or maintaining factors in AN, as it relates to personality traits. Indeed, state-related neurocognitive effects of starvation are profound [17], portending both morphological and functional brain perturbations [18]. As such, the careful delineation of state versus trait related personality variables in AN is of critical importance, since some evidence suggests a change in personality trait expression in those with AN upon recovery [19]. While most studies of personality structure in those with AN have been conducted in outpatient settings [7], or those recovered from the illness [10], an important gap currently relates to the personality structure of AN patients in acute settings.

Urgent hospitalizations are often required in the treatment of AN, given the propensity for rapid medical complications [2]. Broadly speaking, these admissions can be effective over the short-term [20], and particularly in those patients whose life-threatening condition requires involuntary treatment [21]. However, hospitalization admissions typically impact mostly on weight restoration and regularization of clinical parameters (i.e., blood tests [22]), rather than on the cognitive symptoms of AN. In fact, it is well-known that about one-third of inpatients with AN significantly improve their weight but not their overall eating symptomatology, as measured by EDI-2 upon discharge [23]. Therefore, it would be of clinical importance to identify early predictors of treatment response with respect to patients' eating psychopathology, independently of patients' clinical improvement. This would allow to sustain the improvement of both weight and clinical parameters over time.

A core feature of AN is encapsulated in the drive for thinness (DT), which refers to the ubiquitous and relentless pursuit of the thin ideal. An elevated drive for thinness is typical of those affected by both AN and bulimia nervosa (BN); in fact, sufferers report marked fear of weight gain with the strong tendency to restrictive eating [24 25]. This core dimension of AN appears resistant to improvement during a brief and acute hospitalization, where a period of rapid weight gain is common [26]. Earlier research showed that DT in individuals with AN or BN directly correlates with the degree of eating disorder-related psychopathology, suggesting that DT is a potential predictor of relapse [27]. Additionally, DT is robustly associated with disordered eating and intentional weight loss as well [28]. Interestingly, DT also significantly correlated with those structural brain changes (neuroanatomical signatures) that are early associated with AN in a machine learning approach model [29].

Psychopathological and personality aspects are considered factors influencing treatment response and outcome in programmed hospitalizations [30 31]; notwithstanding, data on emergency hospitalizations are scarce. A better understanding of these variables could allow a greater individualization of treatments and therefore a more positive response to emergency admissions, mostly in regard to this core psychopathological element of the disorder.

The aim of this study is to analyze a group of inpatients with AN whose clinical severity required an emergency admission to an Eating Disorders Unit in order to ascertain as to whether personality traits can be associated with the improvement of eating psychopathology as measured by the DT subscale of the EDI-2 [32]. We expected that more adaptive personality traits upon admission could correlate with the improvement of eating psychopathology modulating patients' fear of weight gain.

Materials and methods

Participants

We consecutively enrolled 113 adult and female inpatients diagnosed with AN both subtypes (79 with restricting AN [R-AN] and 34 with binge-purging AN [BP-AN]) according to DSM-5 criteria [33] between March 2014 and November 2017 at the ward for Eating Disorders of the "Città della Salute e della Scienza" Hospital of the Uni-

versity of Turin, Italy. Participants had to meet the following inclusion criteria: a) age > 18 and < 55 years old; b) female gender; c) no substance dependence; d) no psychosis or psychotic symptoms according to DSM-5 criteria [33].

Participants were all Caucasian. All participants completed the assessments within the first week of hospitalization to minimize confounders due to treatment interventions. All participants provided written informed consent.

The hospitalization intervention

All patients were hospitalized because of emergency reasons; therefore, the aims of this intervention were to achieve medical stabilization and re-feeding and to provide psychosocial interventions in order to motivating patients to the following treatment steps (i.e., partial hospitalization or outpatient services).

Therefore, during hospitalization, patients were provided with individualized treatment plans [34] improving patients' overall motivation to treatment. The clinical team included psychiatrists, clinical psychologists, nurses, a registered dietitian and an internal medicine physician.

Weight restoration (including parenteral and enteral re-feeding when needed) is intended as a first-step intervention in order to minimize the life-threatening risks due to severe malnutrition. Weight restoration is strictly monitored in order to avoid the refeeding syndrome. Five structured meals are provided (breakfast, half-morning snack, lunch, mid-afternoon snack and dinner) and more snacks can be administered according to individualized treatment plans. Blood tests and ECG were frequently performed per clinical evaluation.

Psychiatric visits are intended to assess the presence of psychiatric comorbidities and to investigate the medical issues related to psychopharmacology. Moreover, patients are provided with daily individual motivational sessions, daily individual psychotherapy and weekly psycho-educational and cognitive-behavioral groups in order to improve their compliance, motivation, therapeutic alliance and mobilize as much as possible inpatients' resources. Support to parents or significant others is offered to all patients.

Before discharge, all patients receive detailed clinical information about potential strategies to put in place at home in order to avoid relapses.

Measures

A trained nurse measured patients' height and weight upon admission (T0) and discharge (T1) to calculate Body Mass Index (BMI). Participants were asked to complete the following self-report assessments:

1. the Temperament and Character Inventory (TCI). The TCI [35] is a 240-item self-administered questionnaire divided into 7 dimensions. Four of these dimensions assess temperament: novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (P). The other three dimensions assess character: self-directedness (SD), cooperativeness (C), and self-transcendence (ST). The TCI showed sound psychometric properties [36];
2. State Trait Anxiety Inventory (STAI). The STAI [37] is a well-established 20-item self-report instrument for the state and trait anxiety. All items are rated on a 4-point scale. The STAI measures two types of anxiety: state anxiety, a temporary condition experienced in specific situations, and trait anxiety, a general tendency to perceive situations as threatening. Total scores for state and trait sections separately range from 20 to 80, with higher scores indicating higher levels of anxiety;
3. Beck Depression Inventory (BDI). The BDI [38] is a 13-item self-report questionnaire evaluating depressive symptoms. Scores from 0 to 4 represent minimal depressive symptoms, scores of 5-7 indicate mild depression, scores of 8-15 indicate moderate depression and scores of 16-39 indicate severe depression;
4. Eating disorders inventory-2 (EDI-2). The EDI-2 [32] is a psychometrically sound self-report evaluation of disordered eating patterns, behaviors and personality traits shared by individuals affected by an eating disorder (ED). Ninety-one items and eleven subscales assess both symptoms and psychological correlates of EDs. Each item can be rated on a 6-point response scale; the higher the score, the more elevated eating psychopathology. Drive for thinness (seven items), bulimia (seven items) and body dissatisfaction (nine items) represent the 'symptom index'. Participants were divided in two groups according to the improvement (I-DT) versus worsening (W-DT) of the DT subscale upon hospital discharge;
5. the Eating Disorders Examination Questionnaire (EDE-Q [39]) is a 28-item self-report questionnaire with high internal consistency that provides a measure of characteristics and severity of eating disorder features. Four subscales are available: Restraint, Eating Concern, Shape Concern, and Weight Concern but only the total score has been included in this study.

Statistical analysis

The SPSS 24.0 statistical software package (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp) has been used for data analysis. Paired sample t-test has been used to verify any significant changes occurred between hospital admission and discharge. A repeated measures ANOVA has been conducted to assess DT changes between I-DT and W-DT groups.

Independent samples t-test have been applied to continuous variables (i.e., clinical data and questionnaires). Fisher's exact test has been used for categorical variables to maximize reliability independently of cell counts. Statistical significance has been set at 0.05.

Results

Socio-demographic and clinical characteristics of the sample

Twelve patients had to be excluded since males, 5 patients were discarded given their psychotic comorbidity and 9 patients failed to successfully complete the self-report battery of assessment. Therefore, the total sample was finally composed by 113 women affected by AN both subtypes: 79 with R-AN and 34 with BP-AN. Mean BMI was 14.27 ± 1.8, mean age was 24.5 ± 9.4 years, mean duration of illness was 6.8 ± 8.6 years, and mean duration of hospitalization 36.3 ± 17.1 days.

AN subtypes significantly differed only on duration of illness (R-AN: 5.43 ± 7.72 versus BP-AN 9.64 ± 9.72, t = -2.45, p = 0.016) but not with respect to age, BMI, duration of hospitalization and caloric intake upon admission (data not shown). With respect to general and eating psychopathology, R-AN and BP-AN groups differed in TCI self-directedness, trait-anxiety, and EDE-Q total score (data not shown).

Clinical outcomes for hospitalized patients with AN

Patients significantly improved in BMI, state anxiety and depression at discharge. Trait anxiety did not change in a statistically significant way (Tab. I).

As regards eating psychopathology, patients did not significantly improve on the EDI-2 core subscales (i.e., drive for thinness, bulimia, body dissatisfaction), with the exception of the bulimia subscale (Tab. I); in contrast, the EDE-Q total score showed a significant improvement upon discharge.

Relationship between personality and hospitalization outcome

According to the improvement versus worsening of the DT subscale upon hospital discharge, 46 patients were classified as W-DT (T0 11.89 ± 7.32, T1 14.87 ± 7.23, t = -6.774, p < 0.001) while 67 patients as I-DT (T0 12.95 ± 8.18, T1 10.02 ± 8.1, t = -5.398, p < 0.001). W-DT and I-DT groups had a significant impact on changes in DT (groups x time F 59,801; p < 0.001; see Figure 1).

Only the cooperativeness personality trait was found to significantly differ between W-DT and I-DT groups (see Table II). No other significant differences could be found either on clinical variables, diagnostic subtypes (Fisher's exact test p = 1), or on the TCI and other questionnaires used (Tab. II).

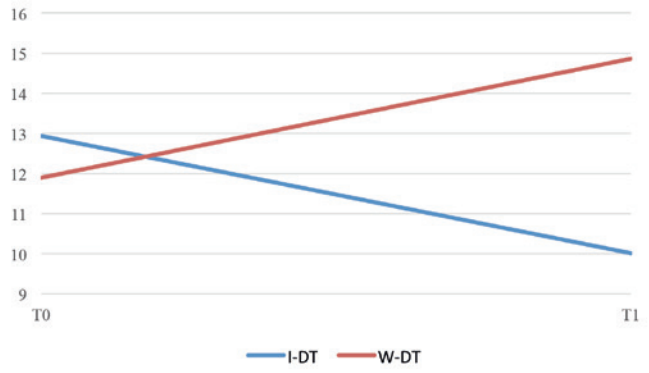
Discussion

A psychopathological characterization of patients with AN is needed in order to provide increasingly effective and individualized treatments for those who suffer from such a severe disorder and tend to be hospitalized after an emergency admission. This study showed that hospitalizations are overall effective in improving eating symptoms; moreover, higher cooperativeness, a char-

TABLE I. *Clinical changes between hospital admission and discharge of patients with anorexia nervosa.*

	AN patients (n = 113)		Test statistics	
	T0	T1	t	p
Weight	37.23(5.69)	39.20(5.04)	-8.473	0.001
BMI	14.27(1.84)	15.05(1.59)	-7.606	0.001
Caloric intake	660.63(338.79)	1570.83(361.41)	-19.723	0.001
EDI-2				
DT	12.54(7.83)	11.92(8.07)	1.307	0.194
B	3.04(4.45)	1.58(2.86)	4.195	0.001
BD	14.73(7.23)	14.41(7.37)	0.697	0.487
STAI-State	55.65(14.31)	51.81(15.96)	3.087	0.003
STAI-Trait	57.59(12.94)	55.43(15.68)	1.842	0.069
BDI	15.78(8.04)	11.59(8.26)	6.024	0.001
EDE-Q-TOT	3.48(1.68)	2.76(1.68)	6.656	0.001

AN: anorexia nervosa; BMI: body mass index; EDI-2: Eating disorders inventory-2; DT: drive for thinness; B: bulimia; BD: body dissatisfaction; STAI: State Trait Anxiety Inventory; BDI: Beck Depression Inventory; EDE-Q-TOT: Eating Disorders Examination Questionnaire total score



I-DT: improved drive for thinness (I-DT); W-DT: worsened drive for thinness

FIGURE 1. *Changes in drive for thinness at hospital admission (T0) and discharge (T1) of the groups with improved (I-DT) versus worsened (W-DT) drive for thinness.*

acter dimension according to the TCI model of personality [35], resulted as associated with the improvement of DT after urgent hospital admission, a core psychopathological dimension of AN, as measured by the EDI-2 [32]. AN is plagued by marked mortality, with a standardized mortality ratio as high as 6 and 20% of deaths caused by suicide [40]. Therefore, hospitalizations are frequently required for both psychiatric and medical acute stabilization. A main goal of hospitalization is weight restoration, since starvation-related medical complications are a leading cause of mortality in AN, and moreover, body weight is a well-known predictor of readmission and relapse [41].

Urgent hospitalization is common in clinical practice and entails treating patients with different degrees of compliance and motivation. Clinical trials usually include patients who seek treatment in order to restore

TABLE II. *Differences in baseline characteristics between patients with anorexia nervosa who improved versus worsened their scores of drive for thinness upon hospital discharge.*

	I-DT (n = 67)	W-DT (n = 46)	Test statistics	
			t	p
Days of hospitalization	35.13(12.06)	38.29(20.80)	-0.847	0.399
BMI	13.86(1.8)	14.38(1.77)	0.839	0.404
Age, years	23.97(9.1)	25.13(9.75)	0.599	0.551
Duration of illness, years	6.7(7.51)	7.53(10.52)	0.450	0.654
Caloric intake	662.50(345.01)	667.12(348.86)	-0.059	0.953
TCI				
NS	16.69(6.38)	15.61(6.62)	-0.809	0.421
HA	20.94(7.69)	20.76(10.54)	-0.100	0.920
RD	13.27(3.98)	11.84(5.01)	-1.556	0.123
P	4.84(2)	4.47(2.69)	-0.781	0.437
SD	23.28(9.24)	21.45(9.55)	-0.945	0.347
C	29.74(9.27)	25.11(12.42)	-2.103	0.038
ST	11.15(6.62)	9.13(7.32)	-1.407	0.163
EDI-2				
DT	11.89(7.32)	12.95(8.18)	-0.645	0.520
B	2.95(4.23)	3.10(4.63)	-0.166	0.869
BD	15.24(6.39)	14.41(7.75)	0.550	0.584
STAI-State	53.89(14.05)	56.26(14.76)	-0.782	0.436
STAI-Trait	58.42(11.54)	56.97(13.78)	0.539	0.591
BDI	14.95(7.33)	16.49(8.42)	-0.921	0.359
EDE-Q-TOT	3.52(1.70)	3.49(1.69)	0.073	0.942

I-DT: improved drive for thinness; W-DT: worsened drive for thinness; BMI: body mass index; TCI: Temperament and Character Inventory; NS: novelty seeking; HA: harm avoidance: RD: reward dependence: P: persistence; SD: self-directedness; C: cooperativeness: ST: self-transcendence; EDI-2: Eating disorders inventory-2; DT: drive for thinness; B: bulimia; BD: body dissatisfaction; STAI: State Trait Anxiety Inventory; BDI: Beck Depression Inventory; EDE-Q-TOT: Eating Disorders Examination Questionnaire total score

their weight and often motivational interviewing is delivered before hospitalization. Therefore, real-world studies (i.e., including patients who are poorly motivated to seek treatment, suddenly hospitalized) are scarce and needed. In this perspective, our study shows that an urgent hospital intervention lasting around 5 weeks is effective in improving weight, bulimic symptoms, caloric intake and eating symptomatology (i.e., EDE-Q total score). Nevertheless, some psychopathological core aspects, i.e., DT, do not improve in all patients. This finding is in line with previous literature showing similar results in both adults [23] and adolescents [26].

Furthermore, this study illustrates the presence of two groups of patients: I-DT and W-DT, namely those patients whose drive for thinness improves or worsens during hospitalization as their weight stabilizes. These groups are largely comparable to one another on character traits measures, with the exception of cooperativeness, which is greater in those patients whose DT improves at discharge. Within Cloninger's model of personality [35], cooperativeness is a character dimension that can be divided into five sub-dimensions: social acceptance *vs* intolerance (C1); empathy *vs* social disinterest (C2); helpfulness *vs* unhelpfulness (C3); compassion *vs* revengefulness (C4); principles vs. self-advantage (C5). Therefore, cooperativeness is a multifaceted and complex construct with multiple clinical implications. For example, it is relevant in the context of therapeutic alliance, which is centrally embedded in all therapeutic modalities in the clinical management of AN and bears much prognostic salience [42]. Also, it can be crucial in intensive and urgent hospitalizations. In fact, patients with AN tend to refuse treatments and to be hardly engaged in the therapeutic relationship.

Cooperativeness has been linked to dropout as well, which is characteristically elevated in patients with AN, alongside its closely correlated treatment-resistance [12]. Earlier research showed that patients who dropout from psychotherapy report lower self-directedness and cooperativeness compared to patients who complete treatment [43]. Further, findings from our group showed that patients with poor cognitive flexibility report also lower scores on cooperativeness and reward dependence than healthy controls [44]. Finally, cooperativeness is linked to impulsive behaviors, including binge eating, with the mediation of anger in bulimia nervosa [16]. Since AN is characterized by high treatment dropout, and poor outcomes [45], future research should investigate whether cooperativeness is correlated with more positive early life experiences; a crucial factor in determining both the extent to which patients trust their treatment [46], and long-term outcome [45].

Our findings are only in part in line with previous research on severe inpatients with AN. For example, Bennett and collaborators [47] found that patients affected by restrictive type AN (R-AN) reported significantly higher cooperativeness than those with binge/purge type AN (BP-AN). The authors suggested that the R-AN group could be more prone than those with BP-AN to accept treatment in the very acute phase of AN [47]. Although the authors focused on patients with BMI lower than 13, personality traits have been suggested to be independent of BMI scores [19]; therefore, different sample sizes could be responsible for this contrasting finding but further research is needed relating to the personality and prognosis of those patients with AN requiring an emergency hospitalization.

Data on the stability of personality traits are mixed. On one hand, personality traits have been found to be stable after recovery [10 19], while other studies suggest a more state-related fluidity of personality [48]. More specifically, cooperativeness is typically elevated in individuals who recovered from AN, as well as harm avoidance and self-directedness [19]. Although longitudinal research is required to shed light on this issue, our findings provide support to this latter hypothesis, given the association found between higher cooperativeness scores and improvement in core eating psychopathology after hospitalization.

Drive for thinness is a core dimension of AN and a relevant maintaining factor; as a consequence, it would be of clinical interest to find eventual predictor of DT improvement. Recent prospective research found that fear of food could predict DT after an intensive ED treatment [49]. In keeping with data on adult [23] and adolescent inpatients [26], no significant improvement could be found over the course of hospitalization although the vast majority of other clinical parameters did improve. From a psychopathological standpoint, this (non) datum further highlights DT as a key-element of AN.

In closing, some limitations can be acknowledged: participants' severity (i.e., BMI and duration of illness) could jeopardize the generalizability of the results, data are limited to treatment seeking individuals, and no follow-up data are available. Nevertheless, these findings could have clinical implications. In fact, given the association between baseline personality and DT after hospitalization, cooperativeness could help patients being more prone to be engaged in treatment, helping patients overcome those eating-related anxiety and fears that substantially hinder recovery from AN [50]. Also, in keeping with earlier literature [6 13], our findings confirm that personality should be taken carefully into account in defining treatment plans.

Conflict of Interest

The authors have no conflict of interests.

References

1. Klump KL, Bulik CM, Kaye WH, et al. *Academy for eating disorders position paper: eating disorders are serious mental illnesses.* Int J Eat Disord 2009;42:97-103.
2. Stheneur C, Ali A, Tric L, et al. *Impact of somatic severity on long-term mortality in anorex ia nervosa.* Eat Weight Disord 2017;22:285-9.
3. Papadopoulos FC, Ekbom A, Brandt L, et al. *Excess mortality, causes of death and prognostic factors in anorexia nervosa.* Br J Psychiatry 2009;194:10-7.
4. Ulfvebrand S, Birgegård A, Norring C, et al. *Psychiatric comorbidity in women and men with eating disorders results from a large clinical database*. Psychiatry Res 2015;230:294-9.
5. Rotella F, Fioravanti G, Ricca V. *Temperament and personality in eating disorders*. Curr Opin Psychiatry 2016;29:77-83.
6. Lilenfeld LR. *Personality and temperament*. Curr Top Behav Neurosci 2011;6:3-16.
7. Fassino S, Abbate-Daga G, Amianto F, et al. *Temperament and character profile of eating disorders: a controlled study with the temperament and character inventory*. Int J Eat Disord 2002;32:412-25.
8. Jáuregui-Lobera I. *Executive functions in anorexia nervosa*. Nutr Hosp 2014;29:500-7.
9. Kaye WH, Wierenga CE, Bailer UF, et al. *Does a shared neurobiology for foods and drugs of abuse contribute to extremes of food ingestion in anorexia and bulimia nervosa?* Biol Psychiatry 2013;73:836-42.
10. Wagner A, Barbarich-Marsteller NC, Frank GK, et al. *Personality traits after recovery from eating disorders: do subtypes differ?* Int J Eat Disord 2006;39:276-84.
11. Kaye WH, Wierenga CE, Knatz S, et al. *Temperament-based treatment for anorexia nervosa*. Eur Eat Disord Rev 2015;23:12-8.
12. Abbate-Daga G, Amianto F, Delsedime N, et al. *Resistance to treatment and change in anorexia nervosa [corrected]: a clinical overview*. BMC Psychiatry 2013;13:294.
13. Segura-García C, Chiodo D, Sinopoli F, et al. *Temperamental factors predict long-term modifications of eating disorders after treatment*. BMC Psychiatry 2013;13:288.
14. Dalle Grave R, Calugi S, Brambilla F, et al. *The effect of inpatient cognitive-behavioral therapy for eating disorders on temperament and character*. Behav Res Ther 2007;45:1335-44.
15. Amianto F, Spalatro A, Ottone L, et al. *Naturalistic follow-up of subjects affected with anorexia nervosa 8 years after multimodal treatment: Personality and psychopathology changes and predictors of outcome*. Eur Psychiatry 2017;45:198-206.
16. Amianto F, Siccardi S, Abbate-Daga G, et al. *Does anger mediate between personality and eating symptoms in bulimia nervosa?* Psychiatry Res 2012;200:502-12.
17. Guillaume S, Gorwood P, Jollant F, et al. *Impaired decision-making in symptomatic anorexia and bulimia nervosa patients: a meta-analysis*. Psychol Med 2015;45:3377-91.
18. Sheng M, Lu H, Liu P, et al. *Cerebral perfusion differences in women currently with and recovered from anorexia nervosa*. Psychiatry Res 2015;232:175-83.
19. Klump KL, Strober M, Bulik CM, et al. *Personality characteristics of women before and after recovery from an eating disorder.* Psychol Med 2004;34:1407-18.
20. Abbate-Daga G, Facchini F, Marzola E, et al. *Health-related quality of life in adult inpatients affected by anorexia nervosa*. Eur Eat Disord Rev 2014;22:285-91.
21. Elzakkers IF, Danner UN, Hoek HW, et al. *Compulsory treatment in anorexia nervosa: a review*. Int J Eat Disord 2014;47:845-52.
22. Kawai K, Yamashita S, Komaki G, et al. *The outcome of treatment for anorexia nervosa inpatients who required urgent hospitalization*. Biopsychosoc Med 2014;8:20.
23. Schlegl S, Diedrich A, Neumayr C, et al. *inpatient treatment for adolescents with anorexia nervosa: clinical significance and predictors of treatment outcome*. Eur Eat Disord Rev 2016;24:214-22.
24. Chernyak Y, Lowe MR. *Motivations for dieting: drive for thinness is different from drive for objective thinness*. J Abnorm Psychol 2010;119:276-81.
25. Peñas-Lledó E, Bulik CM, Lichtenstein P, et al. *Risk for self-reported anorexia or bulimia nervosa based on drive for thinness and negative affect clusters/dimensions during adolescence: a three-year prospective study of the TChAD cohort*. Int J Eat Disord 2015;48:692-9.
26. Fennig S, Brunstein Klomek A, Shahar B, et al. *Inpatient treatment has no impact on the core thoughts and perceptions in adolescents with anorexia nervosa*. Early Interv Psychiatry 2017;11:200-7.
27. Ramacciotti CE, Dell'Osso L, Paoli RA, et al. *Characteristics of eating disorder patients without a drive for thinness*. Int J Eat Disord 2002;32:206-12.
28. Keski-Rahkonen A, Bulik CM, Neale BM, et al. *Body dissatisfaction and drive for thinness in young adult twins*. Int J Eat Disord 2005;37:188-99.
29. Lavagnino L, Amianto F, Mwangi B, et al. *Identifying neuroanatomical signatures of anorexia nervosa: a multivariate machine learning approach*. Psychol Med 2015;45:2805-12.
30. Kästner D, Gumz A, Osen B, et al. *predictors of Outcome in Inpatients with Anorexia Nervosa: A Prospective Multi-Center Study.* Psychother Psychosom 2015;84:255-7.
31. Goddard E, Hibbs R, Raenker S, et al. *A multi-centre cohort study of short term outcomes of hospital treatment for anorexia nervosa in the UK*. BMC Psychiatry 2013;13:287.
32. Garner DM. *Eating disorder inventory 2: professional manual*. Odessa: Psychological Assessment Resources 1991.
33. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*, *5th Edition* 2013.
34. National Institute for Health and Clinical Excellence. *Eating disorders: recognition and treatment. NICE guideline (NG69)* 2017.
35. Cloninger CR, Svrakic DM, Przybeck TR. *A psychobiological model of temperament and character*. Arch Gen Psychiatry 1993;50:975-90.
36. Fossati A, Cloninger CR, Villa D, et al. *Reliability and validity of the Italian version of the temperament and character inventory-revised in an outpatient sample*. Compr Psychiatry 2007;48:380-7.
37. Spielberger CD, Gorsuch RL, Lushene R, et al. *Manual for the state-trait anxiety inventory.* Palo Alto: Consulting Psychologists Press 1983.
38. Beck A, Ward C, Mendelson M, et al. *An inventory for measuring depression*. Arch Gen Psychiatry 1961;4:561-71.
39. Fairburn CG, Beglin SJ. *Assessment of eating disorders: interview or self-report questionnaire?* Int J Eat Disord 1994;16:363-70.
40. Arcelus J, Mitchell AJ, Wales J, et al. *Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies*. Arch Gen Psychiatry 2011;68:724-31.
41. Lund BC, Hernandez ER, Yates WR, et al. *Rate of inpatient weight restoration predicts outcome in anorexia nervosa*. Int J Eat Disord 2009;42:301-5.
42. Graves TA, Tabri N, Thompson-Brenner H, et al. *A meta-analysis of the relation between therapeutic alliance and treatment outcome in eating disorders*. Int J Eat Disord 2017;50:323-40.
43. Fassino S, Daga GA, Pierò A, et al. *Dropout from brief psychotherapy in an-*

orexia nervosa. Psychother Psychosom 2002;71:200-6.

44 Abbate-Daga G, Buzzichelli S, Marzola E, et al. *Clinical investigation of set-shifting subtypes in anorexia nervosa*. Psychiatry Res 2014;219:592-7.

45 Castellini G, Lelli L, Ricca V, et al. *Sexuality in eating disorders patients: etiological factors, sexual dysfunction and identity issues. A systematic review*. Horm Mol Biol Clin Investig 2016;25:71-90.

46 Dunn EC, McLaughlin KA, Slopen N, et al. *Developmental timing of child maltreatment and symptoms of depression and suicidal ideation in young adulthood: results from the National Longitudinal Study of Adolescent Health*. Depress Anxiety 2013;30:955-64.

47 Bennett SL, Gaudiani JL, Brinton JT, et al. *Motivated to survive: high cooperativeness in severe anorexia nervosa*. Eat Disord 2015;23:430-8.

48 Kuipers GS, Hollander SD, van der Ark LA, et al. *Recovery from eating disorder 1 year after start of treatment is related to better mentalization and strong reduction of sensitivity to others.* Eat Weight Disord 2017;22:535-47.

49 Levinson CA, Brosof LC, Ma J, et al. *Fear of food prospectively predicts drive for thinness in an eating disorder sample recently discharged from intensive treatment.* Eat Behav 2017;27:45-51.

50 Murray SB, Loeb KL, Le Grange D. *Dissecting the core fear in anorexia nervosa: can we optimize treatment mechanisms?* JAMA Psychiatry 2016;73:891-2.

JOURNAL OF PSYCHOPATHOLOGY
2018;24:133-140

Original article

A. Brytek-Matera[1], C. Gramaglia[2 3], E. Gambaro[2], C. Delicato[2], P. Zeppegno[2 3]

[1] SWPS University of Social Sciences and Humanities, Katowice Faculty of Psychology Katowice, Poland; [2] Institute of Psychiatry, Università degli Studi del Piemonte Orientale, Novara, Italy;[3] S.C. Psychiatry, Azienda Ospedaliero Universitaria Maggiore della Carità, Novara, Italy

The psychopathology of body image in orthorexia nervosa

Summary

The human body has a complex meaning and role in everybody's life and experience. Body image has two main components: body percept (the internal visual image of body shape and size) and body concept (the level of satisfaction with one's body), whose specific alterations may lead to different conditions, such as overestimation of one's own body dimensions, negative feelings and thoughts towards the body, body avoidance and body checking behavior. Moreover, body dissatisfaction can be associated with a variety of other mental health and psychosocial conditions, but only a few studies have explored the body image construct in orthorexia nervosa (ON). ON is a condition characterized by concern and fixation about healthy eating, with mixed results available in the literature about the presence of body image disorders. The aim of this manuscript is to present the main findings from the literature about the psychopathology of body image in ON. Summarizing, while theoretically the presence of body image disturbances should help clinicians to differentiate ON from eating disorders, further research is needed to confirm this finding. It is not clear whether the body image disorder in ON depends on an altered body percept or body concept, and the relationship between the disordered eating behavior and body image disorder still needs to be disentangled. Further studies regarding the relationship between ON and body image could be helpful to better understand the relevance of body image as a transdiagnostic factor and its potential value as target for treatment interventions.

Key words
Orthorexia nervosa • Eating disorders • Body image

Introduction

The human body has a complex meaning and role in everybody's life and experience. Our bodily being-in-the-world describes an existential position, where the body is both object and subject, and represents a subjective and intersubjective ground of and for experience. The complexity inherent the meaning and role of the human body mirrors itself in the complexity of defining constructs in this field. For instance, the term "body image" is and has been widely used, often in a rather unspecific manner, with a poor discrimination among different dimensions of embodiment, such as body schema, body image and lived body [1], with a consensus still lacking on terminology [2]. Body image should be differentiated from body schema, which is an unconscious model or representation of one's own body that constitutes a standard along which postures and body movements are judged, "a system of sensory-motor capacities that function without awareness or the necessity of perceptual monitoring" [2-4]. The lived body is a phenomenology-derived concept addressing the body experienced from within, the direct experience of one's own body in the first-person perspective, as a spatio-temporal embodied agent in the world [4-8]. According to Schilder, body image can be defined as "the picture of our own body which we form in our mind, that is to say, the way in which the body appears to ourselves" [3]. Allamani and Allegranzi [9] refer to body image as "a complex psychological organization which develops through the

Correspondence
Patrizia Zeppegno
Institute of Psychiatry, Università degli Studi del Piemonte Orientale, via Solaroli 17, 28100 Novara, Italy • Tel./Fax +39 0321 390163/+39 0321 3733121
• E-mail: patrizia.zeppegno@med.uniupo.it

bodily experience of an individual and affects both the schema of behavior and a fundamental nucleus of self-image". Subsequently, Shontz [10] integrated theory and data about cognitive and perceptual aspects of body experience (such as body size estimation) and was the first to consider the body experience as multidimensional. Afterwards, Cash and Pruzinsky [11] defined body image as a multifaceted psychological experience of embodiment, a construct encompassing body-related self-perceptions and self-attitudes, including thoughts, beliefs, feelings, and behaviors. The same authors later conceptualized embodiment beyond body appearance and dissatisfaction, including in the construct body functionality and positive body image, as well [12].

Interestingly, the terminological confusion described above can be found even within the body image research community, where the definition of the construct fluctuates depending on the aim of the researcher [12-15].

Psychopathology of body image

Body image can be defined as the internal representation of one's physical appearance; it is a multidimensional, socio-culturally dependent construct encompassing perceptual, cognitive, affective and behavioral issues [16-18]. At a broad level, body image has two main components [19]: body percept and body concept. The former is the internal visual image of body shape and size, while the latter refers to the level of satisfaction with one's body [19 20].

The specific psychopathology of body image can thus span from disorders in body perception to the consequences of alterations in its cognitive-affective dimensions. Dysfunction in one or more of the body image components can lead to specific problems, such as: overestimation of one's own body dimensions [21-24], negative feelings and thoughts towards the body [25], body avoidance and body checking behavior [26 27]. All these problems can be described with the definition of "body image distortion", which means a disturbed pattern of individuals' experience of their own body weight or shape. As body image, its distortion is a multifaceted construct including cognitive and affective components (concerns and feelings about the body), perception (estimation of body size) and body perception-related behaviors [2].

Experience of own body, together with body attitude, mirrors the individuals' feelings about themselves as persons or social participants. Therefore, an altered body size perception may express people's sense of self-worth; for instance, a sense of body smallness could express a sense of loss of worth and status [28]. Moreover, body concept and the related construct of body dissatisfaction depend on the continuous comparison between one's own body and an "ideal" body, as well as on vulnerability and sensitivity to judgment. Hence, the term "body dissatisfaction" refers to the negative emotions and thoughts elicited by the perceived discrepancy between ideal and current body shape and weight [15 29]. Even though in the last years there has been such a steady increase of female body dissatisfaction that there seems to exist a "normative discontent" [30], body dissatisfaction is generally related to body shape and weight [31], possibly leading to eating disorders (EDs) [32]. Moreover, body dissatisfaction can be associated with a variety of other mental health and psychosocial conditions, including low self-esteem [31], emotional distress [33], depression [34], cosmetic surgery and steroid use [35], social anxiety, and sexual difficulties [32].

The specific abnormalities in lived corporeality described in patients with full-blown EDs, including anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED), have been linked to the individuals' experience of their own body first and foremost as an object being looked at by other people, rather something lived and experienced from a first-person perspective [1]. ED patients may feel alienated from their body, do not 'feel' themselves, and especially they do not feel their own body and emotions [36-42]. Troubles in developing their personal identity may lead to the attempt of trying to define their own selves in terms of the way they are evaluated by others. From this viewpoint, EDs are considered a maladaptive "search for self-hood and a self-respecting identity" [43]. The key role of feeding in the construction of the self, via the phenomenon of "affective attunement" with the caregiver, is an essential step toward the development of a narrative self and a sense of identity [44].

Orthorexia

In 1997, Steven Bratman introduced the term "orthorexia nervosa" (ON) and coined the phrase "health food junkies" to indicate individuals following strict dietary rules intended to promote health, but eventually leading to possible health-detrimental consequences [45]. The term "orthorexia" is a neologism deriving from the Greek ὀρθός, right, and ὄρεξις, appetite; even though literally meaning "correct appetite", it is used to designate an "obsession for healthy and proper nutrition" [45]. Typically, individuals with orthorexic behaviors follow a very rigid diet and reject many foods, due to their composition or elaboration (including those containing significant amounts of fat, sugar, salt, or other undesired components). They may be vegetarians, vegans, frugivores (i.e., eat only fruit) or crudivores (i.e., eat only raw food), and usually refuse to eat away from home, due to lack of trust in food preparation procedures. Such a restrictive dieting attitude may lead to several nutritional deficits and medical complications (e.g. osteopenia, anaemia,

pancytopenia, hyponatraemia, metabolic acidosis and bradycardia), which closely resemble the qualitative and quantitative malnutrition status typical of AN [46]. In addition, individuals with orthorexic behaviors may show feelings of moral superiority and self-righteousness related to their eating patterns and are at risk of social isolation [47].

The prevalence of ON is about 7% in the general population, while higher rates (up to 50%) have been found in "high-risk groups", including healthcare professionals, dietitians or artistic performers [48 49]. According to Dunn et al. [50], the variability in prevalence rates of ON is due to cultural issues or to diagnostic procedures (e.g., ORTO-15 test). Based on proxy categories for ON (seriousness of engagement about healthful eating and medical or social problems secondary to dieting), less than 1% of the US sample could be labeled as suffering from ON, and about 10% could be considered at risk for ON, even though the ORTO-15 scores suggest a prevalence rate of 71%.

It should be noted that despite having often been dubbed as "a disease disguised as a virtue", ON is currently not recognized as an "official" mental disorder [51]. According to the DSM-5, ON would be most appropriately categorized as a distinct subtype of "avoidant/restrictive food intake disorder" (ARFID) [52]. In ON it is not the healthy eating habit per se to be worrisome or pathological, but rather the excessive preoccupation about consuming healthy food, as well as an excessive amount of time spent on food thoughts [48]. Mounting evidence shows that ON shares some clinical features with other mental disorders including AN, obsessive-compulsive disorder, obsessive-compulsive personality disorder, somatic symptom disorder, illness anxiety disorder and psychotic spectrum disorders [53].

Regarding the overlap between ON and EDs, shared features include lack of pleasure about food and eating, perfectionism, anxiety, and the displacement onto food of the sense of control one is not able to achieve with own life. Despite these shared features, ON individuals focus on quality and purity of food, while EDs patients focus on food quantity. The first strive for a pure body, while the latter strive for a body matching an "ideal" of extreme thinness; nonetheless, the literature suggests a much more complex relationship between ON and EDs. Segura-Garcia et al. [54] reported a common comorbidity between ON and EDs (including AN and BN), whose frequency increased over time during a 3-year follow-up study. Another study involving ED patients found that orthorexic behavior was negatively predicted by eating pathology, weight concern, health orientation and appearance orientation [55]. Briefly, ON may precede the onset of a full-syndrome ED, coexist with it, or it may represent its evolution during remission and recovery phases [55].

From a psychopathological viewpoint, orthorexia has been also closely linked to obsessive-compulsive personality/disorder [56] (Fig. 1). Shared features with the obsessive-compulsive disorder spectrum include the presence of recurrent, intrusive thoughts about food and health, related to strong preoccupations with food contamination and purity, as well as the overwhelming need to investigate source, processing and packaging of foods and to arrange food and to eat in a ritualized manner. These behaviors are usually experienced as ego-syntonic in ON [57].

Whether ON is a unique disorder or just a variant of anorexia or obsessive-compulsive disorder is still open to debate [53]. A more thorough understanding is needed about the motivations underlying the behaviors and body perception (e.g., pursuit of an ideal body shape vs. a healthy, pure body), ideation toward eating and food (e.g., worries about quantity vs. quality of food), insight/awareness (subjects with AN try to hide their habits whereas individuals with orthorexic tendencies allegedly show off their behavior) and socio-demographic characteristics (e.g., sex distribution, level of education, access to food-related information). This knowledge will help shedding light on the actual psychopathology at the root of ON [57].

Body image in ON

Due to similarities between ON and EDs, those factors which are widely acknowledged to play a role in the vulnerability, onset and maintenance of EDs (including body image, perfectionism, attachment style, self-esteem ecc.) [58 59], could be implicated also in ON.

A study investigating whether perfectionism, body image, attachment style and self-esteem predicted ON found that higher orthorexic tendencies significantly correlated with higher scores on perfectionism (self-oriented, others-oriented and socially prescribed), appearance orientation, overweight preoccupation, self-classified weight, fearful and dismissing attachment styles [60]. As suggested above, perfectionism could be a potential risk factor for ON, just as it is for the development and maintenance of EDs [58 61]. Interestingly, perfectionism may have an impact on adherence to strict food and dietary rules [45 58], which are shared key features of ON and EDs, but may also lead to a perfectionistic attitude towards one's own body and appearance. Moreover, overweight preoccupation, appearance orientation and the presence of an ED history were identified as significant predictors of ON, with the last one being the strongest predictor. Previous research involving ED patients and healthy controls [54] found that the prevalence of ON is higher in the patients' groups, and more recent studies do not yet allow to exclude that ON belongs to the same spectrum of AN and BN, with patients shifting between these conditions [62 63].

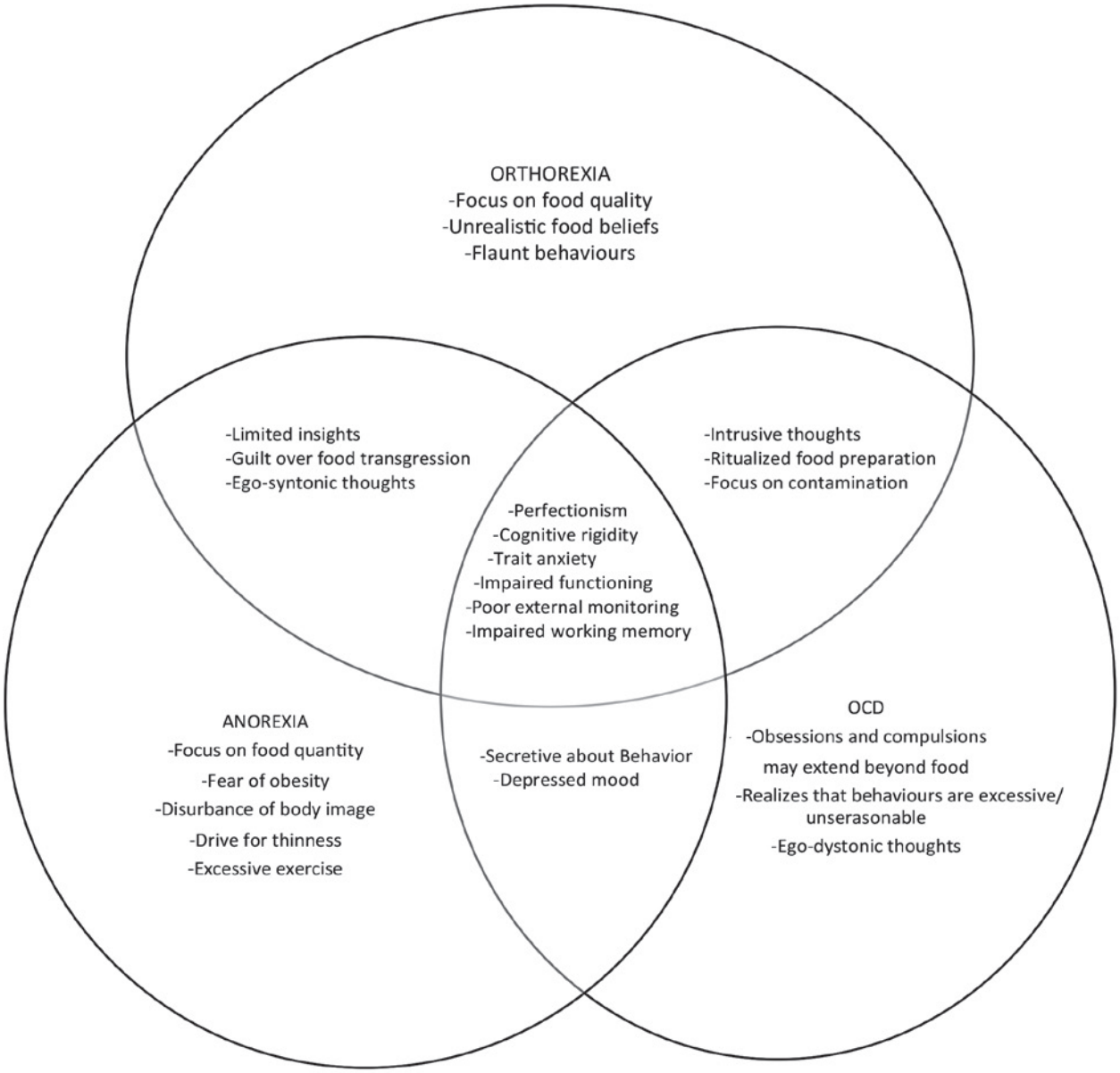


FIGURE 1. *Venn diagram representing the possible relationships between Anorexia Nervosa, Obsessive-Compulsive Disorder (OCD) and Orthorexia (from Vandereycken, 2011, mod.)* [56].

Considering the shared core similarities between AN and BN [57], an interesting perspective about ON is that the strenuous pursuit of a healthy diet may serve as a socially acceptable alternative for the unhealthy drive for thinness. Anyway, a discrepancy seems to exist between some preliminary clinical observations and the theoretical knowledge about ON. Regarding body image, ON individuals should not be concerned with weight loss, and they should not display the negative body image attitudes which are typical of AN and BN patients [45]. Dunn and Bratman's proposed diagnostic criteria identify ON as an independent pathological entity [64] (Tab. I), and do not include features such as body uneasiness, general body/weight dissatisfaction, avoidance and compulsive body-checking behavior, feelings of disconnection from one's own body and concerns about specific body parts. Even though ON may sometimes be associated with weight loss ensuing because of dietary choices, this is not likely the direct consequence of a desire to lose weight as the primary goal

TABLE I. *Dunn & Bratman criteria for orthorexia nervosa (from Dunn, Bratman, 2016, mod.) [64].*

Criterion A. Obsessive focus on "healthy" eating, as defined by a dietary theory or set of beliefs whose specific details may vary; marked by exaggerated emotional distress in relationship to food choices perceived as unhealthy; weight loss may ensue as a result of dietary choices, but this is not the primary goal as evidenced by the following:
A1. Compulsive behavior and/or mental preoccupation regarding affirmative and restrictive dietary practices believed by the individual to promote optimum health
A2. Violation of self-imposed dietary rules causes exaggerated fear of disease, sense of personal impurity and/or negative physical sensations, accompanied by anxiety and shame
A3. Dietary restrictions escalate over time, and may come to include elimination of entire food groups and involve progressively more frequent and/or severe "cleanses" (partial fasts) regarded as purifying or detoxifying. This escalation commonly leads to weight loss, but the desire to lose weight is absent, hidden or subordinated to ideation about healthy eating
Criterion B. The compulsive behavior and mental preoccupation becomes clinically impairing by any of the following:
B1. Malnutrition, severe weight loss or other medical complications from restricted diet
B2. Intrapersonal distress or impairment of social, academic or vocational functioning secondary to beliefs or behaviors about healthy diet
B3. Positive body image, self-worth, identity and/or satisfaction excessively dependent on compliance with self-defined "healthy" eating behavior

of the eating behavior, but rather seems the indirect one of an excessive preoccupation with eating healthy food. Even if the literature on orthorexia nervosa is until now mainly represented by descriptive and anecdotal data and focused primarily on measuring the prevalence of the condition in different countries [48 65 66] and in at-risk groups [48 49 67 68], a few studies are available about ON and body image [69-71].

A study involving male and female university students and examining the predictive model of ORTO-15 in both groups found that in female students lower ORTO-15 scores (greater severity of orthorexic behaviors) were related to a less pathological body image discomfort, while in male students lower ORTO-15 scores were related to less pathological eating patterns [70].

Another study reported that university students with ON were more likely to be engaged in regular physical exercise, more "health conscious", trying to live a healthy routine, afraid of gaining weight and more likely to follow diets, compared to healthy controls. Moreover, they were more likely to monitor their body weight and overestimate their body size [72]. Regarding gender differences, females with orthorexic tendencies were less likely to pay attention to their appearance, while they were more likely to classify themselves as less fit and less healthy than males with orthorexia. Moreover, females with orthorexic preoccupations seemed to have higher fat anxiety, to pay more attention to their body weight and to control their eating behavior more than males.

Contrarily to what described above, a few studies are available suggesting body image concerns and disorders in ON. A positive relationship between ON and body image disturbance has been suggested: Varga and Máté reported that body image disturbances are more severe when more ON features are present [68]. Similarly, an association between orthorexic tendencies and an increased preoccupation with appearance and fears of becoming overweight has been supported by the finding of a negative correlation between the ORTO-15 scores and appearance orientation and overweight preoccupation [48]. Moreover, orthorexic behaviors are also associated with an unhealthy or negative body image among students, regardless of their concern about healthy and appropriate food choices [70 71].

A cross-sectional study investigating the prevalence of ON and EDs in dieticians [73 74] found that about 50% is at risk for ON, and 12.9% for an ED. ON symptoms are associated with eating disturbances as well as with shape and weight concerns [73]. Another study involving nutrition and dietetics students found orthorexic behaviors in 68.2% of them, who had an increased Body Mass Index (BMI), reduced saturated fatty acid intake, increased waist circumference and energy intake [75]. Contrary to this study, Oberle and Lipschuetz [76] found no significant relationship between BMI and ON symptoms among students, while a positive correlation was found between ON symptoms and perceived muscularity, and a negative one between ON symptoms and perceived body fat. In addition, Bundros et al. [77] found a positive association between ON and body dysmorphic disorder among college students; this finding is consistent with a study involving fitness participants with orthorexic tendencies, who showed internalization of the thin ideal, social physique anxiety, body image dissatisfaction and disordered eating [78]. According to Featherstone [79], a slim, muscular body can be regarded as an evidence

that the individual is adhering to an ideal lifestyle; therefore, the failure in matching this body ideal and expectation can give rise to appearance-related anxiety. This anxiety may lead individuals to exert greater control over their diets, to contrast the inner fear of becoming unattractive, being regarded as unhealthy, and losing the opportunity to enjoy an ideal life.

Use of social media has negative effects on body image, depression, social comparison, and disordered eating. For example, a more frequent use of Instagram is associated with a greater tendency to develop ON [80]. An analysis of the #fitspiration tag on Instagram, used to denote images intended to inspire people to become fit and healthy, found that most images of women showed thin and toned bodies with objectifying elements, with negative effects on body image and self-esteem [81].

Conclusions

According to the currently available diagnostic criteria [52 64], ON is an emergent condition that stands out from other EDs for lack of concern with body weight and shape. Further studies on the relationship between ON and nosographically recognized EDs are needed to better understand the correlation among healthy eating, pathologically healthful eating and EDs development. Currently, it cannot be excluded that, at least in some cases, an exaggerated focus on appearance and a fear of becoming overweight might be hidden behind the preoccupation with a healthy diet. Follow-up studies have suggested that ON symptoms may worsen following treatment for other EDs [54 55], suggesting that, for former ED patients, ON may be a compromise to continue controlling food and their body shape and weight, although to a lesser degree than in AN [61].

Summarizing, while theoretically body image discomfort should be able to differentiate ON from other EDs, further research is needed to confirm this finding. At present, some studies [68-70 72-74 82-85] revealed a correlation between ON and body image concerns, in contrast to other studies [45 68 77 86 87] reporting the absence of body image or weight-related concerns in ON subjects. However, one of the limitations of available studies is the difficult assessment of the still uncategorized construct of ON. Indeed, most studies in the field of ON have adopted the ORTO-15 questionnaire, whose possible limitations in detecting the severity of orthorexic behaviors and attitudes have been suggested [88], hence leading to the recommendation of being cautious when interpreting its results as a reliable measure of the prevalence of ON [89]. The ORTO-15 40-points threshold value has a notable predictive capability concerning healthy eating behavior, while it seems less efficient in discriminating the other typical components of ON, that is the presence of obsessive traits [89], suggesting that the ORTO-15 is probably not likely to distinguish between healthy eating and pathologically healthful eating [65].

Future research could potentially benefit from investigations involving larger and more heterogeneous samples to gain more insight into the concept of body image and its association with ON [90]. Some issues deserve to be deepened: from a psychopathological standpoint, it would be interesting to better understand whether the possible body image disorder in ON depends on an altered body percept or body concept; moreover, disentangling the relationship between disordered eating behavior and body image disorders would be helpful also from a clinical standpoint. Addressing these topics would improve knowledge about the relevance of body image as a transdiagnostic factor [91] and its potential value as target for treatment interventions.

Conflict of Interest

The authors have no conflict of interests.

References

1 Stanghellini G, Trisolini F, Castellini G, et al. *Is feeling extraneous from one's own body a core vulnerability feature in eating disorders?* Psychopathology 2015;48:18-24.

2 Gallagher S. *How the body shapes the mind*. Oxford: Oxford UP 2006.

3 Schilder P. *The image and appearance of the human body: studies in the constructive energies of the psyche*. New York: International UP 1950.

4 Husserl E. *Ideen zu einer reinen phänomenologie und phänomenologische philosophie. II. Phänomenologische untersuchungen zur konstitution*. Den Haag: Nijhoff 1912-1915.

5 Merleau-Ponty M. *Phenomenology of perception*, English translation by C Smith. New York: Humanities Press 1996.

6 Stanghellini G, Rosfort R. *Emotions and personhood: exploring fragility – making sense of vulnerability*. Oxford: Oxford UP 2013.

7 Dillon MC. *Merleau-Ponty's ontology*. Evanston: Northwestern UP 1997.

8 Stanghellini G. *Embodiment and schizophrenia*. World Psychiatry 2009;8:1-4.

9 Allamani A, Allegranzi P. *Immagine corporea: dimensioni e misure. Una ricerca clinica* [*Body Image: Dimensions and measures. A clinical research*]. Arch Psicol Neurol Psichiatr 1990;2:171-95.

10 Shontz FC. *Perceptual and cognitive aspects of body experience*. New York, NY: Macmillan 1969.

11 Cash TF, Pruzinsky T. *Body images: development, deviance, and change.* New York, NY: Guilford Press 1990.

12 Cash TF, Pruzinsky T. *Future challenges for body image theory, research, and clinical practice*. In: Cash TF, Pruzinsky T, Eds. *Body image: a handbook of theory, research, and clinical practice* (2nd ed, pp. 509-16). New York, NY: Guilford Press 2002.

13 Cash TF, Smolak L. *Understanding body images: historical and contemporary perspectives*. In: Cash TF, Smolak L, Eds. *Body image: a handbook of science,*

practice, and prevention (2nd ed., pp. 3-11). New York, NY: Guilford Press 2011.

14 Blood SK. *Body work: The social construction of women's body image*. New-York, NY: Routledge 2005.

15 Grogan S. *Body image: understanding body dissatisfaction in men, women and children*. New York, NY: Routledge 2008.

16 Thompson JK. *The (mis)measurement of body image: ten strategies to improve assessment for applied and research purposes*. Body Image 2004;1:7-14.

17 Stewart TM, Williamson DA. *Multidisciplinary treatment of eating disorders part 1: Structure and costs of treatment.* Behav Modif 2004;28:812-30.

18 Thompson JK, Heinberg LJ, Altabe M, et al. *Exacting beauty. Theory, assessment and treatment of body image disturbances.* Washington, DC: American Psychological Association 1999.

19 Slade P. *What is body image?* Behav Res Ther 1994;32:497-502.

20 Slade P, Brodie D. *Body image distortion and eating disorder: a reconceptualization based on the recent literature*. Eur Eat Disord Rev 1994;2:32-46.

21 Waller G, Barnes J. *Preconscious processing of body image cues impact on body percept and concept.* J Psychosom Res 2002;53:1037-41.

22 Cash TF, Deagle EAI. *The nature and extent of body-image disturbances in anorexia nervosa and bulimia nervosa: a meta-analysis*. Int J Eat Disord 1997;22:107-25.

23 Farrell C, Lee M, Shafran R. *Assessment of body size estimation: a review.* Eur Eat Disord Rev 2005;13:75-88.

24 Vocks S, Legenbauer T, Rüddel H, et al. *Static and dynamic body image in bulimia nervosa: mental representation of body dimensions and motion patterns*. Int J Eat Disord 2007;40:59-66.

25 Vocks S, Wächter A, Wucherer M, et al. *Look at yourself: can body image therapy affect the cognitive and emotional response to seeing oneself in the mirror in eating disorders?* Eur Eat Disord Rev 2008;16:147-54.

26 Reas DL, Whisenhunt BL, Netemeyer R, et al. *Development of the Body Checking Questionnaire: a self-report measure of body checking behaviors.* Int J Eat Disord 2002;31:324-33.

27 Shafran R, Fairburn CG, Robinson G, et al. *Body checking and its avoidance in eating disorders*. Int J Eat Disord 2004;35:93-101.

28 Fisher S, Fisher RL. *Body image boundaries and patterns of body perception*. J Abnorm Psychol 1964;68:255-62.

29 Cash TF, Morrow JA, Hrabosky JI, et al. *How has body image changed? A cross-sectional investigation of college women and men from 1983 to 2001.* J Consult Clin Psychol 2004;72:1081-9.

30 Rodin J, Silberstein L, Striegel-Moore R. *Women and weight: a normative discontent*. Neb Symp Motiv 1984;32:267-307.

31 Ricciardelli LA, McCabe MP. *Dietary restraint and negative affect as mediators of body dissatisfaction and bulimic behavior in adolescent girls and boys.* Behav Res Ther 2001;39:1317-28.

32 Cash TF, Grasso K. *The norms and stability of new measures of the multidimensional body image construct.* Body Image 2005;2:199-203.

33 Johnson F, Wardle J. *Dietary restraint, body dissatisfaction, and psychological distress: a prospective analysis*. J Abnorm Psychol 2005;114:119-25.

34 Seigel K, Broman JE, Hetta J. *Behavioral activation or inhibition during emotional stress-implications for exercise habits and emotional problems among young females.* Nord J Psychiatry 2002;56:441-6.

35 Hoffman JM, Brownell KD. *Sex differences in the relationship of body fat distribution with psychosocial variables.* Int J Eat Disord 1997;22:139-45.

36 Stice E, Shaw HE. *Role of body dissatisfaction in the onset and maintenance of eating pathology: a synthesis of research findings.* J Psychosom Res 2002;53:985-93.

37 Fairburn CG, Cooper Z, Shafran R. *Cognitive behavior therapy for eating disorders: a 'transdiagnostic' theory and treatment.* Behav Res Ther 2003;41:509-28.

38 Dalle Grave R. *Eating disorders: progress and challenges*. Eur J Intern Med 2011;22:153-60.

39 Goldschmidt AB, Hilbert A, Manwaring JL, et al. *The significance of overvaluation of shape and weight in binge eating disorder.* Behav Res Ther 2010;48:187-93.

40 Ricca V, Castellini G, Lo Sauro C, et al. *Cognitive behavioral therapy for threshold and subthreshold anorexia nervosa: a three-year follow-up study*. Psychother Psychosom 2010;79:238-48.

41 Grilo CM. *Why no cognitive body image feature such as overvaluation of shape/weight in the binge eating disorder diagnosis?* Int J Eat Disord 2013;46:208-11.

42 Stein KF, Corte C. *Identity impairment and the eating disorders: content and organization of the self-concept in women with anorexia nervosa and bulimia nervosa.* Eur Eat Disord Rev 2007;15:58-69.

43 Bruch H. *Developmental deviations in anorexia nervosa.* Isr Ann Psychiatr Relat Discip 1979;17:255-61.

44 Stern D. *The interpersonal world of the infant: a view from psychoanalysis and developmental psychology*. New York: Basic Books 1985.

45 Bratman S, Knight D. *Health food junkies. Orthorexia nervosa. Overcoming the obsession with healthful eating.* New York: Broadway Books 2000.

46 Park SW, Kim JY, Go GJ, et al. *Orthorexia nervosa with hyponatremia, subcutaneous emphysema, pneumomediastimum, pneumothorax, and pancytopenia*. Electrolyte Blood Press 2011;9:32-7.

47 Catalina Zamora ML, Bote Bonaechea B, García Sánchez F, et al. *Orthorexia nervosa. A new eating behavior disorder?* Actas Esp Psiquiatr 2005;33:66-8.

48 Donini LM, Marsili D, Graziani MP, et al. *Orthorexia nervosa: a preliminary study with a proposal for diagnosis and an attempt to measure the dimension of the phenomenon*. Eat Weight Disord 2004;9:151-7.

49 Bağci Bosi AT, Camur D, Guler C. *Prevalence of orthorexia nervosa in resident medical doctors in the faculty of medicine (Ankara, Turkey).* Appetite 2007;49:661-6.

50 Dunn TM, Gibbs J, Whitney N, et al. *Prevalence of orthorexia nervosa is less than 1%: data from a US sample*. Eat Weight Disord 2017;22:185-92.

51 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders DSM-5, 5th Edition.* American Psychiatric Publishing: Arlington 2013.

52 Attia E, Becker AE, Bryant-Waugh R, et al. *Feeding and eating disorders in DSM-5*. Am J Psychiatry 2013;170:1237-9.

53 Koven NS, Abry AW. *The clinical basis of orthorexia nervosa: emerging perspectives*. Neuropsychiatr Dis Treat 2015;18:385-94.

54 Segura-Garcia C, Ramacciotti C, Rania M, et al. *The prevalence of orthorexia nervosa among eating disorder patients after treatment.* Eat Weight Disord 2015;20:161-6.

55 Brytek-Matera A, Rogoza R, Gramaglia C, et al. *Predictors of orthorexic behaviours in patients with eating disorders: a preliminary study.* BMC Psychiatry 2015;15:252.

56 Vandereycken W. *Media hype, diagnostic fad or genuine disorder? Professionals' opinions about night eating syndrome, orthorexia, muscle dysmorphia, and emetophobia.* Eat Disord 2011;19:145-55.

57 Volpe U, Atti AR, Cimino M, et al. *Beyond anorexia and bulimia nervosa: what's "new" in eating disorders?* Journal of Psychopathology 2015;21:415-23.

58 Brown AJ, Parman KM, Rudat DA, et al.

Disordered eating, perfectionism, and food rules. Eat Behav 2012;13:347.

59 Zachrisson HD, Skårderud F. *Feelings of insecurity: review of attachment and eating disorders.* Eur Eat Disord Rev 2010;18:97-106.

60 Barnes MA, Caltabiano ML. *The interrelationship between orthorexia nervosa, perfectionism, body image and attachment style*. Eat Weight Disord 2017;22:177-84.

61 Bardone-Cone AM, Wonderlich SA, Frost RO, et al. *Perfectionism and eating disorders: current status and future directions.* Clin Psychol Rev 2007;27:384-405.

62 Hrabosky JI, Cash TF, Veale D, et al. *Multidimensional body image comparisons among patients with eating disorders, body dysmorphic disorder, and clinical controls: a multisite study*. Body Image 2009;6:155-63.

63 Barthels F, Meyer F, Pietrowsky R. *Orthorexic eating behavior. A new type of disordered eating.* Ernährungs Umschau 2015;62:156-61.

64 Dunn TD, Bratman S. *On orthorexia nervosa: a review of the literature and proposed diagnostic criteria.* Eat Behav 2016;21:11-7.

65 Varga M, Thege BK, Dukay-Szabó S, et al. *When eating healthy is not healthy: orthorexia nervosa and its measurement with the ORTO-15 in Hungary.* BMC Psychiatry 2014;14:59-70.

66 Gramaglia C, Brytek-Matera A, Rogoza R, et al. *Orthorexia and anorexia nervosa: two distinct phenomena? A cross-cultural comparison of orthorexic behaviours in clinical and non-clinical samples.* BMC Psychiatry 2017;21;17:75.

67 Kinzl JF, Hauer K, Traweger CH, et al. *Orthorexia nervosa in dieticians*. Psychother Psychosom 2006;75:395-6.

68 Varga M, Máté G. *Eating disturbances in orthorexia nervosa*. *XIII annual meeting of the European Association for Consultation-Liaison Psychiatry and Psychosomatics (EACLPP) XXVIII European Conference on Psychosomatic Research (ECPR): a selection of the best abstracts submitted.* J Psychosom Res 2009;68:672-3.

69 Brytek-Matera A, Donini LM, Krupa M, et al. *Erratum to: orthorexia nervosa and self-attitudinal aspects of body image in female and male university students*. J Eat Disord 2016;4:16.

70 Brytek-Matera A, Fonte ML, Poggiogalle E, et al. *Orthorexia nervosa: relationship with obsessive-compulsive symptoms, disordered eating patterns and body uneasiness among Italian university students.* Eat Weight Disord 2017;22:609-17.

71 Brytek-Matera A, Donini LM, Krupa M, et al. *Orthorexia nervosa and self-attitudinal aspects of body image in female and male university students*. J Eat Disord 2015;3:2.

72 Al Kattan, M. *The prevalence of orthorexia nervosa in Lebanese university students and the relationship between orthorexia nervosa and body image, body weight and physical activity (Master thesis).* University of Chester, United Kingdom 2016.

73 Asil E, Saip Sürücüog˘lu M. *Orthorexia nervosa in Turkish dietitians*. Ecol Food Nutr 2015;54:303-13.

74 Tremelling K, Sandon L, Vega GL, et al. *Orthorexia nervosa and eating disorder symptoms in registered dietitian nutritionists in the United States*. J Acad Nutr Diet 2017;117:1612-7.

75 Grammatikopoulou MG, Gkiouras K, Markaki A, et al. *Food addiction, orthorexia, and food-related stress among dietetics students*. Eat Weight Disord 2018;23:459-67

76 Oberle CD, Lipschuetz SL. *Orthorexia symptoms correlate with perceived muscularity and body fat, not BMI.* Eat Weight Disord 2018 May 3. Doi: 10.1007/s40519-018-0508-z.

77 Bundros J, Clifford D, Silliman K, et al. *Prevalence of orthorexia nervosa among college students based on Bratman's test and associated tendencies*. Appetite 2016;101:86-94.

78 Eriksson L, Baigi A, Marklund B, et al. *Social physique anxiety and sociocultural attitudes toward appearance impact on orthorexia test in fitness participants*. Scand J Med Sci in Sports 2008;18:389-94.

79 Featherstone M. *The body in consumer culture*. In: Featherstone M, Hepworth M, Turner SB, Eds. *The body: social process and cultural theory*. London: Sage Publications 1991.

80 Turner PG, Lefevre CE. *Instagram use is linked to increased symptoms of orthorexia nervosa.* Eat Weight Disord 2017;22:277-84.

81 Tiggemann M, Zaccardo M. *'Strong is the new skinny': a content analysis of# fitspiration images on Instagram.* J Health Psychol 2018;23:1003-11.

82 Cuzzolaro M, Vetrone G, Marano G, et al. *The Body Uneasiness Test (BUT): development and validation of a new body image assessment scale*. Eat Weight Disord 2006;11:1-13.

83 Runfola CD, Von Holle A, Trace SE, et al. *Body dissatisfaction in women across the lifespan: results of the UNC-SELF and Gender and Body Image (GABI) studies*. Eur Eat Disord Rev 2013;21:52-9.

84 Carvalheira A, Godinho L, Costa P. *The impact of body dissatisfaction on distressing sexual difficulties among men and women: the mediator role of cognitive distraction*. J Sex Res 2017;54:331-40.

85 Karazsia BT, Murnen SK, Tylka TL. *Is body dissatisfaction changing across time? A cross-temporal meta-analysis.* Psychol Bull 2017;143:293-320.

86 del Mar Bibiloni M, Coll JLI, Pich J, et al. *Body image satisfaction and weight concerns among a Mediterranean adult population.* BMC Public Health 2017;17:39.

87 Moroze RM, Dunn TM, Craig Holland J, et al. *Microthinking about micronutrients: a case of transition from obsessions about healthy eating to near-fatal "orthorexia nervosa" and proposed diagnostic criteria.* Psychosomatics 2015;56:397-403.

88 Missbach B, Hinterbuchinger B, Dreiseitl V, et al. *When eating right, is measured wrong! A validation and critical examination of the ORTO-15 Questionnaire in German*. PLoS One 2015;10:e0135772.

89 Donini LM, Marsili D, Graziani MP, et al. *Orthorexia nervosa: validation of a diagnosis questionnaire.* Eat Weight Disord 2005;10:e28-32.

90 Scheffers M, van Busschbach JT, Bosscher RJ, et al. *Body image in patients with mental disorders: characteristics, associations with diagnosis and treatment outcome*. Compr Psychiatry 2017;74:53-60.

91 Krueger RF, Eaton NR. *Transdiagnostic factors of mental disorders.* World Psychiatry 2015;14:27-9.

JOURNAL OF PSYCHOPATHOLOGY
2018;24:141-147

G. Sampogna[1], V. Del Vecchio[1], M. Luciano[1], V. Giallonardo[1], C. Palummo[1], B. Pocai[1], L. Steardo Jr.[1], D. Bhugra[2], A. Fiorillo[1]

[1] Department of Psychiatry, University of Campania "Luigi Vanvitelli", Naples, Italy; [2] Institute of Psychiatry, Psychology and Neuroscience, King's College, London, UK

Is Internet gaming disorder really a new form of mental disorder? A critical overview

Summary

There is no doubt that the Internet has profoundly modified our daily life, in particular becoming an integral part of young people's life and activities. It is a source for information, a new channel of communication and it is used for various leisure activities. On the other hand, it also carries a potential threat to people's mental health, when people spend excessive amount of time on its use and when time spent gaming online tends to prevail when compared to other activities. The peak time spent on Internet gaming is increasing in young people, with near to 11 hours per day. Computer gaming has been conceptualized as continuum from an enjoyable activity to a pathological and an addictive use. In the new version of the International Classification of Diseases (ICD-11), Gaming Disorder (GD) has been included in the chapter of mental and behavioural disorders. Prevalence rates of Internet Gaming Disorder (IGD) range from 0.2% to 50%, but the true extent of the phenomenon is not yet known due to the lack of specific diagnostic criteria prior to the publication of ICD-11. The inclusion of this new disorder has generated keen debate and raised controversies in the scientific community. Like most behavioural disorders where pathology is identified by variation in norms, it would appear that there is a clear need to define an appropriate boundary between normal Internet gaming and IGD. We believe that considering IGD as proper mental disorder may generate a common ground for assessment, research and development of appropriate treatments. However, high-quality longitudinal multicenter studies are urgently needed in order to identify possible biomarkers of this new disorder and to understand the developmental trajectory of IGD.

Key words

Internet Gaming Disorder • Behavioural addiction • Technology • Impulsivity • Loneliness • Virtual reality

Introduction

There is no doubt that the advent and increased use of Internet around the globe has profoundly modified our daily living and functioning. This has become a major part of the millennial generation (the young people born between 1985 and 2000). The use of social media therefore has become not only a source of keeping in touch but also information and entertainment [1-3]. The latter functions are likely to affect people's mental health and well-being especially when young people spend excessive amount of time on its use to the detriment of other activities. In particular, effects of new technologies on mental health, especially the Internet, have profoundly modified our daily life, becoming an integral part of young people's life [4]. Internet provides information, it is a new way for communication, and also a leisure activity [5 6]. Equally important, it also carries a number of problems and potential threats to mental health, especially when its use starts to dominate people's lives as seen when time spent on gaming online becomes predominant over other daily activities and interferes with daily living. Use of the Internet and computer gaming is a frequent activity for children and adolescents. According to recent US data, adolescents spend more than 11 hours per day using mobile phones or computer, or searching web pages. Computer gaming has been recently

Correspondence

Andrea Fiorillo
Department of Psychiatry, University of Campania "Luigi Vanvitelli", Largo Madonna delle Grazie, 80138 Naples, Italy
• E-mail: andrea.fiorillo@unicampania.it

conceptualized as continuum from an enjoyable activity to pathological and addictive use [7]. As a result of this over-activity and spending increasing amounts of time gaming online, there is a serious concern that vulnerable individuals will go on to develop a full-blown clinical disorder [8 9]. This may lead to a neglect of "real-life" relationships, school or work-related duties, and even basic physical needs, with a detachment from reality and avoidance of social activities. Therefore, Internet gaming is becoming a serious public health concern in Asia where about 30 million internet gamers are recognized as addicted [6 10].

In the new version of the International Classification of Diseases (ICD-11) [11 12] Gaming Disorder (GD) has been included in the chapter of mental and behavioural disorders. Therefore, there is thee need to adapt training curricula and clinical practice to modern patients has been recently stated in the mental health field [13-15]. In fact, many traditional mental disorders, such as catatonia, hysteria or hebephrenia, seem to have disappeared from clinical observation, while new forms of mental health problems emerge regularly [16-18]. The question arises whether these are proper mental disorders or consequences of modern society, such as the ongoing economic downturn and crisis [19], the migration processes [20], the terrorist attacks [21], the use of novel psychoactive substances [22] or response to development of new technologies [23 24].

The decision to include the GD in the ICD-11 has generated debates and caused controversies in the scientific community whether this should have been included or not [25-28]. Criticisms mainly refer to the risk of overpathologizing and overtreating a common behavior of young people [25-27]. On the contrary, the need for early detection and early treatment in young people, based on epidemiological and clinical data [29], remains the main argument in favour of the inclusion of GD among behavioural addictions and mental disorders.

This paper is a critical overview of recent studies on Internet Gaming Disorder (IGD). The epidemiological, clinical and social characteristics of IGD will be described. The psychopathological characteristics of this disorder will also be highlighted.

Methodology

The databases MEDLINE, ISI Web of Knowledge – Web of Science Index, Cochrane Reviews Library and PsychoINFO were searched for papers published in the past few years. The key word "Internet Gaming Disorder" has been matched with "prevalence", "psychopathology", "pharmacological treatments", "psychosocial treatments", and entered in PubMed. Only papers written in English and published in peer-reviewed journals have been included in our analysis. The reference lists of all papers selected in the primary search have been manually searched for other potential manuscripts. Papers have been grouped in four categories: 1) epidemiological studies; 2) papers related to IGD diagnostic characteristics; 3) psychopathological studies; 4) intervention studies.

Results

Epidemiological studies

The prevalence rates of IGD range from 0.2% in Germany to 50% in Korea [10 26 30-34]. According to a large-scale study recently carried out in USA using the American Psychiatric Association (APA) criteria for GD [26], the prevalence rates are 1.0% in young and 0.5% in adult people. The majority of IGD population is between 15 and 20 years, but younger and older people can also be affected [7]. IGD seems to be more frequent in male adolescents, especially among those who have a low level of education, living in Eastern Asian countries, or in those experiencing psychosocial adversities, such as familial difficulties, divorced parents, been bullied or having friends addicted to videogames [35].

Papers related to IGD diagnostic characteristics

In 2013, APA included the diagnosis of IGD in the appendix of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) manual under "Conditions warranting more clinical research before being classified as an official mental disorder" [10 36]. King et al. [37] claimed for the need to define a "gold standard" for the diagnosis of IGD since more than 18 different operational criteria were identified. In fact, several terms defined the same clinical condition, including problematic online gaming, pathological gaming, gaming addiction, excessive gaming, gaming use disorder, videogame addiction, videogame dependency, internet use disorder, pathological internet use, technology use disorder, pathological technology use, compulsive internet use [38].

According to the DSM-5, in order to formulate a diagnosis of IGD, five (or more) of the following symptoms should be present in a 12-month period: 1) preoccupation with internet games; 2) withdrawal symptoms when internet gaming is stopped; 3) need to spend increasing amounts of time in internet games; 4) unsuccessful attempts to control the participation in internet games; 5) loss of interest in previous hobbies and entertainment as a result of internet games; 6) continued excessive use of internet games despite knowledge of psychological problems; 7) deceiving about time spent on internet gaming; 8) escaping negative moods through internet games; 9) loss of a significant relationship, job, or educational or career opportunity because of participation in internet games [10 37 39].

In the eleventh edition of the ICD for the first time a disorder related to the excessive use of videogames has been officially recognized by the medical community among the pathological conditions requiring clinical attention [29]. This new edition of the ICD is published exactly 28 years after the ICD-10, which was published in 1990 and operationalized in 1994. It classified over 2000 diseases and related problems, including a specific chapter on mental disorders. The ICD system is more used by European psychiatrists, mainly because many national laws use this system for the reimbursement of benefits [40]. The "Gaming Disorder" (GD) is included in the chapter of "Disorders due to addicitive behaviours" and is defined as "a persistent or recurring pattern in gambling behaviour that occurs when videogames are prioritized to the point that they take precedence over other interests and daily activities, and continuation or escalation of video-gaming activity despite the occurrence of negative consequences". For being considered a disorder, videogame addiction must result in "significant personal, family, social, educational and/or professional harm".

Psychopathological studies

From a psychopathological viewpoint, the IGD includes two different subtypes: an online form, in which the subject must necessarily be connected to the Internet; and the offline subtype, where the player prefers to be alone [41]. These two forms differ substantially; in fact, people with the online IGD subtype have narcissistic characteristics, are highly competitive with a severe risk of addiction. Moreover, they are exposed to social comparison and tend to consider virtual interactions as real ones. On the other hand, people affected by the offline form are usually covert, dependent, socially withdrawn and highly isolated [40]. However, the differentiation between these two subtypes has not been officially recognized yet and their clinical utility is still debated [29].

The online gaming has been better characterized in terms of physical and psychological consequences. Physical consequences include visual disturbances, postural problems, chronic back pain, weight gain, obesity and increased cardio-metabolic risk. Online gamers report negative consequences on their psychosocial functioning in terms of reduced social interactions, drop in academic or working performances, and reduced attention skills. Moreover, excessive gaming is also associated with poor sleep hygiene, low self-esteem, loneliness, increased aggression and hostility, and reduced verbal memory [6 8 30].

IGD symptoms frequently co-occur with those of other mental disorders especially with those with onset in children or adolescents, such as attention-deficit/hyperactivity disorder (ADHD), conduct disorders, depression, and anxiety. In particular, the relationship between depression and IGD has been deeply investigated, with a higher incidence of depressive symptoms in online gamers [42]. A possible explanation could be that some young depressed patients cope with their negative emotional feelings by playing games on the Internet, while other patients with IGD may experience depressive symptoms as a consequence of social withdrawal from real-life relationships. Obviously, it can also be that depressive disorder and IGD share the same biological liability.

The development and expression of problematic gaming behaviors remains heterogeneous and dependent on multiple interacting factors [8 43 44]. Individuals who are socially isolated or have poor interpersonal skills are particularly attracted to games that allow to develop online relationships and take on new personalities [33]. Moreover, some personality factors, such as low levels of self-esteem, high impulsivity, negative affectivity, and perceived loneliness are associated with a higher risk of developing IGD [45]. Brand et al. [46] have highlighted the role of dysfunctional coping strategies as another risk factor for the development of IGD, suggesting that adolescents not able to cope with everyday life stressors may downregulate their negative emotions through online gaming [45-47] (Tab. I).

Intervention studies

Only a few randomized controlled trials are available for evaluating the efficacy of pharmacological and non-pharmacological treatments in patients with IGD (Tab. II). As regards pharmacological treatment, available studies have investigated the efficacy of bupropion compared to placebo [48 49] or to a no-treatment control condition [50]. In a recent study by Bae et al. [51], a 12-week bupropion treatment improved the severity of IGD as well as the associated clinical symptoms; moreover, a significant correlation between the changes in clinical scales and the changes in brain functional connectivity was found. In another study, bupropion was combined with cognitive-behavioural therapy (CBT) and the association was effective; however, it shall be noted that this study included patients presenting with depression in comorbidity with IGD [52]. Therefore, the limited available data support the use of bupropion in patients with IGD, but these findings should be cautiously considered since samples are small and the follow-up periods are short.

Among psychological approaches, CBT has been proposed as a useful strategy for managing addictive behaviours. In particular, Young et al. [53] tested the efficacy of a CBT-based approach specifically tailored on Internet addiction in 128 patients. At the end of the intervention, a majority of patients reported to be able to manage their symptoms both on short and long-term. In a study by Liu et al. [54], the efficacy of a multi-family group

TABLE I. *Risk factors associated with the development of IGD.*

Author	Year	Risk factors
Petry et al., USA	2015	Low sociability and social competence
Lemmens et al., The Netherlands	2015	Impulsivity
Rho et al., Korea	2015	Time spent in gaming during the week Years spent in playing games Time spent in game community membership Offline community meeting attendance
Brand et al., Germany	2016	Dysfunctional coping strategies
Laconi et al., France	2017	Tendency to escape from reality
Mihara & Higuchi, Japan	2017	Low levels of self-esteem Negative affectivity Perceived loneliness

TABLE II. *Available treatments for patients with IGD.*

Authors, country	Year	Treatment
Pharmacological treatment		
Han et al., China	2010	Bupropion
Han & Renshaw, China	2012	Bupropion compared to placebo
Song et al., South Korea	2016	Bupropion and escitalopram
Nam et al., Korea	2017	Bupropion and CBT
Bae et al., South Korea	2018	12-week bupropion treatment
Non pharmacological treatment		
Young, USA	2013	Cognitive Behavioural Therapy adapted to Internet Addiction, including behavior modification to control compulsive Internet use, cognitive restructuring to identify, challenge, and modify cognitive distortions that lead to addictive use, and harm reduction techniques to address and treat co-morbid issues associated with the disorder
Li & Wang, China	2013	Group CBT of 6-week duration
Wölfling et al., Germany	2014	Standardized cognitive-behavioral therapy program
Liu et al., China	2015	Six-session multi-family group therapy intervention
Park et al., Korea	2016	Cognitive behavior therapy or virtual reality therapy
Santos et al., Brazil	2016	Modified CBT, conducted individually, once a week, over a period of 10 weeks associated with pharmacotherapy
Sakuma et al., Japan	2017	Multimodal therapeutic residential camp, including psychotherapy, psychoeducational therapy, and cognitive behavioural therapy

therapy was tested in patients with IGD and their relatives. At the end of the intervention, patients reported an improvement in addictive behaviours supporting the need to involve parents when adolescents are affected by this mental disorder. Other approaches have been tested more recently in patients with IGD, combining CBT and pharmacotherapy [55-57], or combining CBT with virtual reality [58] or with residential programmes [59]. According to a recent systematic review [60], the extent of benefits of these approaches is not yet clear.

Critical commentary

IGD is a growing public health concern, and as such it should be detected and treated as soon as possible [61-63]. However, the clinical utility of this new diagnostic category in the international classification of mental

disorders is still debated, since it has been argued that this disorder is not adequately supported by evidence-based findings and that online gaming cannot be compared with other behavioural addictions [25-28]. DSM-5 includes the condition in the group requiring further research, whereas the WHO has decided to include it among the list of proper mental disorders. Therefore, a lack of consensus for diagnostic criteria and the lack of reliable assessment tools further limit the utility of such diagnosis in routine clinical practice. Including the GD in the international classification of diseases can impact poorly on the public image of psychiatry, already seen as unscientific and blamed for the over-treatment of many normal conditions [27]. On the other hand, King et al. [28] have highlighted the need to define an appropriate boundary between normal gaming and GD, and recognizing that the new diagnosis of GD does not have a negative impact on normal gaming. Thus, refining criteria for GD diagnosis would benefit from the collaboration of all stakeholders, including gamers who could collaboratively discuss ideas and share perspectives and experiences that may not be immediately evident to researchers and clinicians.

As reported by Kiràly and Demetrovics [29], considering IGD as a proper mental disorder has several advantages in terms of creating a common ground for assessment, research and development of appropriate treatments. The need to recognize this new diagnosis is confirmed by the dangers associated with excessive gaming and by the increasing number of people seeking for specific treatments for their gaming-related problems [28].

The adoption of a formal diagnosis can reduce the stigmatization on the problematic gaming, not considered anymore as a personal weakness. Recognizing a disorder in a classification system represents the first essential step for developing appropriate therapeutic strategies [64]. Further high-quality longitudinal multicenter studies will be helpful in order to identify possible biomarkers of this new disorder and to fully understand the developmental trajectory of such behavioural addiction.

Markey et al. [27] and Przybylski et al. [26] emphasise that videogame addiction represents a growing phenomenon, but its addictive potential is not directly comparable with that of gambling or alcohol, blaming the risk of overtreating normal behaviors adopted by kids and young adults. However, preventive strategies for reducing the maladaptive use of videogames and Internet should be developed and implemented at family, school and individual levels. At the family level, parents need to reduce the time spent using smartphones and tablets when they are at home with their children. It may be useful to improve family communication, avoiding isolation in a real world and seeking social access and links in the virtual world. At school level, awareness campaigns should be carried out in order to provide adolescents with information on benefits and risks related to the use of Internet and of other new technologies. At an individual level, gamers should be made aware of the risk of excessive time spent on gaming activities and should be supported in engaging in real-world and in-persons activities [65].

From a psychopathological viewpoint, this disorder shares common elements with many mental disorders, including personality disorders, major depression, psychoticism, autism, addictions. Therefore, a better characterization of the psychopathological ground of IGD is urgently needed, also in order to establish a treatment plan.

As regards the efficacy of available interventions, the only tested drug is bupropion, whose effects remain unclear. CBT has been extensively studied, but trials conducted so far are of poor quality and lack long-term follow-ups. The quality of study design and consistency of research in the area of behavioural addictions is important as these disorders lie on a continuum between normal and pathological behaviours. Moreover, there is a need to understand which aspects of CBT work better in which patients with IGD, to define the optimal duration of treatment, the format of the intervention (individual or group therapy) and the long-term stability of treatment responses.

Conclusions

IGD represents a new disorder for which mental health professionals and psychiatrists are not yet equipped. Epidemiological naturalistic follow-up studies should be promoted in order to understand the exact incidence rate, the long-term complications, the associated societal and personal burden. IGD has a significant impact on a personal level, but also on a micro- and macro-social level. For these reasons, the introduction of a new diagnostic category in the ICD should be welcomed by the scientific community, since it can represent the basis for a common scientific ground in order to adequately manage and treat these patients. Obviously, implementing research protocols and developing clinical guidelines for the management of this disorder are needed. Finally, national and international associations of stakeholders, scientific societies and policy-makers should work together in order to effectively manage this new disorder of the modern society.

Conflict of Interest

The authors have no conflict of interests.

References

1 Busch V, Leeuw JR. *Unhealthy behaviors in adolescents: multibehavioral associations with psychosocial problems.* Int J Behav Med 2014;21:439-46.

2 Hargittai E. *Digital na(t)ives? Variation in internet skills and uses among members of the 'net generation*. Sociological Inquiry 2010;80:92-113.

3 Zhou R, Fong PW, Tan P. *Internet use and its impact on engagement in leisure activities in China*. PLoS One 2014;9:1-11.

4 Fuchs M, Riedl D, Bock A et al. *Pathological internet use-an important comorbidity in child and adolescent psychiatry: prevalence and correlation patterns in a naturalistic sample of adolescent inpatients*. BioMed Res Int 2018;29:1629147.

5 Barnett J, Coulson M. *Virtually real: a psychological perspective on massively multiplayer online games.* Rev General Psychol 2010;14:167-79.

6 Lukavská K. *The immediate and long-term effects of time perspective on internet gaming disorder.* J Behav Addict 2018;7:44-51.

7 Paulus FW, Ohmann S, von Gontard A, et al. *Internet gaming disorder in children and adolescents: a systematic review.* Develop Med Child Neurol 2018;60:645-59.

8 Rehbein F, Kliem S, Baier D, et al. *Prevalence of internet gaming disorder in German adolescents: diagnostic contribution of the nine DSM-5 criteria in a statewide representative sample*. Addiction 2015;110:842-51.

9 Rehbein F, Kliem S, Baier D, et al. *Systematic validation of internet gaming disorder criteria needs to start somewhere: a reply to Kardefelt-Winther.* Addiction 2015;110:1360-2.

10 Chen KH, Oliffe JL, Kelly MT. *Internet Gaming Disorder: an emergent health issue for men*. Am J Mens Health 2018;1:1557988318766950.

11 https://icd.who.int/browse11/l-m/en

12 Gaebel W, Zielasek J, Reed GM. *Mental and behavioural disorders in the ICD-11: concepts, methodologies, and current status*. Psychiatr Pol 2017;51:169-95.

13 Fiorillo A, Maj M. *The role of psychiatry in modern medicine.* Int Rev Psychiatry 2018;30:169-75.

14 Fiorillo A, Malik A, Luciano M, et al. *Challenges for trainees in psychiatry and early career psychiatrists*. Int Rev Psychiatry 2013;25:431-7.

15 Kendler KS. *The nature of psychiatric disorders*. World Psychiatry 2016;15:5-12.

16 Maj M. *From "madness" to "mental health problems": reflections on the evolving target of psychiatry*. World Psychiatry 2012;11:137-8.

17 De Rosa C, Sampogna G, Luciano M, et al. *Social versus biological psychiatry: it's time for integration!* Int J Soc Psychiatry 2018;1:20764017752969.

18 Arango C, Fraguas D. *Should psychiatry deal only with mental disorders without an identified medical aetiology?* World Psychiatry 2016;15:22-3.

19 Selten JP, van Os J, Cantor-Graae E. *The social defeat hypothesis of schizophrenia: issues of measurement and reverse causality.* World Psychiatry 2016;15:294-5.

20 Kirkbride JB. *Migration and psychosis: our smoking lung?* World Psychiatry 2017;16:119-20.

21 Vostanis P. *New approaches to interventions for refugee children*. World Psychiatry 2016;15:75-7.

22 Schifano F, Orsolini L, Papanti D, et al. *Novel psychoactive substances of interest for psychiatry*. World Psychiatry 2015;14:15-26.

23 Starcevic V, Aboujaoude E. *Cyberchondria, cyberbullying, cybersuicide, cybersex: 'new' psychopathologies for the 21st century?* World Psychiatry 2015;14:197-100.

24 Griffiths KM. *Mental health internet support groups: just a lot of talk or a valuable intervention?* World Psychiatry 2017;16:247-8.

25 Aarseth E, Bean AM, Boonen H, et al. *Scholars' open debate paper on the World Health Organization ICD-11 Gaming Disorder proposal.* J Behav Addict 2017;6:267-70.

26 Przybylski AK, Weinstein N, Murayama K. *Internet Gaming Disorder: investigating the clinical relevance of a new phenomenon.* Am J Psychiatry 2017;174:230-6.

27 Markey PM, Ferguson CJ. *Internet Gaming Addiction: disorder or moral panic?* Am J Psychiatry 2017;174:195-6.

28 King DL, Delfabbro PH, Potenza MN, et al. *Internet gaming disorder should qualify as a mental disorder*. Aust N Z J Psychiatry 2018;1:1-3.

29 Kiràly O, Demetrovics Z. *Inclusion of Gaming Disorder in ICD has more advantages than disadvantages*. J Behav Addict 2017;6:280-4.

30 Kuss DJ, Griffiths MD. *Internet gaming addiction: a systematic review of empirical research*. Int J Ment Health Addict 2012;10:278-96.

31 Kuss DJ. *Internet gaming addiction: current perspectives*. Psychol Res Behav Manag 2013;6:125-37.

32 Festl R, Scharkow M, Quandt T. *Problematic computer game use among adolescents, younger and older adults.* Addiction 2013;108:592-9.

33 Petry NM. *Gaming addiction – how far have we come, and how much further do we need to go?* Addiction 2013;108:600-1.

34 Petry NM, Zajac K, Ginley MK. *Behavioral addictions as mental disorders: to be or not to be?* Ann Rev Clin Psychology 2018;14:399-423.

35 Ferguson CJ, Coulson M, Barnett J. *A meta-analysis of pathological gaming prevalence and comorbidity with mental health, academic and social problems*. J Psychiatr Res 2011;45:1573-8.

36 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (5th ed.)*. Washington, DC: Author 2013.

37 King DL, Haagsma MC, Delfabbro PH, et al. *Toward a consensus definition of pathological video-gaming: a systematic review of psychometric assessment tools.* Clin Psychol Rev 2013;33:331-42.

38 Feng W, Ramo DE, Chan SR, et al. *Internet gaming disorder: trends in prevalence 1998-2016*. Addict Behav 2017;75:17-24.

39 Hussain Z, Griffiths MD, Baguley T. *Online gaming addiction: classification, prediction and associated risk factors.* Addiction Res Theory 2012;20:359-71.

40 Reed GM, Mendonça Correia J, Esparza P, et al. *The WPA-WHO Global Survey of psychiatrists' attitudes towards mental disorders classification*. World Psychiatry 2011;10:118-31.

41 Lemmens JS, Hendriks SJ. *Addictive online games: examining the relationship between game genres and internet gaming disorder*. Cyberpsychol Behav Soc Netw 2016;19:270-6.

42 Rho MJ, Lee H, Lee TH, et al. *Risk factors for Internet Gaming Disorder: psychological factors and internet gaming characteristics*. Int J Environ Res Public Health 2017;15:1.

43 Billieux J, King DL, Higuchi S, et al. *Functional impairment matters in the screening and diagnosis of gaming disorder*. J Behav Addict 2017;6:285-9.

44 Griffiths MD, Kuss DJ, Lopez-Fernandez O, et al. *Problematic gaming exists and is an example of disordered gaming*. J Behav Addict 2017;6:296-301.

45 Mihara S, Higuchi S. *Cross-sectional and longitudinal epidemiological studies of Internet Gaming Disorder: a systematic review of the literature*. Psychiatry Clin Neurosci 2017;71:425-44.

46 Brand M, Young KS, Laier C, et al. *Integrating psychological and neurobiologi-*

cal considerations regarding the development and maintenance of specific Internet-use disorders: An Interaction of Person-Affect-Cognition-Execution (I-PACE) model. Neurosci Biobehav Rev 2016;71:252-66.

47 Hur MH. *Demographic, habitual, and socioeconomic determinants of Internet addiction disorder: an empirical study of Korean teenagers.* Cyberpsychol Behav 2006;9:514-25.

48 Han DH, Hwang JW, Renshaw PF. *Bupropion sustained release treatment decreases craving for video games and cue-induced brain activity in patients with Internet video game addiction*. Exp Clin Psychopharmacol 2010;18:297-304.

49 Han DH, Renshaw PF. *Bupropion in the treatment of problematic online game play in patients with major depressive disorder*. J Psychopharmacol 2012;26:689-96.

50 Song J, Park JH, Han DH, et al. *Comparative study of the effects of bupropion and escitalopram on Internet gaming disorder*. Psychiatry Clin Neurosci 2016;70:527-35.

51 Bae S, Hong JS, Kim SM, et al. *Bupropion shows different effects on brain functional connectivity in patients with internet-based gambling disorder and internet gaming disorder*. Front Psychiatry 2018;9:130.

52 Nam B, Bae S, Kim SM, et al. *Comparing the effects of bupropion and escitalopram on excessive internet game play in patients with major depressive disorder.* Clin psychopharmacol Neurosci 2017;15:361-8.

53 Young KS. *Treatment outcomes using CBT-IA with Internet-addicted patients.* J Behav Addict 2013;2:209-15.

54 Liu Q-X, Fang X-Y, Yane N, et al. *Multi-family group therapy for adolescent Internet addiction: Exploring the underlying mechanisms*. Addict Behav 2015;42:1-8.

55 Wölfling K, Beutel ME, Dreier M, et al. *Treatment outcomes in patients with internet addiction: a clinical pilot study on the effects of a cognitive-behavioral therapy program*. Biomed Res Int 2014;425924.

56 Li H, Wang S. *The role of cognitive distortion in online game addiction among Chinese adolescents*. Child Youth Serv Rev 2013;35:1468-75.

57 Santos VA, Freire R, Zugliani M, et al. *Treatment of internet addiction with anxiety disorders: treatment protocol and preliminary before-after results involving pharmacotherapy and modified cognitive behavioral therapy*. JMIR Research Protocol 2016;5:e46.

58 Park SY, Kim SM, Roh S, et al. *The effects of a virtual reality treatment program for online gaming addiction*. Comput Methods Programs Biomed 2016;129:99-108.

59 Sakuma H, Mihara S, Nakayama H, et al. *Treatment with the Self-Discovery Camp (SDiC) improves Internet gaming disorder*. Addict Behav 2017;64:357-62.

60 King DL, Delfabbro PH, Wu AMS, et al. *Treatment of Internet gaming disorder: an international systematic review and CONSORT evaluation*. Clin Psychol Rev 2017;54:123-33.

61 Laconi S, Pires S, Chabrol H. *Internet gaming disorder, motives, game genres and psychopathology*. Computers Hum Behav 2017;75:652-9.

62 Bass PF. *Gaming addiction: when going online goes off-kilter*. Contemporary Pediatrics 2015;32:16-23.

63 Wartberg L, Kriston L, Zieglmeier M, et al. *A longitudinal study on psychosocial causes and consequences of Internet Gaming Disorder in adolescence*. Psychol Med 2018;6:1-8.

64 Lemmens JS, Valkenburg PM, Gentile DA. *The Internet Gaming Disorder scale.* Psychological Assess 2015;27:567-82.

64 Saunders JB, Hao W, Long J, et al. *Gaming disorder: its delineation as an important condition for diagnosis, management, and prevention*. J Behav Addict 2017;6:271-9.

JOURNAL OF PSYCHOPATHOLOGY
2018;24:148-153

Socio-demographic and clinical characterization of patients with Obsessive-Compulsive Tic-related Disorder (OCTD): an Italian multicenter study

B. Dell'Osso[1-3], B. Benatti[1], E. Hollander[4], J. Zohar[5], L. Dell'Osso[6], N.A. Fineberg[7], M. Marcatili[1], S. Rigardetto[8], M. Briguglio[9], D. Marazziti[6], F. Mucci[6], O. Gambini[3 10], A. Tundo[11], R. Necci[11], D. De Berardis[12 13], R. Galentino[9], S. De Michele[9], C. D'Addario[14 15], D. Servello[9], U. Albert[16], G. Maina[8], D. De Ronchi[16], A.C. Altamura[1], M. Porta[9]

[1] Department of Psysiopathology and Transplantation, University of Milan, Italy; [2] Department of Psychiatry and Behavioral Sciences, Stanford University, CA, USA; [3] "Aldo Ravelli" Center for Nanotechnology and Neurostimulation, University of Milan, Italy; [4] Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine and Montefiore Medical Center, New York, USA; [5] Department of Psychiatry, Chaim Sheba Medical Center, 52621 Tel Hashomer, Israel; [6] Department of Clinical and Experimental Medicine, Section of Psychiatry, University of Pisa, Italy; [7] University of Hertfordshire, Hatfield, UK and Hertfordshire Partnership Foundation Trust, Welwyn Garden City, UK; [8] San Luigi Gonzaga Hospital, Orbassano, University of Turin, Italy; [9] Department of Functional Neurosurgery, IRCCS Galeazzi Hospital, Tourette Center, Milan, Italy; [10] Department of Health Sciences, University of Milan, Italy; [11] Institute of Psychopathology, Rome, Italy; [12] NHS, Department of Mental Health, Psychiatric Service of Diagnosis and Treatment, Hospital "G. Mazzini", ASL 4 Teramo, Italy; [13] Department of Neuroscience, Imaging and Clinical Science, Chair of Psychiatry, University "G. D'Annunzio", Chieti, Italy; [14] Faculty of Bioscience and Technology for Food, Agriculture and Environment, University of Teramo, Italy; [15] Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden; [16] Department of Biomedical and Neuromotor Sciences, Section of Psychiatry, Alma Mater Studiorum University of Bologna, Italy

Summary

In the DSM-5 a new "tic-related" specifier for obsessive compulsive disorder (OCD) has been introduced, highlighting the importance of an accurate characterization of patients suffering from obsessive-compulsive tic-related disorder ("OCTD"). In order to characterize OCTD from a socio-demographic and clinical perspective, the present multicenter study was carried out. The sample consists of 266 patients, divided in two groups with lifetime diagnoses of OCD and OCTD, respectively. OCTD vs OCD patients showed a significant male prevalence (68.5% vs 48.5%; p < .001), a higher rate of psychiatric comorbidities (69.4 vs 50%; p < .001) – mainly with neurodevelopmental disorders (24 vs 0%; p < .001), a lower education level and professional status (middle school diploma: 25 vs 7.6%; full-time job 44.4 vs 58%; p < .001). Moreover, OCTD vs OCD patients showed significantly earlier age of OCD and psychiatric comorbidity onsets (16.1 ± 10.8 vs 22.1 ± 9.5 years; p < .001, and 18.3 ± 12.8 vs 25.6 ± 9.4: p < .001, respectively). Patients with OCTD patients were treated mainly with antipsychotic and with a low rate of benzodiazepine (74.2 vs 38.2% and 20.2 vs 31.3%, respectively; p < .001). Finally, OCTD vs OCD patients showed higher rates of partial treatment response (58.1 vs 38%; p < .001), lower rates of current remission (35.5 vs 54.8%; p < .001) and higher rates of suicidal ideation (63.2 vs 41.7%; p < .001) and attempts (28.9 vs 8.3%; p < .001).

Patients with OCTD report several unfavorable socio-demographic and clinical characteristics compared to OCD patients without a history of tic. Additional studies on larger sample are needed to further characterize OCTD patients from clinical and therapeutic perspectives.

Key words

Obsessive-Compulsive Disorder • Tic Disorder • Obsessive-Compulsive Tic Disorder

Introduction

Obsessive-Compulsive Disorder (OCD) and Tic Disorder (TD) represent disabling, comorbid, chronic and difficult-to-treat conditions, which may affect child and adult patients, associated with high levels of burden for patients and their relatives. Comorbidity between OCD and TD is frequent [1 2], although it can occur in different phases of patient's lifespan (longitudinally) and not necessarily in the same period (cross-sectionally). Moreover, comorbidity between OCD and TD may be at a subclinical level. It has been hypothesized that these disorders and their symptom-dimensions define a specific subtype of disorder, called Obsessive-Compulsive Tic Disorder (OCTD) [3 4]. In the 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [5], OCD has been included in the new category of "OC and related disorders", with the introduction of a new "tic-related" specifier. The introduction of this specifier encourages new investigations on the epidemiology, clinical presentation, disability and therapeutic approach of OCTD [6-10].

Tics and OCD share some phenomenological, autoimmune and neuro-

Correspondence

Beatrice Benatti
University of Milan, Policlinico
via F. Sforza 35, 20122, Milan, Italy
• E-mail: beatricebenatti@gmail.com

biological features [11-13] and often co-occur in affected individuals and relatives.

It has been recently highlighted that OCTD is more frequently associated with early onset, male gender, sensory phenomena and obsessions of symmetry, aggressiveness, hoarding, exactness and sounds, impulsive behaviors and ADHD comorbidity [1 2 6-10 14]. Patients with OCD and comorbid TD accounted for approximately 15% of the primary OCD sample [15] and they are smokers [16] and have a higher rate of previous suicide attempts [17].

According to these features, it seems that patients with comorbid OCD and TD have a more severe phenotype of the disorder, in terms of treatment-resistance, reduced quality of life and levels of disability. Moreover, OCTD patients report a long delay to diagnosis, a high level of functional impairment caused by OC symptoms, a history of multiple treating clinicians and current polypharmacotherapy, with the use of deep brain stimulation in some cases [18].

In order to define socio-demographic and clinical characteristics of patients with OCTD, the present multicenter study has been conducted, including a sample of OCTD patients and a sample of OCD patients with no history of tic. We hypothesized that OCTD patients might exhibit different epidemiologic and clinical characteristics compared to OCD patients with no history of tic.

Methods

The recruitment is still ongoing, with a final target sample of more than 300 OCD patients.

Patients affected by OCD or OCTD of any gender and age were assessed using a novel questionnaire, under validation, developed to better characterize OCTD patients. The questionnaire is composed of 35 questions assessing the following areas: 1) prevalence of OCTD; 2) patient's main socio-demographic features (i.e., age, gender, occupation, level of education, marital status); 3) clinical history (i.e., age at OCD onset, age at TD onset, presence of other psychiatric comorbidities and age at comorbidities' onset, family history, OCD duration of untreated illness - DUI); 4) perceived quality of life, course of illness, current psychotherapy and psychopharmacological therapies, treatment response, presence of past/current suicidal ideation or attempt.

Statistical analysis

In order to compare clinical and demographic features of OCD patients with and without comorbid TD, Pearson Chi-squared tests and Student' *t*-test were used, as appropriate. All analyses were performed using SPSS 24 for Windows software (Chicago, IL) with the level of statistical significance put at 0.05.

Results

The current sample includes 266 adult patients with OCD with and without comorbid TD of either gender and any age, afferent to different psychiatric departments across Italy, distributed as follows: 47 from Policlinico Hospital, Milan; 30 from Galeazzi Hospital, Milan; 16 from San Paolo Hospital, Milan; 60 from Istituto di Psicopatologia, Rome; 30 from Rita Levi Montalcini Department of Neuroscience, Turin; 24 from Department of Neuroscience, Florence; 26 from Teramo Hospital; 33 from Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum University of Bologna.

Main demographic and clinical variables of the study sample are reported in Table I.

In the OCD participating centers, the prevalence of OCD ranges between 5-25%, while in the Tic/Tourette Center the prevalence of OCD is more than 90%.

The sample consists of 132 (51.5%) OCD patients without TD and 124 (48.5%) OCTD patients.

OCTD patients are mainly male (OCTD: 68.5 *vs* OCD: 48.5; $p < .001$), younger (OCTD: 30.7 ± 13.8 *vs* OCD: 37.4 ± 13.4; $p < .001$), with a low level of education and of professional status (OCTD: middle school diploma: 25 *vs* OCD: 7.6%; OCTD: full-time job 44.4 *vs* OCD: 58%; $p < .001$) compared to OCD patients (Figs. 1-2).

OCTD patients report a significantly earlier age at OCD onset (OCTD: 16.1 ± 10.8 *vs* OCD: 22.1 ± 9.5 years; $p < .001$), a earlier age of comorbidities' onset (OCTD: 18.3 ± 12.8 *vs* OCD: 25.6 ± 9.4: $p < .001$), a higher rate of psychiatric comorbidities (OCTD: 69.4 *vs* OCD: 50%; $p < .001$) mainly with neurodevelopmental disorders (e.g. ADHD), compared to OCD patients.

As regards pharmacological treatment (Tab. II), OCTD patients are most frequently treated with D2 antagonist and/or D2, 5-HT2 antagonist treatment compared to OCD patients ($p < .001$). OCTD patients report lower rates of current remission of symptoms (35.5 *vs* 54.8%; $p < .001$), higher rates of suicidal ideation (63.2 *vs* 41.7%; $p < .001$) and suicide attempts (28.9 *vs* 8.3%; $p < .001$), and higher rates of partial treatment response (58.1 *vs* 38%; $p < .001$) compared to OCD patients.

Discussion

The first relevant finding of our study is the different prevalence of OCD and TD in primary OCD *vs* Tic/Tourette centers, indicating that Tic and Tic-related specifier is a consistent phenotype in primary OCD patients, but in primary TD/Tourette patients, comorbid OCD seems the rule rather than the exception [19 20]. Our findings confirm that OCTD defines a more severe phenotype of OCD compared with OCD without Tic. We found a significantly higher male prevalence in the OCTD

TABLE I. *Socio-demographic and clinical features of OCD vs OCTD patients.*

		OCD N = 132	OCTD N = 124
M:F		64 (48.5%): 68 (51.5%)	85 (68.5%)*: 39 (31.5%)
Family history		74 (56.5%)	79 (63.7%)
Psychiatric comorbidity		66 (50%)	86 (69.4%)*
Affective disorders		39 (37.9%)	27 (27%)
Psychosis		3 (2.9)	2 (2%)
Anxiety disorders		11 (10.7%)	16 (16%)
Personality disorders		5 (4.9%)	2 (2%)
Neurodevelopmental disorders		0	24 (24%)*
Eating disorders		2 (3.9%)	0
Poly-comorbidity		4 (3.9%)	11 (11%)
Age		37.4 ± 13.4	30.7 ± 13.8*
Age at OCD onset		22.1 ± 9.5	16.1 ± 10.8 *
Age at TIC onset		-	12 ± 9.5
Age at comorbity onset		25.6 ± 9.4	18.3 ± 12.8 *
DUI (months)		64.6.4 ± 88.6	60.8 ± 77.8
Married		49 (37.4%)	36 (29%)
Professional status	Unemployed	32 (24.4%)	22 (17.7%)
	Full-time	76 (58%)*	55 (44.4%)
	Part-time	2 (1.5%)	3 (2.4%)
	Retired	6 (4.6%)	4 (3.2%)
	Student	15 (11.5%)	40 (32.3%)*
Level of education	Middle school diploma	10 (7.6%)	31 (25%)*
	High school diploma	67 (51.1%)	62 (50%)
	University degree/master degree	54 (41.2%)*	31 (25%)

Values for categorical and continuous variables are expressed as N (%) and mean ± SD, respectively
** p < .001*

group, compared to the OCD without TD group. This finding seems to be consistent with most of the current literature indicating a male preponderance in tic-related OCD [7]. As regards the onset of first OCD symptoms, we found an earlier onset in OCTD patients compared to OCD patients without tics. This finding is in line with Diniz et al. [21], which found that patients with OCD and Tic Symptoms (TS) presented an earlier age at onset compared to OCD patients without tics.

Moreover, we found that psychiatric comorbidity rate was significantly higher in OCTD patients compared to the group without TD. OCTD patients showed a significantly higher comorbidity with neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder and autism spectrum disorders. This finding is consistent with previous research from Coffey and colleagues and Lewin and coauthors, showing a higher prevalence of comorbid neurodevelopmental disorders both in children and adults with OCTD, when compared to OCD patients without TD [19 22].

Previous studies and ICOCS reports showed significant positive correlation between the number of comorbid DSM-IV-TR Axis I-disorders and OCD severity and duration of illness [15 23]. In the present study, the OCTD subgroup showed an overall higher severity of illness. This is the first study exploring socio-demographic features of OCTD patients; in particular, OCTD patients showed significantly lower rates of university/master education and full-time employment compared to OCD patients without TD. It should be that the burden of OCTD se-

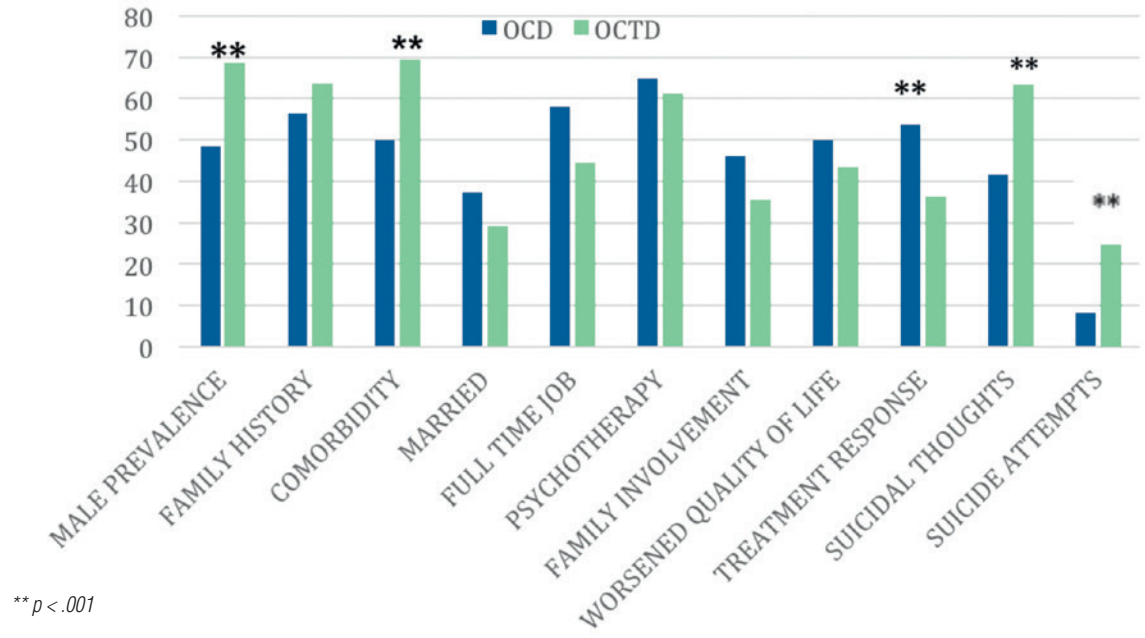
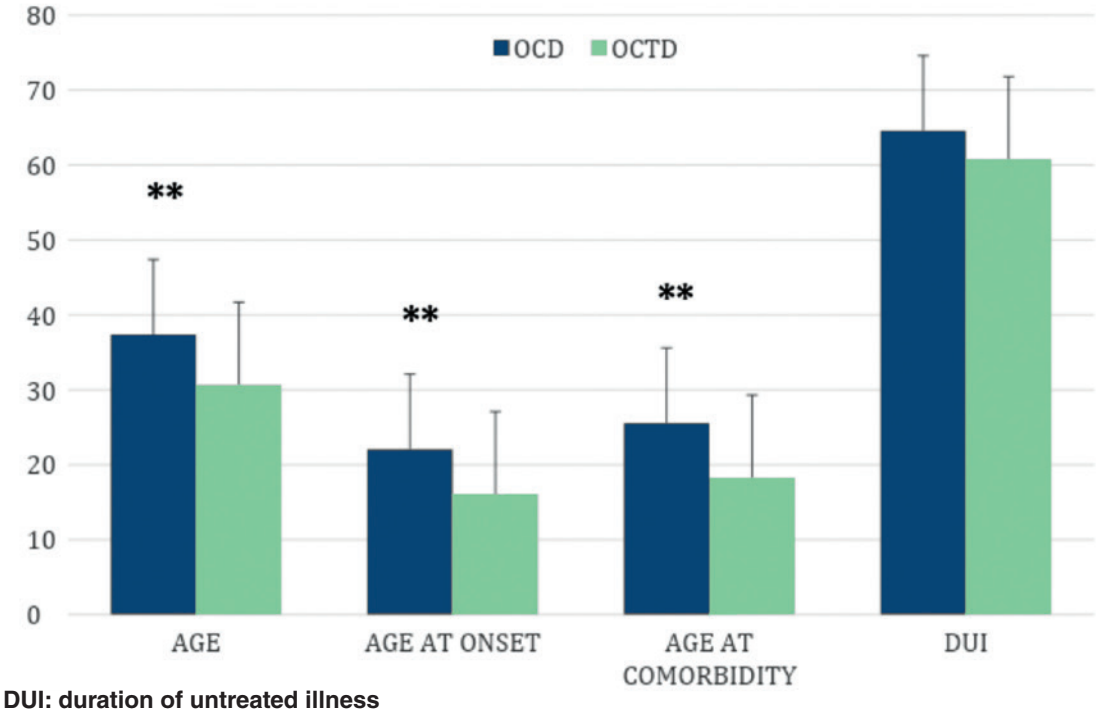


FIGURE 1. *Summary of categorical variables in OCD vs OCTD patients.*

TABLE II. *Treatment related variables (prior and current) in OCD vs OCTD patients.*

	OCD N = 132	OCTD N = 124
Previously treated in other medical centers	89 (67.9%)	84 (68.3%)
Psychotherapy	85 (64.9%)	76 (61.3%)
Psychopharmacological treatment (current)	126 (96.2%)	122 (98.4%)
Antidepressants	119 (90.8%)	112 (90.3%)
D2 antagonist and/or D2, 5-HT2 antagonist treatment	50 (38.2%)*	92 (74.2%)*
Mood stabilizers	32 (24.4%)	29 (23.4%)
Gaba receptor agonist	41 (31.3%)*	25 (20.2%)
Family involvement	60 (46.2%)	44 (35.5%)
Worsened quality of life	65 (50%)	54 (43.5%)
Current treatment responders	70 (53.8%)*	45 (36.3%)
Current partial treatment responders	49 (38%)*	72 (58.1%)*
Residual tic symptoms	-	35 (36.5%)
Residual OCD symptoms	48 (82.8%)*	60 (62.5%)*
Residual OCD + tic	-	27 (27.8%)
Current remission	69 (54.8%)*	44 (35.5%)*
Past remission	43 (37.4%)*	72 (60%)*
Treatment resistance	17 (13.2%)	22 (17.9%)
Suicidal thoughts	20 (41.7%)*	24 (63.2%)*
Suicide attempts	4 (8.3%)*	11 (28.9%)*

Values for categorical variables are expressed as N (%)
** p < .001*



DUI: duration of untreated illness
*** p < .001*

FIGURE 2. *Summary of continuous variables in OCD vs OCTD patients.*

verity could have had a role on both education and employment, as previously noted on quality of life and psychosocial functioning [18 24 25].

In terms of clinical features, the administered questionnaire included a specific section investigating treatment response and symptoms' remission. In this respect, a higher rate of OCTD patients was treated with an D2 antagonist and/or D2, 5-HT2 antagonist treatment, showing less favorable characteristics, such as lower current treatment response rate, higher current partial response rates, and lower current remission rates, compared to OCD patients without TD. This finding is consistent with previous literature reporting specific higher severity features for OCTD patients [1].

Finally, another relevant novel finding of the present study concerns suicidality. OCTD patients showed significantly higher rates of lifetime suicidal ideation and attempts compared to OCD without TD subgroup. A previous ICOCS study on suicide attempts in OCD patients showed higher rates of suicide attempts in patients with psychiatric and medical comorbidities, who had TD and Tourette as more frequent comorbid conditions [17].

The present study has some limitations, such as the lack of information on the severity of the disorder (measured with specific psychopathological scales) and the cross-sectional assessment design. Further follow-up studies are needed to better characterize long-term course of OCTD patients, their functional impairment and treatment response.

Conclusions

Based on the present findings, a tailored, personalized and multidisciplinary treatment seems a priority in the management of OCTD patients, given their early onset and long-term disabling course.

Conflicts of Interest

Bernardo Dell'Osso: speaker's fee from Lundbeck, Angelini and FB Health.

Joseph Zohar: Grant/research support from Lundbeck, Brainsway, Servier and Pfizer; consultant or on advisory boards for Servier, Pfizer, Abbott, Lilly, Actelion, AstraZeneca, Janssen and Roche; speakers' bureaus for Lundbeck, Roch, Lilly Servier, Pfizer, Brainsway, Sunpharma and Abbott.

Orsola Gambini: took part in a European multicentre study sponsored by Medtronic about DBS in OCD. The study is concluded, results are under elaboration.

Domenico de Berardis: speaker's fee from Lundbeck, Angelini, Janssen and Eli-Lilly

A. Carlo Altamura: Speaker's fee from Lundbeck, Angelini and Janssen.
Beatrice Benatti, Eric Hollander, Liliana Dell'Osso, Naomi A. Fineberg, Matteo Marcatili, Sylvia Rigardetto, Matteo Briguglio, Donatella Marazziti, Federico Mucci, Antonio Tundo, Roberta Necci, Roberta Galentino, Sara De Michele, Claudio D'Addario, Domenico Servello, Umberto Albert, Giuseppe Maina, Diana de Ronchi, Mauro Porta: Nothing to Declare.

References

1. Gomes De Alvarenga PG, De Mathis MA, Dominguez Alves AC, et al. *Clinical features of tic-related obsessive-compulsive disorder: results from a large multicenter study*. CNS Spectrums 2012;17:87-93.
2. Ferrao YA, De Alvarenga PG, Hounie AG, et al. *The phenomenology of obsessive-compulsive symptoms in Tourette Syndrome*. In: Martino D, Leckman JF, Eds. *Tourette Syndrome*. New York, NY: Oxford University Press 2013.
3. Yu D, Mathews CA, Scharf JM, et al. *Cross-disorder genome-wide analyses suggest a complex genetic relationship between Tourette's syndrome and OCD*. Am J Psychiatry 2015;172:82-93.
4. Stein DJ, Kogan CS, Atmaca M, et al. *The classification of obsessive-compulsive and related disorders in the ICD-11*. J Affect Disord 2016;190:663-74.
5. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, 5th edition*. Arlington, VA: American Psychiatric Association 2013.
6. Pinto R, Monzani B, Leckman JF, et al. *Understanding the covariation of tics, attention-deficit/hyperactivity, and obsessive-compulsive symptoms: A population-based adult twin study*. Am J Med Genet B Neuropsychiatr Genet 2016,171:938-47.
7. Leckman JF, Grice DE, Barr LC, et al. *Tic-related vs non-tic-related obsessive compulsive disorder*. Anxiety 1994-1995;1:208-15.
8. Eichstedt JA, Arnold SL. *Childhood-onset obsessive-compulsive disorder: a tic-related subtype of OCD?* Clin Psychol Rev 2001;21:137-57.
9. Roessner V, Becker A, Banaschewski T, et al. *Tic disorders and obsessive compulsive disorder: where is the link*? J Neural Transm Suppl 2005;:69-99.
10. Brakoulias V, Androutsos C. *The clinical utility of the tic-related obsessive-compulsive disorder diagnostic specifier*. Aust N Z J Psychiatry 2015;49:1060.
11. Browne HA, Hansen SN, Buxbaum JD, et al. *Familial clustering of tic disorders and obsessive-compulsive disorder*. JAMA Psychiatry 2015;72:359-66.
12. Zilhão NR, Olthof MC, Smit DJ, et al. *Heritability of tic disorders: a twin-family study*. Psychol Med 2017;47:1085-96.
13. Grados MA, Mathews CA. *Clinical phenomenology and phenotype variability in Tourette Syndrome*. J Psychosom Res 2009;67:491-6.
14. Dell'Osso B, Marazziti D, Albert U, et al. *Parsing the phenotype of obsessive-compulsive tic disorder (OCTD): a multidisciplinary consensus*. Int J Psychiatry Clin Pract 2017;21:156-9.
15. Lochner C, Fineberg NA, Zohar J, et al. *Comorbidity in obsessive-compulsive disorder (OCD): a report from the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS).* Compr Psychiatry 2014;55:1513-9.
16. Dell'Osso B, Nicolini H, Lanzagorta N, et al. *Cigarette smoking in patients with obsessive compulsive disorder: a report from the International College of Obsessive Compulsive Spectrum Disorders (ICOCS).* CNS Spectr 2015;20:469-73.
17. Dell'Osso B, Benatti B, Arici C, et al. *Prevalence of suicide attempt and clinical characteristics of suicide attempters with obsessive-compulsive disorder: a report from the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS).* CNS Spectr 2018;23:59-66.
18. Scalone L, D'Angiolella LS, Mantovani LG, et al. *Obsessive compulsive tic disorder: appropriate diagnosis and treatment as key elements to improve health and rationalize use of resources.* Epidemiol Biostat Public Health 2017;14:e12661-1-10.
19. Lewin AB, Chang S, McCracken J, et al. *Comparison of clinical features among youth with tic disorders, obsessive-compulsive disorder (OCD), and both conditions*. Psychiatry Res 2010;178:317-22.
20. Porta M, Saleh C, Zekaj E, et al. *Why so many deep brain stimulation targets in Tourette's syndrome? Toward a broadening of the definition of the syndrome*. J Neural Transm 2016;123:785-90.
21. Diniz JB, Rosario-Campos MC, Hounie AG, et al. *Chronic tics and Tourette Syndrome in patients with obsessive-compulsive disorder*. J Psychiatr Res. 2006; 40:487–493.
22. Coffey BJ, Miguel EC, Biederman J et al. *Tourette's disorder with and without obsessive-compulsive disorder in adults: are they different?* J Nerv Ment Dis 1998;186:201-6.
23. Fineberg NA, Hengartner MP, Bergbaum C, et al. *Lifetime comorbidity of obsessive-compulsive disorder and subthreshold obsessive-compulsive symptomatology in the community: impact, prevalence, socio-demographic and clinical characteristics*. Int J Psychiatry Clin Pract 2013;17:188-96.
24. Højgaard DRMA, Skarphedinsson G, Nissen JB, et al. *Pediatric obsessive-compulsive disorder with tic symptoms: clinical presentation and treatment outcome.* Eur Child Adolesc Psychiatry 2017;26:681-9.
25. de Vries FE, Cath DC, Hoogendoorn AW et al. *Tic-Related Versus Tic-Free Obsessive-Compulsive Disorder: Clinical Picture and 2-Year Natural Course*. J Clin Psychiatry. 2016;77(10):e1240-e1247.

Original article

JOURNAL OF PSYCHOPATHOLOGY
2018;24:154-163

Factors associated with increased suicide risk in Obsessive-Compulsive Disorder

U. Albert[1], M. Speciani[1], D. De Ronchi[1], A.R. Atti[1], G. Maina[2], Z. Bélteczky[3], M. Pompili[4], Z. Rhimer[5]

[1] Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy; [2] Rita Levi Montalcini Department of Neuroscience, University of Torino, Italy;[3] Department of Psychiatry, Sántha Kálmán Szakkórház, Nagykálló, Hungary; [4] Department of Neurosciences, Mental Health and Sensory Organs, Suicide Prevention Center, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy; [5] Department of Clinical and Theoretical Mental Health, Kútvölgyi Clinical Center, Semmelweiss University, Budapest, Hungary

Summary

Objectives

Obsessive-Compulsive Disorder (OCD) is in itself at greater risk for suicide (suicidal ideation, suicide attempts and completed suicide) as compared to the general population. However, the majority of individuals with OCD do not have current or lifetime suicidal ideation nor did attempt suicide in their lifetime.

Methods

The present paper aims to provide an updated review on factors (socio-demographic and personal factors, OCD-related variables, comorbidities, emotion-cognitive factors, and biological variables) contributing to the increased suicide risk in patients with OCD.

Results

Several factors have been found to be strongly associated with suicide risk in patients with OCD, such as the severity of OCD, the unacceptable thoughts symptom dimension, having a comorbid Axis I disorder (Bipolar Disorder, Major Depressive Disorder, Substance Use Disorder), the severity of comorbid depressive and anxiety symptoms, a previous history of suicide attempts, having high levels of alexithymia and hopelessness.

Conclusions

Several contributing factors should be evaluated and identified in the clinical practice in order to improve early detection of suicide risk. Risk identification and stratification of risk remain essential components of suicide prevention and should guide the clinical approach to patients with OCD. Whether and how these risk factors for suicide in patients with OCD work together, and whether the specific factors act as moderators or mediators, remains to be fully clarified.

Key words

Obsessive-Compulsive Disorder (OCD) • Suicide • Risk factors

Introduction

Obsessive-Compulsive Disorder (OCD) has been considered for long time a disorder without a notable suicide risk. According to recent meta-analyses, patients with OCD may actually be considered at risk for suicidal ideation, suicide attempts and committed suicide.

Harris et al. [1] found that patients with OCD has 10-times higher risk of suicide compared to the general population. Khan et al. [2] estimated the incidence of suicide attempts among subjects with anxiety disorders, and found a 4% incidence in the subset of patients with OCD. This is a notable result as these patients were enrolled in clinical trials and, since the risk of suicidal behaviors is often an exclusion criterion, it means they were likely not deemed at risk. In more recent years, two independent systematic reviews [3 4] confirmed a significant association between OCD, suicidal ideation and suicide attempts.

The concept that patients with OCD are not at risk of committing or attempting suicide, with the clinical consequence of underestimating and un-

Correspondence

Umberto Albert
Department of Biomedical and Neuromotor Science, Section of Psychiatry, University of Bologna, viale C. Pepoli 5, 40123 Bologna, Italy
• Tel. +39 051 2083058 • Fax +39 051 521030 •
E-mail: umberto.albert@unibo.it

dertreating this aspect, has been questioned. Clinicians should consider that patients affected from OCD are at risk and all aspects of suicidality should be evaluated in these patients. However, having a mental disorder is one of the contributing factors for suicide risk; other risk factors can interact with the diagnosis of OCD and determining the risk of suicide in each subject.

The present paper aims to provide an updated review of the literature concerning the relationship between suicide risk and OCD. Specifically, we will focus our attention on factors (socio-demographic and personal factors, OCD-related variables, comorbidities, psychopathological and biological variables) contributing to the increased suicide risk in OCD (either in terms of suicidal ideation, suicidal attempts, or completed suicides).

Methods

We performed a systematic review of the literature by searching PubMed from the date of the first available article to January 8, 2018. The search terms [suicide] OR [suicidality] OR [suicide attempts] OR [suicidal ideation] OR [suicidal thoughts] were combined with [OCD] OR [obsessive*compulsive disorder] OR [obsessive*compulsive symptoms]. We included: 1) studies with appropriate definition of OCD (diagnosis made through specific structured interviews and/or established international criteria); 2) performed in adolescents and/or adults; 3) with a cross-sectional or prospective designs; 4) performed in clinical samples or in the general population (epidemiological studies); 5) which employed a quantitative measure of suicidality; and/or 6) reported an outcome measure of the association between suicidality and OCD (e.g. odds ratios) or examined factors associated with suicidality.

Estimates of suicide risk in OCD

A recent systematized review of the available literature [4] investigated suicide risk in OCD patients in both clinical and epidemiological samples; estimates of suicidal ideation and suicide attempts rates in clinical samples were based on 37 studies while 14 epidemiological studies provided data on the association in the general population between a baseline diagnosis of OCD and suicidal ideation or suicide attempts.

Suicidal ideation and suicide attempts in OCD: clinical samples

The prevalence of current suicidal ideation ranges between 6.4 [5] and 75% [6] with an estimated mean of 25.9% (median: 15.6%) [4]; while the lifetime suicidal ideation is estimated to be 44.1% (median: 36.4%) [4], varying from 26.3 [7] to 73.5% [8]. Lifetime suicide attempts rate is estimated at 14.2% (median 10.8%) [4], ranging from 6 [9] to 51.7% [10].

Concerning family history of suicide, the rates of suicide attempts range from 11.5 [11] to 27.1% [12] (mean 17.9, median 18.2%) [4] and rates of completed suicide among family members varying between 8.9 [13] and 16.1% [14].

Suicidal ideation, suicide attempt and suicide rates in OCD: epidemiological samples

All epidemiological studies (among which three performed on national registers – the Swedish National Patient Register [15], the Danish Register [16] and the British National Psychiatric Morbidity Survey [17]) found that OCD increases significantly the odds of having a lifetime suicidal ideation as compared to the general population [OR ranging from 1.9 (CI 1.3-2.8) to 10.3 (CI 5.37-19.8)]; the increased risk remains significant even after controlling for demographic variables and comorbid psychiatric disorders [Adjusted Odds Ratio ranging from 3.8 (CI 2.8-5.1) to 5.58 (CI 2.7-11.6)] [4]. Having a history of OCD is associated with an increased risk of lifetime suicide attempts [OR from 1.6 (CI 1.0-2.6) to 9.9 (CI 4.5-21.8)], although it is not clear whether this increased risk remains significant when controlling for comorbid psychiatric disorders[4].

The two prospective studies on national registers [15 16] reported a higher risk of death by suicide in patients with OCD than expected [OR: 3.02 (CI 1.85-4.63) to 9.83 (CI 8.72-11.08)], and results remained significant even for pure OCD [OR: 13.18 (CI 10.76-16.16)].

Data coming from the analysis of prevalence rates and odds ratios show that, at least in part, suicide risk in OCD is influenced by several other psychiatric disorders, including unipolar and bipolar depression. Additionally, a substantial proportion of OCD patients never manifest suicidal ideation in their lifetime, even when the severity of the disorder is significant. This implies that a number of potential contributing factors to the increase of suicide risk are to be screened and identified. Risk identification and stratification of risk remain essential for suicide prevention and should guide the clinical approach to subjects with psychiatric disorders.

In the following paragraphs, we will present data concerning which factors are associated with a higher risk of suicidal ideation, attempting suicide or committing suicide in individuals with OCD. Socio-demographic and personal factors, OCD-related variables, comorbidities, psychopathological variables (emotion-cognitive and temperamental factors) as well as biological variables will be presented separately.

Factors associated with increased risk of suicide

Socio-demographic and personal characteristics

Table I shows the socio-demographic or personal factors associated with the increased suicide risk in pa-

TABLE I. *Socio-demographic variables or personal factors found to be associated with increased suicide risk in OCD patients.*

Factor	Suicidal ideation	Suicide attempts	Completed suicides
Male gender	Maina et al., 2006 [18]		Fernandez de la Cruz et al., 2017 [15]
Female gender		Fernandez de la Cruz et al., 2017 [15]	
Older age	Maina et al., 2006 [18]		
Marital status: single	Torres et al., 2011 [14]	Alonso et al. 2010 [27]	
No children	Torres et al., 2011 [14]		
Poor educational level, lower social class	Maina et al., 2006 [18] Torres et al., 2011 [14]		
Childhood trauma	Ay & Erbay, 2018 [21]	Khosravani et al., 2017 [6]	

tients with OCD. Being male is a risk factor for both suicidal ideation and for death by suicide [15 18], while being female is a risk factor for lifetime suicide attempts [15], confirming data from the general population [19].

Having a low educational level, being older, having a low social economic status and not having children have been found to be significant risk factors for current and lifetime suicidal ideation [14 18].

As regards the impact on marital status of suicide risk, Torres et al. [14] reported a significant correlation between being single and a higher risk of lifetime suicide attempts, contrasting with data by Maina et al. [18]. An explanation may be that the family plays an important supportive role in OCD, tackling suicide-related sentiments when they emerge, urging patients to seek for professional help.

Another factor associated with increased risk of suicide (both suicidal ideation and suicide attempts) is a personal history of childhood trauma [6 21]. In particular, childhood sexual abuse predicts later suicidal ideation and attempts among individual with OCD [6 21].

OCD-related variables

The disorder-specific (OCD-related) variables associated with increased suicide risk in patients with OCD are reported in Table II.

Six studies investigated the relationship between OCD severity (in terms of Y-BOCS total score) and suicidal ideation/suicide attempts showing that higher levels of illness severity are associated with higher rates of lifetime suicide attempts [12 23] and suicidal ideation [18 24-26]. Whether or not the effect is mediated by the concomitant presence of comorbid depression, the chronicity of

TABLE II. *Disorder-specific (OCD-related) variables found to be associated with increased suicide risk in OCD patients.*

Factor	Suicidal ideation	Suicide attempts
Severity of OCD: Y-BOCS total scores	Maina et al., 2006 [18] Balci & Sevincok, 2010 [26] Hung et al., 2010 [24] Gupta et al., 2014 [25]	Velloso et al., 2016 [12] Dhyani et al., 2018 [23]
Contamination/washing dimension	Gupta et al., 2014 [25]	
Symmetry/ordering dimension	De Berardis et al., 2014 [13] Gupta et al., 2014 [25]	Alonso et al., 2010 [27]
Unacceptable thoughts	Balci & Sevincok, 2010 [26] Torres et al., 2011 [14] Kim et al., 2016 [30] Velloso et al., 2016 [12] Khosravani et al., 2017 [10]	Velloso et al., 2016 [12] Khosravani et al., 2017 [10]
Hoarding dimension	Torres et al., 2011 [14]	Chakraborty et al., 2012 [29]
Poor insight	Gupta et al., 2014 [25] De Berardis et al., 2015 [11]	
Premenstrual worsening of OCD symptoms	Moreira et al., 2013 [33]	Moreira et al., 2013 [33]

OCD: Obsessive-Compulsive Disorder; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale

the disorder/duration of untreated illness or other mediating factors is to be fully understood.
OCD is a heterogeneous disorder, with several symptom dimensions. Contrasting findings have been found on the role of obsessive thinking/compulsive behaviour and suicidal ideation. In particular, Gupta et al. [25] found a positive significant association between contamination obsessions/washing behaviors and lifetime suicidal ideation, while other studies identified the presence of symmetry as risk factor [13 25 27]. Alonso et al. [27] found that symmetry obsessions/ordering symptoms are associated with lifetime suicide attempts. Chaudhary et al. [28] have observed that suicidality is most common in patients reporting obsessions on cleanliness and contamination (57%), religious obsessions (45%), sexual obsessions (33%) and repeated rituals (31%). Hoarding obsessions and compulsions predicted lifetime suicide attempts in one study [29]. A clear association between unacceptable (aggressive, sexual, or religious obsessions) thoughts and suicidal behaviors has been found [10 12 14 26 30], both in terms of suicidal ideation and suicide attempts. Moreover, suicidal ideation was predicted by lack of insight [11 25]. Moreira et al. [33] investigated the worsening of OCD symptoms in the premenstrual period as risk factor for suicidal ideation and suicide attempts. This relationship might be due to the hormonal changes preceding the menstrual period, which may heighten patients' susceptibility to obsessions/compulsions cycle, causing an exacerbation of symptoms.

Comorbidities

The impact of psychiatric or medical comorbidities on suicide risk or suicidal behaviors in patients with OCD has been extensively investigated (Tab. III). Having at least one current or lifetime comorbid mental disorder impacts on suicidal behaviors [12 15 34 35], in terms of higher number of suicide attempts and higher prevalence of suicidal thoughts [34].
Several studies have analyzed the effects of specific comorbidities and suicidal behaviors. In particular, patients with OCD and comorbid bipolar disorder [36-38] or major depressive disorder (MDD) [14 18 26 39-41] have an increased risk of suicidal attempts and suicidal ideation; moreover, patients with MDD and OCD have an increased risk of lifetime suicide attempts [14 27 39 41]. Furthermore, the severity of depressive symptoms is positively associated with suicidal ideation and lifetime suicide attempts in patients with OCD [10 12 14 18 24-28 30].
As regards the impact of comorbidity with anxiety disorders on suicidal behaviors, having a PTSD or GAD increases the risk of suicidal ideation and lifetime suicide attempts [14 42]. On the other hand, the presence of comorbid anxiety disorders seems to be a protective factor for completed suicides [15]. The severity of comorbid anxiety disorders is correlated with suicidal ideation [14 18 24-26 43] and with suicide attempts [12 14], although this has not been confirmed by Weingarden et al. [43].
Patients with a comorbid substance and alcohol use disorders show a higher risk of suicidal ideation [7 14 36], suicide attempts [7 15 36] and death by suicide [15].
A significant correlation was found between cigarette smoking and suicide attempts in OCD patients by Dell'Osso et al. [44]. In particular, the risk of suicide is higher in former cigarette smokers with OCD.
A significant association between higher lifetime suicide attempts and comorbid eating disorders in OCD was found by Sallet et al. [50]. The prevalence of lifetime suicide attempts was higher in bulimic-OCD patients (33%), followed by anorexic-OCD patients (19%), and then by binge eating disorder-OCD patients (16%).
Personality disorders are correlated to a higher risk of both suicide attempts and completed suicide in patients with OCD, although it is unclear whether specific personality disorders account for this increased risk [15].
Suicidal ideation increases the risk of attempting suicide [23 39] and a history of previous suicide attempts is strongly related to later suicidal ideation, suicide attempts and even death by suicide [15 27 39]. Moreover, in the Swedish study that used a matched case-cohort design with a follow-up of 44 years, authors found that a previous suicide attempt increases the risk of 4.7 for death by suicide in patients with OCD [15]. A positive family history for suicide attempts is also correlated with both suicidal ideation and suicide attempts in OCD patients [12].
Only one study [35] found that also comorbid medical disorders may be associated with increased risk of suicide; in fact, subjects who attempted suicide had more comorbid medical disorders than individuals who never attempted suicide.

Psychopathological variables

Several different psychopathological variables are associated with increased suicide risk in OCD patients (Tab. IV). De Berardis et al. [11] found a significant association between suicidal ideation and inflated responsibility in individuals with OCD and alexithymia, independently from depressive symptoms. Alexithymia is a multifaceted construct including difficulty in identifying and describing feelings, difficulty in distinguishing feelings from bodily sensations, reduction in fantasy, and concrete and minimally introspective thinking. Alexithymia itself is associated with suicidal ideation [11 13 30] and lifetime suicide attempts [30]. Moreover, a study found that alexithymic individuals with OCD exhibit dysregulation of the cholesterol balance [13], which in turn is associated with suicidal ideation. Although the exact relationship between alexithymia, altered lipid profile and suicide in OCD is not clear, it is possible that the increased risk for suicide is mediated by the alterations of cholesterol levels associated with alexithymia.

TABLE III. *Comorbidities found to be associated with increased suicide risk in OCD patients.*

Factor	Suicidal ideation	Suicide attempts	Completed suicides
Current/lifetime comorbid psychiatric disorders	Torres et al., 2013 [34]	Torres et al., 2013 [34] Velloso et al., 2016 [12] Dell'Osso et al., 2017 [35] Fernandez de la Cruz et al., 2017 [15]	
Comorbid Bipolar Disorder	Fineberg et al., 2013 [36]	Fineberg et al., 2013 [36] Ozdemiroglu et al., 2015 [37] Saraf et al., 2017 [38]	
Comorbid Mood Disorders/ Comorbid Major Depressive Disorder	Maina et al., 2006 [18] Kamath et al., 2007 [39] Maina et al., 2007 [40] Balci & Sevincok, 2010 [26] Torres et al., 2011 [14] Viswanath et al., 2012 [41]	Kamath et al., 2007 [39] Alonso et al., 2010 [27] Torres et al., 2011 [14] Viswanath et al., 2012 [41]	
Severity of comorbid depressive symptoms	Maina et al., 2006 [18] Kamath et al., 2007 [39] Balci & Sevincok, 2010 [26] Hung et al., 2010 [24] Torres et al., 2011 [14] Gupta et al., 2014 [25] Kim et al., 2016 [30] Khosravani et al., 2017 [10]	Kamath et al., 2007 [39] Alonso et al., 2010 [27] Velloso et al., 2016 [12]	
Comorbid PTSD/GAD (and other anxiety disorders)	Torres et al., 2011 [14] Fontenelle et al., 2012 [42]	Torres et al., 2011 [14] Fontenelle et al., 2012 [42]	Fernandez de la Cruz et al., 2017 [15]
Severity of comorbid anxiety symptoms	Maina et al., 2006 [18] Balci & Sevincok, 2010 [26] Hung et al., 2010 [24] Torres et al., 2011 [14] Gupta et al., 2014 [25] Weingarden et al., 2016 [43]	Torres et al., 2011 [14] Velloso et al., 2016 [12] Weingarden et al., 2016 [43]	
Substance/alcohol use disorders	Gentil et al., 2009 [7] Torres et al., 2011 [14] Fineberg et al., 2013 [36]	Gentil et al., 2009 [7] Fineberg et al., 2013 [36] Fernandez de la Cruz et al., 2017 [15]	Fernandez de la Cruz et al., 2017 [15]
Cigarette smoking (former)		Dell'Osso et al., 2015 [44]	
Comorbid eating disorders		Sallet et al., 2010 [50]	
Personality disorders		Fernandez de la Cruz et al., 2017 [15]	Fernandez de la Cruz et al., 2017 [15]
Lifetime psychiatric hospitalizations		Dell'Osso et al., 2017[35]	
Suicidal ideation		Kamath et al., 2007 [39] Dhyani et al., 2018 [23]	
Previous suicide attempts	Kamath et al., 2007 [39]	Kamath et al., 2007 [39] Alonso et al., 2010 [27]	Fernandez de la Cruz et al., 2017 [15]
Family history for suicide attempts	Velloso et al., 2016 [12]	Velloso et al., 2016 [12]	
Medical comorbidities		Dell'Osso et al., 2017 [35]	

PTSD: Post-Traumatic Stress Disorder; GAD: Generalized Anxiety Disorder

TABLE IV. *Psychopathological variables found to be associated with increased suicide risk in OCD patients.*

Factor	Suicidal ideation	Suicide attempts
Inflated responsibility	De Berardis et al., 2015 [11]	
Ego-dystonic perfectionism	Kim et al., 2016 [30]	Kim et al., 2016 [30]
Alexithymia	Kim et al., 2016 [30] De Berardis et al., 2014 [13] De Berardis et al., 2015 [11]	Kim et al., 2016 [30]
Shame	Weingarden et al., 2016 [43]	
Hopelessness	Kamath et al., 2007 [39] Balci & Sevincok, 2010 [26] Gupta et al., 2014 [25]	Dhyani et al., 2018 [23]
Hostility	Gupta et al., 2014 [25]	

Kim et al. [30] found an association between suicidal behaviors and perfectionism, defined as a tendency to set extremely high personal standards and being critical of themselves in a perpetuating cycle of dissatisfaction. Weingarden et al. [43] found a significant association between shame and suicidal ideation in OCD patients and hypothesized that shame may strengthen the destabilizing effects of egodystonic emotions and acts.

Also hopelessness and hostility can impact on suicidal ideation and suicide attempts in patients with OCD [23 25 26 39]. In particular, Gupta et al. [25] found a correlation between hostility and suicidal ideation and found that the Beck Hopelessness Scale (BHS) predicts suicidal ideation in patients with OCD better than the Y-BOCS [23]. Khosravani et al. [6] found that the presence of early maladaptive schemas, such as mistrust/abuse schemas, is significantly correlated with an increased risk for suicidal ideation and suicide attempts in patients with OCD. Cyclothymic affective temperament represents a major risk factor for suicide in patients with OCD [8] as in patients with MDD [51 52].

Biological variables

In addition to the well documented serotonergic dysregulation in OCD [3 54], two recent studies reported a statistically significant correlation between lower HDL-Cholesterol levels and suicidality in OCD patients; De Berardis et al. [13] found a statistically significant correlation between lower HDL-C levels, alexithymia, and higher suicidal ideation, while Aguglia et al. [55] found a significant correlation between higher lifetime suicide attempts and lower HDL-C levels and higher blood levels of triglycerides. While the two studies investigated two different dimensions of suicidality, they agree on specific serum lipid alterations that seem to correlate with suicidal behavior. No other biological variables have been investigated concerning the risk for suicide in OCD.

Discussion

Patients with OCD are at high risk for suicide, and not only due to the presence of other comorbid mental disorders [3 4]. This new evidence is in contrast with the former assumption that patients with OCD are not exposed to suicidal risk. Therefore, clinicians should always evaluate the suicidal risk in patients with OCD in terms of suicidal ideation, past history of suicide attempts and family history of suicide (attempts and/or committed). Suicidality is a dynamic dimension, and the use of specific instruments, such as the Columbia Suicide Severity Rating Scale (C-SSRS) for evaluating the different dimension analysis of suicidal ideation and its severity, should be implemented in clinical practice[56]. Clinicians dealing with OCD patients should keep in mind that most patients may not spontaneously report suicidal ideation, and a direct inquire is mandatory as it is generally considered to be when interviewing subjects with a major depressive episode.

The majority of patients with OCD do not have current or lifetime suicidal ideation nor did attempt suicide in their lifetime. This implies that identifying predictors of suicidal ideation and suicide attempts in OCD could result in improving our ability to screen subjects at greater risk needing intensive and careful monitoring. Of course, early recognition and diagnosis of OCD and effective pharmacological and psychological treatments of the disorder remain essential for the prevention of suicidality. We do not have pharmacological agents with an evidence-based demonstration of effectiveness in treating suicidality, apart from lithium in affective disorders and clozapine in schizophrenia. Therefore, the evaluation of risk factors remains crucial for suicide prevention.

Concerning sociodemographic factors, we found male gender, older age and poor socioeconomic status to be associated with suicide risk. The possible explanations for higher suicide mortality of males may be the more common use of alcohol and violent suicide method by

males and the higher prevalence of borderline personality disorder in women [20], which is more frequently correlated with attempted suicides than with completed ones. Some of the data taken in consideration may actually support this hypothesis, as Fernandez de la Cruz et al. [15] actually found overlapping confidence intervals between genders in OR for suicide attempts after adjustments for personality disorders.

Since no significant difference was found between age at diagnosis, suicidal ideation in older age may be considered a consequence of OCD which has not been resolved, and therefore which could have had a long-standing negative impact on quality of life. As of the poorer educational level as a risk factor, this specific group of subjects may lack the means or the knowledge to further understand their illness, or to recognize when to seek help in case of exacerbations, which may impact their quality of life and the course of the illness.

When examining OCD-related variables, we found that severity of symptoms and the specific symptom dimension of aggressive obsessions are related to higher suicide risk. It is possible that other factors, such as hopelessness, could mediate the effect of specific symptom dimensions on suicide risk. It may be that individuals with a higher severity of symptoms, or higher severity of specific symptom dimensions (such as thoughts that are deemed unacceptable, or symptoms that severely impact a multitude of aspects of their day-to-day life, such as hoarding symptoms), are more likely to feel hopeless, and therefore may consider – or even act – against their own self in an attempt to regain control of their life. In this context, lack of insight may play a role as a risk factor as proper insight could promote a deeper knowledge and understanding of the illness, which could therefore lead to the better use of all the means available to patients to get help and appropriate treatment.

From our review of the literature we found that comorbid disorders (and, specifically, comorbid depression – both in major depressive disorder but also in bipolar disorder) are predictors of higher suicide risk. Clinicians should always inquire about suicidal ideation or previous suicide attempts in individuals with comorbid depression, keeping in mind that often these individuals are affected by bipolar disorder and that the pharmacological treatment for OCD (moderate-to-high doses of SSRIs) may worsen suicidal ideation, induce mixed states and expose the patient to a higher risk of committing suicide. Comorbid substance use disorders are also significant risk factors for suicidality. It may be that the development of an addiction to a substance and the distress caused by egodystonic obsessions and compulsions in OCD may work in synergy and amplify each other. Substance abuse may therefore be considered, in OCD patients who develop addiction, as a mean to escape from their obsessions and compulsions through the intoxication of the mind, which could cause an exacerbation of symptoms as soon as the effect of the substance wears off, thus reinforcing the cycle, eventually leading some patient to consider, attempt or even complete suicide. Comorbid cigarette smoking seems also to be a risk factor; it may be hypothesized that those who are at a higher risk for smoking are at a higher risk for impulsive behaviors [45]; however, those who are no longer smoking may be those who are either determined enough to make long-term, definitive choices (both healthier choices, such as no longer smoking, but also harmful ones, such as attempting suicide), or they may be those who no longer feel that they have an easily accessible mean, such as a cigarette, to help coping with the stress of OCD symptoms and behaviors. Smoking could be not an important contributing factor for the elevated suicidality of OCD patients as, in spite of the fact that smoking is a risk factor for all forms of suicidal behavior both on clinical [46] and on population level [47], it has been repeatedly shown that OCD patients smoke much less than other psychiatric patients and the general population [48 49]. Further studies are needed to better understand the relationship between smoking and suicidality in OCD patients.

Comorbid somatic diseases are also associated with suicidality in OCD. Since the presence of medical comorbidities is associated with an increased risk of suicide attempt [35], it is possible that the treatment of medical comorbidities could strongly affect the risk for suicide attempts in OCD patients, and should be a priority, although this assumption needs to be further confirmed.

Concerning psychopathological variables, from our review of the literature we identified hopelessness and personality traits, such as alexithymia or ego-dystonic perfectionism, as emotion-cognitive factors increasing the risk of suicide in individuals with OCD. Regretfully, it is not common in clinical practice to screen for the presence of these factors, nor it is routine clinical practice to distinguish between ego-dystonic perfectionism from OCD symptoms. Some clinicians with a cognitive-behavioral background may assess cognitive constructs such as inflated responsibility and evaluate its impact on the severity of the disorder (including suicide risk). Given that suicide risk is higher in people with these cognitive-emotional risk factors, we suggest adding their evaluation in the baseline assessment of individuals presenting with severe OCD.

Early maladaptive schemas, such as mistrust/abuse schemas, are also predictors of suicidality. Mistrust/abuse schema refers to an attitude recognized by avoidance of relationships with others for fear of being betrayed or misled, which in turn may be related

to having suffered from physical and/or sexual abuse experiences, severe punishments or living in an emotionally or physically unsafe environment[6]. This finding is particularly interesting and clinically useful if considered together with results concerning the role of childhood trauma and comorbid PTSD as two independent risk factors for suicide behaviors in OCD. Addressing adverse childhood experiences in patients at higher risk for suicide because of having suffered a childhood trauma could result in reduced suicide rates.

Very few biological variables have been investigated concerning suicide risk and OCD; only low HDL-cholesterol levels have been found associated with an increase in suicidal ideation and suicide attempts. A possible explanation could be that altered cholesterol levels may impact vascular serotonin sensitivity, neuronal membrane balance and viscosity, and this may result in decreased serotonin activity, which could lead to more impulsive behaviors, such as suicidal ideation and attempts. Further studies are needed to better assess the cause and effect relationship between suicidality and altered serum lipid levels.

A few studies evaluated the relative weight of each risk factor in increasing risk suicide risk: family history for suicidality [12], previous suicide attempts [15] and comorbid major depression or bipolar disorder [14] appear the most important risk factors and should not be disregarded when assessing individuals with OCD.

Another under investigated area in OCD is whether addressing and modifying one risk factor result in reducing rates of suicide attempts. We could identify only one study investigating the effects of an intervention on risk factor modification; in this study, a one-session anxiety sensitivity cognitive concerns intervention produced significantly greater reduction in anxiety sensitivity, and changes in anxiety sensitivity cognitive concerns mediated the changes in suicidality at one-month follow-up [57]. Unfortunately, no other studies assessed or proposed similar interventions on other risk factors.

We strongly advocate future similar longitudinally studies examining whether specific programs and interventions on risk factors will result in a reduced suicide risk in OCD patients, as some identified risk factors, such as severity of the disorder, comorbid depression (or other disorders), cigarette smoking, alexithymia and hopelessness, among others, are all potentially modifiable (e.g. simple interventions such as smoking cessation programs could reduce suicide risk).

A general limitation of this review is that several of the identified risk factors were not confirmed in other studies; moreover, the statistical procedure of several studies did not allow for the control of potentially confounding factors, so that many identified predictors of suicide ideation or attempts in OCD may actually result to be proxies to other true independent risk factors. Notwithstanding these limitations, we think that our contribution could be of great value to clinicians in that it could prompt a greater attention to suicide risk in OCD.

Conclusions

Patients with obsessive-compulsive disorder have a greater risk for suicide (suicidal ideation, suicide attempts and completed suicide) as compared to the general population, and this increased risk is even greater in individuals who have specific characteristics, which we may assume are risk factors for suicidality in OCD. These factors should be routinely assessed in clinical practice: the severity of OCD, the symptom dimension of unacceptable (aggressive, sexual, religious obsessions) thoughts, having a comorbid Axis I disorder (especially bipolar disorder or major depressive disorder, but also substance use disorder), the severity of comorbid depressive and anxiety symptoms, a previous history of suicide attempts, and some psychopathological variables, such as alexithymia and hopelessness, all increase the risk of having suicidal ideation or attempting suicide. Whether and how these risk factors for suicide in OCD work together, and whether the specific factors act as moderators or mediators, remains to be elucidated. Nevertheless, identifying individuals who are at greater risk could result in improving our ability to prevent suicide in OCD.

Conflict of Interest

The authors have no conflict of interests.

References

1 Harris EC, Barraclough B. *Suicide as an outcome for mental disorders. A meta-analysis.* Br J Psychiatry 1997;170:205-28.

2 Khan A, Leventhal RM, Khan S, et al. *Suicide risk in patients with anxiety disorders: a meta-analysis of the FDA database.* J Affect Disord 2002;68:183-90.

3 Angelakis I, Gooding P, Tarrier N, et al. *Suicidality in obsessive compulsive disorder (OCD): a systematic review and meta-analysis.* Clin Psychol Rev 2015;39:1-15.

4 Albert U, De Ronchi D, Maina G, et al. *Suicide risk in Obsessive-Compulsive Disorder and exploration of risk factors: a systematic review*. Curr Neuropharmacol 2018. Doi: 10.2174/1570159X16666180620155941. [Epub ahead of print]

5 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.

6 Khosravani V, Kamali Z, Jamaati Ardakani R, et al. *The relation of childhood trauma*

to suicide ideation in patients suffering from obsessive-compulsive disorder with lifetime suicide attempts. Psychiatry Res 2017;255:139-45.

7 Gentil AF, de Mathis MA, Torresan RC, et al. *Alcohol use disorders in patients with obsessive-compulsive disorder: the importance of appropriate dual-diagnosis*. Drug Alcohol Depend 2009;100:173-7.

8 Hantouche EG, Angst J, Demonfaucon C, et al. *Cyclothymic OCD: a distinct form?* J Affect Disord 2003;75:1-10.

9 Chia BH. *A Singapore study of obsessive compulsive disorder.* Singapore Med J 1996;37:402-6.

10 Khosravani V, Sharifi Bastan F, Samimi Ardestani M, et al. *Early maladaptive schemas and suicidal risk in an Iranian sample of patients with obsessive-compulsive disorder.* Psychiatry Res 2017;255:441-8.

11 De Berardis D, Serroni N, Campanella D, et al. *Alexithymia, responsibility attitudes and suicide ideation among outpatients with obsessive-compulsive disorder: an exploratory study.* Compr Psychiatry 2015;58:82-7.

12 Velloso F, Piccinato C, Ferrão Y, et al. *The suicidality continuum in a large sample of obsessive-compulsive disorder (OCD) patients.* Eur Psychiatry 2016;38:1-7.

13 De Berardis D, Serroni N, Marini S, et al. *Alexithymia, suicidal ideation, and serum lipid levels among drug-naïve outpatients with obsessive-compulsive disorder.* Rev Bras Psiquiatr 2014;36:125-30.

14 Torres AR, Ramos-Cerqueira AT, Ferrão YA, et al. *Suicidality in obsessive-compulsive disorder: prevalence and relation to symptom dimensions and comorbid conditions.* J Clin Psychiatry 2011;72:17-26.

15 Fernández de la Cruz L, Rydell M, Runeson B, et al. *Suicide in obsessive-compulsive disorder: a population-based study of 36 788 Swedish patients.* Mol Psychiatry 2017;22:1626-32.

16 Meier SM, Mattheisen M, Mors O, et al. *Mortality among persons with Obsessive-Compulsive Disorder in Denmark.* JAMA Psychiatry 2016;73:268-74.

17 Torres AR, Prince M, Bebbington PE, et al. *Obsessive Compulsive Disorder: prevalence, comorbidity, impact, and help-seeking in the British National Psychiatric Morbidity Survey of 2000*. Am J Psychiatry 2006;163:1978-85.

18 Maina G, Albert U, Rigardetto S, et al. *Suicidio e disturbo ossessivo-compulsivo.* Giornale Italiano di Psicopatologia 2006;12:31-7.

19 Mościcki EK. *Gender differences in completed and attempted suicides.* Ann Epidemiol 1994;4:152-8.

20 Skodol AE, Bender DS. *Why are women diagnosed borderline more than men?* Psychiatr Q 2003;74:349-60.

21 Ay R, Erbay LG. *Relationship between childhood trauma and suicide probability in obsessive-compulsive disorder.* Psychiatry Res 2017;261:132-6.

22 Turecki G, Brent DA. *Suicide and suicidal behaviour.* Lancet 2016;387:1227-39.

23 Dhyani M, Trivedi JK, Nischal A, et al. *Suicidal behaviour of Indian patients with obsessive compulsive disorder.* Indian J Psychiatry 2018;55:161-6.

24 Hung TC, Tang HS, Chiu CH, et al. *Anxiety, depressive symptom and suicidal ideation of outpatients with obsessive compulsive disorders in Taiwan.* J Clin Nurs 2010;19:3092-101.

25 Gupta G, Avasthi A, Grover S, et al. *Factors associated with suicidal ideations and suicidal attempts in patients with obsessive compulsive disorder.* Asian J Psychiatr 2014;12:140-6.

26 Balci V, Sevincok L. *Suicidal ideation in patients with obsessive-compulsive disorder.* Psychiatry Res 2010;175:104-8.

27 Alonso P, Segalàs C, Real E, et al. *Suicide in patients treated for obsessive-compulsive disorder: a prospective follow-up study.* J Affect Disord 2010;124:300-8.

28 Chaudhary RK, Kumar P, Mishra BP. *Depression and risk of suicide in patients with obsessive-compulsive disorder: a hospital-based study.* In Psychiatry J 2016;25:166-70.

29 Chakraborty V, Cherian AV, Math SB, et al. *Clinically significant hoarding in obsessive-compulsive disorder: results from an Indian study.* Compr Psychiatry 2012;53:1153-60.

30 Kim H, Seo J, Namkoong K, et al. *Alexithymia and perfectionism traits are associated with suicidal risk in patients with obsessive-compulsive disorder.* J Affect Disord 2016;192:50-5.

31 Ducasse D, Loas G, Dassa D, et al. *Anhedonia is associated with suicidal ideation independently of depression: a meta-analysis.* Depress Anxiety 2018;35:382-92.

32 Abramovitch A, Pizzagalli DA, Reuman L, et al. *Anhedonia in obsessive-compulsive disorder: Beyond comorbid depression.* Psychiatr Res 2014;216:223-9.

33 Moreira L, Bins H, Toressan R, et al. *An exploratory dimensional approach to premenstrual manifestation of obsessive-compulsive disorder symptoms: a multicentre study*. J Psychosom Res 2013;74:313-9.

34 Torres AR, Shavitt RG, Torresan RC, et al. *Clinical features of pure obsessive-compulsive disorder.* Compr Psychiatry 2013;54:1042-52.

35 Dell'Osso B, Benatti B, Arici C, et al. *Prevalence of suicide attempt and clinical characteristics of suicide attempters with obsessive-compulsive disorder: a report from the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS).* CNS Spectr 2017;1-8.

36 Fineberg NA, Hengartner MP, Bergbaum C, et al. *Lifetime comorbidity of obsessive-compulsive disorder and subthreshold obsessive-compulsive symptomatology in the community: impact, prevalence, socio-demographic and clinical characteristics.* Int J Psychiatry Clin Pract 2013;17:188-96.

37 Ozdemiroglu F, Sevincok L, Sen G, et al. *Comorbid obsessive-compulsive disorder with bipolar disorder: a distinct form?* Psychiatry Res 2015;230:800-5.

38 Saraf G, Paul I, Viswanath B, et al. *Bipolar disorder comorbidity in patients with a primary diagnosis of OCD.* Int J Psychiatry Clin Pract 2017;21:70-4.

39 Kamath P, Reddy YC, Kandavel T. *Suicidal behavior in obsessive-compulsive disorder*. J Clin Psychiatry 2007;68:1741-50.

40 Maina G, Salvi V, Tiezzi MN, et al. *Is OCD at risk for suicide? A case-control study.* Clinical Neuropsychiatry 2007;4:117-21.

41 Viswanath B, Narayanaswamy JC, Rajkumar RP, et al. *Impact of depressive and anxiety disorder comorbidity on the clinical expression of obsessive-compulsive disorder*. Compr Psychiatry 2012;53:775-82.

42 Fontenelle LF, Cocchi L, Harrison BJ, et al. *Towards a post-traumatic subtype of obsessive-compulsive disorder*. J Anxiety Disord 2012;26:377-83.

43 Weingarden H, Renshaw KD, Wilhelm S, et al. *Anxiety and shame as risk factors for depression, suicidality, and functional impairment in Body Dysmorphic Disorder and Obsessive Compulsive Disorder*. J Nerv Ment Dis 2016;204:832-9.

44 Dell'Osso B, Nicolini H, Lanzagorta N, et al. *Cigarette smoking in patients with obsessive compulsive disorder: a report from the International College of Obsessive Compulsive Spectrum Disorders (ICOCS).* CNS Spectr 2015;20(5):469-73.

45 Bloom EL, Matsko SV, Cimino CR. *The relationship between cigarette smoking and impulsivity: A review of personality, behavioral and neurobiological assessment*. Addiction Research and Theory 2014;22:386-97.

46 Poorolajal J, Darvishi N. *Smoking and suicide: a meta-analysis.* Plos One

2016;11:e0156348. Doi: 10.1371/journal pone 0156348.

47 Döme P, Kapitány B, Ignits G, et al. *Tabacco consumption and antidepressant use are associated with the rate of completed suicide in Hungary: an ecological study.* J Psychiatric Res 2011;43:488-94.

48 Abramovitch A, Pizzagalli DA, Geller DA, et al. *Cigarette smoking in obsessive-compulsive disorder and unaffected parents of OCD patients.* Eur Psychiatry 2015;30:137-44.

49 Sharma P, Gale TM, Fineberg NA. *Clinical correlates of tobacco smoking in OCD: a UK, case-controlled, exploratory analysis.* J Behav Addict 2012;1:180-5.

50 Sallet PC, de Alvarenga PG, Ferrão Y, et al. *Eating disorders in patients with obsessive-compulsive disorder: prevalence and clinical correlates.* Int J Eat Disord 2010;43:315-25.

51 Rihmer Z, Akiskal KK, Rihmer A, et al. *Current research on affective temperaments.* Curr Opin Psychiat 2010;23:12-18.

52 Innamorati M, Rihmer Z, Akiskal H, et al. *Cyclothymic temperament rather than polarity is associated with hopelessness and suicidality in hospitalized patients with mood disorders.* J Affect Disord 2015;170:161-5.

53 Grove G, Coplan JD, Margolin L, et al. *The neuroanatomy of 5-HT dysregulation in obsessive-compulsive disorder.* CNS Spectrum 1996;1:16-22.

54 Nakao T, Okada K, Kanba S. *Neurobiological model of obsessive-compulsive disorder: evidence from recent neuropsychological and neuroimaging findings.* Psychiatry Clin Neurosci 2014;68:587-605.

55 Aguglia A, Albert U, Maina, G. *Serum lipids and lifetime suicide attempts in patients with obsessive-compulsive disorder*. J Obsessive Compuls Relat Disord 2017;15:1-6.

56 Posner K, Brown GK, Stanley B, et al. *The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults.* Am J Psychiatry 2011;168:1266-77.

57 Raines AM, Short N, Allan NP, et al. *Examination of a brief anxiety sensitivity cognitive concerns intervention on suicidality among individuals with obsessive-compulsive symptoms.* Contemp Clin Trials 2015;45:191-5.

Original article

JOURNAL OF PSYCHOPATHOLOGY
2018;24:164-179

Traumatic brain injury and suicide risk

A. Nardella[1], G. Falcone[1], A. Padovano[1], L. Bonanni[1], D. Erbuto[1], D. Lester[2], M. Pompili[1]

[1] Department of Neurosciences, Mental Health and Sensory Organs, Suicide Prevention Center, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy; [2] The Richard Stockton University, NJ, USA

Summary

Among the various consequences of traumatic brain injury (TBI), evidence supports the notion that individuals exposed to such events may be at higher risk of suicide. We therefore aim at reviewing the literature by focusing on possible association between TBI and features of the suicidal spectrum, such as suicidal ideation, suicide attempts and completed suicides. We carried out a computerized search for reports of studies involving TBI and suicide risk. A total of 35 reports provide data with preliminary support of this association. Seven articles showed a direct correlation between TBI and completed suicides. Thirteen articles have shown a direct relationship between TBI and suicide attempts; five articles demonstrated a positive correlation with suicidal ideation and suicidality. We also found negative results failing to show a correlation between TBI and completed suicides (one article), suicide attempts (one article) and suicidality (one article). In addition, one article showed that patients who received psychological treatment (CBT therapy) after suffering a head injury showed a significant reduction in suicidal ideation.

These preliminary findings encourage further testing of the association between TBI and suicide risk regardless of the psychiatric history. Furthermore, those who have a history of psychiatric illness before the TBI present a greater risk of suicide than those who do not have psychiatric precedents.

Key words

Traumatic brain injury • Suicide risk • Psychiatric history • Prevention

Introduction

Traumatic brain injury (TBI) [1-5] is defined as a change in neural functioning as a result of an external force which acts on the brain, either directly or indirectly [5]. In Europe, the incidence of TBI is around 235 cases per 100,000 inhabitants per year [6]. Head injuries, in terms of frequency and the use of medical resources, are one of the major health problems and the leading cause of death in people aged 15-44. In Italy, the hospitalization rate is about 250-300 cases per 100,000 inhabitants each year[7], which is in line with other European countries [8-12]. The most frequent causes of head injuries in Europe are road accidents (10-56%), accidental falls (31-62%), interpersonal aggression (6-34%), suicide (12%), and other causes (9-15%) [13-19].

After a TBI, most patients have a complete resolution within a few weeks or months, while about 10-25% will have persistent symptoms accompanied by social and occupational consequences based on the severity of the initial neurological trauma [19-32]. These symptoms, defined as post-concussive syndrome (PCS), include somatic, cognitive and emotional disorders (such as headaches, increased fatigue, sleep disturbances, balance disorders, mood and behavioral changes) [33]. People with a history of head injury have a suicide risk ranging from 1.55 to 4.05 times higher than the general population [34-38].

The association between TBI and suicide has been evaluated in several studies. In particular, a higher rate of suicide among people with brain injuries has been found [39-40], although the sample sizes are small. TBI and

Correspondence

Maurizio Pompili
Department of Neurosciences, Mental Health & Sensory Organs, Suicide Prevention Center, Sant'Andrea Hospital, Sapienza University of Rome, via di Grottarossa 1035, 00189 Rome, Italy • E-mail: maurizio.pompili@uniroma1.it

suicide share some risk factors, namely being male, with young age, living in unfavorable social conditions and having and abuse of alcohol and drugs [41-43]. Therefore, it is of interest to understand the extent to which *TBI itself* is a risk factor for suicide.

The above-mentioned background encouraged the present overview of research pertaining to suicidal risk in relation to TBI. Given the relatively early state of this area of inquiry, we viewed our task as gathering and critically appraising the available research relevant to the topic, with the aim of formulating a hypothesis to be tested with further research.

By reviewing selected articles we identified some specific fields of interest. We also consulted a number of international experts in the field to determine whether the studies selected were relevant for discussing preventive measures for suicide risk in TBI. The authors and experts consulted performed a careful analysis of the literature data and agreed on a number of key subjects relevant to the aim of this paper.

We will therefore review studies dealing with the impact of TBI on completed suicide, attempted suicide, suicidal ideation and suicide risk as a whole. The aim of this paper is to evaluate the role of TBI as a risk factor for suicide and stimulate further discussion on the field of prevention of suicidal behaviour in TBI.

Studies evaluating the impact of TBI on completed suicide

The relationship between TBI and suicide has been confirmed in several studies. In a retrospective cohort study [44], it has been found that people with TBI had a 3-times higher risk of dying by suicide than people without a history of TBI (SMR: 2.95; CI 95%; 1.42-5.43).

In particular, Brenner et al. [45] studied 7,850,472 veterans. Veterans with a previous TBI were 1.55 times more likely to die by suicide than those without TBI ($p < 0.0001$): those with concussion or cranial fracture were 1.98 times more likely to die by suicide ($p = 0.0002$) and those with cerebral contusion or traumatic intracranial hemorrhage were 1.34 times more likely to die by suicide ($p = 0.006$) as compared to those without a TBI.

Richard et al. [46] found that the association between TBI and death by suicide was higher if the trauma occurred in adulthood [(HR) = 2.53, 95% CI: 1.79-3.59] compared to adolescence [(HR) = 1.57, 95% CI: 1.09-2.26] or infancy [(HR) = 1.49, 95% CI: 1.04-2.14]. The death by suicide was higher in subjects with male gender (HR: 4.69 *vs* 1.00), with the more serious injuries [HR = 2.77, 95% CI: 2.01-3.83], and with a mental disorder prior to the trauma. In a study conducted in Finland [47], it was found that the interval between the TBI and suicide was shorter if the individual had a prior psychiatric disorder. Patients with TBI had a higher risk of premature death in general and by suicide in the 6 months after a TBI compared to the general population. Death by suicide occurred significantly more often in TBI patients than in general population (OR = 3.3; CI 95%: 2.9-3.7) [47].

In a 20-year follow-up study carried out in Canada [48], the authors found 667 suicide deaths after a median of 9.3 years since the TBI (a rate of 31 suicides per 100,000 patients annually).

In Denmark, Teasdale and Enberg [49] found standardized mortality ratios for suicide that were higher in patients with concussion (3.02, 95% CI: 2.82-3.25), cranial fracture (2.7, 95% CI: 2.01-3.59) and brain lesions (4.1, 95% CI: 3.33-4.93) compared to the general population. Standardized mortality ratios for suicide were greater among females than male subjects in all groups. The suicide rate was higher in those aged 21-60, with substance abuse and with prolonged hospitalization [< 1 week (HR): 3.51, 95% CI: 2.08-5.92; > 3 months (HR): 4.85, 95% CI: 2.97-7.92).

Only one study by Shavelle et al. [50], including 2,320 subjects with intellectual disability, found that TBI increased the overall mortality risk (SMR = 3.1; CI 95% 2.5-3.7), but not by suicide compared to the general population.

Studies evaluating the impact of TBI on attempted suicide

The association between having a TBI and suicide attempts have been evaluated in several longitudinal and cohort studies. In particular, Fonda et al. [51] found, in a cohort study including 273,591 veterans (42,392 [16%] with TBI and 231,199 [84%] without TBI), a 4-times higher risk of attempted suicide for those with TBI (hazard ratio = 3.76, 95% CI: 3.15-4.49). Moreover, veterans with TBI more frequently had a psychiatric disorder than those without TBI. Comorbidity with psychiatric disorders explained 83% of the association between TBI and attempted suicide, with PTSD having the largest impact.

Brenner et al. [52] studied 133 veterans and they found that veterans with a previous suicide attempt and TBI did not show any learning over the course of the Iowa Gambling Test (IGT) unlike all the other groups. No differences were found on other aspects of executive function.

Several studies [53-57] have found a positive association between having a TBI and suicidal attempts after adjusting for any comorbid psychiatric disorder, demographic variables and quality of life.

In several longitudinal studies, it has been confirmed that rates of suicide attempts, suicidal ideation and of depressive symptoms were higher in patients with a TBI than in the general population [58 59].

Homafair et al. [60] explored the relationship between TBI, executive dysfunction and suicide attempts, and found that patients attempting suicide had a higher level of perseveration than subjects without a previous suicide attempts ($p = 0.04$).

Illie et al. [61] found a statistically significant difference in psychological distress, suicidal ideation and suicide attempts in TBI patients compared to patients without TBI. However, in a study on the impact of PTSD and TBI on suicidal attempts, after adjusting for age and gender, the odds of a suicide attempt for subjects with PTSD were 2.8 (95% CI: 1.5, 5.1), while it was 1.03 if TBI was considered alone. When the impact of PTSD and TBI were evaluated together, only PTSD was significant [62].

Studies evaluating the impact of TBI on suicidal ideation

Several factors have been investigated as possible predictors of suicidal ideation in patients suffering from TBI. In particular, it was found that the trauma mode [63] and sleep quality [64] are significant factors.

In a study by Gunter et al. [65], having a TBI was found to be a risk factor for suicidal ideation or behaviour ($p \leq 0.007$, OR = 2.63, 95% CI: 1.30-5.35), together with other factors such as Caucasian ethnicity ($p \leq 0.001$, OR = 5.98, 95% CI: 2.38-14.97), depressive symptoms ($p \leq 0.003$, OR = 1.13, 95% CI: 1.04-1.23), childhood trauma ($p \leq 0.008$, OR = 2.70, 95% CI: 1.30-5.61) and avoidant personality ($p \leq 0.028$, OR = 2.97, 95% CI: 1.12-7.87).

Wisco et al. [66] examined the association between TBI history and suicidal ideation and found that TBI was significantly associated with suicidal ideation only in male veterans (RR = 1,55). Moreover, multiple TBIs and TBI with loss of consciousness, depressive symptoms and PTSD were more strongly associated with suicidal ideation.

In a longitudinal study, it was reported that people with TBI are at higher risk to report suicidal ideation, even one year after the trauma [67].

Moreover, the mediating role of anger and depressive symptoms has been explored as an explanation for suicidal ideation in patients with TBI. It was found that TBI significantly predicted anger (B = 11.845, SE = 5.281, $p = 0.026$); anger significantly predicted depression (B = 0.020, SE = 0.002, $p < 0.001$) and depression significantly predicted suicide risk (B = 0.788, SE = 0.178, $p < 0.001$) [68].

An association between disinhibition and suicidal behavior was found 6 and 12 months after the TBI ($p = 0.045$, $p = 0.033$, respectively) [69]. Bryan et al. [70] found that TBIs were significantly associated with increases in depression and PTSD symptom intensity. TBIs were also associated with a greater incidence of lifetime suicidal thoughts or behaviors. Greater suicide risk was related to the number of TBIs (β [SE] = 0.214 [0.098]; $p = 0.03$) after correcting for the influence of depression, PTSD, and TBI symptom intensity. Cumulative TBIs were also associated with a higher severity of depressive symptoms ($\beta = 0.580$ [0.283]; $p = 0.04$).

Studies evaluating the impact of TBI on suicide risk

The association between suicide risk and presence of TBI has been confirmed in several studies with veterans. In particular, Brenner et al. [71] found that veterans with TBI were 3.6 times more likely to report suicide risk, even after correcting for the number of psychiatric diagnoses (95% CI: 1.4, 9.0; $p = 0.007$). This finding has been confirmed in another study [72], showing that depressive and PTSD symptoms were significantly associated with increased suicide risk among patients with a diagnosis of TBI ($p < 0.001$). Moreover, veterans at greater risk of suicide exhibited post-TBI symptoms more frequently than those with no or low risk, including blurred vision, seizures, memory difficulties or problem-solving difficulties and difficulty in managing stress [73].

The association between suicide risk and TBI has been confirmed also in samples with college students [74], even after controlling for other well-known risk factors such as depression, perceived burdensomeness, thwarted belongingness, and acquired capability.

Only one study did not confirm the association between TBI and suicide risk [75]. Simpson and Tate [76] found no relationship between injury severity and suicide risk.

Discussion

The present review aimed to investigate the relationship between TBI and suicide and, in particular, the relationship between head injuries and suicidal ideation, suicide behaviors, suicide attempts and completed suicides. According to our findings, TBI is a risk factor for suicidal ideation, suicide attempts and deaths by suicide. In particular, the consequences of TBI can include psychological distress, depression and suicidal behavior. Furthermore, suicide and TBI share several common risk factors such as younger age, male sex, substance use and aggression. The present findings are consistent with previous reviews [79-81].

It is important to understand how TBI can indirectly increase the risk of suicidal ideation and behaviors, suicide attempts and complete suicide. Head injuries, especially mild ones, cause an indirect increase in suicide risk mediated by the worsening of depressive symptoms and aggressiveness [68].

Other factors can explain the increased risk of suicidal behaviours in patients with TBI, such as the increase in levels of TNF-α and the alteration of sleep quality.

Moreover, the suicidal risk is even higher in patients with TBI and a history of mental and substance abuse disorders.

Therefore, in order to avoid the onset of suicidal ideation and suicide attempts, it is extremely important to detect and appropriately treat TBI and its consequences. In particular, in patients with TBI, it is the frequent development of post-traumatic amnesia and hopelessness,

which represent *per se* a relevant risk factor for suicide [79]. It is necessary to promote screening programs for an early identification of patients at higher suicide risk, using the TBI-4 scale [73].
Several studies were conducted on war veterans. Veterans with a history of TBI and PTSD [51] are at greater risk of suicide than those without a history of TBI [34 45 57 71]. According to Barnes et al. [75], if PTSD and TBI are associated with a higher risk of suicide than PTSD alone, the added risk is attributable to the severity of the PTSD symptoms. A greater risk of dying by suicide has been shown in children, adolescents and adults with a history of TBI compared with those with no TBI [46 61]. The risk of death by suicide is greater in subjects who suffered from TBI in adulthood compared to those experiencing TBI in childhood or adolescence [46].

Psychopathological implications

Traumatic brain injury is an alteration in brain function, or other evidence of brain pathology, caused by an external force [79]. Neurotrauma can cause brain alterations that result in neuropsychiatric sequelae and functional deficits in those who experience such injuries. The brain regions most frequently affected by TBI damage are the frontal cortex and the subfrontal white matter, the basal ganglia and the diencephalon, the rostral cerebral trunk and temporal lobes including the hippocampus. In relation to the post-TBI brain damage, there is a consequent profile of neurobehavioural sequelae characterized by cognitive deficits (memory, attention, executive function, speed of information processing), personality changes (better characterized as dysexecutive syndromes involving social behavior, cognition and motivated behavior) and increased rates of psychiatric disorders, including mood disorders, sleep disorders, substance abuse, psychotic syndromes and post-traumatic stress disorder [80].

Limitations

This review has several limitations, which must be acknowledged. Firstly, it was not possible to carry on a meta-analysis due to the variety of methodologies adopted in the included studies. Second, only studies published in English and in peer-reviewed journals were considered. Furthermore, although our approach was comprehensive, we did not attempt a systematic analysis which may have left out of this review possible papers of interest. We chose to report those studies available in the literature that could support a broad analysis of the topic so as to offer a tutorial paper. After a careful and systematic search, we extrapolated from those studies with the aim of formulating a hypothesis to be tested with further research.

Conclusions

Although TBI represents a risk factor for suicidal ideation and suicide attempts, patients with a history of psychiatric illness prior to the TBI present a higher risk than those who do not have psychiatric precedents, and they die by suicide sooner after the initial evaluation than those who do not have psychiatric precedents [46]. Indeed, it is important to note how subjects with a TBI, not only have an increased risk of developing suicidal behaviors, but they also die by suicide earlier than others regardless of the presence or absence of a psychiatric history.

Conflict of Interest

The authors have no conflict of interests.

References

1 Faul M, Xu L, Wald MM, et al. *Traumatic brain injury in the United States.* Atlanta, GA: National Center for Injury Prevention and Control, Centers for Disease Control and Prevention 2010.

2 Hyder AA, Wunderlich CA, Puvanachandra P. et al. *The impact of traumatic brain injuries: A global perspective*. NeuroRehabilitation 2007;22:341-53.

3 Langlois JA, Rutland-Brown W, Thomas KE. *Traumatic brain injury in the United states: Emergency department visits, hospitalizations, and deaths.* Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention, Division of Acute Care, Rehabilitation Research and Disability Prevention, National Center for Injury Prevention and Control 2004.

4 Langlois JA, Rutland-Brown W, Wald MM. *The epidemiology and impact of traumatic brain injury: a brief overview.* J Head Trauma Rehab 2006;21:375-8.

5 Santiago LA, Oh BC, Dash PK, et al. *A clinical comparison of penetrating and blunt traumatic brain injuries.* Brain Inj 2012;26:107-25.

6 Tagliaferri F, Compagnone C, Korsic M, et al. *A systematic review of brain injury epidemiology in Europe.* Acta Neurochir (Wien) 2006;148:255-68.

7 Servadei F, Verlicchi A, Soldano F, et al. *Descriptive epidemiology of head injury in Romagna and Trentino. Comparison between two geographically different Italian regions.* Neuroepidemiology 2002;21:297-304.

8 Engberg AW, Teasdale TW. *Traumatic brain injury in Denmark 1979-1996. A national study of incidence and mortality.* Eur J Epidemiol 2001;17:437-42.

9 Firsching R, Woischneck D. *Present status of neurosurgical trauma in Germany.* World J Surg 2001;25:1221-3.

10 Kay A, Teasdale G. *Head injury in the United Kingdom.* World J Surg 2001;25:1210-20.

11 Brell M, Ibanez J. *Minor head injury management in Spain: a multicenter national survey.* Neurochirugia (Astur) 2001;12:105-24.

12 Masson F, Thicoipe M, Aye P, et al. *Epidemiology of severe brain injuries: a prospective population-based study.* J Trauma 2001;51:481-9.

13 Servadei F, Antonelli V, Betti L, et al. *Regional brain injury epidemiology as the basis for planning brain injury treatment. The Romagna (Italy) experience.* J Neurosurg Sci 2002;46:111-9.

14 Meerhoff SR, de Kruijk JR, Rutten J, et

al. *Incidence of traumatic head or brain injuries in catchment area of Academic Hospital Maastricht in 1997.* Ned Tijdschr Geneeskd 2000;144:1915-8.

15 Ingebrigtsen T, Mortensen K, Romner B. *The epidemiology of hospital-referred head injury in northern Norway.* Neuroepidemiology 1998;17:139-46.

16 Andersson EH, Bjorklund R, Emanuelson I, et al. *Epidemiology of traumatic brain injury: a population based study in western Sweden.* Acta Neurol Scand 2003;107:256-9.

17 Kay AD, Thornhill S, Teasdale GM. *The head injured adult – who cares?* Br J Neurosurg 2001;15:508-10.

18 Alaranta H, Koskinen S, Leppanen L, et al. *Nationwide epidemiology of hospitalized patients with first-time traumatic brain injury with special reference to prevention.* Wien Med Wochenschr 2000;150:444-8.

19 Kleiven S, Peloso PM, von Holst H. *The epidemiology of head injuries in Sweden from 1987 to 2000.* Inj Control Saf Promot 2003;10:173-80.

20 Masson F, Thicoipe M, Aye P, et al. *Epidemiology of severe brain injuries: a prospective population-based study.* J Trauma 2001;51:481-9.

21 Stulemeijer M, van der Werf SP, Jacobs B, Biert J, et al. *Impact of additional extracranial injuries on outcome after mild traumatic brain injury.* J Neurotrauma 2006;23:1561-9.

22 Stålnacke BM, Elgh E, Sojka P. *One-year follow-up of mild traumatic brain injury: cognition, disability and life satisfaction of patients seeking consultation.* J Rehabil Med 2007;39:405-11.

23 Lannsjö M, af Geijerstam JL, Johansson U, et al. *Prevalence and structure of symptoms at 3 months after mild traumatic brain injury in a national cohort.* Brain Inj 2009;23:213-9.

24 Bryant RA, Creamer M, O'Donnell M, et al. *Sleep disturbance immediately prior to trauma predicts subsequent psychiatric disorder.* Sleep 2010;33:69-74.

25 Konrad C, Geburek AJ, Rist F, et al. *Long-term cognitive and emotional consequences of mild traumatic brain injury.* Psychol Med 2011;41:1197-211.

26 Hartvigsen J, Boyle E, Cassidy JD, et al. *Mild traumatic brain injury after motor vehicle collisions: what are the symptoms and who treats them? A population-based 1-year inception cohort study.* Arch Phys Med Rehabil 2014;95:286-94.

27 Carroll LJ, Cassidy JD, Peloso PM, et al. *Prognosis for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury.* J Rehabil Med 2004(Suppl 43):84-105.

28 Wood RL. *Understanding the "miserable minority": a diasthesis-stress paradigm for post-concussional syndrome.* Brain Inj 2004;18:1135-53.

29 Iverson GL. *Outcome from mild traumatic brain injury.* Curr Opin Psychiatry 2005;18:301-17.

30 Stulemeijer M, van der Werf S, Borm GF, et al. *Early prediction of favourable recovery 6 months after mild traumatic brain injury.* J Neurol Neurosurg Psychiatry 2008;79:936-42.

31 Hou R, Moss-Morris R, Peveler R, et al. *When a minor head injury results in enduring symptoms: a prospective investigation of risk factors for postconcussional syndrome after mild traumatic brain injury.* J Neurol Neurosurg Psychiatry 2012;83:217-23.

32 Cassidy JD, Cancelliere C, Carroll LJ, et al. *Systematic review of self-reported prognosis in adults after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis.* Arch Phys Med Rehabil 2014;95:132-51.

33 Caplain S, Blancho S, Marque S, et al. *Early detection of poor outcome after mild traumatic brain injury: predictive factors using a multidimensional approach a pilot study.* Front Neurol 2017;12;8:666.

34 Brenner LA, Ignacio RV, Blow FC. *Suicide and traumatic brain injury among individuals seeking Veterans Health Administration services.* J Head Trauma Rehabil 2011;26:257-64.

35 Harrison-Felix CL, Whiteneck GG, Jha A, et al. *Mortality over four decades after traumatic brain ijury rehabilitation: a retrospective cohort study.* Arch Phys Med Rehabil 2009;90:1506-13.

36 Ventura T, Harrison-Felix C, Carlson N, et al. *Mortality after discharge from acute care hospitalization with traumatic brain injury: a population-based study.* Arch Phys Med Rehabil 2010;91:20-9.

37 Teasdale TW, Engberg AW. *Suicide after traumatic brain injury: a population study.* J Neurol Neurosurg Psychiatry 2001;71:436-40

38 Faul M, Xu L, Wald MM, et al. *Traumatic brain injury in the United States: emergency department visits, hospitalizations and deaths 2002-2006.* Centers for Disease Control and Prevention, National Center for Injury Prevention and Control 2010.

39 Harris EC, Barraclough B. *Suicide as an outcome for mental disorders. A meta-analysis.* Br J Psychiatry 1997;170:205-28.

40 Achté KA, Lönnqvist J, Hillbom E. *Suicides following war brain-injuries.* Acta Psychiatr Scand Suppl 1971;225:1-94.

41 Moscicki EK. *Identification of suicide risk factors using epidemiologic studies.* Psychiatr Clin North Am 1997;20:499-517.

42 Engberg A. *Severe traumatic brain injury: epidemiology, external causes, prevention, and rehabilitation of mental and physical sequelae.* Acta Neurol Scand Suppl 1995;164:1-151.

43 Diekstra RF. *The epidemiology of suicide and parasuicide.* Acta Psychiatr Scand Suppl 1993;371:9-20.

44 Harrison-Felix CL, Whiteneck GG, Jha A, et al. *Mortality over four decades after traumatic brain injury rehabilitation: a retrospective cohort study.* Arch Phys Med Rehabil 2009;90:1506-13.

45 Brenner LA, Ignacio RV, Blow FC. *Suicide and traumatic brain injury among individuals seeking veterans health administration services.* J Head Trauma Rehabil 2011;26:257-64.

46 Richard YF, Swaine BR, Sylvestre MP, et al. *The association between traumatic brain injury and suicide: are kids at risk?* Am J Epidemiol 2015;182:177-84.

47 Fazel S, Wolf A, Pillas D, et al. *Suicide, fatal injuries, and other causes of premature mortality in patients with traumatic brain injury: a 41-year Swedish population study.* JAMA Psychiatry 2014;71:326-33.

48 Fralick M, Thiruchelvam D, Tien HC, et al. *Risk of suicide after a concussion.* CMAJ 2016;188:497-504.

49 Teasdale TW, Engberg AW. *Suicide after traumatic brain injury: a population study suicide after traumatic brain injury: a population study.* J Neurol Neurosurg Psychiatry 2001;71:436-40.

50 Shavelle RM, Strauss D, Whyte J, et al. *Long-term causes of death after traumatic brain injury.* Am J Phys Med Rehabil 2001;80:510-6.

51 Fonda JR, Fredman L, Brogly SB et al. *Traumatic brain injury and attempted suicide among veterans of the wars in Iraq and Afghanistan.* Am J Epidemiol 2017;186:220-6.

52 Brenner LA, Bahraini N, Homaifar BY, et al. *Executive functioning and suicidal behavior among veterans with and without a history of traumatic brain injury.* Arch Phys Med Rehabil 2015;96:1411-8.

53 Silver JM, Kramer R, Greenwald S, et al. *The association between head injuries and psychiatric disorders: findings from the New Haven NIMH Epidemiologic Catchment Area Study.* Brain Inj 2001;15:935-45.

54 Schneider AL, Hostetter TA, Homaifar BY, et al. *Responses to traumatic brain injury screening questions and suicide attempts among those seeking Veterans Health Administration Mental Health Services.* Front Psychiatry 2016;19;7:59.

55 Simpson G, Tate R. *Clinical features of suicide attempts after traumatic brain injury.* J Nerv Ment Dis 2005;193:680-5.

56 Oquendo MA, Friedman JH, Grunebaum MF, et al. *Suicidal behavior and mild traumatic brain injury in major depression.* J Nerv Ment Dis 2004;192:430-4.

57 Gutierrez PM, Brenner LA, Huggins JA. *A preliminary investigation of suicide risk in psychiatrically hospitalized veterans with traumatic brain injury.* Arch Suicide Res 2008;12:336-43.

58 Fisher LB, Pedrelli P, Iverson GL, et al. *Prevalence of suicidal behaviour following traumatic brain injury: longitudinal follow-up data from the NIDRR Traumatic Brain Injury Model Systems.* Brain Inj 2016;30:1311-8.

59 Kesinger MR, Juengst SB, Bertisch H, et al. *Acute trauma factor associations with suicide risk across the first 5 years after traumatic brain injury.* Arch Phys Med Rehabil 2016;97:1301-8.

60 Homaifar BY, Brenner LA, Forster JE, et al. *Traumatic brain injury, executive functioning, and suicidal behavior: a brief report.* Rehabil Psychol 2012;57:337-41.

61 Ilie G, Mann RE, Boak A, et al. *Suicide risk, bullying and other conduct and mental health correlates of traumatic brain injury in adolescents.* PLoS One 2014;9:e94936.

62 Brenner LA, Ignacio RV, Blow FC. *Suicide and traumatic brain injury among individuals seeking Veterans Health Administration services.* J Head Trauma Rehabil 2011;26:257-64.

63 Bethune A, da Costa L, van Niftrik CHB, et al. *Suicidal ideation after mild traumatic brain injury: a consecutive Canadian sample.* Arch Suicide Res 2017;21:392-402.

64 DeBeer BB, Kimbrel NA, Mendoza C, et al. *Traumatic brain injury, sleep quality, and suicidal ideation in Iraq/Afghanistan era veterans.* J Nerv Ment Dis 2017;205:512-6.

65 Gunter TD, Chibnall JT, Antoniak SK, et al. *Childhood trauma, traumatic brain injury, and mental health disorders associated with suicidal ideation and suicide-related behavior in a community corrections sample.* J Am Acad Psychiatry Law 2013;41:245-55.

66 Wisco BE, Marx BP, Holowka DW, et al. *Traumatic brain injury, PTSD, and current suicidal ideation among Iraq and Afghanistan US veterans.* J Trauma Stress 2014;27:244-8.

67 Mackelprang JL, Bombardier CH, Fann JR, et al. *Rates and predictors of suicidal ideation during the first year after traumatic brain injury.* Am J Public Health 2014;104:e100-7.

68 Stanley IH, Joiner TE, Bryan CJ. *Mild traumatic brain injury and suicide risk among a clinical sample of deployed military personnel: Evidence for a serial mediation model of anger and depression.* J Psychiatr Res 2017;84:161-8.

69 Juengst SB, Kumar RG, Arenth PM, et al. *Exploratory associations with tumor necrosis factor-α, disinhibition and suicidal endorsement after traumatic brain injury.* Brain Behav Immun 2014;41:134-43.

70 Bryan CJ, Clemans TA. *Repetitive traumatic brain injury, psychological symptoms, and suicide risk in a clinical sample of deployed military personnel.* JAMA Psychiatry 2013;70:686-91.

71 Brenner LA, Hostetter TA, Barnes SM, et al. *Traumatic brain injury, psychiatric diagnoses, and suicide risk among Veterans seeking services related to homelessness.* Brain Inj 2017;31:1731-5.

72 Bryan CJ1, Clemans TA, Hernandez AM, et al. *Loss of consciousness, depression, posttraumatic stress disorder, and suicide risk among deployed military personnel with mild traumatic brain injury.* J Head Trauma Rehabil 2013;28:13-20.

73 Palladino B, Montgomery AE, Sommers M, et al. *Risk of suicide among veterans with traumatic brain injury experiencing homelessness.* J Military Veterans Health 2017;25:34-8.

74 Bryson CN, Cramer RJ, Schmidt AT. *Traumatic brain injury and lifetime suicide risk: Applying the interpersonal-psychological theory perspective.* Death Stud 2017;41:399-405.

75 Barnes SM, Walter KH, Chard KM. *Does a history of mild traumatic brain injury increase suicide risk in veterans with PTSD?* Rehabil Psychol 2012;57:18-26.

76 Simpson GK, Tate RL, Whiting DL, et al. *Suicide prevention after traumatic brain injury: a randomized controlled trial of a program for the psychological treatment of hopelessness.* J Head Trauma Rehabil 2011;26:290-300.

77 Wasserman L, Shaw T, Vu M, et al. *An overview of traumatic brain injury and suicide.* Brain Inj 2008;22:811-9.

78 Harris EC, Barraclough BM. *Suicide as an outcome for medical disorders.* Medicine (Baltimore) 1994;73:281-96.

79 Menon D, Schwab K, Wright D, et al. *Position statement: definition of traumatic brain injury.* Arch Phys Med Rehabil 2010;91:1637-40.

80 McAllister TW. *Neurobiological consequences of traumatic brain injury.* Dialogues Clin Neurosci 2011;13:287-300.

POSITIVE FINDINGS

Completed suicide Author, year	Study	Sample	Aims
Teasdale & Engberg, 2001	Population study	145,440 patients admitted for TBI between the years 1979 and 1993: patients with concussion (n = 126, 114), with a cranial fracture (n = 7,560),with a cerebral contusion or traumatic intracranial haemorrhage (n = 11,766)	To evaluate the suicide rate in a group of Danish patients with a history of TBI
Mainio et al., 2007		1,877 suicide victims	To study the prevalence of TBI among suicides and to evaluate the association of suicide, TBI and psychiatric disorders
Harrison-felix et al., 2009	Retrospective cohort study	1,678 TBI patients admitted to Craig Hospital within 1 year of injury (between 1961 to 2002)	To investigate mortality in patients with TBI
Brenner et al, 2011	Observational retrospective study	81 veterans with a history of suicide attempts between October 2004 and February 2006	To examine the association between suicide attempt history among veterans with PTSD and/or TBI
Fazel et al.; 2014		218,300 patients with a previous TBI studied between 1969-2009 compared to 2,163,190 controls; and 150,513 TBI patients with siblings without TBI compared with 237,535 sibling controls without TBI	To evaluate premature mortality in TBI patients vs general population
Richard et al., 2015		134,629 children aged 0-17 years	To evaluate the association between TBI and the subsequent risk of suicide deaths in a population of children
Fralick et al., 2016	Longitudinal cohort study	235,110 patients who received a diagnosis of concussion from 1st April 1992 to 31st March 2012 (weekend concussion n = 39,940; weekday concussion n = 195,170)	To evaluate if concussion could influence long-term risk of suicide

Material and methods	Follow-up	Results
Subjects identified in a computerized National Bureau of Health register of hospitalizations which documents all admissions to hospital in Denmark since 1979	14 years	0.62% (895) of TBI patients died from suicide. The standardized mortality ratios for suicide showed that the incidence was increased relative to the general population and was lower for patients injured before the age of 21 or after 60. There was a significantly higher risk of suicide among patients with cerebral contusions or traumatic intracranial haemorrhages than those with concussion or cranial fractures. In all diagnosis groups the ratios were higher for females than for males
This study examines all the suicides during the years 1988-2004 in a province of Finland	16 years	Among all suicides, 103 (5.5%) had sustained a TBI. Patients with TBI died by suicide within 3 years after TBI (this time interval was shorter if the subject had a psychiatric disorder before TBI)
Social Security Death Index was used to determine features of patients. Death certificates were used to identify causes of death	40 years	130 deaths occurred after 1-year post injury (mortality rate: 7.7%) Standardized mortality ratio was 1.51 (95% C.I.:1.25-1.78). 10 deaths caused by suicide. TBI patients are 3 times more like to commit suicide than general population
81 cases and 160 matched controls randomly selected from a Veterans Affairs Medical Center clinical database. Inclusion criteria: Veterans Affairs health care services received and an electronic medical record note reporting a suicide attempt		PTSD history was associated with an increased risk for a suicide attempt (OR = 2.8). No differences between those with and without a history of TBI emerged
Evaluation of mortality rate in TBI compared to general population and to unaffected siblings of TBI patients		11,053 premature deaths occurred in TBI population. Compared with controls and with unaffected siblings, the OR was respectively 3.2 (CI 95%, 3.0-3.4) and 2.6 (CI 95%, 2.3-2.8). There were 522 deaths by suicide. Compared with controls, OR was 3.3 (CI 95%; 2.9-3.7). Compared with unaffected siblings, OR was 2.3 (CI 95%; 1.9-2.9)
The cohort was assembled using information from 4 provincial administrative databases. Those 4 databases were the physician billing claims database from the Quebec Health Insurance Board, the hospital admission and discharge database (MEDECHO), the Quebec Institute of Statistics database and the Quebec Coroner Database	21 years	The study found a higher risk of suicide for people who sustained a TBI during adulthood [(HR): 2.53] rather than during adolescence [(HR) = 1.57] and childhood [(HR) = 1.49]. Males who sustained a TBI were at a much higher risk for suicide than females [(HR): 4.69 *vs* 1.00]. More severe injuries were associated with a higher risk of suicide than low severity injuries [(HR): 2.77 *vs* 2.18]. Sustaining repeated injuries increased the risk of suicide for children [(HR) = 1.23], adolescents [(HR) = 1.41] and adults [(HR) = 1.61]
Data were extracted from the Office of the Registrar General database. Cause of death was assessed by death certificates	20 years	667 patients committed suicide, with a median follow-up of 9.3 years (31 suicides/100,000 subjects annually). 519 suicides occurred after weekday concussion (29 suicides/100,000 subjects annually; ≥ 3-times the general population) and 148 after weekend concussion (39 suicides/100 000 subjects annually; ≥ 4 times the general population). Weekend concussion was associated with a greater risk of suicide than weekday concussion (RR = 1.36; CI 95% 1.14-1.64)

Attempted suicide			
Author, year	**Study**	**Sample**	**Aims**
Jonathan et al., 2001		5,034 participants in the Epidemiologic Catchment Area Study	To explore the relationship between a history of TBI and suicide attempts
Oquendo et al., 2004		325 patients with a diagnosis of major depressive episode. 44% of them had an history of TBI	To evaluate the relationship between suicidal behavior, depression and mild traumatic brain injury
Simpson and Tate et al., 2005		172 outpatients with TBI from the Liverpool Hospital Brain Injury Rehabilitation Unit (BIRU) in Sydney aged between 16 and 61	To study demographic, temporal and clinical parameters for the suicide attempts after TBI
Gutierrez et al., 2008		22 veterans who suffered head injury and hospitalized in psychiatric department between 1968 and 2005 (4 subjects had preexisting brain injury between 1971 and 2003)	To evaluate suicidal behavior in patients psychiatrically hospitalized with history of TBI
Homaifar et al., 2012	Pilot study	Veterans with TBI with previous suicide attempts (n=18) and with no history of suicide attempts (n 29)	To evaluate if there was an association between executive dysfunction, TBI and suicide
Bryan et Clemans, 2013	Observational study	161 military personnel evaluated or treated for suspected head injury at a TBI's military clinic in Iraq	To identify if there is an increase in suicide risk among military personnel with a single or no TBIs and those with multiple lifetime TBIs
Gunter et al., 2013		418 community-supervised offenders served by office Iowa's Sixth Judicial District	To determine which factors differentiate suicidal ideation and actions group from control group in community corrections sample

Material and methods	Follow-up	Results
		361 (7.2%) of the participants had a history of TBI. Suicide attempts were more frequent in patients with a history of TBI compared with subjects without TBI (8.1% *vs* 1.9%, p = 0.0001).
Hamilton Depression Rating Scale (HAM-D) was used for depression; Beck Hopelessness Scale (BHS) was used for hopelessness. Suicidal ideation was assessed with the Beck Scale for Suicide Ideation (BSS). Suicide attempts were assessed with the Suicide Intent Scale and Lethality Rating Scale		Subjects with TBI presented a higher rate of suicide attempts compared with subjects without TBI (60% *vs* 47%). 80% of the TBI suicide attempters made the first attempt after TBI
Beck Hopelessness Scale (BHS) and Beck Scale for Suicide Ideation (BSS) were used to assess levels of hopelessness and suicide ideation	24 months	43 patients (25%) attempted suicide: 14 patients made a pre-injury attempt, 29 patients made a post-injury attempt. The authors found a high frequency of post-TBI attempts compared to the period before the trauma (30% pre-injury *vs* 70% post-injury). The main mode of attempting suicide was overdose (62.5%), followed by cutting (17.5%). Patients with a post-TBI history of psychiatric disorders and substance abuse were 21 times more likely to have an attempt post-TBI (OR: 20.62, CI 5.10-83.40) compared with people without the same post-TBI history
Suicide ideation and suicide attempts were evaluated. The Lethality of Suicide Attempts Rating Scale (LSARS) was used to characterize suicidal behaviors		72.7% of patients presented suicide ideation during at least one hospitalization. 27.3% of subjects cmade at least one suicide attempt after TBI. The number of attempts per person was between 1 and 5 (median: 2)
Executive function was evaluated with different scales: making decision with Iowa Gambling Task (IGT); impulsivity with Immediate and Delayed Memory Test (IMT/DMT); abstract reasoning with Wisconsin Card Sorting Test (WCST). Previous suicide attempts and suicidal ideation were evaluated with Columbia Suicide History Form		66% of patients without a history of suicide attempts reported suicidal ideation. Abstract reasoning, especially perseveration, was the only measure which differed significantly between the two groups (p value = 0.04). Patients with suicide attempts had higher level of perseveration than patients with no prior suicide attempts
4-item Suicidal Behaviors Questionnaire–Revised, 5-item depression subscale of the Behavioral Health Questionnaire–20, PTSD Checklist–Military Version, history clinical interview (Military Acute Concussion Evaluation), physical examination		The number of TBIs was significantly associated with an increase in depression, PTSD, and TBI symptom severity. The number of TBIs was also correlated with an increased incidence of lifetime suicidal thoughts or behaviors (no TBIs, 0%; single TBI, 6.9%; and multiple TBIs, 21.7%; p =.009). Greater suicide risk was associated with the number of TBIs (β [SE] =.214 [.098]; p =.03) after checking of the effects of depression, PTSD, and TBI symptom severity. Depression was also correlated with cumulative TBIs (β =.580 [.283]; p = 0.04)
Alcoholism Revised (SSAGA-II) to assess substance use and co-occurring disorders, Hare Psychopathy Checklist Screening Version (PCL:SV) to assess psychopathy and Achenbach Adult Self Report (ASR) to evaluate the subject's attention to the six-month period before the interview		Three groups obtained: the control group with no suicide ideation or actions (n = 235, 56%), the ideator group with suicidal ideation without suicidal actions (n = 70, 17%) and the actor group with suicide-related actions regardless of suicidal ideation (n = 113, 17%). Caucasian race, depressive symptoms, TBI, childhood trauma and avoidant personality characterized the actor and ideator group more than the control group; moreover, the same five items associated with antisocial lifestyle and lifetime anxiety disorder distinguished the actor group from the control group

Attempted suicide			
Author, year	**Study**	**Sample**	**Aims**
Ilie et al., 2014		4,685 students (aged 11-20) with and without a life time TBI (respectively n = 882; n = 3,803)	To explore whether there is a relationship between TBI and psychiatric disease in adolescent population
Brenner et al., 2015	Observational study	133 veterans: 48 without suicide attempt (SA) or TBI; 51 with TBI, but without SA; 12 with SA, but without TBI; 22 with SA and TBI	To explore the relationship between executive dysfunction and suicide attempt history in a high-risk sample of veterans with moderate to severe TBI
Fonda et al., 2016	Cohort study	273,591 veterans deployed in support of three military operation (OEF/OIF/OND), who received health care from the Veterans Affairs (VA) between April 2007 and Sept. 2012; 42,392 (16%) with TBI and 231,199 without TBI.	To evaluate the possible mediating role of common comorbid psychiatric conditions in the association between TBI and suicide attempt
Schneider et al., 2016		1,097 veterans	To determine whether a positive screen on the TBI-4 is associated with increased risk for suicide attempt within 1-year post-screening
Fisher et al., 2016	Longitudinal study	Patients presenting at Traumatic Brain Injury Model System hospital within 72 h of brain injury (n = 8,547 for suicide attempts; n = 3,192 for suicidal ideation; n = 3,182 for depression)	To evaluate the prevalence of depression and suicidal behaviour in TBI patients
Kesinger et al., 2016		3,575 patients with TBI enrolled in Traumatic Brain Injury Model System (TBIMS) National Database	To explore if there is a relationship between severity of TBI/ extracranial injuries and suicide ideation/suicide attempts
Suicidal ideation			
Simpson et al., 2002		172 out-patients with TBI from the Liverpool Hospital Brain Injury Rehabilitation Unit (BIRU) in Sydney (Australia)	To evaluate the suicidal ideation, suicide attempts, hopelessness and other clinical correlates after TBI

Material and methods	Follow-up	Results
Measures were: assessment of TBI; Mental/ emotional Health with General Health Questionnaire (GHQ12); suicide ideation and suicide attempts; asking help through a crisis help-line/ website; need to receive pharmacological treatment for anxiety, depression or both; evaluation of conduct behaviours		There was a significantly difference in suicide ideation and attempts between adolescents with and without TBI (suicide ideation: AOR = 1.93, CI = 95% 1.42-2.63, p value ≤ 0.001; suicide attempts: AOR = 3.39, CI 95% 2.15-5.35, p value ≤ 0.001)
Iowa Gambling Test (IGT), Immediate and Delayed Memory Test, State-Trait Anger Expression Inventory-2, Wisconsin Card Sorting Test		Veterans with a history of both SA and TBI demonstrated a lack of learning over the course of the IGT, unlike all the other groups. No significant differences were identified on other measures of executive functioning among the groups
TBI exposure: VA primary TBI screen and comprehensive TBI evaluation; Suicide attempt and outcome: ICD-9 injury E codes (E950–E959); Covariates: sex, race (white, black, other, unknown/missing), age, marital status (single, married, or divorced/separated/other), and psychiatric conditions (using ICD-9 diagnosis code)	From April 2007 to September 2012	545 attempted suicides, more frequently among veterans with TBI (n = 227, 0.54%) than those without TBI (n = 318, 0.14%). Veterans with TBI had higher proportion of each psychiatric condition than those without TBI (from 16% *vs* 5% for substance-use disorder to 63% *vs* 10% for PTSD). Co-occurring psychiatric conditions mediated 83% of the association between TBI and attempted suicide: PTSD had the largest impact (73% of the association)
The TBI-4 was administered to 1,097 veterans at the time of mental health intake. Follow-up data regarding suicide attempts for one year post-mental health intake were obtained from suicide behavior reports (SBRs) in Veteran electronic medical records (EMRs)	1 year	468 participants screened positive on Question 2 (Have you ever been knocked out or unconscious following an accident or injury?) of TBI-4. 7 (1,5%) of them made a suicide attempt 1-year post-assessment (*vs* 0% in those who did not endorse this item)
Patient Health Questionnaire (PHQ-9) was used to assess depression and suicidal ideation. Previous suicide attempts were self-reported by patients. Patients were evaluated at 1,2, 3, 10, 15 and 20 years after brain injury		Suicidal ideation and depression rates were, respectively, 7-10% and 24.8-28.1% 20 years after brain injury. The prevalence of suicide attempts was 0.8-1.7% at the end of follow-up. The highest rates of suicidal ideation and depression were registered after 5 years form TBI. Patients with head injury presented a greater risk of suicide attempts, suicidal ideation and depression than general population
PHQ-9 was used to evaluate suicidal ideation. Suicide attempts were assessed with an interview. Severity of TBI and extracranial injuries were evaluated respectively with Abbreviated Injury Scale head score and with Injury Scale (non-head). Measures were assessed at 1st, 2nd and 5th year after TBI		8.2% of subjects presented with suicide ideation without suicide attempts. 3.0% committed at least one suicide attempt during 5 years after TBI. There was a relationship between severe extracranial injury and suicide ideation (OR = 2.73 CI 95%, 1.55-4.82; p value = 0.001), and between use of alcohol and drugs and suicide ideation (OR = 1.69 CI 95%, 1.11-2.86; p value = 0.015)
Hopelessness and suicide ideation were assessed using the Beck Hopelessness Scale (BHS) and the Beck Scale for Suicidal Ideation (BSS)		35% patients had moderate-severe levels of hopelessness, 23% had suicidal ideation and 17.4% attempted suicide after TBI. No relationship was found between injury severity and suicidality

Suicidal ideation			
Author, year	**Study**	**Sample**	**Aims**
Wisco et al., 2014		824 male and 825 female U.S. veterans	To evaluate the relationship between TBI history and suicidal ideation in a group of U.S. veterans
Mackelprang et al., 2014	Recruitment phase of a clinical trial	559 patients admitted to Harborview medical Center (Seattle) for TBI between June 2001 and March 2005	To assess the rate of suicidal ideation in patient with TBI
Bethune et al., 2016		871 patients in an urban tertiary care ED enrolled at 3 months post injury, between 1998 and 2012	To clarify psychosocial and injury features contributing to suicidal ideation (SI) after concussion or mTBI and the time it takes to develop
DeBeer et al., 2017	Observational study	145 Iraq/Afghanistan veterans within the Central Texas Veterans Health Care System	To evaluate whether sleep quality influence the association between TBI history and current suicidal ideation
Suicidality			
Brenner, Ignacio et al., 2011	Observational retrospective study	7,850,472 veterans who received care between fiscal years 2001 to 2006: 49,626 with a history of TBI (12,159 with concussion or cranial fracture and 39,545 with cerebral contusion/traumatic intracranial hemorrhage), and 389,053 patients without TBI	To evaluate any association between death by suicide and history of traumatic brain injury (TBI) diagnosis among individuals receiving care within the Veterans Health Administration
Bryan, Clemans, Hernandez et al., 2013	Observational study	158 military personnel as outpatients TBI clinic in Iraq: 135 (85.4%) with diagnosis of mTBI and 23 (14.6%) without	To determine which clinical outcomes were associated with suicidality in military personnel with mTBI
Juengst et al., 2014		74 patients with TBI (acute cerebrospinal fluid (CSF) levels of TNF-α: n = 37 *vs* n =15 controls; acute serum levels of TNF-α: n = 48 *vs* n = 15 controls; chronic serum levels of TNF-α: n = 48 *vs* n = 15 controls)	To measure the association between high level of Tumor Necrosis Factor-α (TNF-α), disinhibition and suicidal behaviour
Suicidality			
Bryson et al., 2017	Observational study	42 college students self-reported a history of TBI (42 controls matched)	To investigate the association between TBI and suicide, assessing the weight of TBI in the risk of suicide TBI and whether the Interpersonal-Psychological Theory of Suicide can be applied to TBI status

Material and methods	Follow-up	Results
TBI history was assessed using a structured interview. The prime-MD Patient Health Questionnaire was used to evaluate depressive symptoms. The Mini-International Neuropsychiatric Interview, English version 5.0 (M.I.N.I.) was used to evaluate suicidality		TBI was significantly associated with suicidal ideation among male (RR = 1,55), but not female, veterans. In addition, multiple TBI and TBI with loss of consciousness were more strongly associated with suicidal ideation. Depressive symptoms and PTSD were associated with greater risk of ideation in both groups (male and female)
PHQ-9 was used to evaluate suicidal ideation. A structured telephone interview was conducted at month 1-6-8-10 and 12 after brain injury		25% of patients reported suicidal ideation during the first year after brain injury. Rate of ideation was highest (10%) during months 2 and 8. Patients with history of previous suicide attempts presented a risk 5 times more to have suicidal ideation after injury than patients without a history of a suicide attempt (OR: 4.81; 95% CI: 2.83-8.17)
Psychiatric (DSM-IV, MMSE, General Health Questionnaire) and social-demographic (clinical interview) assessments at 3 and 6 months after injury. The Rivermead Post-Concussion Disorder Questionnaire (RPDQ) to record the post concussion syndrome symptoms	At 3 and 6 months post injury	SI emerged in 6.3% of patients at 3 months and in 8.2% at 6 months. It was independently associated with speaking English as a second language and injury mechanism (motor vehicle crashes/passenger) at 3 and 6 months, and with history of depression and marital status at 3 months only
Defense and Veterans Brain Injury Center Brief Traumatic Brain Injury Screening Tool, Pittsburgh Sleep Quality Index, Beck Scale for Suicide Ideation		Sleep quality influenced the effect of TBI history on current suicidal ideation (indirect effect = 0.0082): individuals with history of TBI suffered worse sleep quality, which was also associated with increased suicidal ideation
ICD-9 (Diagnosis of TBI), National Death Index (vital status or dates/causes of death)		Veterans with a history of TBI were 1.55 times more likely to die by suicide than those without a history of TBI. Those with concussion/cranial fracture were 1.98 times more likely to die by suicide and cerebral contusion/traumatic intracranial hemorrhage were 1.34 times more likely to die by suicide, compared to those without an injury history. The presence of psychiatric disorders or demographic factors didn't explain this increased risk
4-item Suicidal Behaviors Questionnaire–Revised, 5-item Depression subscale of the Behavioral Health Measure-20, PTSD Checklist–Military Version, Insomnia Severity Index, 2008 TBI Task Force's criteria of the Department of Defense and Department of Veterans Affairs		Depression and its interaction with PTSD symptoms were significantly associated with increased suicidality among patients with diagnosis of mTBI. Decreased probability for any suicidality was correlated with a longer duration of loss of consciousness
TNF-α levels were collected for 12 months after TBI. Frontal System Behaviour Scale (FrSBe) Disinhibition Subscale and PHQ-9 were used to assess respectively disinhibition and suicidal behavior		Acute CSF level of TNF-α was associated with suicidal behaviour at 12 months from TBI ($p = 0.014$). Acute and chronic serum TNFα level was not related with suicidal behaviour but was significantly associated with disinhibition at 6 months post-injury (respectively $p = 0.009$; $p = 0.029$). Disinhibition was associated with suicidal behaviour at 6 and 12 months (respectively $p = 0.045$; $p = 0.033$)
Depression Anxiety Stress Scale – 21, Interpersonal Needs Questionnaire, Acquired Capability for Suicide Scale, Suicidal Behaviors Questionnaire-Revised		Higher suicide risk emerged in individuals with a TBI than those without, even accounting for the relative influence of 2 strong suicide risk factors (i.e., depression, perceived burdensomeness, thwarted belongingness, and acquired capability). The interaction of perceived burdensomeness, acquired capability and thwarted belongingness (IPTS) was significantly associated with suicide risks

Author, year	Study	Sample	Aims
Suicidality			
Palladino et al., 2017		103 homeless veterans with TBI	To evaluate the associations between suicide risk and physical, psychological, social and military characteristics among homeless veterans with TBI
NEGATIVE FINDINGS			
Completed suicide			
Shavelle et al.; 2001		2,320 subjects who had TBI at the age of 10 or more and with a mental disability after TBI followed-up between 1988 and 1997	To assess causes of death in patients with previous TBI vs in general population
Attempted suicide			
Brenner et al., 2017	Observational study	309 veterans seeking homeless services: 282 with a history of TBI and 27 without a history of TBI	To find out any difference in negative psychiatric results among veterans seeking homeless services, with and without a history of traumatic brain injury (TBI)
Suicidal ideation			
Stanley et al., 2016		149 military service members referred to a TBI clinic within a military hospital in Iraq during a 6-month span in 2009	To determine if the relationship between mild TBI and suicide risk is statistically accounted for by anger and depression symptoms
Suicidality			
Barnes et al., 2012		92 male veterans in treatment for PTSD between 2006 and 2010 at a Midwestern Veterans Affairs Medical Center; 46 of these patients had sustained an mTBI	To investigate whether mTBI increases suicide risk beyond the risk associated with PTSD alone
Treatment			
Simpson & Tate, 2011	Randomized controlled trial	17 patients with severe TBI (aged 18 or older at injury and current < 65 years) and moderate/severe levels of hopelessness and/or suicide ideation (BHS-Beck Hopelessness Scale)	To evaluate the efficacy of a psychological treatment (CBT therapy) to reduce the hopelessness after severe TBI

TBI: Traumatic Brain Injury; PHQ-9: Patient Health Questionnaire

Material and methods	Follow-up	Results
TBI-4 Questionnaire and Ohio State University TBI Identification Method (OSU TBI-ID) were used to find positive subjects for TBI. MINI International Neuropsychiatric Interview (MINI) was used to investigate the presence of psychiatric disorders including suicidal ideation	1 year (December 2010-September 2011)	Veterans with high risk of suicide reported significantly more frequently the following TBI related symptoms than those with no or low risk: blurred vision (81.8 *vs* 45.7%), seizures (36.4 *vs* 4.3%) and difficulty with memory/problem-solving (81.8 *vs* 37%) and managing stress (63.6 *vs* 27.2%). Veterans with PTSD had 8 times the odds of being at high risk for suicide
Subjects were identified from a database with people who received assistance from the California Department of Developmental Services. Death information were extracted from annual computer register	9 years	TBI subjects presented higher risk of death than general population (SMR = 3.1; CI 95% 2.5-3.7). 3% of patients had attempted suicide before TBI. 2 suicides occurred during the follow-up period
The Ohio State University TBI-Identification Method (structured interview); the MINI international neuropsychiatric interview (short, structured diagnostic interview)		Veterans with a history of TBI received significantly more psychiatric diagnoses (p = 0.0003), and showed higher risk for suicide (p = 0.007) than those without a history of TBI
Mild TBI diagnosis was confirmed by a licensed clinical psychologist or physician during a clinical interview. Suicide risk was assessed utilizing the Suicidal Behaviors Questionnaire (SBQ-R). Anger was assessed utilizing the mood scale module of the Automated Neuropsychological Assessment Metrics (ANAM). Depression symptoms were assessed utilizing the Behavioral Health Measure-20 (BHM-20)	6 months	The relationship between mild TBI and suicide risk is fully mediated by anger and depression symptoms: mild TBI significantly predicted anger; anger significantly predicted depression symptoms and depression symptoms significantly predicted suicide risk
PTSD Scale assesses *DSM-IV-TR* PTSD diagnostic criteria; SCID-I to detect current and/or lifetime presence of Axis I psychiatric disorders. *Self-report measures:* BDI-II for assessing depressive symptoms; the PCL-S (PTSD Checklist Stressor Specific Version) instructs patients to rate the severity of their PTSD symptoms in relation to a specific traumatic stressor		No significant differences emerged in the assessed risk factors suggesting that, if PTSD and mTBI are associated with greater suicide risk relative to PTSD alone, the added risk is attributable to PTSD symptom severity
Participants were aged between 18 and 65 years, experienced post traumatic amnesia more than 1 day and moderate/severe hopelessness (evaluated with the Beck Hopelessness Scale) and/or suicide ideation (evaluated with the Beck Scale for Suicide Ideation)	3 months	The treatment group improved with a reduction of 6 BHS points, whereas the wait-list group increased scores by 1 BHS point. Was also observed a significant reduction in suicide ideation scores in the treatment group

Original article

JOURNAL OF PSYCHOPATHOLOGY
2018;24:180-186

The interplay between cannabis use and suicidal behaviours: epidemiological overview, psychopathological and clinical models

F. Bartoli[1], S. Lev-Ran[2 3], C. Crocamo[1], G. Carrà[1 4]

[1] Department of Medicine and Surgery, University of Milano Bicocca, Monza, Italy; [2] Dual Diagnosis Clinic, Lev-Hasharon Medical Center, Pardesiya, Israel; [3] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [4] Division of Psychiatry, University College, London, UK

Summary

Objectives
The clinical and psychopathological relationships between substance use and suicidal behaviours are deserving growing attention. Understanding and identifying factors that may be associated with suicidal behaviours can help clinicians to early detect high-risk individuals.

Methods
We conducted a narrative review, summarising main epidemiological data from longitudinal studies, on the potential association between cannabis use and suicidal behaviours. In addition, we discuss possible psychopathological models that may explain and disentangle this clinical relationship.

Results
Individuals who use cannabis, the most common psychoactive drug apart from alcohol and nicotine, may have higher risk of suicidal behaviours. Despite the mixed findings, evidence seems to suggest that an early and heavy cannabis use may be associated with suicidal ideation, attempt, and completion.

Conclusions
Findings from our review show that it is likely that cannabis is associated with increased rates of suicidal behaviours. This relationship could be explained by the reciprocal influence of cannabis on severity of depression, psychotic features, and impulsivity. Cannabis may play a key role in the complex clinical pathways that link mental disorders and suicide-related behaviours. Nevertheless, various potential mechanisms and contributing factors to this association remain to be investigated.

Key words
Cannabis • Suicide • Epidemiology • Psychopathology

Introduction
According to the World Health Organization [1], suicide is a global phenomenon, representing the 17th leading cause of death in 2015. In the European Union, out of the 4.9 million deaths reported in 2014, 58,000 (1.2%) were due to intentional self-harm [2]. In addition, evidence from the National Vital Statistics System show that between 1999 and 2014 age-adjusted suicide rates in the United States raised from 10.5 to 13.0 per 100,000 individuals in the general population [3]. Thus, suicide represents a public health problem, and it seems correlated with different clinical, psychological, biological and environmental risk factors, although no effective predictive algorithms for clinical practice are available [4]. Nevertheless, understanding and identifying factors that may be associated with suicidal behaviours could help clinicians to early detect high-risk individuals and assist them in screening for treatment [4].

Correspondence
Giuseppe Carrà
Department of Medicine and Surgery, University of Milano Bicocca,via Cadore 48, 20900 Monza, Italy, Italy
• E-mail: giuseppe.carra@unimib.it

In recent years, the possible relationship between substance use and suicidal behaviours has been investigated. Mood and substance use disorders are the most frequent mental disorders among suicide decedents worldwide [5]. In addition, cannabis, following nicotine and alcohol, is the most commonly used psychoactive substance both in the United States and in Europe, with particularly high misuse rates among young people [6 7]. Mixed results have been produced by studies analysing the possible detrimental effect of cannabis on health, making difficult to clarify whether, how, and to what extent cannabis is harmful. Negative effects are heterogeneous and may include a range of consequences in terms of brain development, mental disorders, use of other illicit drugs, school performance and lifetime achievement [8]. In particular, cannabis misuse may explain a portion of the complex interplay between mental illness and suicidality. Individuals who have attempted suicide show structural and functional brain changes similar to those found in cannabis users [9]. Moreover, high rates of cannabis use are common among individuals suffering from any mental disorders [10 11]. For example, data from the NESARC study [12] indicated that rates of cannabis use and cannabis use disorder among individuals with 12-month mental illness were 9.9 and 4.0%, respectively, as compared with 1.6 and 0.4% among individuals without any mental illness. In particular, the likelihood of having a cannabis use disorder for individuals with 12-month mental illness was over three times higher, after adjusting for sociodemographic characteristics and other substance use disorders. Potential effects of cannabis on suicidality have been analysed in different mental disorders, including major depression [13], anxiety [14], bipolar [15], and psychotic disorders [16]. Consistently, toxicology reports have shown high cannabis rates amongst suicide decedents by non-overdose methods, and chronic, heavy cannabis use has been found to be associated with suicidal ideation, attempt, and completion [17]. A relatively recent meta-analysis [17] estimated that chronic cannabis use could predict suicidality. In particular, cannabis use was associated with any suicidal behaviours, including suicidal ideation (Odds ratio [OR] = 1.43; 95% Confidence Interval [CI]: 1.13-1.83), suicide attempts (OR = 2.23; 95% CI: 1.24-4.00), and suicide death (OR = 2.56; 95% CI: 1.25-5.27). Nevertheless, the lack of homogeneity in the measurement of cannabis exposure and, at least partially, of systematic controlling for known risk factors, temper these findings. Consistently, a systematic review of epidemiological evidence on adverse effects of cannabis use, has pointed out that it is still unclear whether a regular cannabis use may increase the risk of death, including it due to suicide [18].

An epidemiological understanding is certainly required to clarify the nature of the clinical relationship between cannabis use and suicidal behaviours, as well as significance, consistency, and strength of this association. In particular, epidemiological research has attempted to establish whether a causal relationship may be postulated, clarifying the role of associated psychopathology, common among both cannabis users and suicidal individuals. In addition, it should be clarified whether certain mediators or moderators (the so-called *third factors*) might better explain the association between cannabis use and suicidal behaviours. These clinical, environmental, genetic factors may have an independent effect on both behaviours, thus confounding and influencing the association.

In this paper, we provide a narrative overview on the potential association between cannabis use and suicidal behaviours. In particular, we review findings of main longitudinal studies published in this field, discussing possible psychopathological models that may explain and disentangle this clinical relationship.

Methods

We conducted a narrative review including main population-based longitudinal studies. Studies had to analyse the direction of the association between cannabis use and any suicidal behaviours (suicidal ideation, attempts, completion), as well as the possible interplay of this relationship on individual psychopathological characteristics. We excluded studies selecting only special populations, such as individuals with mental disorders or those with substance use disorders. We searched on PubMed for articles written in English and indexed during the last 10 years (ranging from January 2008 to May 2018). Our search strategy included the following terms: *('Cannabis' or 'Marijuana') and ('Suicide' or 'Suicidal') and ('Longitudinal' or 'Cohort' or 'Prospective')*.

Results

Our search strategy identified a preliminary pool of 80 studies. Among these, seven longitudinal studies [19-25], analysing the association between cannabis use and different suicidal behaviours, met our inclusion criteria. We found that most of studies reported a significant association between cannabis use and subsequent suicidal behaviours. An integrative analysis of participant-level data from three large, long-running, longitudinal studies conducted in Australia and New Zealand [19], tested the association between the maximum frequency of cannabis use before the age 17 and various young adult psychosocial sequelae, including suicide attempts. After adjustment for confounders, daily cannabis users during adolescence had an increased odds of suicide attempts (adjusted OR = 6.83; 95% CI: 2.04 to 22.90), along with

other adverse outcomes, including reduction in school proficiency and risk of cannabis dependence or other illicit drugs use. Moreover, data from the Young in Norway longitudinal study [20], a population-based sample of 2,033 individuals followed up over a 13-year period, from their early teens to their late twenties, showed that exposure to cannabis by itself, though not leading to depression, was associated with later suicidal thoughts and attempts. Consistently, the Mexican Adolescent Mental Health Survey [21], estimating the prospective associations between substance use and incident suicide-related behaviours, showed that an early and a high frequency of cannabis use were associated with both suicide ideation and attempt. In addition, data gathered over the course of the Christchurch Health and Development Study, based on 938 individuals born in an urban region of New Zealand, estimated that using cannabis several times a week led to suicidal ideation in susceptible males, though, suicidal ideation did not lead to cannabis use in either males or females [22]. Gender differences were found also from waves 1 and 2 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) [23] based on 31,549 participants. This study showed that daily cannabis use was associated with an increased incidence of suicidality among men (adjusted OR = 4.28; 95% CI: 1.32 to 13.82), but not among women (adjusted OR = 0.75; 95% CI: 0.28-2.05). On the other hand, suicide ideation or attempts were associated with subsequent cannabis use among women (adjusted OR = 2.34; 95% CI: 1.42 to 3.87) but not among men (adjusted OR = 1.10; 95% CI: 0.57 to 2.15).

Other studies did not show any relationship between cannabis use and suicidal behaviours. The prospective cohort of the Collaborative Study of the Genetics of Alcoholism (COGA) [24], based on 3,277 individuals, reported that an early cannabis use was unrelated to the onset of suicidal ideation or suicide attempt. Similarly, no effect of suicidal ideation or suicide attempt on the onset of cannabis use was found. In addition, an important longitudinal study [25] investigating more than 50,000 men conscripted for Swedish military service, found 600 cases of suicides or deaths from undetermined causes at a 33-year follow-up. Findings showed that, despite a crude effect of cannabis use on risk of suicide was found (crude OR = 1.62; 95% CI: 1.28 to 2.07), this association was not confirmed after adjustment for relevant confounders (adjusted OR = 0.88; 95% CI: 0.65 to 1.20). The authors concluded that it is unlikely that cannabis use – either directly or because of mental health problems – may have a strong effect on completed suicide risk. Although there was a significant association between cannabis use and suicide, this relationship was likely to be attributable to correlated psychological and behavioural features.

Discussion

Summary and interpretation of findings

Over the years, epidemiological evidence has produced conflicting results, making it complex to identify a valid and reliable clinical model for subjects who use cannabis and have a greater risk of suicide ideation or attempt. In this narrative review, we pointed out that cannabis may be associated with increased rates of suicidal behaviours, despite mixed findings are available from different longitudinal studies. Heterogeneity of findings across studies could obviously involve methodological differences, in terms of study design, index population, follow-up duration, assessment methods. In addition, it should be considered that, in terms of toxicology, cannabis is a complex compound, with different active agents (phytocannabinoids) leading to various psychotropic effects. Delta-9-tetrahydrocannabinol (THC) explains most of the psychotropic and psychotomimetic effects of cannabis, while cannabidiol (CBD) may have anxiolytic, mood stabilizing, and antipsychotic effects [26]. For this reason, future, prospective, cohort studies should benefit from specific biochemical analyses of different phytocannabinoids concentration to clearly characterize possible dose-response effects between cannabis use and adverse outcomes, including suicidality [27]. Moreover, epidemiological research did not consider different methods for cannabis consumption, e.g., joints, bowls, bongs, edibles or drinks [28], despite these may potentially impact on related acute and chronic effects of cannabis, as well as on patterns of drug use [29]. Thus, the lack of a sufficient amount of longitudinal studies taking into account cannabis potency and routes of administration does not allow estimating if these factors could influence the individual risk of suicide. Consistently, the possible role of cannabis legal status as an environmental factor that can prevent or shape life consequences for cannabis users should be considered [30]. Country-level legalization or prohibition of cannabis represent key environmental factors that may influence outcomes of cannabis use, including those related to mental health and risk of suicide. Legislation changes in several countries may thus provide "natural" experiments on the effects of general population exposure to cannabis, giving the unique opportunity to monitor the related effects on mental health [31]. Studies that attempted to analyse the relationship between country-level cannabis legalization/prohibition and rates of suicide, can be taken as an example of this approach. A relatively recent study [32] estimated the association between cannabis use and completed suicide, showing that the legalization of medical cannabis does not affect suicide rates. No association between the number of "medical cannabis" registrants (used

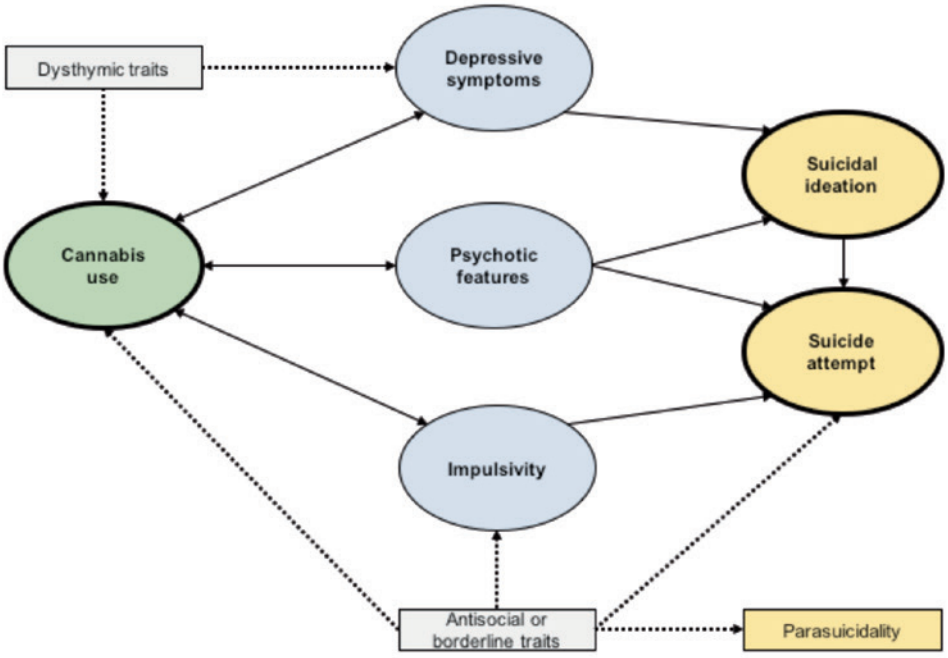
as a proxy measure of cannabis use) and completed suicide was found after controlling for multiple known, potential confounders. Consistently, relatively recent data from the National Vital Statistics System's Mortality Detail Files [33], analysed pre- and post- legalization trends in US states where medical cannabis was legalized. After adjustment for economic conditions, state policies, and state-specific linear time-period trends, the association between legalizing medical cannabis and suicides was not statistically significant. However, suicide rates decreased after medical cannabis legalization as compared with states that did not legalize it. In particular, although estimates for women were less precise, legalization was associated with a significant suicide rate reduction among men aged 20 to 29 years and those aged 30 to 39 years, respectively.

Psychopathological implications

Despite epidemiological research produced mixed results and the lack of sufficient evidence to support the hypothesis of an independent role of cannabis on suicide risk, it is important to identify psychopathological models that may at least partially explain the perceived association found in crude models. Subjects misusing cannabis may have an increased risk of psychopathological conditions, possibly leading to a higher risk of suicidal behaviours (suicidal ideation, suicide attempt, completed suicide). On the other hand, cannabis use may be the consequence of pre-existing clinical conditions, independently correlated with increased suicidality. Cannabis, along with alcohol and other substances, may represent one of the facilitators of the clinical progression from non-structured suicidal thoughts to emergent suicide ideation and attempts [4]. Recent findings actually support the hypothesis that cannabis users are vulnerable to perceived burdensomeness and thwarted belongingness, preliminarily confirming that difficulties in interpersonal functioning may serve as potential pathways through which daily cannabis use may lead to greater suicide risk [34].

From a clinical perspective, it should be considered that different psychopathological links may explain the interplay between cannabis use and suicidal behaviours (Fig. 1).

First, subjects experiencing depressive features, particularly those with pre-existing dysthymic traits or experiencing hopelessness [35], may use cannabis to relieve symptoms. This perspective is certainly consistent with the self-medication hypothesis [36], postulating that



The association between cannabis use and suicidal behaviours may be explained by impairment on depressive symptoms, psychotic features, and impulsivity (continuous lines), which may have bidirectional links with cannabis use. In addition, personality traits (dotted lines) may independently cause both cannabis use and suicidal behaviours.

FIGURE 1. *Relationship between cannabis use and suicidal behaviours: psychopatological models.*

individuals may use illicit substances in order to relieve symptoms such as affective dysregulation, apathy, and anhedonia. According to this model, cannabis use would occur in a context of self-regulation vulnerability and individual difficulties in controlling subjective emotions, affects, relationships, and self-care [37 38]. Moreover, a relationship between cannabis use and suicidal behaviours has been highlighted in subjects with additional risk factors, including stressful life events, interpersonal problems, poor social support, lonely lives, and feelings of hopelessness [16]. This can represent the first step of a vicious circle in which cannabis use might impair, regardless of temporary improvement, depressive symptoms, increasing the degree of anhedonia and apathy. It has been reported that subjects with lifetime depression, under the influence of cannabis, more often experience sadness, anxiety and paranoia, being less likely to report happiness or euphoria [39]. Consistently, negative symptoms are considered key features of depression in cannabis users, characterizing the so-called "amotivational syndrome", which combines affective flattening and loss of emotional reactivity [40]. In particular, hopelessness may represent the most important clinical and psychopathological mediator of the complex interplay between depression, suicide risk and cannabis use [35]. Nevertheless, evidence that cannabis use itself may independently trigger depressive symptoms are only partially convincing. For example, a three-year-follow-up longitudinal study, including 8,598 Swedish men and women, aged 20-64, did not show any association between cannabis use and incidence of depression/anxiety [41]. Consistently, a recent longitudinal study [42] showed that in mid-adolescence, anhedonia – an important psychopathological trait indicative of inability to experience pleasure and linked with suicide-related behaviors [43] – might be correlated with subsequent increase of cannabis use, despite, conversely, cannabis use did not appear to be associated with subsequent anhedonia. On the other hand, a recent study reported that the monozygotic twin using cannabis was more likely to report both major depression and suicidal ideation, as compared with twin who used cannabis less frequently [13]. Nevertheless, it has been argued that cannabis use is probably related to both depression and suicidal behaviours, through a constellation of mechanisms, involving genetic predisposition as well as social and environmental factors [44]. In particular, shared genetic influences seem to underlie the association of early-onset cannabis use with both depression and suicidality [45].

Second, psychotic symptoms also play a role as potential mediators of the clinical association between cannabis use and suicidal behaviours. Both neurobiological models [46] and epidemiological evidence support the role of cannabinoids as a possible risk factor for psychosis, showing that cannabis might influence, in a dose-dependent manner, the onset of schizophrenia and other psychotic disorders [47]. A concomitant increase in the severity of positive symptoms can be expected as an acute and chronic effect of THC [48], inducing psychotomimetic symptoms, delusions and auditory hallucinations, which may be the core signal of suicidal risk in individuals suffering from psychotic disorders [49 50]. Consistently, a relatively recent meta-analysis has shown that a continued cannabis use after the psychosis onset, may predict, along with other adverse outcomes, more severe positive symptoms as compared with individuals who discontinued cannabis use or never used it [51]. In addition, cannabis can have an indirect effect on the overall symptoms' severity and on the individual suicide risk, since cannabis use is one of main determinants of medication non-adherence [52].

A third important element is the effect of cannabis on impulsivity. It is known that elevated impulsivity may facilitate the transition from suicidal thoughts to suicidal behaviours [53]. Consistently, cannabis use is associated with changes in impulse control and hostility in daily life [54 55]. Despite the unsolved issue as to whether impulsivity is a trait preceding cannabis consumption or, the other way, cannabis itself exacerbates impulsivity, reduced prefrontal volumes and differences in white matter integrity have been identified in cannabis users [56]. This might explain the likelihood of impulsive and non-planned suicidal attempts in subjects with mental disorders misusing cannabis. Indeed, data from two community-based twin samples from the Australian Twin Registry [57] showed that cannabis use is associated with unplanned suicide attempts, but not with planned ones, even after controlling for other substance use disorders. Finally, illicit substance use is common among subjects with personality disorders, especially antisocial and borderline ones. Recent cross-sectional data from the Norwegian Institute of Public Health Twin Study of Mental Health [58] showed that subjects with antisocial or borderline personality disorders are more likely to use cannabis or suffering from a cannabis use disorder. In particular, it has been shown that the shared genetic risk between depression and cannabis dependence may be largely explained by genetic effects of antisocial personality disorder [59]. Thus, the clinical relationship between cannabis use and suicidality in some personality disorders can be considered a false association, since both substance use and suicidal tendencies are likely to be direct consequences of individual traits, rather than linked through a causal or bidirectional relationship. In addition, it should be considered that individuals with personality disorders might be vulnerable to parasuicidal behaviours and manipulative/impulsive

suicidal threats and/or gestures, with low lethality and lack of medical consequences, rather than suicidal behaviours [60 61].

Conclusions

Over the years, disentangling psychopathological issues underlying the relationship between co-occurring substance use disorders and behaviours has represented a key challenge of research in psychiatry [62]. Despite mixed findings deriving from main epidemiological evidence, our review shows that cannabis use may be clinically associated with an increased risk of suicide. However, the various mechanisms as well as contributing factors to this association remain to be clarified. Cannabis seems to have a role in the complex clinical pathways that link mental disorders and suicide-related behaviours. Cannabis may influence or trigger psychopathological features associated with increased suicidality. The association between cannabis use and suicidal behaviours may be due to an impairment on depressive symptoms, psychotic features, and impulsivity, which may have bidirectional links with cannabis use. In addition, personality traits and characteristics may independently cause both cannabis use and suicidal behaviours, thus determining a false association. Nevertheless, it is likely that the psychopathological relationship between cannabis use and suicidal behaviours cannot be explained by a single clinical model, even taking into account the possible role of overlapping genetic influences [45]. Future research should consider the possible association between increasing potency of cannabis and suicidality [31], the potential anxiolytic, antidepressant, antipsychotic effects of CBD [26], as well the possible influence of various routes for cannabis consumption [29].

Conflict of Interest

The authors have no conflict of interest to declare.

References

1. World Health Organization. *Suicide data* (http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/, accessed June 7th, 2018).
2. Eurostat. *Almost 60 000 suicides in the EU*. (http://ec.europa.eu/eurostat/web/products-eurostat-news/-/DDN-20170517-1, accessed June 7th, 2018).
3. Curtin SC, Warner M, Hedegaard H. *Increase in suicide in the United States, 1999-2014*. NCHS Data Brief 2016;241:1-8.
4. Turecki G, Brent DA. *Suicide and suicidal behaviour*. Lancet 2016;387:1227-39.
5. Conner KR, Bridge JA, Davidson DJ, et al. *Metaanalysis of mood and substance use disorders in proximal risk for suicide deaths*. Suicide Life Threat Behav 2017. Doi: 10.1111/sltb.12422. [Epub ahead of print]
6. Center for Behavioral Health Statistics and Quality. *2016 National survey on drug use and health: detailed tables*. Rockville: Substance Abuse and Mental Health Services Administration 2017.
7. European Monitoring Centre for Drugs and Drug Addiction. *European Drug Report 2017: trends and developments*. Luxembourg: Publications Office of the European Union 2017.
8. Volkow ND, Compton WM, Weiss SR. *Adverse health effects of marijuana use*. N Engl J Med 2014;371:879.
9. Clarke MC, Coughlan H, Harley M, et al. *The impact of adolescent cannabis use, mood disorder and lack of education on attempted suicide in young adulthood*. World Psychiatry 2014;13:322-3.
10. Carrà G, Clerici M. *Dual diagnosis – policy and practice in Italy*. Am J Addict 2006;15:125-30.
11. Carrà G, Bartoli F, Brambilla G, et al. *Comorbid addiction and major mental illness in Europe: a narrative review*. Subst Abus 2015;36:75-81.
12. Lev-Ran S, Le Foll B, McKenzie K, et al. *Cannabis use and cannabis use disorders among individuals with mental illness*. Compr Psychiatry 2013;54:589-98.
13. Agrawal A, Nelson EC, Bucholz KK, et al. *Major depressive disorder, suicidal thoughts and behaviours, and cannabis involvement in discordant twins: a retrospective cohort study*. Lancet Psychiatry 2017;4:706-14.
14. Buckner JD, Joiner TE Jr, Schmidt NB, et al. *Daily marijuana use and suicidality: the unique impact of social anxiety*. Addict Behav 2012;37:387-92.
15. Carrà G, Bartoli F, Crocamo C, et al. *Cannabis use disorder as a correlate of suicide attempts among people with bipolar disorder*. Bipolar Disord 2015;17:113-4.
16. Serafini G, Pompili M, Innamorati M, et al. *Can cannabis increase the suicide risk in psychosis? A critical review*. Curr Pharm Des 2012;18:5165-87.
17. Borges G, Bagge CL, Orozco R. *A literature review and meta-analyses of cannabis use and suicidality*. J Affect Disord 2016;195:63-74.
18. Calabria B, Degenhardt L, Hall W, et al. *Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use*. Drug Alcohol Rev 2010;29:318-30.
19. Silins E, Horwood LJ, Patton GC, et al. *Young adult sequelae of adolescent cannabis use: an integrative analysis*. Lancet Psychiatry 2014;1:286-93.
20. Pedersen W. *Does cannabis use lead to depression and suicidal behaviours? A population-based longitudinal study*. Acta Psychiatr Scand 2008;118:395-403.
21. Borges G, Benjet C, Orozco R, et al. *Alcohol, cannabis and other drugs and subsequent suicide ideation and attempt among young Mexicans*. J Psychiatr Res 2017;91:74-82.
22. van Ours JC, Williams J, Fergusson D, et al. *Cannabis use and suicidal ideation*. J Health Econ 2013;32:524-37.
23. Shalit N, Shoval G, Shlosberg D, et al. *The association between cannabis use and suicidality among men and women: a population-based longitudinal study*. J Affect Disord 2016;205:216-24.
24. Agrawal A, Tillman R, Grucza RA, et al. *Reciprocal relationships between substance use and disorders and suicidal ideation and suicide attempts in the Collaborative Study of the Genetics of Alcoholism*. J Affect Disord 2017;213:96-104.
25. Price C, Hemmingsson T, Lewis G, et al. *Cannabis and suicide: longitudinal study*. Br J Psychiatry 2009;195:492-7.
26. Atakan Z. *Cannabis, a complex plant: different compounds and different effects on individuals*. Ther Adv Psychopharmacol 2012;2:241-54.
27. Freeman TP, Mokrysz C, Curran HV. *Rethinking dose-response effects of cannabis use in adolescence*. Lancet Psychiatry 2014;1:416.

28 Schauer GL, King BA, Bunnell RE, et al. *Toking, vaping, and eating for health or fun: marijuana use patterns in adults, US, 2014*. Am J Prev Med 2016;50:1-8.

29 Baggio S, Deline S, Studer J, et al. *Routes of administration of cannabis used for nonmedical purposes and associations with patterns of drug use*. J Adolesc Health 2014;54:235-40.

30 Reiman A, Earleywine M, Corva D. *Rethinking dose-response effects of cannabis use in adolescence*. Lancet Psychiatry 2014;1:416-7.

31 Murray RM, Quigley H, Quattrone D, et al. *Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis*. World Psychiatry 2016;15:195-204.

32 Rylander M, Valdez C, Nussbaum AM. *Does the legalization of medical marijuana increase completed suicide?* Am J Drug Alcohol Abuse 2014;40:269-73.

33 Anderson DM, Rees DI, Sabia JJ. *Medical marijuana laws and suicides by gender and age*. Am J Public Health 2014;104:2369-76.

34 Buckner JD, Lemke AW, Walukevich KA. *Cannabis use and suicidal ideation: test of the utility of the interpersonal-psychological theory of suicide*. Psychiatry Res 2017;253:256-9.

35 Serafini G, Pompili M, Innamorati M, et al. *The Association between cannabis use, mental illness, and suicidal behavior: what is the role of hopelessness?* Front Psychiatry 2013;4:125.

36 Khantzian EJ. *The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence*. Am J Psychiatry 1985;142:1259-64.

37 Khantzian EJ. *The self-medication hypothesis of substance use disorders: a reconsideration and recent applications*. Harv Rev Psychiatry 1997;4:231-44.

38 Potvin S, Stip E, Roy JY. *Schizophrenia and addiction: an evaluation of the self-medication hypothesis*. Encephale 2003;29:193-203.

39 Arendt M, Rosenberg R, Fjordback L, et al. *Testing the self-medication hypothesis of depression and aggression in cannabis-dependent subjects*. Psychol Med 2007;37:935-45.

40 Bersani G, Bersani FS, Caroti E, et al. *Negative symptoms as key features of depression among cannabis users: a preliminary report*. Eur Rev Med Pharmacol Sci 2016;20:547-52.

41 Danielsson AK, Lundin A, Agardh E, et al. *Cannabis use, depression and anxiety: a 3-year prospective population-based study*. J Affect Disord 2016;193:103-8.

42 Leventhal AM, Cho J, Stone MD, et al. *Associations between anhedonia and marijuana use escalation across mid-adolescence*. Addiction 2017;112:2182-90.

43 Winer ES, Drapeau CW, Veilleux JC, et al. *The Association between anhedonia, suicidal ideation, and suicide attempts in a large student sample*. Arch Suicide Res 2016;20:265-72.

44 Huckins LM. *Linking cannabis use to depression and suicidal thoughts and behaviours*. Lancet Psychiatry 2017;4:654-6.

45 Agrawal A, Lynskey MT. *Cannabis controversies: how genetics can inform the study of comorbidity*. Addiction 2014;109:360-70.

46 Bloomfield MA, Ashok AH, Volkow ND, et al. *The effects of Δ(9)-tetrahydrocannabinol on the dopamine system*. Nature 2016;539:369-77.

47 Marconi A, Di Forti M, Lewis CM, et al. *Meta-analysis of the association between the level of cannabis use and risk of psychosis*. Schizophr Bull 2016;42:1262-9.

48 D'Souza DC, Ranganathan M, Braley G, et al. *Blunted psychotomimetic and amnestic effects of delta-9-tetrahydrocannabinol in frequent users of cannabis*. Neuropsychopharmacology 2008;33:2505-16.

49 Kjelby E, Sinkeviciute I, Gjestad R, et al. *Suicidality in schizophrenia spectrum disorders: the relationship to hallucinations and persecutory delusions*. Eur Psychiatry 2015;30:830-6.

50 Wong Z, Öngür D, Cohen B, et al. *Command hallucinations and clinical characteristics of suicidality in patients with psychotic spectrum disorders*. Compr Psychiatry. 2013;54:611-7.

51 Schoeler T, Monk A, Sami MB, et al. *Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis*. Lancet Psychiatry 2016;3:215-25.

52 Foglia E, Schoeler T, Klamerus E, et al. Cannabis use and adherence to antipsychotic medication: a systematic review and meta-analysis. Psychol Med 2017;47:1691-705.

53 Klonsky ED, May A. *Rethinking impulsivity in suicide*. Suicide Life Threat Behav 2010;40:612-9.

54 Ansell EB, Laws HB, Roche MJ, et al. *Effects of marijuana use on impulsivity and hostility in daily life*. Drug Alcohol Depend 2015;148:136-42.

55 Trull TJ, Wycoff AM, Lane SP, et al. *Cannabis and alcohol use, affect and impulsivity in psychiatric out-patients' daily lives*. Addiction 2016;111:2052-9.

56 Wrege J, Schmidt A, Walter A, et al. *Effects of cannabis on impulsivity: a systematic review of neuroimaging findings*. Curr Pharm Des 2014;20:2126-37.

57 Delforterie MJ, Lynskey MT, Huizink AC, et al. *The relationship between cannabis involvement and suicidal thoughts and behaviors*. Drug Alcohol Depend 2015;150:98-104.

58 Gillespie NA, Aggen SH, Neale MC, et al. *Associations between personality disorders and cannabis use and cannabis use disorder: a population-based twin study*. Addiction 2018;113:1488-98.

59 Fu Q, Heath AC, Bucholz KK, et al. *Shared genetic risk of major depression, alcohol dependence, and marijuana dependence: contribution of antisocial personality disorder in men*. Arch Gen Psychiatry 2002;59:1125-32.

60 Black DW. *The natural history of antisocial personality disorder*. Can J Psychiatry 2015;60:309-14.

61 Söderberg S. *Personality disorders in parasuicide*. Nord J Psychiatry 2001;55:163-7.

62 Carrà G, Bartoli F, Clerici M, et al. *Psychopathology of dual diagnosis: new trumpets and old uncertainties*. J Psychopathol 2015;21:390-9.

JOURNAL OF PSYCHOPATHOLOGY
2018;24:187-191

Original article

G. Ciocca[1], C. Solano[1], L. D'Antuono[2], L. Longo[3], E. Limoncin[1], E. Bianciardi[3], C. Niolu[3], A. Siracusano[3], E.A. Jannini[1], G. Di Lorenzo[3]

[1] Chair of Endocrinology and Sexual Medicine (ENDOSEX), Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy; [2] Independent Researcher, Brussels, Belgium; [3] Chair of Psychiatry, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

Hypersexuality: the controversial mismatch of the psychiatric diagnosis

Summary

Hypersexuality is characterized by intrusive fantasies and thoughts regarding sex, excessive sexual behaviours, and the inability to control one's own sexuality, resulting in an impairment of relational and social life. While several clinical histories and empirical research consider hypersexuality as a disorder, the last version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) does not include hypersexuality as a psychopathological category in se. This has generated controversy among clinicians and researchers and a mismatch with the 11th revision of the International Classification of Diseases (ICD-11). However, different theoretical models are related to hypersexuality, i.e. the compulsivity model, the impulsivity model and the addiction model. This paper addresses the psychopathology of hypersexuality, including treatment and related comorbid conditions.

Key words

Hypersexuality • Comorbidity • Treatment • ICD-11 • DSM-5

Introduction

Sexual behaviour represents a fundamental aspect of human life, mainly involving pleasure, reproduction and couple relationships. Sexual physiology consists of several phases according to the gender and problems can occur in some cases. The most common sexual problems are erectile dysfunction and premature ejaculation in males and anorgasmia or sexual pain in females [1]. In some cases, the main cause of a sexual impairment is hypoactive sexual desire disorder, i.e. lack of libido, that causes a decrease of sexual activity. On the contrary, hypersexuality includes excess of sexual activities, the obsession toward sex and its consequences. Hypersexual behaviours include excess of compulsive masturbation, pornography, sexual behaviour with consenting adults, cybersex or telephone sex use and strip clubs attendance [2].

In the last years, the debate was on whether to include hypersexuality within the last version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), with some proposals based on diagnostic criteria, but to date the psychiatric nosography has not considered hypersexuality a mental disorder *per se*. On the contrary, the World Health Organization has recently proposed to include hypersexuality within the last version of the International Classification of Diseases (ICD-11) as a disorder of sexual compulsive behaviour (compulsive sexual behaviour disorder, CSBD) [3]. This generates a mismatch and controversy for the clinical and diagnostic praxis. Is hypersexuality a disorder for psychiatrists and clinical psychologists? In 2010, prominent American psychiatrist M.P. Kafka proposed the criteria to detect hypersexuality [4], but the American Psychiatric Association (APA) still does not include this condition as a category of mental disorder, although the debate is currently open [5]. However, the impossibility to diagnose hypersexuality according to DSM-5 criteria does not mean that this condition does not exist, since several empirical data

Correspondence

Giorgio Di Lorenzo
Chair of Psychiatry, Department of Systems Medicine, University of Rome Tor Vergata, via Montpellier 1, 00133 Rome, Italy
• E-mail: di.lorenzo@med.uniroma2.it

and the clinical practice demonstrate a large pathological spectrum characterizing this particular sexual condition [6]. The aim of the current paper is to highlight the main theoretical models and the state of art of hypersexuality in the field of psychopathology.

Theories of hypersexuality

Theoretical debate concerning the hypersexuality started with Freud's psychoanalytic theories. In particular some authors in this field discussed about the relationship between life instinct and death instinct in sexual addiction [7]. From this perspective, hypersexual/addicted subjects attempt to antagonize depressive states and death anxiety with the life instinct through sexual activities, although in a deregulated way. Hence, hypersexual behaviours can be bona fide considered a defensive behaviour against death anxiety [8].
However, other theoretical models were developed based on different aspects leading to hypersexual disorder: the compulsive sexual behaviour, the sexual impulsivity, and the sexual addiction.

Compulsivity model

Coleman described and defined hypersexuality as a compulsive sexual behaviour through a parallelism with the phenomenology of obsessive-compulsive disorder (OCD), characterized by repetitive and intrusive thoughts and then the repetition of sexual experiences. These experiences are described by an increase of arousal before – and a decrease after – a sexual act [9]. According to this model, thoughts and images constitute the obsession, while the acting constitutes the compulsion. However, this psychopathological mechanism in hypersexuality is ego-syntonic [6].

Impulsivity model

According to this model, the hypersexual behaviour is due to the failure to resist to sexual drive, and to the incapacity to delay the sexual gratification [6]. Based on the impulsivity model, the hypersexuality is thus caused by impulse dyscontrol, although this proposal has been largely criticized. Many hypersexual subjects, in fact, carefully plan their sexual activities and behaviours. Moreover, the reward system related to the pleasure experience would reinforce the hypersexual behaviour [10]. However, according to some studies, sexual impulsivity and sexual compulsivity are factors characterizing hypersexuality together and not separately [10].

Addiction model

The addiction model is considered the most valid to explain the hypersexual disorder. The parallelism between hypersexuality and the common addiction disorders was made in the past [11]. The symptomatology concerns the increase of sexual activity together with the development of the disorder, while abstinence symptoms as depression, anxiety, and blame are associated to the decrease of sexual conducts [11]. Moreover, as in other forms of addiction, hypersexual subjects spend a particular amount of time looking for novel sexual partners and compromise their social and relational life, without taking into account potential negative consequences as the sexually transmitted diseases.

ICD-11 *versus* DSM-5

The categorial approach towards mental disorders regards both the ICD and the DSM classifications, however the ICD proposed to include hypersexuality as a condition in its last version (ICD-11). Hypersexuality has an estimated prevalence of 2-6%, with males being the most affected [12 13]. This high prevalence, in absence of specific diagnostic criteria, drove some clinicians and epidemiologists to categorize and propose hypersexuality as a distinct disorder. In particular, the World Health Organization proposed to describe hypersexuality as a compulsive sexual behaviour disorder (CSBD), describing it in the ICD-11 as follows:

Compulsive sexual behaviour disorder is characterized by a persistent pattern of failure to control intense, repetitive sexual impulses or urges resulting in repetitive sexual behaviour. Symptoms may include repetitive sexual activities becoming a central focus of the person's life to the point of neglecting health and personal care or other interests, activities and responsibilities; numerous unsuccessful efforts to significantly reduce repetitive sexual behaviour; and continued repetitive sexual behaviour despite adverse consequences or deriving little or no satisfaction from it. The pattern of failure to control intense, sexual impulses or urges and resulting repetitive sexual behaviour is manifested over an extended period of time (e.g., 6 months or more), and causes marked distress or significant impairment in personal, family, social, educational, occupational, or other important areas of functioning. Distress that is entirely related to moral judgments and disapproval about sexual impulses, urges, or behaviours is not sufficient to meet this requirement [14].

Moreover, an additional controversial aspect is the position of CSBD among the impulse control disorders together with pyromania, kleptomania and intermittent explosive disorder, as also the various substance impulse control disorders [14]. According to the ICD-11 classification, the only conditions to be excluded when diagnosing CSBD are paraphilic disorders. The ICD-11 made also a further specification concerning the terminology: hypersexuality or hypersexual disorder is better defined as compulsive sexual behaviour disorder.

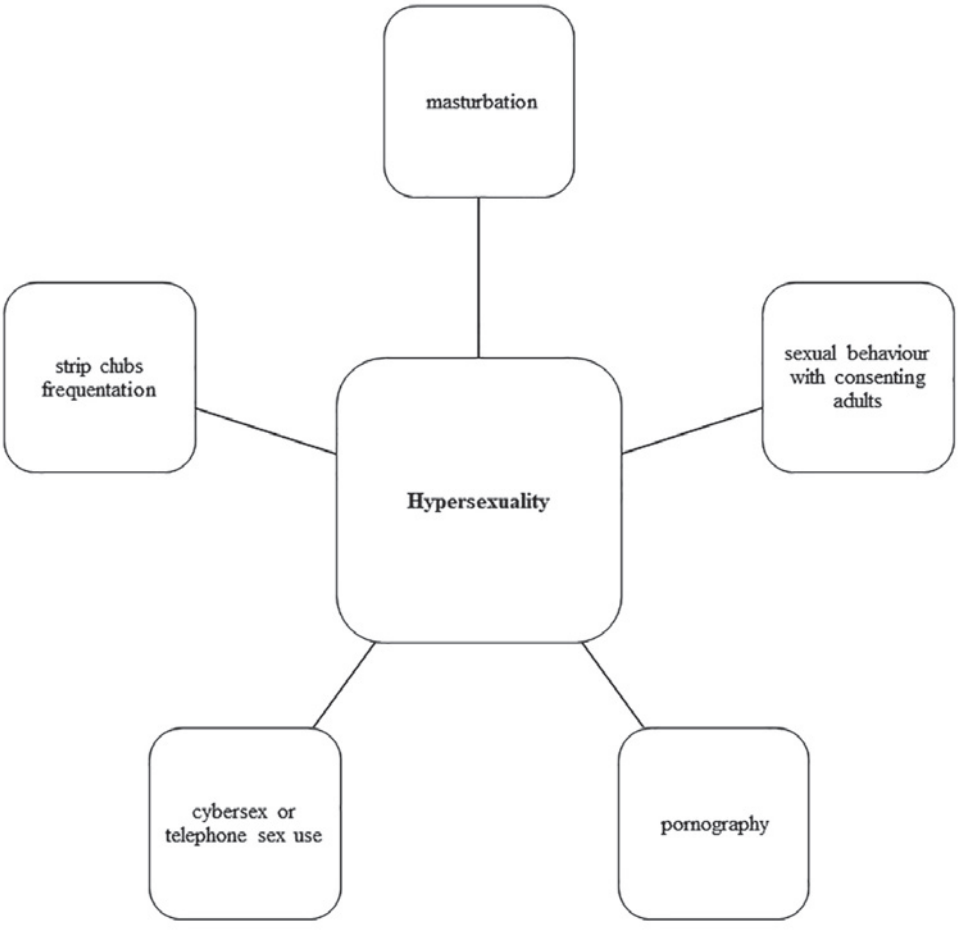
On the other hand, hypersexuality was considered for inclusion as a psychiatric disorder within the section of sexual dysfunctions of the DSM-5. The DSM-5 Working Group on Sexual and Gender Identity Disorders proposed possible detailed criteria [4]. Also in this case, as for the ICD-11, the clinicians of DSM-5 considered the possible differential diagnosis with paraphilic disorders. Both ICD-11 criteria as putative DSM-5 criteria isolate hypersexuality from paraphilias. However, hypersexuality is not a pathological category of DSM-5 for several reasons, including insufficient evidence, studies or clinical trials on hypersexual subjects, and the potential misuse of this delicate diagnosis in forensic settings [10 15].

Hypersexuality and comorbid disorders

Hypersexuality is very often present along with different comorbid disorders, that make the diagnostic process more complex and question the official nosography. In fact, hypersexual disorder was found in comorbidity with other psychiatric and physical conditions, particularly in males, such as anxiety and mood disorders, substance use disorder, attention-deficit hyperactivity disorder (ADHD) [16-18]. Moreover, some studies , and that hypersexuality correlates with narcissistic, borderline, antisocial, avoidant, obsessive-compulsive, and passive-aggressive personality disorders; a high comorbidity with paranoid personality disorder was also found [16 19].

To make the differential diagnosis, it is necessary to distinguish hypersexuality from paraphilic disorders. Comparing to paraphilias, hypersexual subjects and hypersexual behaviours do not concern inanimate objects, animals, parts of the body, etc. [20]. However, paraphilic patients can also develop hypersexual disorder along with elements of compulsivity, obsession and distress.

Finally, hypersexual behaviours should also be distinguished from other medical conditions, neuropsychi-



The figure shows the sexual activities involved in hypersexuality cases in a deregulated and pathological way.

FIGURE 1. *Sexual behaviours and hypersexuality.*

atric diseases, neurodegenerative disorders and from iatrogenic effects of some medications [4 21].

Treatments

Following the idea of hypersexuality as a mental disorder, some possible treatments can be considered along the pharmacological and psychotherapeutic continua [22]. The first includes the noradrenergic and serotoninergic reuptake inhibitors, or simply selective serotonin reuptake inhibitor [23]. On the other hand, also opiate agonists were experimentally verified for compulsive sexual behaviour in a retrospective study [24]. Psychological therapies for hypersexuality are mainly follow cognitive-behavioural approaches, although psychodynamic psychotherapy focused on trauma and the family of origin have also been considered useful [2]. Moreover, different styles of group or couple therapy were also found to be useful [2 22]. Also mindfulness has proven to be effective in people seeking help for hypersexual behaviour [25]. In any case, it is also important the treatment of comorbid conditions, such as substance abuse, mood and anxiety disorders [2]. This aspect represents a crucial point to take into account for the treatment of hypersexual subjects.

Conclusions

If most of social media recently claimed that "hypersexuality is a mental disorder that regards the compulsive sexual behaviour", based on our article the issue remains controversial. The psychiatric community sees the hypersexuality as a pathological condition, and different psychological treatments were empirically proven. Therefore, many psychiatrists and clinical psychologists prompt to include hypersexuality in the psychiatric nosography, although some doubts still persist. The first doubt concerns the differential diagnosis. Is hypersexuality an isolated disorder? Or the sexual addiction is a consequence of another mental disease, as manic phases of bipolar disorder or the effect of substance abuse? The compulsive sexual behaviour can be considered a psychotic sign or the onset of a first episode of psychosis [26] in the young while an iatrogenic effect of Parkinson's therapy in the elderly [27]. However, these comorbid conditions could be considered into the diagnostic process to detect a primary diagnosis excluding the other consequent pathologies.

In other words, if hypersexuality is not better accounted for by another mental disorder, it could be considered a category *per se*. This is the case of many mental diseases as addiction and eating disorders. In this regard, when two pathologies are present together, we talk of dual diagnosis. Therefore, it is crucial to take into account the concept of dual diagnosis involved also in hypersexual disorder when we adopt a categorial diagnostic method [28].

In conclusion, we believe that when individuals use sex, sexual behaviour and sexual activities as a therapy for another disorder, such as anxiety or depression, that could be considered as an index of discomfort. In the same manner, when a subject suffering from a specific mental disorder, such as bipolar disorder or schizophrenia, the hypersexual behaviour can be considered a manifestation of those primary diagnoses. If APA will include hypersexuality as a disorder, it is important to define a criterion that clearly specifies whether the disorder is present alone or in comorbidity, as it has been partially proposed [4]. On the other hand, many theories and hypothesis try to explain the origin and the correct definition of hypersexuality according to different approaches, although all studies conclude that more research and clinical studies are necessary to be able to categorize hypersexuality as a specific disorder.

Conflict of Interest

The authors declare no conflict of interest.

References

1 Ciocca G, Limoncin E, Di Tommaso S, et al. *Attachment styles and sexual dysfunctions: a case-control study of female and male sexuality*. Int J Impot Res 2015;27:81-5.

2 Kaplan MS, Krueger RB. *Diagnosis, assessment, and treatment of hypersexuality*. J Sex Res 2010;47:181-98.

3 Potenza MCG M, Voon V, Kor A, et al. *Is excessive sexual behaviour an addictive disorder?* Lancet Psychiatry 2017;4:663-4.

4 Kafka MP. *Hypersexual disorder: a proposed diagnosis for DSM-V.* Arch Sex Behav 2010;39:377-400.

5 Kraus SW, Krueger RB, Briken P, et al. *Compulsive sexual behaviour disorder in the ICD-11.* World Psychiatry 2018;17:109-10.

6 Garcia FD, Thibaut F. *Sexual addictions*. Am J Drug Alcohol Abuse 2010;36:254-60.

7 Watter DN. *Existential issues in sexual medicine: the relation between death anxiety and hypersexuality.* Sex Med Rev 2018;6:3-10.

8 Ciocca G, Limoncin E, Lingiardi V, et al. *Response regarding existential issues in sexual medicine: the relation between death anxiety and hypersexuality.* Sex Med Rev 2018;6:335-6.

9 Coleman E, Raymond N, McBean A. *Assessment and treatment of compulsive sexual behavior.* Minn Med 2003;86:42-7.

10 Walton MT, Cantor JM, Bhullar N, et al. Hypersexuality: a critical review and introduction to the "Sexhavior Cycle". Arch Sex Behav 2017;46:2231-51.

11 Orford J. *Hypersexuality: implications for a theory of dependence.* Br J Addict Alcohol Other Drugs 1978;73:299-10.

12 Klein V, Rettenberger M, Briken P. *Self-reported indicators of hypersexuality and its correlates in a female online sample.* J Sex Med 2014;11:1974-81.

13 Kuzma JM, Black DW. *Epidemiology, prev-*

alence, and natural history of compulsive sexual behavior. Psychiatr Clin North Am 2008;31:603-11.

14 WHO. *International Classification of Diseases (ICD-11)*. 2018 (https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/1630268048).

15 Kafka MP. *What happened to hypersexual disorder?* Arch Sex Behav 2014;43:1259-61.

16 Raymond NC, Coleman E, Miner MH. *Psychiatric comorbidity and compulsive/impulsive traits in compulsive sexual behavior.* Compr Psychiatry 2003;44:370-80.

17 Kafka MP, Hennen J. *A DSM-IV Axis I comorbidity study of males (n = 120) with paraphilias and paraphilia-related disorders.* Sex Abuse 2002;14:349-66.

18 Niolu C, Lisi G, Siracusano A. *Sexual dysfunctions and mood and anxiety disorders*. In: Jannini EA, Siracusano A, Eds. *Sexual dysfunctions in mentally ill patients*. New York, NY: Springer 2018.

19 Black DW, Kehrberg LL, Flumerfelt DL, et al. *Characteristics of 36 subjects reporting compulsive sexual behavior*. Am J Psychiatry 1997;154:243-9.

20 Di Lorenzo G, Gorea F, Longo L,et al. *Paraphilia and paraphilic disorders*. In: Jannini EA, Siracusano A, Eds. *Sexual dysfunctions in mentally ill patients*. New York, NY: Springer 2018.

21 Bereau M. *Hypersexuality in neurological disorders: from disinhibition to impulsivity.* Front Neurol Neurosci 2018;41:71-6.

22 Hook JN, Reid RC, Penberthy JK, et al. *Methodological review of treatments for nonparaphilic hypersexual behavior.* J Sex Marital Ther 2014;40:294-308.

23 Coleman E, Gratzer T, Nesvacil L, et al. *Nefazodone and the treatment of nonparaphilic compulsive sexual behavior: a retrospective study*. J Clin Psychiatry 2000;61:282-4.

24 Raymond NC, Grant JE, Coleman E. *Augmentation with naltrexone to treat compulsive sexual behavior: a case series.* Ann Clin Psychiatry 2010;22:56-62.

25 Reid RC, Bramen JE, Anderson A, et al. *Mindfulness, emotional dysregulation, impulsivity, and stress proneness among hypersexual patients*. J Clin Psychol 2014;70:313-21.

26 Ciocca G, Usall J, Dolz M, et al. *Sexual dysfunctions in people with first-episode psychosis assessed according to a gender perspective*. Riv Psichiatr 2015;50:239-44.

27 Nakum S, Cavanna AE. *The prevalence and clinical characteristics of hypersexuality in patients with Parkinson's disease following dopaminergic therapy: a systematic literature review.* Parkinsonism Relat Disord 2016;25:10-6.

28 Luciano M, Sampogna G, Del Vecchio V, et al. *Critical evaluation of current diagnostic classification systems in psychiatry: the case of DSM-5.* Riv Psichiatr 2016;51:116-21.

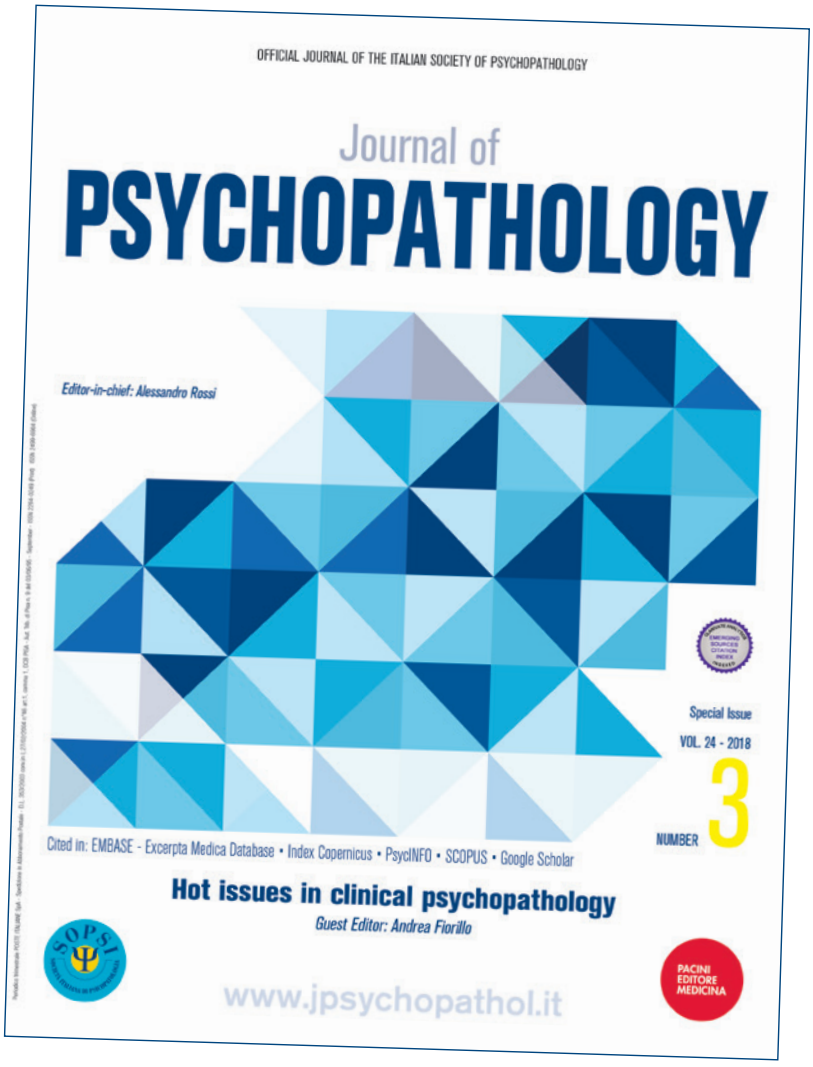
News

Società Italiana di Psicopatologia (SOPSI) and **Pacini Editore Srl** are pleased to announce that **Journal of Psychopathology** has been accepted for indexing in the

Emerging Sources Citation Index, a new edition of Web of Science

Content in ESCI is under consideration by Clarivate Analytics, the owner of Web of Science, for additional indexing on the platform, including for the Science Citation Index Expanded, the Social Sciences Citation Index, and the Arts & Humanities Citation Index.

The quality and depth of content Web of Science offers to researchers, authors, publishers, and institutions sets it apart from other research databases. The inclusion of **Journal of Psychopathology** in the Emerging Sources Citation Index demonstrates our dedication to providing the most relevant and influential **Psycopathology/Psychiatry** content to our community.



The Journal of Psychopathology publishes contributions in the form of monographic articles, news, update articles in clinical psychopharmacology, forums in the field of psychiatry. The material submitted should not have been previously published, and should not be under consideration (in whole or in part) elsewhere; it must conform with the regulations currently in force regarding research ethics. If an experiment on humans is described, a statement must be included that the work was performed in accordance with the principles of the 1983 Declaration of Helsinki. The Authors are solely responsible for the statements made in their paper, and must specify that consent has been obtained from patients taking part in the investigations and for the reproduction of any photographs. For studies performed on laboratory animals, the authors must state that the relevant national laws or institutional guidelines have been adhered to. Only papers that have been prepared in strict conformity with the editorial norms outlined herein will be considered for publication. Eventual acceptance is conditional upon a critical assessment by experts in the field, the implementation of any changes requested, and the final decision of the Editor.

Conflict of Interests. In the letter accompanying the article, Authors must declare whether they obtained funds, or other forms of personal or institutional financing – or if they are under contract – from Companies whose products are mentioned in the article. This declaration will be treated by the Editor as confidential, and will not be sent to the referees. Accepted articles will be published accompanied by a suitable declaration, stating the source and nature of the financing.

SOPSI - Società Italiana di Psicopatologia and Pacini Editore srl inform readers and users of the Journal of Psychopathology, that the published articles reflect only the research and the opinion of the authors signing the contents. These articles therefore do not represent and do not in any way constitute indications or guidelines of the SOPSI itself. This differs from the texts and contents that are explicitly declared as official institutional matrix and published in the appropriate sections of the Journal, which are dedicated to the Guidelines of SOPSI.

The Journal of Psychopathology is sent to SOPSI members, subscribers, doctors, health professionals, exclusively for professional training and improvement and to inform and promote activities and products / services, strictly related to the professional activities of users, always ensuring a strong affinity between the message and the user's interest. Please read the Privacy Policy at the following link: http://www.pacinimedicina.it/privacy-policy-informativa-privacy/. For communications / information: info@pacinieditore.it

General instructions

– *Online submission*: authors are requested to submit their manuscripts to: **submission.jpsychopathol.it**
Manuscripts should be accompanied by the "Permission form" downloadable from the website, signed by all authors to transfer the copyright.
– *Software and text*: please saving files in.DOC or in.RTF format.
– *Illustrations*: a) send pictures in separate files from text and tables; b) software and format: preferably send images in.TIFF or.JPEG or.PDF format, resolution at least 300 dpi (100 x 150 mm).

The text must be written in English. The paper must include:

1. **title**;
2. **summary** (Summary should be about 3000 typewritten characters (including spaces). It should be divided into 4 sections: Objectives, Methods, Results, Conclusions);
3. **a set of key words**;
4. **legends for tables and figures** (each figure and/or each table on separate pages);
5. **authors are invited to suggest 3 national or international** referees for their article.

The *first page* of the manuscript must also contain the names of the Authors and the Institute or organisation to which each Author is affiliated; the category under which the Authors wish the work to be published (although the final decision rests with the Editor); the name, mailing address, and telephone and fax numbers of the Author to whom correspondence and the galley proofs should be sent.

Tables (in 3 copies) must be limited in number (the same data should not be presented twice, in both the text and tables), typewritten one to a page, and numbered consecutively with Roman numerals. In the text and legend to the tables, Authors must use, in the exact order, the following symbols:, †, ‡, ¶,, ††, ‡‡ …

Figures, please strictly follow the above-mentioned instructions.

The *references* must be limited to the most essential and relevant references, identified in the text by Arabic numbers in upper script and listed at the end of the manuscript in the order of mention. The first 3 Authors must be indicated, followed by et al. Journals should be cited according to the abbreviations set out by *Index Medicus*.
Examples of the correct format for bibliographic citations:
Journal articles:
Schatzberg AF, Samson JA, Bloomingdale KL, et al. *Toward a biochemical classification of depressive disorders, X: urinary catecholamines, their metabolites, and D-type scores in subgroups of depressive disorders.* Arch Gen Psychiatry 1989;46:260-8.
Books:
Kaplan HI, Sadock BJ. *Comprehensive textbook of Psychiatry.* Baltimore: Williams & Wilkins 1985.
Chapters from books or material from conference proceedings:
Cloninger CR. *Establishment of diagnostic validity in psychiatric illness: Robins and Guze's method revisited.* In: Robins LN, Barret JE, editors. *The validity of psychiatric diagnosis.* New York: Raven Press 1989, pp. 74-85.

Acknowledgements and the citation of any grants or other forms of financial support should be provided at the end of the paper, after the list of references.

Notes to the text, indicated by asterisks or similar symbols, should appear at the bottom of the relevant page.

Mathematical terms and formulae, abbreviations, and units of measure should conform to the standards set out in *Science* 1954;120:1078.

Drugs should be referred to by their chemical name; the commercial name should be used only when absolutely unavoid-

able (capitalizing the first letter of the product name and giving the name of the pharmaceutical firm manufacturing the drug, town and country).

Authors are required to correct and return galley proofs of their paper within 2 days of receipt.

Specific instructions for the various categories of papers:

1. Editorials: only upon invitation by the Editor-in-chief or the Editorial Board are brief discussions on general and practical aspects of topics of current interest. The text must not exceed 10 typewritten pages (2000 typewritten characters).

2. Original articles (which may also include invited articles). The text should be subdivided into the following sections: Introduction, Materials and methods, Results, and Discussion and Conclusions. The manuscript should not exceed 40.000 typewritten characters, including the summary, tables, figures and references (max 35). Summary should be no more than 3000/3500 typewritten characters (please strictly follow the above-mentioned instructions). In the Objective(s) section, the aim (or the aims) of the work must be clearly summarised (i.e., the hypothesis the Authors aim to verify); in the Method(s) section, the Authors must report the context of the study (i.e., general paediatrics, Hospital, Specialist Centre …), the number and the kind of subjects under analysis, the kind of treatment and of statistical analysis used. The Results section should refer to the results of the study and of the statistical analysis. In the Conclusion(s) section should report the significance of the results as related to clinical implications.

3. Brief articles: this space is dedicated to brief communications of clinical and experimental data and to preliminary data of ongoing research of particular interest. The manuscript should not exceed 20.000 typewritten characters, including the summary, tables, figures and references (max 10).

4. Case reports: brief articles (maximum 4000/4500 typewritten characters) in which clinical original experiences from medical practice are described.

5. Assessment and instruments in psychopathology. This section hosts articles on psychological and psychopathological assessment instruments aiming at improving knowledge of psychological functioning of those subjects with mental and behavior disorders in different reference models. The use of such instruments is not limited to clinical population but also includes non-clinical and general population. This section also accepts studies on validation and translation into Italian of instruments, new assessment instruments and competing studies of new assessment instruments with other procedures of assessment than psychopathological constructs. The manuscript should not exceed 40.000 typewritten characters, including the summary, tables, figures and references (max 35).

6. Clinical psychopharmacotherapy: articles reporting the latest developments in the area of drug therapy should be subdivided into the following sections: Introduction, Materials and Methods, Results, and Discussion and Conclusions. The text must not exceed 30.000 typewritten characters including the references, tables, figures, and summary (3000/3500 typewritten characters, excluding figure legends and table captions).

Subscriptions

The Journal of Psychopathology is published quarterly. Annual subscription: € 70,00 for Italy; € 85,00 for all other countries; € 30,00 for single issues (when available). All correspondence concerning subscriptions (including payments) should be addressed to: Journal of Psychopathology, Pacini Editore Srl, Via Gherardesca 1, 56121 Pisa (Italy) – Tel. + 39 050 313011 – Fax + 39 050 3130300
abbonamenti@pacinieditore.it - www.pacinieditore.it

Articles in open access, information for authors including editorial standards for the preparation of manuscripts and submission and Publisher's note also available on-line: www.jpsychopathol.it

Printed by Pacini Editore - September 2018
Journal printed with total chlorine free paper and water varnishing